December 1, 2017

Hello,

We hope you enjoy this detailed look at our global research program. We have the premier ALS research program in the world, led by the premier ALS scientist in the world, Dr. Lucie Bruijn. We are the largest private funder of ALS research in the world and thanks to the ALS Ice Bucket Challenge, we are spending three times as much on ALS research as we were before the summer of 2014. Since our research program was founded in 1985, our focus has led to significant ALS research breakthroughs.

Our approach is simple: we fund the best, most promising research anywhere in the world. This approach has led to some of the biggest research discoveries in the history of ALS. We also inspire and initiate innovative partnerships across all sectors – government, industry, academia, and other non-profit organizations. Thanks to our donors, we are currently funding nine global collaborations.

Research is a critical part of our mission. We are also the leading organization providing care services for people living with ALS around the country, as well as advocating for increased funding for ALS research and improved public policies. Everything we do supports our mission of finding treatments and a cure for ALS.

If you’d like to learn more about our global research program, including what specific research projects and/or clinical trials are occurring in your area, please visit our website at alsa.org/research.

Thank you for your interest and support. We are committed to creating a world without ALS.

Sincerely,

Calaneet Balas
President and CEO
The ALS Association
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Acknowledgements

Thank you to our Chapters – especially North Carolina, Golden West, St. Louis Regional, and Rocky Mountain – for all their valuable input and revisions. This was a large team effort involving the Chapters, along with National Development, Communications, Chapter Relations, Advocacy, Executive, Research, and Care Services teams.

*Customizable by chapter
RESEARCH TALKING POINTS, NARRATIVE & STRATEGIC INITIATIVES
SUMMARY

The ALS Association’s global research program has remained at the forefront of ALS research since its inception in 1985. We are the largest private funder of ALS research worldwide, and our efforts have led to some of the most promising and significant advances in ALS research. Our approach is global – the world is our lab – enabling us to fund the top ALS researchers worldwide and ensure that the most promising research continues to be supported. We fund projects across the research pipeline, from basic research through clinical trials, and our support has led to several potential treatments currently in clinical trials. Since the ALS Ice Bucket Challenge in 2014, we have tripled the amount we spend in research every year – from $6 million to over $18 million – and we are committed to maintaining – and even increasing – this level.

OUR HISTORY

Since its inception in 1985, The ALS Association’s global research program has led the way on ALS research. The program was established by Robert Abendroth, one of the founders of The ALS Association and long-standing member of the Board of Trustees. The program was originally modeled after a National Institutes of Health (NIH)-style program that funded basic research grants. When The ALS Association decided to expand our research funding, Mr. Abendroth invited Dr. Tom Maniatis, a world renowned geneticist and molecular biologist, to lead and assemble an advisory board of experts to help identify critical gaps in ALS research. In 2001, they recruited Dr. Lucie Bruijn, to run the global research program and to expand our grant portfolio to include translational research studies, our postdoctoral fellowship, and clinical trial programs. As the program expanded, it was renamed Translational Research Advancing Therapies for ALS, or TREAT ALS™.

Today, Dr. Bruijn serves as the Chief Scientist of The ALS Association and continues to build programs to support The ALS Association’s research goals. She is recognized as an international leader in the field and represents The ALS Association on several scientific and research committees worldwide. Dr. Bruijn and ALS Association CEO Calaneet Balas direct the TREAT ALS™ global research program with guidance from The ALS Association’s Research Committee.
OUR APPROACH TO RESEARCH

Through TREAT ALS™, we are dedicated to a collaborative and global approach. Since our inception, we continue to accomplish significant advances in ALS research. Everything we do works toward discovering ALS treatments and a cure. We do not fund one laboratory, but instead take a global approach in funding the most promising researchers worldwide, whose projects span the entire research pipeline. This covers a wide breadth of scientific focus areas – each is critical to advancing research – while spurring innovation along the way.

Collaboration is the cornerstone of our research program. Rather than conducting research in our own proprietary laboratory, our unique approach to advancing ALS research involves forging partnerships among academic institutions, industry (pharmaceuticals and biotech firms), government, and other nonprofit organizations. We host yearly scientific workshops and symposia to bring the foremost ALS experts together to discuss and explore various ALS research topics, leading to the generation of novel research ideas.

We also focus on the future of ALS research by supporting and attracting bright, young scientists to the ALS field. We foster their creative ideas and hard work to incite advances and propel them to the next level to start their own ALS research laboratories.

HOW WE WORK

Through TREAT ALS™, we maintain a large grant portfolio. All studies funded through the organization undergo competitive review. Every year, we receive hundreds of grant applications, and the number of applications received has doubled since the ALS Ice Bucket Challenge. Leading experts in ALS and related fields from around the world review our grant program to select the most promising ALS projects. Our grant review process is rigorous, following policies and procedures that are in place to maintain the utmost integrity of the research program. Members of our Research Committee provide oversight for final approval of the grants, and the Board of Trustees gives the final approval.

OUR ACHIEVEMENTS

To date, The ALS Association has funded more than $128 million in ALS research. Currently, we are funding over 113 projects in nine countries, all selected through our competitive peer review process, involving top ALS scientists. We are the largest private funder of ALS research worldwide. Our unrelenting focus has resulted in some of the greatest ALS research discoveries in history. From the earliest stages of our program, The ALS Association has recognized novel approaches that have led to significant ALS research breakthroughs.
EXAMPLE OF OUR TRACK RECORD OF SUCCESS

The ALS Association has a strong track record of success when it comes to advancing research. The ALS Association was the first to invest in antisense technology targeting the second most common genetic cause of ALS: SOD1. We supported antisense research despite the high risk of the technology not coming to fruition. Our initial investment of $1.5 million to ALS researchers propelled the concept all the way from an academic laboratory in partnership with industry to testing the approach in the clinic. Currently, a clinical trial for people carrying the SOD1 mutation is ongoing, with plans to begin a clinical trial targeting C9orf72, the most common genetic cause of ALS, in the near future.

Our translational approach facilitates the development of potential antisense treatments not only for ALS, but also for other neurodegenerative diseases. In this way, the value of our initial investment has ballooned from $1.5 million to more than $100 million. In December 2016, the FDA approved antisense technology targeting spinal muscular atrophy, a common neuromuscular disease, which is the leading genetic cause of death in infants and toddlers. This is the first approved treatment for this fatal disorder. This success gives us much hope for the future of antisense therapies targeting ALS.

THE FUTURE

Building on success, our research program continues to evolve with an increased focus on people living with the disease. Driven by a sense of urgency, we are driving drug development while leveraging innovative partnerships with industry, the investment community, and federal agencies. In the years ahead, we will see an increase in the number of clinical trials, as many of the newer approaches in gene therapy continue to expand. Through engagement with the Federal Drug Administration (FDA) and the voice of people living with the ALS, clinical trial design and biomarker programs will be enhanced.

We are in an era of precision medicine that targets an individual patient’s disease process and takes into account individual variability in genes, environment, and lifestyle. As a result, many more large collaborative partnerships will emerge focusing on collecting clinical data closely linked to gene sequencing aimed at improving clinical trial design. Through our consortium initiatives, new therapeutic targets will be identified leading to new treatment approaches.

Treatments that significantly change the course of ALS and ultimately halt the disease continue to be a high priority in our programs. Improving the lives of people living with ALS is also a primary focus. In recognition of the interdependence of care and research, we will continue to leverage our clinical network to conduct a variety of qualitative and quantitative research with our clinics to help to improve patient care, communications, and mobility for those living...
GENERAL PROGRESS POINTS

• In August 2014, millions of people participated in the ALS Ice Bucket Challenge — raising awareness and donating more than $115 million to The ALS Association.

• The ALS Association continues to be a global leader in advancing ALS research. With the generous support of our donors, we are currently funding more than 113 active ALS research projects in nine countries (as of February 2018).

• In The ALS Association’s history, we have committed over $128 million to research.

• Due to the huge funding boost from generous donors during the ALS Ice Bucket Challenge, so far we have committed more than $84 million to research alone, not including investments in the other core pillars of The ALS Association. This commitment is focused on specific projects and large global initiatives to help drive progress toward finding treatments and a cure for ALS. For more information visit: www.alsa.org/ibcspending/

• We feel privileged with this great responsibility to spend these dollars wisely, transparently, and in ways that make the most impact on the fight against this disease.

• We are committed to maximizing all donations from the ALS IBC and beyond by partnering with other organizations to fund research, along with tremendous efforts by our ALS advocates and volunteers across the country. It is important to keep up the momentum to contribute to funding the most promising ALS research all over the world!

IN 2017, THE ALS ASSOCIATION:

• Committed an $18 million research budget to support promising projects all over the globe.

• Supported over 159 projects in 10 countries.

• Advanced ALS research to better understand the disease and contributed to the knowledge base of ALS research in the scientific community, where important results and comprehensive ALS reviews were published in top scientific journals by researchers and clinicians we funded.

• Invested in numerous ALS clinical trials through our Clinical Trial Pilot Program, facilitated partnerships between academia and industry to propel ideas from the lab into clinical trials, and invested in clinical trial infrastructure to ensure that trials are carried out at the highest level.

The ALS Ice Bucket Challenge of August 2014 raised more than $115 million for The ALS Association.
Many new clinical trials we are funding began enrollment, such as the growth factor stem cell trial “CNS10-NPC-GNDF” at Cedars-Sinai Medical Center, Amylyx Pharmaceuticals’ phase I/II CENTAUR trial across the country, and a phase II clinical trial in Italy and at Massachusetts General Hospital testing drug RNS60.

Saw great advancement and more collaborations between the research strategic initiatives we support, including an exciting partnership between Answer ALS, Project MinE, and the New York Genome Center for Genomics of Neurodegenerative Disease (CGND) to share genomic sequencing information to speed their efforts toward new ALS treatments and a cure.

Funded six new bright, young scientists through our Milton Safenowitz Postdoctoral Fellowship Program and two new clinician scientists through fellowship awards in partnership with the American Academy of Neurology (AAN).

Key advancements were made in wearable sensor and brain computer interface technology by our Assistive Technology Challenge winners – Pison Technology and the Donders Institute for Brain, Cognition, and Behavior.

ALS researcher Dr. Don Cleveland won the $3 million 2018 Breakthrough Prize in Life Sciences, allowing him to continue his work in ALS antisense technology. Successes of antisense therapy in other neurodegenerative diseases, such as spinal muscular atrophy, all stemmed from our initial investment in this work.

NINE NEW STRATEGIC INITIATIVES SUPPORTED

Strategic initiatives are large global collaborations focused on the understanding of the disease, targeting new therapies, expediting clinical trials, and making RNA and DNA sequencing data available to the entire ALS research community. These initiatives will generate data and resources available for researchers globally. Central to all the major new collaborations are the people living with ALS.

In October 2014, The ALS Association announced initial ALS Ice Bucket Challenge spending decisions designed to ignite four new strategic initiatives – Project MinE, New York Genome Center for Genomics of Neurodegenerative Diseases (NYGC CGND), the Neuro Collaborative, and ALS Accelerated Therapeutics (ALS ACT) – to advance progress towards finding treatments for ALS.

Since then, The ALS Association has announced its support for five new collaborative strategic teams – CReATe Consortium, Genomic Translation for ALS Clinical Care (GTAC), Answer ALS, NeuroLINCS, and ALS ONE.

TWO NEW ALS ANTISENSE DRUGS

Antisense therapy, which The ALS Association has supported since 2004, prevents the production of proteins involved in disease, with the aim to slow or stop disease progression in people living with ALS.

The Neuro Collaborative is one of the major research strategic initiatives made possible by the ALS Ice Bucket Challenge. Its scientists have developed antisense drugs targeting two of the most common ALS genes, SOD1 and C9orf72.

This progress can be directly attributed to The ALS Association’s early investment of SOD1 antisense technology. The SOD1 antisense clinical trial started in early 2016, led by Biogen and Ionis Pharmaceuticals and is currently
A C9orf72 antisense trial is slated to start in the near future.

- Our investment in this innovative technology also translates to other neurodegenerative diseases, making our impact even greater. In December 2016, the FDA approved the antisense drug SPINRAZA™ to treat a broad range of people with spinal muscular atrophy (SMA), a common, fatal genetic disease in children.

**NEK1 now ranks among the most common genes that contribute to the disease.**

**FOUR GENES IDENTIFIED SINCE THE ALS ICE BUCKET CHALLENGE**

- Identifying ALS genes that contribute to ALS disease allows scientists to target them for therapy, essentially increasingly the likelihood that a TREATMENT will be found.

- Four new ALS genes that contribute to the development of the disease have been identified in the last two years, two of which, **NEK1 and C2orf2**, were announced in July 2016. (Note: the four genes identified since the ALS IBC are NEK1, C2orf2, TUBA4A, and TBK1.)

- Researchers who are part of Project MinE’s global gene sequencing effort identified **NEK1, which now ranks among the most common genes that contribute to the disease.** The study involved contributions from more than 80 researchers in 11 countries.

- Global collaboration among scientists, which was made possible by ALS Ice Bucket Challenge donations, led to these important gene discoveries.

**WHY SUPPORT FOR RESEARCH IS CRITICAL**

- There is renewed hope in ALS science circles these days. The excitement is fueled in part by important new discoveries. In recent years, researchers have pinpointed a key genetic cause of the disease and begun sorting through, to an unprecedented degree, the way that a gene mutation plays out inside the brain’s motor neurons.

- We have tripled the amount of money allocated to research in the years since the Ice Bucket Challenge, leading to greater scientific output and a greater understanding of the disease pathways and potential strategies for new therapies.

- To get a drug from preclinical trials to market costs between $50M and $100M on average, according to the U.S. Department of Health and Human Services (HHS).

- It can take between $2 billion and $3 billion to develop one new pharmaceutical treatment from an idea to an approved drug.

- A clinical trial is the best way for researchers to find effective treatments, and, equally important, to weed out...
useless or harmful ones. Clinical trials are costly and may last months. When the treatment being tested proves to not be effective, it can be sorely disappointing. But **clinical trials have proven to be the most reliable, and ultimately the fastest, way to discover treatments that really work.**

- Unfortunately, **people with ALS will pass away while waiting for experimental treatments to slowly crawl through the approval process**, and some promising drugs are simply shelved because companies run out of money trying to finance multiple long and expensive clinical trials.

- **The ALS Association funds top ALS researchers all over the globe**, forming lasting global collaborations, and encouraging data sharing to avoid duplication. We invest in innovation, technologies, and partnerships, exploring all aspects of the disease across the research pipeline, from idea through phase II clinical trials.

- Funding from The ALS Association over the past 30 years has contributed to a better understanding of ALS, **funded all the major ALS gene discoveries**, improved care for people living with the disease, and explored new treatment approaches in clinical trials.

- Our work is not done. Researchers are close to major ALS scientific breakthroughs and therapies. They are motivated to finish the work they started! **Together, we can help them get there.**

For questions or more information, please contact Jill Yersak, Ph.D., Associate Director of Research Communications, at jyersak@alsa-national.org.
THE ALS ICE BUCKET CHALLENGE

In August 2014, millions of people around the world dumped buckets of ice water on their heads to raise awareness and funds in support of the ALS community. The result was staggering – The ALS Association welcomed 2.5 million new donors, the majority of them millennials, and received $115 million in just six weeks; at least $100 million more was donated to other ALS organizations around the world. It was the most important moment in the history of ALS since Lou Gehrig’s farewell speech more than 75 years ago. Ultimately, the ALS Ice Bucket Challenge became the single biggest act of collaborative grassroots fundraising in history. This all stemmed from the efforts of three young men living with ALS, who inspired their communities, celebrities, and the world to join the fight against, and bring awareness to this devastating disease.

The ALS Ice Bucket Challenge became the single biggest act of collaborative grassroots fundraising in history.

ALS ICE BUCKET CHALLENGE AND RESEARCH

The ALS Ice Bucket Challenge and the infusion of funding it generated has had a significant impact on advancing ALS research globally. Since 2014, The ALS Association has invested more than $84 million in the most promising research projects. The ALS Association research budget more than tripled to an all-time high of $19 million, which propelled the organization to become the largest ALS research funder outside the U.S. federal government in any single year in the world. We proudly fund diverse, cutting-edge research through our competitive TREAT ALS™ global research program in laboratories around the world, rather than just one laboratory. With your help, we funded more than 180 critical projects in 11 countries in the last year alone, in addition to a total of nine global collaborative initiatives that would not have been possible without the ALS Ice Bucket Challenge. Through collaborations with government, industry, academia, and other nonprofit organizations, The ALS Association aims to accelerate drug development so that people living with ALS receive treatments faster.
The ALS Association has announced nine important research strategic initiatives since the ALS Ice Bucket Challenge to advance the search for treatments and a cure for the disease. In this document, we have included details on the goals of each initiative, along with information on The ALS Association’s role and funding commitments.

Strategic initiatives are large global collaborations focused on the understanding of the disease, targeting new therapies, expediting clinical trials, and making RNA and DNA sequencing data available to the entire ALS research community. These initiatives will generate data and resources available for researchers globally. Central to all the major new collaborations are the people living with ALS.

Learn more about each strategic initiative here:

PROJECT MINE

$1.4 million commitment partnered with Greater New York and Georgia Chapters

An international, large-scale research initiative devoted to discovering genetic causes of ALS and to ultimately finding a cure. The goal is to identify genes associated with ALS by performing whole genome sequencing on at least 15,000 ALS patients plus 7,500 healthy controls worldwide, resulting in an open-source ALS genome database, in conjunction with the collection of skin samples to make ALS patient-induced pluripotent stem cell (iPSC) lines. Our funding supports the U.S. arm of this initiative, led by Jonathan Glass, M.D. (Emory University) and John Landers, Ph.D. (University of Massachusetts Medical School). Funding announced in October 2014.

NEW YORK GENOME CENTER—CENTER FOR GENOMICS OF NEURODEGENERATIVE DISEASES (NYGC CGND)

$2.5 million commitment partnered with Greater New York Chapter matched with an additional $2.5 million contributed by the Tow Foundation

A consortium that is a collaboration between numerous global laboratories capable of generating and analyzing thousands of DNA sequences from people with ALS. The goal is to discover new genetic contributors of ALS to then translate into clinical solutions for ALS. It houses all data in a central repository that is freely available to the research community worldwide. Funding announced in October 2014.

GENOMIC TRANSLATION FOR ALS CARE (GTAC)

$3.5 million commitment partnered with Greater New York Chapter

A collaboration between Biogen and Columbia University Medical Center (CUMC) to better identify new targets for treatment development, in order to understand how different genes contribute to various clinical forms of ALS. This will translate into clinical trials that are more focused. This project will follow 1,500 people with ALS.
and collect detailed clinical data, sequence their DNA and store blood cell samples to generate iPSCs. This study will allow correlation of ALS clinical symptoms to genetic causes and help stratify patients for future clinical trials. Funding announced in August 2015.

**CReATe**

Clinical Research in ALS and Related Disorders for Therapeutic Development (CReATe) Consortium: $450K commitment for biomarker study and biorepository and an $835,937 commitment to Drs. Paul Taylor, Jinghui Zhang, and Michael Benatar for DNA sequencing

A Rare Diseases Clinical Research Consortium (RDCRC) that forms part of the National Institutes of Health (NIH) Rare Diseases Clinical Research Network. The goal of CReATe is to identify new genes and novel disease pathways linked to ALS and related disorders. In addition to sequencing samples collected from study participants, CReATe is building a resource of biosamples that have attached detailed clinical information, providing a unique and critical resource for biomarker development. The biorepository will enable the discovery and validation of biomarkers relevant to therapy development for patients with ALS and related disorders. In partnership with The ALS Association, CReATe is funding pilot biomarker projects using this resource, as well as other biorepositories, including the Northeast ALS Consortium (NEALS) biorepository supported by The ALS Association. Funding announced September 2015.

• **CReATe Connect: All ALS organizations associated with CReATe are a part of Connect**

  A part of the Rare Diseases Clinical Research Network (RDCRN) Contact Registry, CReATe Connect is an international online system to help facilitate communication between doctors/scientists and patients and their families. CReATe Connect provides a means for patients with these rare diseases (and their family members) to indicate their willingness to be contacted in the future about clinical research opportunities and to receive updates on the progress of research and new educational opportunities sponsored by CReATe.

**NEUROLINCS**

$2.5 million commitment partnered with the Greater Philadelphia Chapter

A partnership with NIH’s National Institutes of Neurological Disorders and Stroke (NINDS). This National Institutes of Health (NIH)-funded collaborative effort is between various research groups with expertise in iPSC technology, disease modeling, OMICS methods, and computational biology. The goal is to use iPSC lines from ALS patients and healthy controls and OMICS methods to identify unique cell signatures that are specific to various subtypes of motor neuron diseases, in order to better develop therapies and design clinical trials. Funding announced July 2016.

**ALS ACCELERATED THERAPEUTICS (ALS ACT)**

$10 million commitment matched with an additional $10 million contributed by ALS Finding a Cure®

A novel academic-foundation-industry partnership with ALS Finding a Cure, initiated with researchers from
General Electric (GE) Healthcare and four academic NEALS sites to accelerate treatments for people living with ALS. It is using the following strategies to develop new therapeutic approaches for ALS: supporting development of neuroimaging tools as potential ALS biomarkers; supporting projects focused on decreasing the production of misfolded proteins, and reversing neuroinflammation, two major contributors to the disease process; supports NeuroBANK™ (see below); and supporting Phase IIA pilot clinical trials with relevant biomarkers aimed at developing novel high-potential ALS treatments. A TDP 43 PET Tracer Grand Challenge was launched as part of ALS ACT. Funding announced October 2014.

- **NeuroBANK™: funding under ALS ACT – further expanded in August 2016**
  A patient-centric clinical research platform and central repository that sets the framework to allow for standardization of ALS patient information (including proteomic, genomic, and clinical data) that is linked across simultaneously running research studies, locations, and modalities. It is designed to host, curate, and disseminate this information. Global Unique Identifier (GUID) technology generates a patient-specific character string that securely identifies a patient without revealing their true identity. Neurobank™ is part of NYGC projects, GTAC, and Answer ALS.

**NEURO COLLABORATIVE**

**A $5 million commitment in October 2014 - funding through The ALS Association with contributions from the Orange County and Wisconsin Chapters. To date, we have committed a total of $8 million.**

An initiative founded as a collaboration between three leading California laboratories aimed at discovering and developing new potential ALS therapies that can be delivered to pharmaceutical companies for further development. The three laboratories are the Svendsen Laboratory at Cedars-Sinai in Los Angeles, which will develop and maintain a Motor Neuron Core Facility to create iPSC lines from people with ALS that will be openly shared; the Cleveland Laboratory at the University of California San Diego, which will spearhead the development of antisense therapy against the C9orf72 gene, the most common genetic cause of ALS; and the Finkbeiner laboratory at the Gladstone Institutes, which is affiliated with University of California San Francisco, which will further develop robotic technology for screening drugs in motor neuron cell culture. The Cleveland laboratory is collaborating with Martin Marsala, M.D., at the University of California San Diego and Brian Kaspar, Ph.D., at the Research Institute at Nationwide Children’s Hospital in Ohio. In 2014, The ALS Association Golden West Chapter, along with Advisory Trustees Jim Barber and Linda Della, partnered with the National ALS Association to build the Neuro Collaborative concept. For more information, [click here](#).

Funding announced October 2014.
ANSWER ALS

The ALS Association contributed to its development/business plan and is a partner with Team Gleason and others to advance this initiative. We plan to contribute funds as the program evolves.

An initiative spearheaded by Steve Gleason to challenge ALS researchers to come up with a solid plan to find a cure for ALS. Its strategy includes two impact goal arms. One is designed for immediate impact to help ALS patients live more productive lives by supporting affordable assistive technologies and services. The other arm is designed to contribute to the ultimate impact to fund a collaborative effort to bring together the world’s best ALS researchers to find a treatment or a cure in the next five-10 years. As part of this initiative, all DNA samples from participants will be sequenced by the New York Genome Center (NYGC), which will be funded through ALS Association research programs. In addition, NeuroBANK™ will be an integral part of the program. Projects funded as part of ALS ACT, the Neuro Collaborative, and NeuroLINCS form an important foundation for Answer ALS. Partnership announced in September 2015.

ALS ONE – MASSACHUSETTS ALS PARTNERSHIP

The ALS Association partnered with ALS ONE and ALS Finding a Cure to fund $2 million each for specific clinical and research initiatives to maximize collaborations to find treatments and a cure for ALS.

An initiative founded by Kevin Gosnell, a person who passed away from ALS, to bring together leading neurology experts and care specialists in Massachusetts to leverage their institutions’ strengths to expedite progress toward finding a treatment for ALS by 2020 while improving care now. Institutional partnerships include Massachusetts General Hospital, the ALS Therapy Development Institute (ALS TDI), the University of Massachusetts Medical School, and Compassionate Care ALS. Under the ALS ONE umbrella, we fund research projects of Dr. Steven Perrin from ALS TDI, Dr. Nazem Atassi from Mass General, and Dr. Robert Brown from U. Mass Medical School. Partnership announced January 2016. Funding announced in November 2016.
CURRENT PROJECTS
The ALS Association Is Accelerating Progress Toward Treatments

The ALS Association’s TREAT ALS™ Global Research Program

113 Active Research Projects
In an effort to accelerate progress toward finding treatments and a cure for ALS, The ALS Association is currently funding 113 active research projects all over the globe.

Active Projects by Location
- Arizona 4
- California 15
- D.C. 1
- Florida 9
- Georgia 2
- Illinois 5
- Indiana 1
- Louisiana 1
- Maine 1
- Massachusetts 21
- Maryland 11
- Michigan 3
- Minnesota 1
- Missouri 4
- New York 6
- Ohio 3
- Oregon 1
- Pennsylvania 6
- South Carolina 1
- Tennessee 4
- Virginia 1
- Wisconsin 1

Australia 1
Chile 1
Finland 1
Germany 1
Ireland 1
Italy 2
Switzerland 1
United Kingdom 3

Winter 2018
We support a wide breadth of scientific focus areas – each is critical to advancing ALS research.

Harnessing Innovative Ideas:
Basic research at the lab bench to find therapeutic targets

Translating Concepts to Therapies:
Drug development and biomarker discovery

Advancing Treatments to Patients:
Clinical trials, assistive technology, patient care

Thirteen Scientific Focus Areas
- Disease Mechanisms
- Environmental Factors / Epidemiology
- Disease Models
- Genetics
- Cognitive Studies
- Natural History Studies
- Assistive Technology
- Clinical Studies
- Stem Cells
- Precision Medicine
- Biomarkers
- Drug Development
- Nanotechnology

For more information, visit:
www.alsa.org/research/our-approach
www.alsa.org/research/focus-areas
2015 NONPROFIT SPENDING ON RESEARCH
The ALS Association Is the Largest Nonprofit Funder of ALS Research in the U.S.

2015 Nonprofit Spending on ALS Research

<table>
<thead>
<tr>
<th>Organization</th>
<th>Research Dollars Spent</th>
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<tbody>
<tr>
<td>The ALS Association</td>
<td>$16,608,607</td>
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<tr>
<td>MDA</td>
<td>$12,000,000</td>
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<tr>
<td>ALS TDI*</td>
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<tr>
<td>Les Turner Foundation</td>
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<tr>
<td>Project ALS</td>
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<td>ALS Therapy Alliance</td>
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<tr>
<td>ALS Worldwide</td>
<td>$183,675</td>
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<tr>
<td>Answer ALS*</td>
<td>$99,429</td>
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</table>

Research Dollars Spent on ALS Scientific Discovery

Information from 990/annual report finances from 2015

Note: Graph represents funding supporting approved peer-reviewed research grants
*ALS TDI & Answer ALS = total program service expenses to operate. They do not fund outside research grants

2015 FEDERAL GOVERNMENT SPENDING ON RESEARCH
The ALS Association Leads the Effort in Advocating U.S. Government Spending in ALS Research.

<table>
<thead>
<tr>
<th>Government Agency</th>
<th>Research Dollars Spent</th>
</tr>
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<tbody>
<tr>
<td>Overall NIH</td>
<td>$49,500,000</td>
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<tr>
<td>NIH NINDS</td>
<td>$35,900,000</td>
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<tr>
<td>CDC National ALS Registry</td>
<td>$7,141,179</td>
</tr>
<tr>
<td>DoD ALS Research Program</td>
<td>$7,500,000</td>
</tr>
</tbody>
</table>

Research Dollars Spent on ALS Scientific Discovery

Note: In 2015, the NIH invested $49.5 million in ALS research, of which $35.9 million was from the NINDS. Also, in 2015, the CDC was appropriated $7.7 million for the National ALS Registry and the DoD was appropriated $7.5 million for the ALS Research Program

Key:
MDA: Muscular Dystrophy Association
ALS TDI: ALS Therapy Development Institute
NIH: National Institutes of Health
NINDS: National Institute of Neurological Disorders and Stroke
CDC: Centers for Disease Control and Prevention
DoD: Department of Defense

Winter 2018
The ALS Association’s collaborative and global approach to funding research continues to lead to significant advances by top ALS researchers all over the world.

**THE WORLD IS OUR LAB**
We fund novel, promising research around the globe covering all scientific focus areas, spurring innovation along the way.

- **Harnessing Innovative Ideas**
- **Translating Concepts to Therapies**
- **Advancing Treatments to Patients**

**TREATMENTS & CURES**

1. **Funded Global Research Projects in 10 Countries:** 159+
2. **Current Research Budget:** $18 Million
   - The ALS Association is the highest nonprofit research funder in the U.S.
3. **Global Strategic Initiatives:** 9
4. **New Genes Identified Since the ALS Ice Bucket Challenge (IBC) to Develop New Therapies:** 4
5. **Clinician Scientists Funded in 2017:** 2
6. **New Postdoctoral Fellows Funded in 2017:** 6
7. **Actively Recruiting ALS Clinical Trials:** 65+
8. **MILLION**
   - $84+ Million
   - Dedicated to research since the ALS IBC to advance treatments and a cure
9. **Two Potential New Antisense Drugs and Numerous Other Drugs on the Horizon Aimed to Slow or Stop the Progression of ALS**

Winter 2018
INSPIRING PARTNERSHIPS
Collaboration is the cornerstone of our research program. We partner with academia, industry, government, and other nonprofit organizations.

Impact: We lead by spurring long-lasting collaborations among researchers across all sectors, leading to globally shared data, protocols, and research samples to accelerate research progress.

MAXIMIZING INVESTMENTS
We secure matching gifts to significantly increase donor investment from the ALS IBC and beyond.

Impact: Our original $1.5 million investment in antisense technology infused an additional $100 million and one FDA-approved drug for spinal muscular atrophy, SPINRAZA™, and two potential new ALS drugs targeting SOD1 and C9orf72.

WORKING WITH TOP ALS EXPERTS
We collaborate with top ALS scientists, clinicians, consultants, entrepreneurs, and executives to create and lead an exceptional research program.

Impact: Our highly competitive research program funds the most ALS research dollars of any ALS nonprofit, $19 million in 2016, and is held to rigorous standards to drive innovation.

ATTRACTING YOUNG, BRIGHT SCIENTISTS
We encourage young scientists to enter and remain in ALS research and are dedicated to their continued success.

Impact: Over 90 percent of our postdocs remain in ALS research to start their own labs and mentor more young researchers.

INVESTING IN CLINICAL TRIALS
We sponsor ALS clinical trials to accelerate drugs through the drug pipeline as quickly as possible.

Impact: Currently, we are funding eight ALS interventional clinical trials. We have helped countless drugs move from ideas into trials. Cedars-Sinai’s combined stem cell-gene therapy trial, which started this year, is just one example.

CHAMPIONING PEOPLE LIVING WITH ALS
People living with ALS are at the center of everything we do and must receive the best care and support possible.

Impact: Last year, we funded five clinical management projects focused on improving care for people living with ALS and their families. We awarded two winners of the ALS Assistive Technology Challenge, driving innovation!
Thanks to our generous donors, The ALS Association awards various research projects throughout the year as part of its competitive Translational Research for ALS (TREAT ALS™) Portfolio, which include the following:

- **Multiyear Investigator-Initiated Grants** to established investigators.

- **One-year Starter Grants** to investigators new to the ALS field or senior postdoctoral fellows establishing their own independent position.

- **Milton Safenowitz Postdoctoral Fellowships** to encourage and facilitate promising young scientists to enter the ALS field. Fellows work with a senior mentor and receive extensive exposure to the ALS research community through meetings and presentations.

- **Strategic Challenges** are crowdsourcing initiatives such as the ALS Assistive Technology Challenge to help people living with ALS communicate with ease (partnered with Prize4Life) and the TDP43 PET Tracer Grand Challenge to discover a biomarker to track TDP43 in the body (partnered with ALS Finding a Cure®).

- **Strategic Calls** that invite researchers to submit collaborative projects that address research gaps, areas of high risk-high reward, and/or areas that provide novel opportunities. Includes funding of **Strategic Initiatives** that are large, collaborative research programs. For more information, visit the strategic initiative page and refer to the strategic initiative talking points.

- **Clinical Development Fellowships**, in partnership with the American Academy of Neurology (AAN), to support ALS clinician-researchers focused on projects involving people living with ALS.

- **Lawrence and Isabel Barnett Drug Development Program** fosters collaborations with companies/academia to fund milestone-driven research focused on preclinical studies to move treatment approaches closer to the clinic. Funding specifications and project criteria vary for each specific request for proposals.

- **Pilot Clinical Trials** to support up to and including phase II clinical trials that are associated with a comprehensive biomarker program to test novel, high-potential treatment approaches in people with ALS.

- **Clinical Management Awards** to fund research for improving clinical, psychological, and social management of ALS, focusing on both people living with ALS and their caregivers.

For questions, please contact Dr. Lucie Bruijn, ALS Association Chief Scientist, at lucie@alsa-national.org.
The ALS Association Provides Funding at Every Stage of the Research Pipeline

DEVELOPMENT
Biomarkers are any measurable substance that changes in quantity, either appearing or disappearing over time, with a change in the body's state. Examples are a chemical change in your blood, urine or cerebral spinal fluid, and structural change or chemical change in your brain. They are used to diagnose diseases and track effectiveness of potential treatments. Currently, there are no approved biomarkers for ALS. **The ALS Association currently funds 34 active biomarker projects with a total contribution of approximately $17 million in grants.**

**IMPACT ON ALS**

Today, researchers rely on clinical trial outcome measures such as the ALS Functional Rating Scale – Revised (ALSFRS-R), forced vital capacity (FVC), and others. Once developed, their potential is immense. Right now, the average time to ALS diagnosis is one year. We need to do better. Biomarkers will make ALS diagnosis faster and more accurate. They will also allow physicians the ability to track the disease in real time as ALS progresses in a patient, allowing for more proactive and targeted care. Clinical trials will be more easily stratified, allowing clinicians to test specific populations of people that have a high potential for the therapy to be effective. Biomarkers will also be used to track a person’s response to therapy. It will show whether a drug is hitting its target in the central nervous system and is working properly. Biomarkers will accelerate drug development of new treatment for ALS by making the clinical trials more efficient. This, in turn, increases a potential therapy’s value to pharmaceutical companies, as it will be readily apparent if the therapy is working as designed.

“The ALS Association is committed to supporting biomarker discovery. Identifying biomarkers is an extremely important step in the drug development pipeline to accelerate the discovery of novel treatments and a cure for ALS. We support a number of exciting biomarker research studies in addition to the TDP-43 Biomarker Grand Challenge, all aimed at pioneering and moving the ALS biomarker field rapidly forward.”

– Chief Scientist Dr. Lucie Bruijn
TDP-43 protein is present in aggregates (large clumps of protein) that are found in the brain and spinal cord of people with ALS, and other neurodegenerative diseases, such as Alzheimer’s disease and frontotemporal dementia. Dr. Miller’s team is developing a positron emission tomography (PET) biomarker that is a fluorescent tracer that attaches to TDP-43 protein aggregates and can be observed in real time by PET imaging. The goal is for the tracer to not only contribute to the basic scientific understanding of TDP-43 disease processes, but also to ALS drug development targeting TDP-43 aggregates. Outcomes for drug development will not only impact ALS, but also could apply to other neurodegenerative diseases where TDP-43 aggregates are also observed.

Principle Investigator: Timothy Miller, M.D., Washington University, St. Louis
Funding Award: $500,000 over two years

“Our team at Washington University and St. Louis University is very enthusiastic about developing a PET tracer for TDP-43, which has such important implications for future clinical studies.” – Dr. Timothy Miller
Stem cells have the ability to divide for indefinite periods in a dish, providing an unlimited supply of cells to study. They can give rise to any specialized cell type in the body, including motor neurons and support neurons called glia, which are both lost in ALS. There are different types of stem cells, such as induced pluripotent stem cells (iPSCs), which are typically created from adult skin cells or blood. When derived from a person living with ALS, iPSCs are transformed into motor neurons, exactly reflecting the person’s genetic makeup – like an avatar in a dish.

The ALS Association currently funds 16 stem cell grants with a total contribution of approximately $11 million.

**IMPACT ON ALS**

iPSCs have emerged as the most significant source of stem cells for ALS research and are important sources of neurons to model the disease in a dish. They have the potential to identify new disease pathways and individual susceptibilities to disease that cannot be revealed with other models. They serve as exceptionally valuable tools to find new treatments based on a person’s unique genetic makeup. Neurons derived from iPSCs can be tagged with fluorescent markers to allow tracking of individual neurons over time. This allows researchers to conduct drug screens to find compounds that improve the health of neurons, identifying a potential therapy. Motor neurons derived from iPSCs are even being used in parallel to people living with ALS (from which the cells are derived) during clinical trials to help predict whether a trial drug will positively impact the health of motor neurons.

“iPSCs have emerged as exceptionally valuable tools for modeling disease, screening for new therapies, and finding new treatments based on a person’s unique genetic makeup.”

– Dr. Lucie Bruijn, Chief Scientist, The ALS Association
**Principle Investigator:** Dr. Clive Svendsen, Cedars-Sinai, Los Angeles, Calif.

**Funding Award:** $1.6 million over one year

“Funding from The ALS Association has allowed us to generate a set of valuable ALS iPSC lines and develop robust protocols for making motor neurons from them. As they are the cells that die in ALS, they should help us understand the underlying mechanisms of disease.” – Dr. Clive Svendsen

The Neuro Collaborative is a synergistic research model based in three laboratories in California that are working in collaboration to bring together complementary expertise to advance the understanding of ALS and to develop and expedite ALS therapeutic approaches. One arm of the Collaborative is Dr. Svendsen’s laboratory, which focuses on the establishment of a stem cell and motor neuron core facility to create and store clinical-grade iPSCs, which will be shared openly with the ALS research community, including with large collaborative initiatives such as Answer ALS, the Northeast ALS Consortium (NEALS), the National Institutes of Health (NIH), and the California Institute for Regenerative Medicine (CIRM), among others. The team is developing enhanced, standardized techniques that turn iPSCs into a range of motor neurons and genetically modify them to light up fluorescently to allow researchers to view and track individual motor neuron health over time. The iPSCs will be used for discovering the causes of ALS, developing new drugs through drug screening using a patient's own motor neurons, and creating clinical-grade lines of iPSCs to be used in cutting-edge stem cell therapy trials that are underway at Cedars-Sinai and other institutions.
Researchers have demonstrated that 10 percent of ALS cases are familial, meaning the disease gene is inherited. The other 90 percent of ALS cases are sporadic, meaning they do not know the underlying cause. It is likely that a percentage of the sporadic cases are familial, but those genes are yet to be uncovered. In recent years, there has been a large boom in genome sequencing (where all of a person's DNA is sequenced) due to decreased cost (approximately $2,000 per genome) and advances in sequencing technology. Currently, more than 30 ALS genes have been identified, and counting. The ALS Association supports big initiatives all over the world that are working toward closing the genetic gap to identify all possible ALS genes.

**IMPACT ON ALS**

Gene discovery represents opportunities for new therapeutic targets, thereby increasing the number of potential ALS therapies. Importantly, insights gained from studying genetic forms of ALS are likely to benefit those with sporadic ALS. For example, new model organisms based on newly identified genes are developed to better understand and discover novel disease pathways – information that can be tested and possibly applied to all ALS cases. These new genetic discoveries allow scientists to study disease in ways that would otherwise not have been possible. In addition, identified genetic mutations can be corrected using cutting-edge gene therapy that aims to slow or stop the progression of ALS. Antisense technology designed to correct the two most commonly inherited genes – SOD1 and C9orf72 – is in clinical and preclinical trial phases, respectively. New gene editing technology, such as CRISPR, may also add value in the ALS treatment landscape.

“The ALS Association is committed to supporting genome sequencing and the next frontier of gene discovery. The more genes we uncover, the more potential therapeutic targets we will have, leading us closer to our goal – to discover effective treatments and a cure for this devastating disease.”

– Dr. Lucie Bruijn, Chief Scientist of The ALS Association
Project MinE is an international, large-scale research initiative dedicated to discovering genetic causes of ALS and to ultimately finding a cure. It was founded by Bernard Muller and Robbert Jan Stuit, both entrepreneurs and people living with ALS, who teamed up to change the genetic landscape of ALS. The ALS Association initially committed $1 million to fund the U.S. arm of this global initiative, which now includes 17 countries. Project MinE’s activities are rooted in the theory that genes are thought to contribute, directly or indirectly, to most cases of ALS. The goal is to sequence 15,000 people with ALS and 7,500 healthy people for a total of 22,500 genomes. Already, Project MinE has identified two new ALS genes – NEK1 and C21orf2 – discoveries that were published in back-to-back articles in top journal *Nature Genetics* – a collaborative effort of 80 researchers in 11 countries that included Drs. Landers and Glass in the U.S. As of August 2017, Project MinE has achieved 38 percent of its goal, sequencing a total of 8,347 genomes and counting. There is still much more left to be done! Sequencing just one person’s genome costs $2,000.

For more information on Project MinE, click here.
For more information on Landers’s project, click here.
For more information on genetics, click here.

**Principle Investigators:** Dr. John Landers (left), University of Massachusetts Medical School, Worcester, Mass., and Dr. Jonathan Glass (right), Emory University, Atlanta

**Current Funding Award:** $671,385

*Since Project MinE received a $1 million grant from The ALS Association in the wake of the ALS Ice Bucket Challenge, we were able to expand our operation significantly. Your support has made a profound impact!*

– Dr. John Landers
In 2016, a significant number of ALS research discoveries, advances in clinical trials, collaborations, and strategic initiatives all accelerated the pace of discovery in finding treatments and a cure for ALS.

Here are 10 of 2016’s BIGGEST advances in ALS research! Seven out of 10 were funded by The ALS Association.

1. The U.S. Food and Drug Administration (FDA) reviews and accepts a New Drug Application (NDA) for Radicava™ for the treatment of ALS in 2016. On May 5, 2017, the FDA approves Radicava™ — the first treatment for ALS in over 20 years. With our ALS Drug Development Guidance document in hand, the ALS Association’s Advocacy team worked with the FDA to speed the approval process. It is yet to be seen how Radicava™ will impact people with ALS in the U.S.

2. The Neurological Clinical Research Institute (NCRI) imaging team at Massachusetts General Hospital (MGH) led by Dr. Nazem Atassi, supported under The ALS Association’s ALS ACT, uses PET (Positron Emission Tomography) imaging to successfully scan the first person living with ALS to measure inflammation in the brain, a promising first step in this imaging biomarker study. Since then, many more people have participated in the study.

3. Dr. Aaron Gitler and his researcher colleagues, supported by The ALS Association, identifies a new therapeutic target called Spt4*, designed to reduce toxicity associated with C9orf72 ALS, adding to the growing list of potential ALS therapeutics.

4. Investigators at Cedars-Sinai gain approval from the FDA to test the safety of a combination stem cell—gene therapy in a clinical trial that began in 2017—research the The ALS Association has supported since 2003. Cedars-Sinai is a certified Treatment Center of Excellence, meeting The ALS Association’s rigorous standards with their comprehensive, collaborative approach to patient care and services.

5. The discovery of the NEK1 gene, now known to be among the most common genes that contribute to the development of ALS, makes headlines around the globe. More than 80 researchers in 11 countries out of Association-supported Project MinE conducted the largest-ever study of inherited ALS. This discovery of NEK1 has provided researchers with an important new target for therapy development.

6. IBM’s Watson supercomputer discovers five new ALS genes. IBM’s collaboration with the Barrow Neurological Institute in Phoenix shows the power of Big Data and the potential for advanced computing to speed up progress toward treatments and a cure.

7. Global collaborations ALS ONE and NeuroLINCS are announced, supported by millions in funding from The ALS Association. These two initiatives will leverage resources and help generate the data researchers need to continue their important work.

8. Brainstorm Cell Therapeutics reports positive results in the NurOwn® stem cell phase II trial in the U.S. and then announces a larger phase III trial to begin in 2017.

9. One of the nation’s largest precision medicine programs, Genomic Translation for ALS Care (GTAC), begins enrollment in October 2016, in collaboration with nine centers at universities and hospitals across the United States. The ALS Association committed $3.5 million in Ice Bucket Challenge-raised money to this exciting collaborative effort.

10. At the International ALS/MND Symposium in Dublin, a leading University of Miami ALS researcher and the pharmaceutical company Orphazyme announce the successful completion of a phase II trial of Arimoclomol* for inherited SOD1-ALS. The ALS Association has long supported this trial to move the needle forward for people living with familial ALS.
Research supported and funded by The ALS Association in 2017 accelerated momentum toward treatments and a cure. Our grants funded research being led by top ALS scientists and clinicians; enrollment in ALS clinic trials is higher than ever; ALS drug development is taking off; assistive technology is advancing rapidly, and new biomarkers to track ALS progression and improve diagnosis are being discovered.

Here are the biggest research advances in 2017 – all funded by The ALS Association.

Clinical Trials and Studies
The Nuedexta trial showed significant palliative effects on speech, swallowing, and salvation; Pimozide demonstrated promise in animal studies and in a short human trial; and the Ezogabine trial made progress. Computer models designed by Origent Data Sciences to predict disease progression improved; our ability to determine the rate of decline more accurately progressed using the ATLIS test; the IMPACT ALS survey furthered our understanding of ALS burden; and we learned that it can be safe and tolerable for people with ALS to exercise. Many new clinical trials also started to enroll.

Assistive Technology
Our investments in assistive technology led to key advances in wearable sensor and brain computer interface technology by our Assistive Technology Challenge winners, and continue to empower people with ALS. In addition, the ALS Hackathon brought students together to develop exciting new assistive technology ideas to help people living with ALS.

Drug Development
Three organizations – Answer ALS, Project MinE, and New Genome Center for Genomics of Neurodegenerative Disease (CGND) ALS Consortium began sharing genome sequencing information to speed efforts toward new ALS treatments and a cure. The NYGC CGND expanded, launched a new clinical database, and made data from 2,500+ samples available to global researchers. In addition, Aquinnah Pharmaceuticals’ stress granule research and the Neuro Collaborative Brain Bot project advanced through new pharma partnerships.

Breakthrough Prize in Life Sciences
ALS researcher Dr. Don Cleveland won the $3 million 2018 Breakthrough Prize in Life Sciences, allowing him to continue work in ALS antisense technology. Successes of antisense therapy in other neurodegenerative diseases were reported that all stemmed from our initial investment in this work. “I’m incredibly grateful to the ALS Association for their support – right from the beginning and continuing to today – that enabled the success that is now being celebrated.” – Dr. Don Cleveland

Biomarkers
Researchers are working to develop a unique imaging biomarker to track TDP-43, a protein found in almost all ALS cases, discovered a new urinary biomarker to help monitor ALS disease progression, and a new biomarker discovery paves the way toward the upcoming C9orf72 antisense clinical trial. In addition, a new ALS biomarker was reported to help researchers better understand survival of people living with C9orf72-associated ALS.

Basic research
Research in 2017 provided a deeper understanding of the contributions of upper motor neurons to ALS; provided critical insight into sporadic ALS disease pathways; and brought new perspective to the role of immune response in ALS brain pathology. It also identified new genes and disease pathways associated with ALS that could potentially be targeted by therapeutics and shed new light on FUS disease pathways.

ALS Association News
The TREAT ALS drug development program was renamed The Lawrence and Isabel Barnett Drug Development Program in honor of the Barnett family legacy. Six postdoctoral fellowship grants were awarded under the Milton Safenowitz Postdoctoral Fellowship Program, while 2 clinical fellows were funded in partnership with the American Academy of Neurology. Updates to ALS Online Genetics Database (ALSoD) began, and the National ALS Biorepository launched as part of the National ALS Registry. Dr. John Ravits won the Sheila Essey Award. Top scientific journals publish major comprehensive reviews by The ALS Association-funded researchers.

For more detailed information on the 2017 research advances we fund, read our blog here.
The ALS Association is committed to biomarker discovery, as their potential is immense. Identifying biomarkers is vital to improving diagnosis, following disease progression, tracking response to therapy, and make clinical trials more efficient. Our support of the TDP-43 Biomarker Grand Challenge Program is just one example.

**ASSISTIVE TECHNOLOGY**

The ALS Association is working to develop accessible, portable devices for people living with ALS, in order to help them maintain a high quality of life. The ALS Assistive Technology Challenge winners we announced in December 2016 are dedicated to achieving this!

**ENVIRONMENTAL FACTORS**

Multiple factors in one’s lifestyle and surroundings, such as smoking and military service, are the only known ALS risk factors. The ALS Association champions multiple efforts to better understand these risk factors and drive discovery of other factors that may contribute to ALS.

**NATURAL HISTORY STUDIES**

These studies are important to understanding the natural disease course of familial (inherited) ALS. The ALS Association is supporting several natural history studies of SOD1 and C9orf72 ALS, which are critical to helping inform patient care and clinical testing of new treatment approaches.

**CLINICAL STUDIES**

The ALS Association supports clinical management grants to improve the lives of people living with ALS and their caregivers, along with clinical trials to accelerate treatments through the drug development pipeline.

**COGNITIVE STUDIES**

There is a great deal of evidence that cognitive impairment is connected to ALS, such as overlap with frontotemporal dementia (FTD). The ALS Association is committed to improving understanding of why and how this connection takes place.
GENETICS
The number of genes identified to cause familial ALS has multiplied since the discovery of SOD1. Many efforts are underway to identify more ALS genes and target them for therapy. The ALS Association continues to make significant investments in identifying new genes and has supported all the major ALS gene discoveries in history.

DISEASE MECHANISMS
ALS is a complicated disease involving multiple disease pathways. The ALS Association encourages research to discover novel pathways. Understanding how ALS disease works on many biological levels is necessary to identify potential therapeutic targets.

NANOTECHNOLOGY
There is growing interest in using nanotechnology as a delivery tool for ALS therapeutics, and we are on the cutting edge, funding this exciting technology.

DRUG DEVELOPMENT
The ALS Association is supporting development of several different treatment approaches, including small molecules, stem cells, and gene therapy. Our early support of antisense drugs in 2004 has paid off! Antisense therapies have already proven effective in spinal muscular atrophy (SMA), are in trial for SOD1 and are starting in the near future targeting C9orf72.

STEM CELLS
Stem cell technology is progressing rapidly, and The ALS Association is spearheading work on several critical fronts to advance this key research tool.

DISEASE MODELS
The ALS Association’s research portfolio supports a variety of model systems used for understanding disease pathways and testing promising compounds.

PRECISION MEDICINE
The ALS Association has helped establish and currently supports several partnerships and precision medicine programs to aid in the identification of new disease genes and targets for drug therapy.

Learn more on the Scientific Focus Area Page.
A
agonist
A drug that increases neurotransmitter activity by
directly stimulating the nerve cell receptors.

ALS Functional Rating Scale – Revised (ALSFRS-R)
A survey of questions that assesses the impact of ALS
on activities of daily living. It is often used as a primary
outcome measure of ALS clinical trials.

amino acid
One of the 20 building blocks of protein.

antibody
A defense protein that binds to foreign molecules to
allow their elimination.

antigen
A substance that is capable of causing the production
of antibodies. Antigens may or may not lead to an
allergic reaction.

antioxidant
A chemical compound or substance that inhibits
oxidation.

assay
An investigative procedure (i.e., experiment) in the
laboratory.

ataxia
Loss of balance.

atrophy
The progressive loss of muscle mass, or wasting,
caused by reduction in the size or number of muscle
cells. It is one of the later symptoms of ALS.

axon
The long, hairlike extension of a nerve cell that carries
a message to the next nerve cell.

B
blood-brain barrier (BBB)
A protective barrier formed by the blood vessels and
glia of the brain. It prevents some substances in the
blood from entering brain tissue.

bradykinesia
Slowness of movement.

bulbar muscles
The muscles that control speech, chewing, and
swallowing.

C
central nervous system (CNS)
The brain and spinal cord combined.

cerebrospinal fluid (CSF)
A clear fluid that covers and protects the brain and
spinal cord.

chromosome
A visible carrier of the genetic information.

corticospinal tract
The bundle of nerves that reach from the motor area
of the brain (see cortex) to the spinal cord, connecting
to the nerves that go out to control the muscles.

CRISPR/Cas9
Genome editing technology that allows the
permanent modification of genes within an organism.
By delivering the Cas9 nuclease bound to a synthetic
guide RNA into a cell, the cell’s genome can be cut
at the designed/desired location. This allows existing
genes to either be removed or added in. CRISPR
stands for Clustered Regulatory Interspaced Short
Palindromic Repeats.
DNA
Deoxyribonucleic acid. Hereditary material that encodes genetic information.

dysarthria
Impaired speech and language due to weakness or stiffness in the muscles used for speaking.

dyskinesia
Abnormality or impairment of voluntary movement.

dysregulation; dysregulate
An impairment of a physiological regulatory mechanism; to cause a dysfunctional level of an activity or chemical in an organism by disrupting normal function.

dysphagia
Difficulty in swallowing.

dystonia
A slow movement or extended spasm in a group of muscles.

electroencephalogram (EEG)
A method of recording the brain's continuous electrical activity by means of electrodes attached to the scalp.

Embryonic stem cells
Embryonic stem cells are the “blank slates” of an organism, capable of developing into all types of tissue in the body.

enzyme
A protein that acts as a catalyst in mediating and speeding a specific chemical reaction.

excitotoxic
An agent that excites neurons which can, over time, lead to neuronal death.

fasciculation
Small, involuntary, irregular, visible contractions of individual muscle fibers. Often seen in the legs, arms, and shoulders of persons with ALS. This is often described by people with ALS as “persistent rolling beneath the skin.”

Forced Vital Capacity (FVC)
The amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible. It is measured by a test called spirometry, a type of pulmonary function test. The percent force vital capacity is often used as criteria to participate in an ALS clinical trial.

free radicals
Chemicals that are highly reactive and can oxidize other molecules (i.e., superoxide).

gene
Genes are the basic biological units of heredity. They are composed of DNA.

genome
All of the genetic information; all of the hereditary material possessed by an organism.

genotype
The genetic makeup (i.e., DNA code) of an individual.

glutamate
Glutamate is one of the most common amino acids found in nature. It is the main component of many proteins, and is present in most tissues. Glutamate is also produced in the body and plays an essential role in human metabolism. It is a primary excitatory neurotransmitter in the human CNS.

hyperreflexia
Excessive response of muscle reflexes when a normal stimulus is applied.

hyporeflexia
Weak or absent muscle response when a normal stimulus is applied.
immune system
A complex system that is responsible for distinguishing us from everything foreign to us and for protecting us against infections and foreign substances. The immune system works to seek and kill invaders.

incidence
The occurrence of new cases of a condition. The incidence rate describes the frequency with which cases are identified. Incidence is commonly measured in new cases per 1,000 (or 100,000) of population at risk per year.

induced pluripotent stem cells (iPSCs)
A type of pluripotent stem cell that can be generated directly from adult cells.

inflammation
The nonspecific immune response that occurs in reaction to any type of bodily injury. It is a stereotyped response that is identical whether the injurious agent is a pathogenic organism, foreign body, ischemia, physical trauma, ionizing radiation, electrical energy or extremes of temperature.

inflammatory disease
A disease that is characterized by activation of the immune system to abnormal levels that lead to disease.

intrathecal
Injection into the innermost membrane surrounding the central nervous system. Usually done by lumbar puncture.

interventional trial
Type of trial or clinical research study in which exposure to a potential therapy or drug is assigned and being tested. It is used to determine the effectiveness and safety of a potential treatment.

investigator
A person who carries out a scientific study. A researcher.

in vitro
In an artificial environment outside the living organism, such as in a dish or test tube in the laboratory.

in vivo
In a living organism, such as a mouse or human.

lower motor neurons
Nerve cells (motor neurons) originating in the spinal cord that connect to muscles, conduct signals to allow muscle movement.

molecule
The smallest unit of a substance that can exist alone and retain the character of that substance.

motor neuron
A neuron that conveys impulses initiating muscle contraction or glandular secretion.

motor neuron disease (MND)
A group of disorders in which motor nerve cells (neurons) in the spinal cord and brain stem deteriorate and die. ALS is the most common motor neuron disease.

muscle atrophy
Loss of muscle fiber volume characterized by a visible decrease in muscle size. This occurs because muscles no longer receive impulses or signals from nerve cells.

mutation
A permanent change, a structural alteration, in the DNA or RNA. Mutations can be caused by many factors, including environmental insults such as radiation and mutagenic chemicals. Mutations are sometimes attributed to random chance events.

myelin
A fatty substance that surrounds and insulates the axon of some nerve cells to help speed nerve transmission. It is important for proper function of the nervous system.
Nervous system
The system of cells, tissues, and organs that regulates the body's responses to internal and external stimuli. In vertebrates it consists of the brain, spinal cord, nerves, ganglia, and parts of the receptor and effector organs.

Neuron
Neurons are the nerve cells which make up the central nervous system. They consist of a nucleus, a single axon which conveys electrical signals to other neurons and a host of dendrites which deliver incoming signals.

Neurotransmitters
Chemical substances that carry impulses from one nerve cell to another, found in the space (synapse) that separates the transmitting neuron's terminal (axon) from the receiving neuron's terminal (dendrite).

Observational study
Type of trial in which enrolled participants are observed. Outcome measures (i.e. measures of strength or function) may be part of the observation. No treatment/drug is given. It is often used to learn about trends of symptoms, the course of disease, and can include biomarker studies.

Oxidative stress
Accumulation of destructive molecules called free radicals can lead to motor neuron death. Free radicals damage components of the cells' membranes, proteins or genetic material by "oxidizing" them – the same chemical reaction that causes iron to rust.

Phenotype
The observable characteristics of an individual resulting from the expression of genes. This may be directly observable (eye color) or apparent only with specific tests (blood type). Some phenotypes, such as the blood groups, are completely determined by heredity, while others are readily altered by environmental agents.

Pluripotent stem cells
Human pluripotent stem cells are a unique scientific and medical resource. They can develop into most of the specialized cells and tissues of the body, such as muscle cells, nerve cells, liver cells, and blood cells. They are self-renewing, making them readily available for research and, potentially, for treatment purposes. Scientists derive these unique cells from human embryos, from fetal tissue, or from adult tissue (in the case of induced pluripotent stem cells (iPSCs)).

Positron emission tomography (PET) scan
A computer-based imaging technique that provides a picture of the brain's activity rather than its structure. The technique detects levels of injected glucose labeled with a radioactive tracer.

Potassium channel
A type of ion channel that forms potassium-selective pores that span the cell membrane, thereby helping transport potassium across the cell membrane. They are found in most cell types and control a variety of cell functions.

Precision medicine
A tailoring of medical treatment to the individual characteristics of each person, while taking into account individual variability in genes, environment, and lifestyle for each person. In precision medicine programs, researchers aim to learn as much as possible from each unique person living with ALS.
Protein
Proteins are large molecules required for the structure, function, and regulation of the body’s cells, tissues, and organs. Each protein has unique functions. Proteins are essential components of muscles, skin, bones, and the body as a whole. Protein is also one of the three types of nutrients used as energy sources by the body.

Proteomics
The study and identification of the proteins produced by the genetic instructions carried by a cell.

Protocol
A precise and detailed plan for the study of a biomedical problem or for a regimen of an experimental therapy.

Qualitative
Relating to measuring or measurement of the quality of something, such as its size, appearance, etc.

Quantitative
Relating to measuring or measurement of the quantity (amount) of something.

RNA
Ribonucleic acid. The primary function of RNA is to act as a messenger carrying instructions from DNA for controlling protein synthesis within a cell.

Sclerosis
A hardening within the nervous system, especially of the brain and spinal cord, resulting from degeneration of nervous elements such as the myelin sheath.

Sialorrhea
Drooling.

Spinal cord
Part of the central nervous system extending from the base of the skull from the brain stem through the vertebrae of the spinal column. It carries information from the body’s nerves to the brain and signals from the brain to the body.

Stem cells
Cells that can differentiate into many different cell types when subjected to the right biochemical signals. Stem cells are a promising new therapeutic approach to treating central nervous system disorders. The most versatile stem cells, called pluripotent stem cells, are present in the first days after an egg is fertilized by sperm. Researchers believe they can coax stem cells to become whatever tissues patients need. Stem cells come from embryos, bone marrow, and umbilical cords. View the stem cell glossary to learn more.

Stratify
To arrange or classify.

Superoxide dismutase
An enzyme that destroys superoxide, which is a highly reactive form of oxygen. With ALS, 20 percent of the total population of patients have mutations in the gene for copper/zinc superoxide dismutase type SOD1. SOD1 normally breaks down free radicals, but mutant SOD1 is unable to perform this function.

Synapse
A tiny gap between the ends of nerve fibers across which nerve impulses pass from one neuron to another; at the synapse, an impulse causes the release of a neurotransmitter, which diffuses across the gap and triggers an electrical impulse in the next neuron.

Synergistic
Interaction or cooperation between two or more substances or organizations to produce a greater combined effect.

Toxicity
The extent, quality or degree of being poisonous.
transgenic
An organism whose sperm or egg contains genetic material originally derived from an organism other than the parents or in addition to the parental genetic material.

translational research
Studies that apply findings from basic science discovered in the lab to relevant disease therapies that enhance patient well-being.

trophic factor
One of a class of proteins that help keep cells healthy.

U

upper motor neurons
Nerve cells (motor neurons) originating in the brain’s motor cortex and running through the spinal cord.

V

vector
The agent used (by researchers) to carry new genes into cells. Plasmids currently are the vectors of choice, though viruses and other bacteria are increasingly being used for this purpose.

For more ALS vocabulary, visit The ALS Association online, found at:
www.alsa.org/research/our-approach/glossary
Neil Thakur became Executive Vice President of Mission Strategy in May 2018. He leads the advocacy, care services, and research programs for the Association.

Prior to joining the Association, Neil served in the National Institutes of Health (NIH) Office of the Director, where he supported NIH governance and helped make NIH research more open and less burdensome. He managed the world’s largest policy to make biomedical research papers publicly accessible and co-chaired the White House taskforce that lead to the requirement that all federal science agencies adopt similar policies. He also spent a year on detail to the U.S. Senate Special Committee on Aging, raising awareness about quality issues in long-term health care, particularly around Alzheimer’s care and pharmaceuticals.

Prior to his time at NIH, Neil worked with health systems in many capacities. He was Assistant Director of Health Services Research and Development at the Department of Veterans Affairs (VA), leading an evaluation service for the VA health system and represented the VA research service in setting clinical performance measures. In his post-doctoral fellowship, he studied the interactions between jails, Medicaid and behavioral health care, and how changes in health financing impacted people’s utilization of these systems. During graduate school, he worked throughout the Connecticut behavioral health system, helping to implement managed care and health information systems, and raise tens of millions of dollars in competitive grants.

Neil won many awards for his government service, including several NIH Director’s Awards, and the Secretary for Health and Human Services’ award for Meritorious Service, the second highest award that the Secretary can bestow. He holds a Ph.D. in Health Policy from Yale University School of Public Health and completed a NIMH postdoctoral fellowship in mental health services research at the Cecil G. Sheps Center for Health Services Research at the University of North Carolina at Chapel Hill. He lives in Maryland with his wife, Jen.
Dr. Jill Yersak, Director, Mission Strategy, joined The ALS Association in 2015. Reporting to Neil Thakur, she helps oversee the strategy of projects and programs in the Association’s mission – research, care, and advocacy. She is also responsible for communicating ALS research in an accessible way by developing and maintaining research information tailored to people living with ALS, their caregivers, and loved ones. She supports both ALS Association National and chapters in all departments with research information needs, including donor outreach. As a part of the Research Communications team, she played a large part in implementing The ALS Association’s research website redesign and the mission toolkit.

Dr. Yersak received her bachelor’s degree in Biology at Ursinus College in Collegeville, Pa. After college, she served as a research technician at the Children’s Hospital of Philadelphia in the department of Human Genetics and Molecular Biology, focused on a pediatric genetic disease called 22q11.2 Deletion Syndrome. She then went onto complete her Ph.D. at Thomas Jefferson University in Philadelphia, with a focus on a neurodegenerative disease called Kennedy’s Disease. Dr. Yersak then moved to Providence, R.I. to complete her postdoctoral fellowship under the mentorship of Dr. Anne Hart in the Neuroscience department. During this time, she spearheaded a project to generate precise ALS C. elegans models (which are microscopic worms), co-wrote a successfully-funded ALS Association grant based on this project, and mentored several graduate and undergraduate students. Dr. Yersak then went on to work at her alma mater, Thomas Jefferson University, as coordinator of the Postbaccalaureate Pre-Professional Program in the Graduate School of Biomedical Sciences, where she helped manage the program, in addition to counseling students in medical school and career placement.

Dr. Yersak is dedicated to mentorship, outreach, and advocacy in her community. She served on the Board for the Association for Women in Science in Philadelphia, where she championed young women to join and gain success in the STEM (science, technology, engineering, and mathematics) fields. During her time as a postdoctoral fellow, Dr. Yersak volunteered at the local ALS Multidisciplinary Clinic where she worked closely with people living with ALS and their caregivers, along with the multidisciplinary team, and local R.I. chapter. There she launched a National ALS Registry Program in R.I., where she significantly increased Registry enrollment. In 2014, she received the ALS Leadership Award presented by The ALS Association R.I. Chapter for her service to the chapter to raise ALS awareness.