New Therapies for Amyotrophic Lateral Sclerosis: Challenges and Next Steps

Report Summary

HEALTHCARE AND HUMAN SERVICES POLICY, RESEARCH, AND CONSULTING—WITH REAL-WORLD PERSPECTIVE.

Prepared for: The Amyotrophic Lateral Sclerosis Association
Submitted by: The Lewin Group, Inc.

May 10, 2016
New Therapies for Amyotrophic Lateral Sclerosis: Challenges and Next Steps

A. Progressive and Fatal Disease

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease of the brain and the spinal cord that causes progressive muscle weakness and eventually death. More than 12,000 Americans have a definite diagnosis of ALS.

The most common symptoms of ALS are muscle weakness and atrophy in the arms or legs, slurred speech, difficulty chewing or swallowing, cognitive disorders, and neurobehavioral problems. However, people with ALS exhibit high variability in their symptoms and patterns of progression of the disease. Ultimately, people with ALS lose the ability to move, speak, eat, and breathe. While the rate of progression of ALS varies, it is usually fatal within 2-5 years of symptom onset.

ALS has various genetic and environmental causes. Certain genetic mutations that are linked mostly to familial (inherited) ALS account for only about 5-10% of ALS cases. The other 90-95% of ALS cases are sporadic, that is, occurring apparently randomly in people with no family history of the disease. Aside from familial ALS, the only established risk factors for ALS to date are age and sex. The disease is more common in older adults and in males.

The causes for sporadic ALS are largely unknown, but appear to be associated with both genetic and environmental risk factors. Recent research indicates that it is possible to identify potentially causative mutations in roughly 15% of patients with sporadic ALS.

Early and accurate diagnosis of ALS is difficult to achieve due to the various steps used to reach a diagnosis. The average time from onset of symptoms to confirmation of diagnosis of ALS in the U.S. is about 16-18 months. There is no single, gold-standard test for ALS. Rather, it is diagnosed through a series of tests to rule out other diseases that can be mistaken for ALS, especially during its early stages.

The costs associated with ALS are high. According to a 2012 report conducted by The Lewin Group and sponsored by The Muscular Dystrophy Association using commercial insurance data from 2008 to 2010, the total estimated annual cost of ALS in the U.S. was approximately $256 million to $433 million in 2010 dollars, including medical expenses, non-medical expenses, and loss of income.

B. Limited Therapeutic Options

There is no cure for ALS. Only one medication, riluzole, has been shown to be effective and safe in slowing the progression of ALS. It does not modify the ALS disease process and does not strengthen muscles or improve ALS symptoms. Riluzole’s effects are only moderate and are not sustainable; it typically increases survival by about 2-3 months. Riluzole was approved by the FDA in 1995.

Although they do not slow the ALS disease process, other treatments can help extend survival, improve quality of life, and maintain daily function of ALS patients. These include invasive and
non-invasive ventilation (breathing support) and certain forms of nutrition therapy. Other interventions help to manage symptoms, including those for drooling, airway mucus accumulation, pain, various mental health disorders, insomnia, and spasticity. Assistive devices can help with communication disorders, ambulation, and other functions of daily living, along with physical therapy, occupational therapy, and speech therapy.

Although more than 30 clinical trials of drugs and biological therapies for ALS have been conducted over the past 20 years, none has demonstrated the ability to modify the progression of the disease in humans. Several recent, large ALS clinical trials have failed to achieve improved patient outcomes. Despite promising results in laboratory and animal testing, these drugs did not show any clinical benefits for patients, and are no longer active for ALS research.

The difficulty of developing an effective therapy for ALS starts with the nature of ALS as a complex, multifactorial disease that presents itself in various ways across patients. Given the rarity of ALS, there are relatively few human subjects available for enrollment in clinical trials, and those patients are spread over numerous ongoing trials. The heterogeneity of the disease and lack of diagnostic biomarkers limits the ability to identify patient subgroups that are more likely to respond to investigational therapies in clinical trials.

C. Renewed Interest in ALS Research

Breakthroughs in genomics, recent discoveries of numerous genetic mutations linked with ALS, and other technological advances over the last decade have fueled research into ALS disease processes, diagnosis, and treatment. The avenues of promising research involve, for example, biomarkers to diagnose and treat the disease, use of stem cells to identify potential drug targets and to deliver growth factors or other protections to spinal neurons, and applications of precision medicine to identify therapies for patients with particular forms of ALS. There is greater emphasis on enhancing the quality of life and disease management for ALS patients, including providing ALS care in multidisciplinary settings for symptom management and enabling as much patient autonomy as possible throughout the course of the disease. Many of these efforts involve collaborations of academic researchers, government agencies, industry, patient organizations, and others.

D. Challenges to Development of Treatments for ALS

The full report addresses a range of interrelated challenges to development of new therapies for ALS. Among these are the rarity of the disease, its poorly understood causes and disease pathways, lack of validated biomarkers to identify and track the disease and impact of potential therapies, inadequately identified molecular targets for such therapies, insufficient animal and other models for understanding the disease and testing potential therapies, insufficient elucidated regulatory pathways for development of therapies, and the costs and timelines required to develop and validate new therapies. Several of the main challenges are briefly described, below.

Causes of ALS

Gaps in understanding of the causes of ALS pose great challenges to drug development for ALS, including the basis for biomarker development, identification of potential drug targets, validation...
of reaching these targets, and such matters as clinical trial design and patient identification for enrollment into clinical trials.

Researchers have achieved a much improved, yet far from complete, understanding of several specific genetic mutations that cause familial ALS. Four genetic mutations are linked to approximately 65% of cases of familial ALS: C9orf72, Cu/Zn superoxide dismutase 1 (SOD1), fused in sarcoma (FUS), and TAR DNA binding protein gene (TARDBP). The irregularity in patterns of inheritance of ALS complicates the identification of the genetic basis of ALS. Also, various phenotypes (expressed forms) of ALS can result from the same genetic mutation. Genome-wide association studies (GWAS) continue to be conducted to identify candidate genes that increase the risk of certain phenotypes (expressed forms) of ALS, and significant advances in genome sequencing are accelerating research into the genetic basis of ALS.

Various environmental causes and risk factors for sporadic ALS have been proposed and investigated, but remain inadequately validated. These include, for example, exposure to certain toxins, infectious diseases, dietary factors, level of physical activity, trauma, and behavioral and occupational factors. However, other than older age and male sex, environmental risk factors are inadequately validated.

**Biomarkers**

Biomarkers are objectively measured variables or traits that are used as indicators of a biological state or process. A major challenge in ALS is the absence of validated biomarkers that can be used in detection of presymptomatic ALS, diagnosis, prognosis (estimate natural course of disease), target activation (whether a therapy engages the intended molecular or other disease locus), prediction (whether a particular type of patient will respond to a given treatment), monitoring of treatment response, and other ways. Biomarker advancement is essential for pursuing new therapies in ALS. Diagnostic biomarkers would help to identify patients who truly have ALS, even at early stages of the disease. They could be useful in selecting patients for clinical trials and to more efficiently determine which potential therapies have greater likelihoods of success during each stage of clinical trials, thereby reducing financial risk of continued investigation of new therapies.

**Disease Models**

Cell-based, animal-based, and other types of disease models are essential for studying the disease processes of ALS and testing potential new therapies. Disease models are essential in development of new therapies because they allow researchers to gain practical insights into how a patient with ALS might respond to certain therapeutic strategies and whether there is a scientific basis for pursuing these in humans. There is no single model for ALS that appropriately encompasses all pathological and behavioral aspects of the disease. While mouse and other animal models have been essential in expanding our understanding of certain disease processes in ALS, they have been less helpful to date in predicting clinical outcomes of potential new therapies for ALS. Induced pluripotent stem cells (iPSCs) show some promise as another potential disease model. These are adult cells that have been genetically retrofitted to resemble embryonic stem cells, and therefore have the capability of developing into various cell types in the body. By increasing the menu of models available, researchers can develop a repertoire that represents the diversity of ALS and its disease processes.
**Target Engagement and Validation**

An inadequacy in development of ALS therapies is validation and engagement of molecular targets or other disease loci for such therapies. Most proposed therapies for ALS do not have a validated target. As such, researchers cannot determine whether a drug has engaged the intended target at the molecular level, aside from whether it yields improved patient outcomes. Target activation biomarkers, as well as disease progression biomarkers, can be useful in early clinical trials to determine whether a particular drug is engaging its molecular target and benefiting all or certain trial participants. If so, those findings can inform enrollment of patients into subsequent trials who are most likely to benefit from that treatment. Researchers can design a trial with a smaller sample size and shorter duration that still has the potential to show efficacy in modifying disease progression.

**Risks of New ALS Drug Development**

The cost of developing and gaining market approval for new drugs and biological therapeutics can be lengthy and very costly, with estimated per-drug averages ranging from the low hundreds of millions of dollars to more than $2.6 billion, nearly half of which is cost of capital (or “time costs”). The high costs of drug development and the high ratio of failures to successes places great risk on drug development decisions, particularly for a rare disease with poorly understood etiology, inadequately characterized therapeutic targets, and a short life expectancy curtailing lifelong drug consumption, yielding limited and uncertain prospects for return on investment.

**Regulatory Guidance for Patient-Focused Drug Development**

The lack of success in developing drugs and biologics for ALS suggests that FDA guidance that is informed by multistakeholder input would help to clarify and improve the predictability of the regulatory pathway for new therapies. Among the development challenges are the limitations imposed by the rarity and heterogeneity of ALS, current inadequacies in disease models, biomarkers, target engagement, and understanding of patient perspectives on benefit/risk tradeoffs of investigational therapies, as well as concerns about clinical trial design and patient selection and enrollment, selection of endpoints, and the regulatory review flexibility for new product applications. In recent years, the FDA has provided guidance documents to encourage drug development for unmet medical needs and to clarify pathways for the development of therapies for rare diseases. The agency has published guidance on pharmacogenomics data submissions and aspects related to validation of biomarkers, clinical trial endpoints for approval of certain therapies, patient-reported outcome measures, and adaptive clinical trials. Under authorities in the Food and Drug Administration Safety and Innovation Act (FDASIA), The ALS Association is leading an effort among ALS stakeholders to draft drug development guidance for industry that will be submitted to the FDA to inform an official guidance.

**Consideration of Additional Regulatory Pathway**

Certain long-standing and newer initiatives have greatly improved the drug development process for rare and severe conditions. The Orphan Drug Act of 1983 has proven to be highly successful in incentivizing development and marketing of orphan drugs, particularly in recent years. The FDA has several other programs that are intended to facilitate and speed development and review of new drugs and biologics to address unmet medical needs related to treating serious or life-threatening...
conditions, including fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation.

Currently proposed legislation before Congress is intended to encourage development of “dormant therapies” for certain unmet medical needs. Although such drugs were found ineffective or were not otherwise pursued for their originally intended indications, they may have potential applications for unmet medical needs; however, their limited or expired patent protection may discourage industry sponsorship of further development. The Dormant Therapies Act is intended to build on the Orphan Drug Act by encouraging drug sponsors to invest in developing potential therapies, including the typically high costs of clinical trials, that might not otherwise be pursued.

E. Recommendations for Advancing Development of ALS Treatments

1. **Increase support for comprehensive risk assessment for ALS** to understand genetic, epigenetic, environmental, occupational, sociodemographic, and other risk factors contributing to diverse ALS phenotypes.

   a. Conduct large, stratified case control genome-wide association studies (GWAS) to identify, with increased statistical power, the genetic risk factors associated with various ALS phenotypes.

   b. Conduct whole-genome sequencing of ALS patients with well-characterized phenotypes and controls.

   c. Conduct systematic, multicenter analyses of ALS populations, stratified by known genetic risk factors, age of onset, and other phenotypic characteristics, versus appropriate controls, to establish the risks of environmental exposures.

   d. Conduct analyses of large, general population-based registries to determine environmental, behavioral, and social risk factors for ALS.

   e. Conduct longitudinal analyses of ALS populations to determine genetic, environmental, and other factors (e.g., medications) associated with disease progression and survival.

   f. Continue to develop and expand genotypic and phenotypic classification of ALS.

2. **Develop highly diverse ALS models** based on species and other attributes to answer particular research questions, e.g., cells for molecular processes and rodents for testing candidate therapies.

   a. For these models, develop a broad range of outcome measures to track various aspects of disease processes, ranging from molecular processes, histopathology, motor function, cognitive function, and survival.

   b. These models should include more diverse genetic mouse models as well as models in cells, worms, insects, fish, and other mammals.

   c. Continue to expand and develop resources for mouse models, including the National ALS Mouse Model Repository at The Jackson Laboratory.

   d. Recognizing the limited success of translating efficacy from mouse models to human disease, pursue use of mouse models introduced with human-derived
induced pluripotent stem cells (iPSCs) that have been differentiated into ALS motor neuron and astrocytes for testing of investigational therapies. Use human tissues to validate pathways and targets identified in such models.

e. Among the sources to inform development and characterization of ALS models, draw on the National ALS Registry, National ALS Biorepository, and such other biorepositories as those of the Clinical Research in ALS and Related Disorders for Therapeutic Development (CREATe) Consortium and the Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS).

f. Catalog the expanding number of pre-clinical models with systematically characterized strengths, weaknesses, and other attributes for representing particular molecular, cellular, physiological, and behavioral ALS phenotypes. This expanding catalog could build on the Alzforum ALS Mouse Models Database.

g. Encourage non-competitive sharing of ALS models with transparent, rigorous studies to validate their respective phenotypic attributes, and develop standard operating practices and best practices for using these models.

h. Learn from preclinical modeling used in other neurodegenerative diseases via collaboration with researchers in those disease areas.

3. Develop and validate ALS biomarkers, including protein-based biomarkers alone and in combination with neurophysiological and neuroimaging biomarkers, for presymptomatic identification, diagnosis, prognosis, prediction of therapeutic efficacy, monitoring of disease progression, and patient care planning.

a. Increase emphasis on identification and validation of presymptomatic biomarkers that can be used for earlier identification of ALS (or other motor neuron conditions) and earlier intervention to slow the onset or progression of symptomatic motor neuron demise. This work could start with early biomarker identification in people with known heritable risk of ALS and should extend to those at risk for sporadic ALS.

b. Implement presymptomatic and diagnostic biomarkers to increase efficiency in patient selection for clinical trials by helping to identify patient subgroups that are more likely to respond to particular investigational therapies targeted to disease processes in those subgroups.

c. Conduct longitudinal studies of known and candidate biomarkers to determine their natural history over the course of disease progression and their sources of variability in order to better inform their research and clinical utility.

d. Facilitate precompetitive academic, industry, and governmental collaborations to advance development and validation of biomarkers.

4. Develop a national infrastructure for sharing of patient data and biosamples across registries, biobanks and other collection initiatives.

a. Standardize data definitions and collection processes to encourage collection of complete samples.
b. Assign unique identifiers, e.g., globally unique identifiers (GUID), to patients to facilitate appropriate sharing of biosamples and data and to protect patient anonymity.

c. Develop an electronic platform on which researchers can search for, access, and communicate with others regarding patient biosamples and data.

5. **Develop and validate targets** for pharmacologic, gene, and cellular therapies.

   a. Such targets include, e.g., inflammation factors, kinases, mutant genes, and specific cell populations (i.e., stem cell replacement of motor neurons and astrocytes).

   b. Tailored interventions are targeted to blocking expressions of mutant genes that lead to motor neuron demise; these interventions include, for example, using antisense oligonucleotides (ASOs), antibodies, small molecules, or genetic engineering to target SOD1, C9orf72, or ATXN2 mutations.

6. **Facilitate collaboration** of academic researchers, industry, government and others, including patient groups, to advance ALS research in disease mechanisms, biomarker development, therapeutic target validation, and clinical trials of investigational therapies.

   a. Leverage the complementary attributes and approaches of academic researchers and industry, helping to orient preclinical research and investigation of candidate therapies toward greater likelihood of translation into humans, lowering the risk of drug development.

   b. Form early partnerships and gain input from regulatory agencies and patients (e.g., on patient-centered endpoints for clinical trials) to increase the efficiency and relevance of development and testing of new ALS therapies.

   c. Increase funding from combinations of philanthropic sources, industry matching funds, and government research support.

   d. Continue to build on and adapt research partnership models in ALS, including The ALS Association’s drug development contracts between academia and industry and Target ALS, which funds research consortia of academic and industry researchers, and Department of Defense Amyotrophic Lateral Sclerosis Research Program (ALSRP) funding of preclinical research for which industry collaboration is encouraged.

7. **Enhance substantive patient engagement** through interactive, targeted education of patients on the personal, population, and societal benefits of their participation in ALS research, e.g., in clinical trial planning and design and enrollment in clinical trials, registries and databases, and donation for postmortem studies.

   a. In direct and early collaboration with the FDA and industry, involve patients in clinical trial design to ensure use of trial endpoints that are important to patients; include patient representatives or advocates in clinical trial collaborations; and continue researching patient preferences and treatment goals.

   b. Provide ongoing support for patient involvement in research including protection of personal health information, informed consent, and related matters.
c. Encourage patient involvement in registries (e.g., the National ALS Registry) that can facilitate research about the causes and risk factors of ALS, enrollment in clinical trials, and other benefits.

d. Develop infographics, video, and other means to convey to patients the importance of certain inadequately understood aspects of their ability to contribute to research by participating in clinical trials, including in control groups; providing biosamples; and donating their bodies postmortem.

8. Increase research and development of symptomatic therapies for ALS that can help to extend survival, improve quality of life, and maintain daily function.

a. This research should include, but not be limited to, respiratory management and nutritional therapies; management of mental health disorders, sialorrhea, spasticity, and sleep disorders; and use of assistive devices for communication and mobility.

b. Symptomatic therapies should be assessed for comparative effectiveness and safety in various ALS patient subgroups.

9. Continue to develop patient-centered FDA drug development guidance to assist sponsors and other stakeholders for the development and gaining of regulatory approval of drugs and biological products for treatment of ALS.

a. Such guidance should result from collaboration of the FDA and other government agencies, particularly NIH and CDC; researchers from academic institutions and industry, The ALS Association and other patient advocacy organizations, clinicians, and patients and their caregivers.

b. The guidance should span development of drugs and biological products from preclinical development through clinical trial phases, marketing approval, and post-market study. It should address such matters as benefit-risk tradeoffs from patient perspectives; diagnosis of ALS; biomarkers for ALS; clinical trial endpoints, including patient-reported outcome measures; clinical trial design, implementation, and reporting; and the quality and consistency of review of applications for new drugs and biological products for ALS.

c. The guidance would clarify and improve the predictability of the development for ALS and the regulatory pathway for gaining market approval of new therapies. As such, it should improve the efficiency and lower the risk of developing and validating therapies for ALS.

d. Once completed, the guidance should be updated to reflect evolving understanding of ALS disease mechanisms and natural history, including aspects of genotypic and phenotypic diversity, and the entry of potential therapies with new forms of therapeutic action.

10. Establish a new regulatory pathway for dormant therapies to encourage the development of treatments for ALS and other rare conditions of high unmet need.

a. Provide for FDA authority to designate as a dormant therapy a new treatment that meets such criteria as: is intended to treat an unmet medical, has potential for clinically significant improvements in patient outcomes, lacks sufficient patent
protection to incentivize its development, and does not include active ingredients that have been approved previously by the FDA.

b. Determine a fixed period of market exclusivity, starting upon regulatory approval, from generic and follow-on competition that is sufficient to encourage development of the therapy while enabling, via competition or other means, affordable access to such therapies in an acceptably timely manner.

c. Require sponsors of approved dormant therapies to waive certain rights to patents of the approved dormant therapy at the end of the market exclusivity period.