EVALUATION OF THE ALS ASSOCIATION GRANT PROGRAMS

Executive Summary Report

May 2019

ALS ASSOCIATION

RTI INTERNATIONAL

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1. INTRODUCTION

The ALS Association will soon be celebrating the 5-year anniversary of the Ice Bucket Challenge (the Challenge hereafter) campaign. Within the first 6 weeks after the Challenge launched in August 2014, the Association received $115 million in donations (The ALS Association, 2016), which amplified its grant funding capacity. Funding records from the Association indicate that between 2014 and 2018, the Association awarded nearly $90 million toward research grants around the world, in addition to funding for clinical care centers and advocacy initiatives. In 2018, the Association reported $19 million in research grant spending (The ALS Association, 2019a). By comparison, the Association's research grants totaled $6.6 million in 2013 and $3.9 million in 2012 (issuu, 2013), which illustrates the sharp trajectory of the Association's research investments after the Challenge.

Clearly, the most important beneficiaries of ALS research discoveries are those who have ALS currently or may face an ALS diagnosis in the future. Gene identification, new therapeutics, and clinical trials have some of the most direct impacts on current and future people living with ALS. Since the Challenge, the Association has funded research leading to actual discoveries and clinical improvements in these areas. For example, following the Challenge:

- Association-funded researchers identified five new genes that contribute to ALS, including KIF5A, C21orf2, NEK1, TBK1, and TUBA4A (Nicolas et al., 2018; The ALS Association, 2018).
- The Association contributed funding to 17 ALS-related clinical trials (The ALS Association, personal communication, February 13, 2019b). For example, the Association funded The Neuro Collaborative, which developed new "antisense" drug therapies that target two common ALS genes and are being tested in clinical trials (The ALS Association, 2018; Washington University School of Medicine, 2018), as well as several trials for drug therapies (e.g., Barrow Neurological Institute, 2018; Wainger, 2018) and an e-Health program promoting healthy weight in people living with ALS (Massachusetts General Hospital, 2018).

As the Association embarks on new campaigns to fund the fight against ALS, it aims to further understand the impact that its grant investments have had since the first Challenge. Thus, the Association partnered with RTI International, a nonprofit research institute, to evaluate its grant programs by assessing the accomplishments of Association grantees.

In consultation with the Association, RTI designed the evaluation to answer three main research questions:

- What has been the impact of ALS Association funding on research output since 2014?
- Have grantees been able to leverage their ALS Association funding into follow-on funding since 2014?
- What has been the impact of ALS Association funding on researcher collaborations since 2014?

The evaluation used a mixed-methods approach that included the following components to address these research questions:

- **Secondary data collection and analysis** to describe grantee publications and follow-on funding;
- **A grantee survey** to measure their self-reported research accomplishments, external grant applications and awards, and collaborations; and
- **Key informant interviews** with Association-funded researchers, advocates, and clinicians to contextualize funding impacts from their perspective.

RTI developed this report, and the Association approved its contents. To contextualize the geographic spread of the Association's funding efforts, Section 2 plots total spending on research grants and the number of researchers funded since 2014, as well as the availability of ALS treatment centers before and after the Challenge. Remaining sections of the report describe methods, results, and insights from secondary data analysis (Section 3), the grantee survey (Section 4), and key informant interviews (Section 5). A final discussion section synthesizes the findings (Section 5). Overall, notable insights from this evaluation include the following:

Key Insights

- After the Challenge, the Association funded 29 new ALS Certified Treatment Centers of Excellence, 20 new Recognized Treatment Centers, and 7 new affiliated clinics to increase availability of ALS care.
- Key informant clinicians described how the Association's clinical program grants fostered more multidisciplinary, holistic services. Clinical improvements included home visits, caregiver support, nutrition services, social services, and health navigation.
- Between 2014 and 2018, the Association awarded over 300 grants to over 200 different scientists for ALS research.
- The number of ALS researchers funded through the Challenge grew from 42 in 2014 to 237 grantees in 2018.
- Grantees reported that their Association funding accelerated their research productivity and enabled them to form collaborations with not only other researchers but also clinicians and people living with ALS.
- One of the most common achievements that grantees reported was identification of new therapeutic targets. Participants also reported gene discovery, initiation or completion of one or more clinical trials, and identification of new biomarkers. Section 4 describes results from the grantee survey, which asked researchers about these new discoveries.
- The number of journal articles authored by the Association's research grantees and co-authorships between grantees both increased markedly between 2014 and 2018. Publications signal advancements in knowledge, and co-authorships reflect transmission of knowledge that may help accelerate science in the ALS field.
- Researchers we interviewed highlighted their achievements in gene discovery and assistive technology for people with ALS.
- National Institutes of Health (NIH) funding among the Association's research grantees increased between 2014 and 2018, mirroring the upward trajectory of donations to the Association and its subsequent research investments.

2. GRANT AWARD PROGRAMS

The ALS Association's global research program supports a wide range of research initiatives to advance treatment and care for ALS. The Association's portfolio aims to support scientific discovery, career growth, and collaboration across academic, government, nonprofit, and industry sectors, according to the Association's Research Toolkit (The ALS Association, 2017). The Association provided documentation of its research and clinical care spending from 2014 through 2018, and we used these records to plot the number of researchers funded and the geographic spread of research grant awards and clinical care funding.

From 2014 through 2018, the Association awarded nearly $81.2 million across 275 research grants in the United States, and another $8.5 million was awarded internationally. Figure 1 maps the geographic distribution of these research funds.

In addition, the Association has two clinical grant programs, the Certified Treatment Center of Excellence (CTCE) and Recognized Treatment Center (RTC) programs (The ALS Association, no date). CTCEs provide multidisciplinary ALS care that meets standards of care and participate in ALS-related research. RTCs provide multidisciplinary care at the same level as CTCEs, but they typically do not offer clinical trials or other research studies on-site. In addition to CTCEs and RTCs, local chapters of the Association work closely with other ALS clinics called Affiliated Clinics.

The number of CTCEs, RTCs, and Affiliated Clinics grew from 100 before the Challenge to 156 after this campaign (Figure 2). By investing in this expansion in treatment centers, the Association endeavors to increase access to ALS care for patients and their families. Funding to the CTCEs doubled from $12,500 to $25,000 per center. In addition, the ALS Challenge enabled the Association to fund $5,000 per RTC; the Association was not able to provide this funding before the Challenge (The ALS Association, personal communication, February 13, 2019c). Many of the Association chapters also provide grants to their clinics in addition to the national CTCE and RTC grants.

Figure 1. Geographic Distribution of The ALS Association Research Grant Funding, 2014–2018

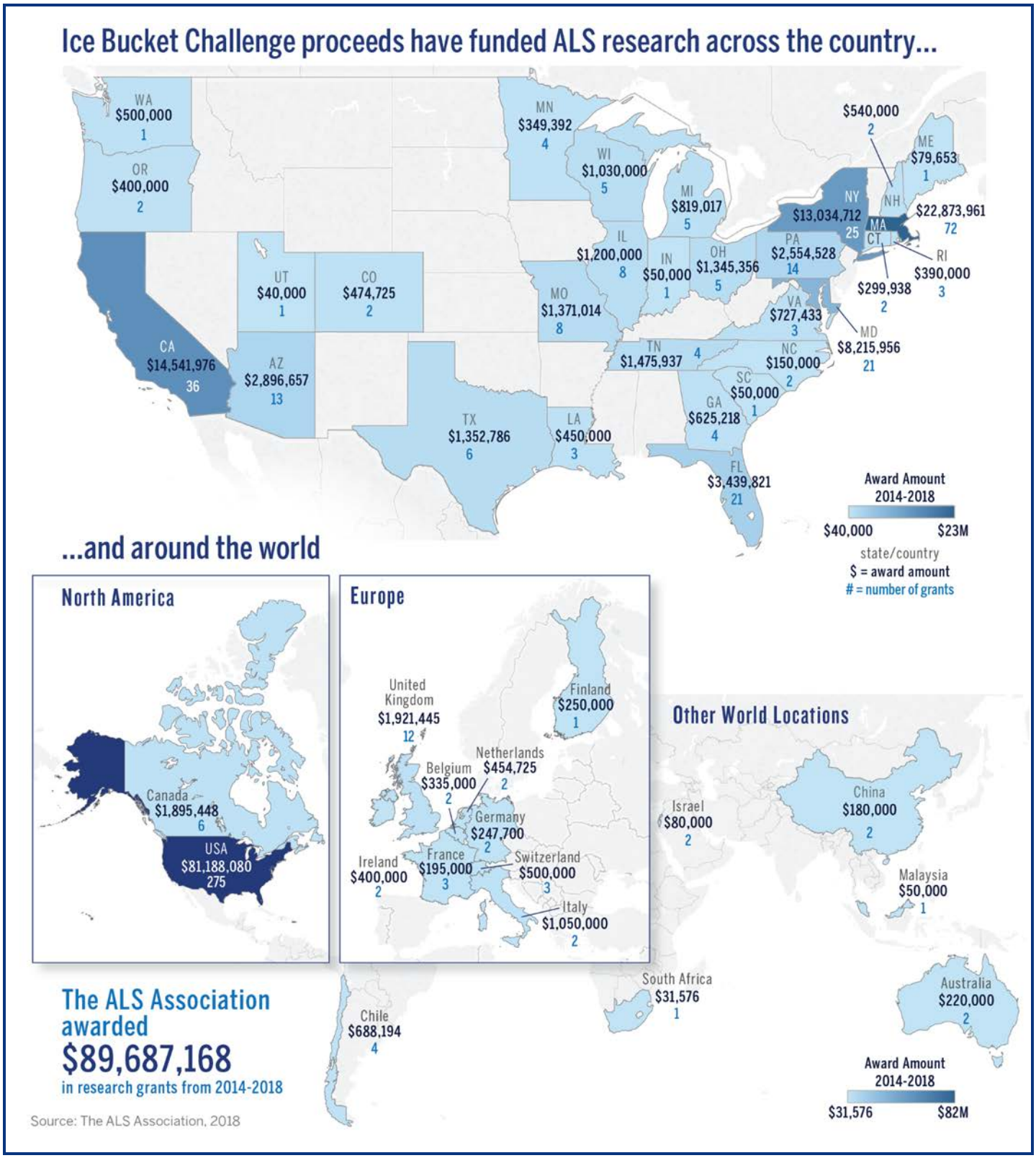
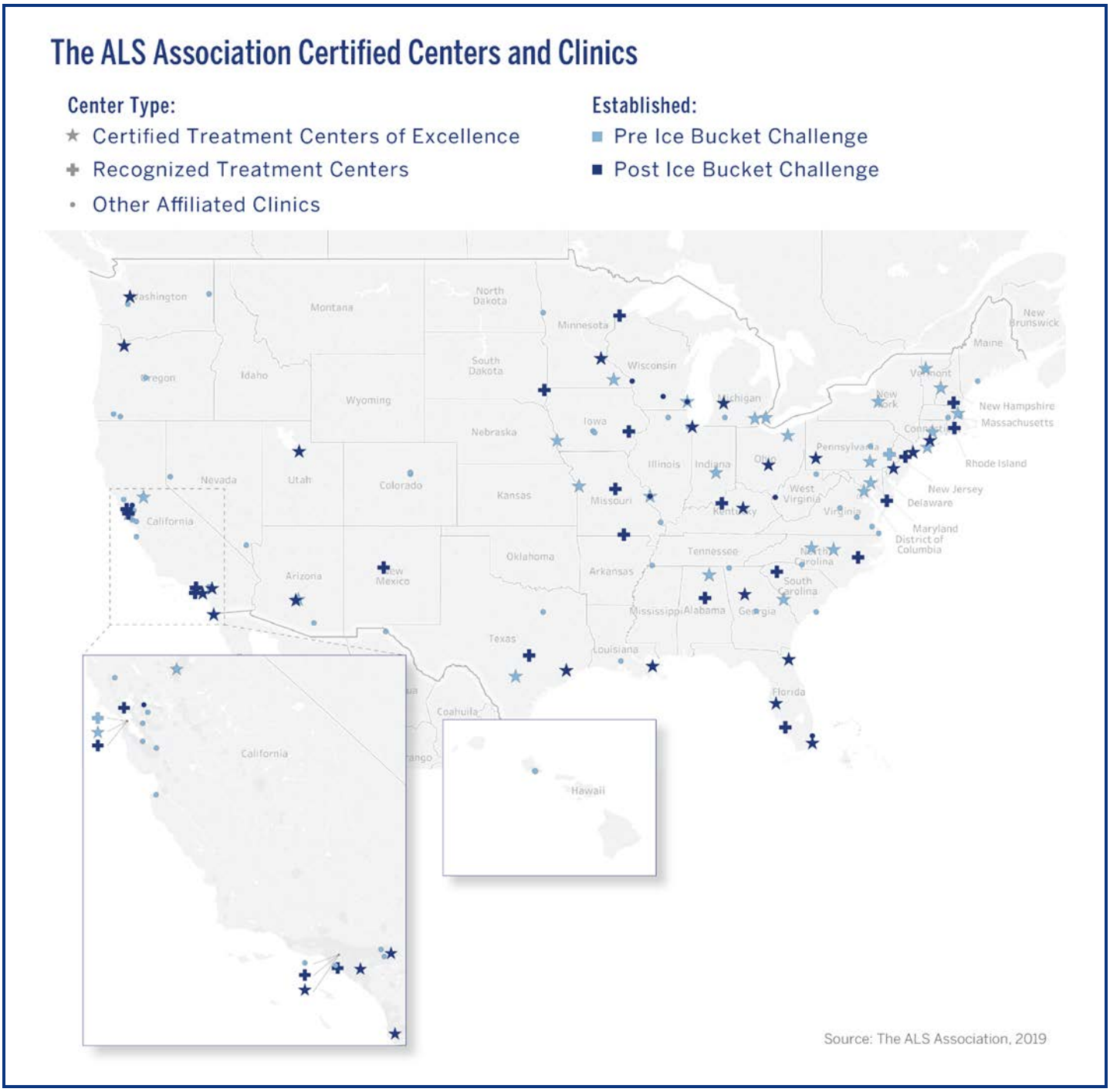


Figure 2. The ALS Association's Treatment Centers and Clinics Before and After the Ice Bucket Challenge



3. SECONDARY DATA ANALYSIS

AIMS

From 2014 through 2018, The ALS Association awarded over 322 grants to 237 different scientists for ALS research.[1] In line with the main research questions guiding this evaluation (see Section 1), we aimed to understand whether these Association grants have

1. effectively leveraged funding from the NIH,
2. led to changes in the research publication output of its grantees,
3. led to changes in the collaboration patterns of grantees, and
4. leveraged funding from other potential sources (other funders of grantees).

To investigate the first aim, the most salient information was the total amount of annual funding being provided by the NIH to Association grantees. Upon recognition of the surge in funds provided by the Association, other funders may react in a number of ways. One possibility is that the Association's investments reveal new opportunities to the NIH, while on the other extreme, the NIH may perceive that the Association funds have fulfilled a need that requires little additional support and thus divest in the Association grantees and reallocate those funds elsewhere.

A bibliometric analysis addressed aims two through four by investigating the total annual number of journal articles published from 2014 through 2018, changes in co-authorships among grantees on those publications, and the identification of other funders that were acknowledged on this set of publications. Scientific publishing is commonly referred to as the "currency" of the academic community. Journal articles and other types of publications represent a quantifiable unit of output produced by a researcher, and each new publication adds to the body of knowledge and enables science to progress. Scientific progress toward novel treatments for ALS relies on the foundations of knowledge that are catalogued within the scientific literature, either building directly on prior knowledge or by recombining it in novel ways. As knowledge accumulates, the number of opportunities for combining knowledge that were previously distinct grows exponentially, thus also increasing the likelihood of "breakthroughs" in scientific discovery or application.

METHODS

The Association provided RTI with a dataset that included the complete set of grants used for the evaluation, which contained grantee names, project titles, award dates, and other relevant grant information. RTI used this dataset to collect information on NIH grants awarded to each of the Association's grantees and academic publications authored by each grantee.

NIH Funding Analysis

RTI collected NIH grant records from NIH RePORTER that were awarded from 2014 through 2018 to the Association's grantees, regardless of whether the Association's grantee was listed as the "contact PI" or another PI or project leader on the NIH grant. The set of NIH grant records contains funding amounts provided by the NIH as well as counts of awards. From this set of NIH grant records, RTI calculated the total annual dollar amount of NIH funding that was distributed to the Association's grantees and tabulated annual counts of new NIH grants that were awarded to the Association's grantees from 2014 through 2018.

[1] Because of timing with respect to the availability of data, the scope of this analysis was limited to 232 Association grantees who had received an award at the time the secondary data were collected.

The chief limitation of the analysis is the high likelihood that not all 2018 NIH grant records had been added to RePORTER at the time the data were collected by RTI in January 2019. Notably, the dip in NIH funding awarded to the Association grantees from 2017 to 2018 could be caused by a delay in the appearance of some 2018 grant records in NIH RePORTER.

A secondary, and more subtle limitation, which has little bearing on the primary aim of investigating the total amount of NIH funding awarded to the Association's grantees, is the inability to attribute NIH grants to awards made previously by the Association. First, we are unable to observe whether the NIH was aware of awards made by the Association, and second, there are (varying) time lags from the moment that grantees receive funds from the Association to the time that they may have produced results from research conducted using those funds, which they may leverage in their grant applications to the NIH. In principle, both events could induce investments from the NIH. Although it is impossible to determine definitively whether the NIH funds would have been allocated as they were in the absence of the Association's investments, certain inferences can be made with relative safety. For example, the NIH's increases in total funding awarded to Association grantees lend credibility to the quality of the Association's investments. Because the NIH has more options for funding allocations than it has the budget for, it must select and choose those investments that seem most promising. The NIH's investment in the Association's grantees thus reveals confidence in the opportunities posed by these grantees. These investment decisions made by the NIH further suggest that the Association has successfully identified and funded talented and promising researchers and that these researchers are likely to make effective use of both sources of funds.

Bibliometric Analysis

For this analysis, RTI collected publications indexed in Clarivate Analytics Web of Science authored by the Association grantees. Once we identified these publications, which involved the nontrivial task of disambiguating author names as they appear in the Web of Science records and matching them to the appropriate Association grantees, we calculated the number of scientific journal articles authored by Association grantees from 2014 through 2018 based on the publication year of the articles. From this set of publications, RTI also extracted instances of co-authorship among grantees and the acknowledgements of funders who supported the research. These data are indexed in Web of Science indexes within publication records, whenever available, because it is common practice for authors, when publishing a journal article, to acknowledge the funders who supported their research.

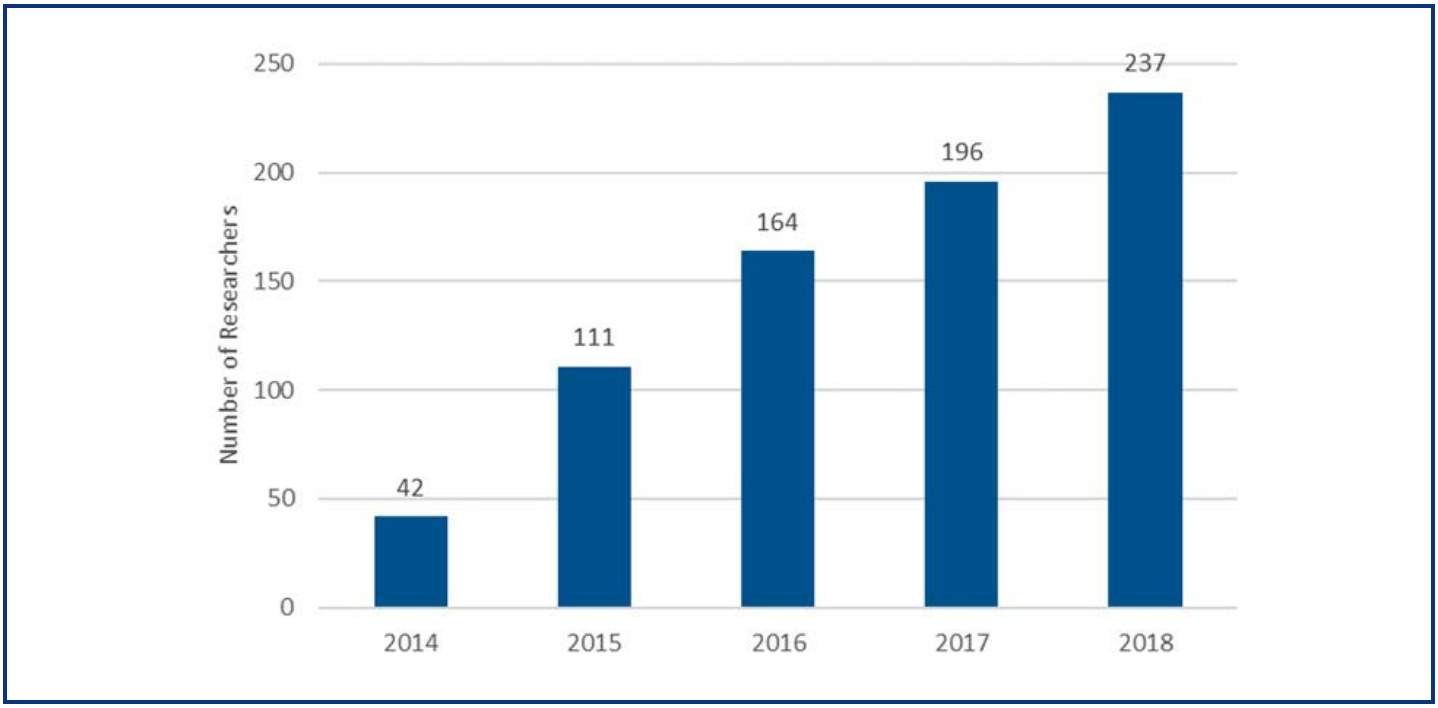
Limitations include some inevitable error in the disambiguation of author names and the inability to accurately link or attribute publications to specific grants made by the Association. However, the number of instances of misattribution of a publication to a given grantee is trivial for the analysis presented here and insufficient to appreciably alter any of the network diagrams. Furthermore, the conclusions of this analysis are not contingent on the attribution of articles to specific grants. A great number of factors affect the ability to attribute specific publications to prior awards, notably the long and highly variable lags from receiving funds to conducting research, from obtaining results to submitting a manuscript, and from reviewing the initial manuscript to publication.

Disambiguation of funder names is also imperfect and is an arduous task considering that in this dataset the Association was acknowledged in over 60 different ways and the NIH was acknowledged in over 1,000 different ways. However, these data can also be challenging to analyze because funders are voluntarily acknowledged by the authors, which results in unsystematized underreporting. It is impossible to determine the total number of articles funded by the Association, given that for some articles the Association's support is in no way acknowledged. Therefore, although tabulating precise counts of funding acknowledgement instances may result in undercounts, some valuable insights can be gleaned from the funding acknowledgements data that do exist. For example, the trends in the number of articles acknowledging the Association may convey important information.

RESULTS

From 2014 to 2018, the Association funded 237 unique grantees. Figure 3 illustrates the growth in the number of funded researchers over time. As stated earlier, remaining results from the secondary analysis focus on 232 of these grantees who had received an award at the time the secondary data were collected.

Figure 3. Cumulative Number of Researchers Funded Since the Ice Bucket Challenge



Leveraged NIH Investment

We analyzed how the Association leveraged its sizable investment with funds from the United States' biggest health research funder, the NIH. We examined the trends in NIH funding dollar amounts awarded to 232 Association grantees and trends in new NIH grants awarded to Association grantees.

Based on data available from NIH RePORTER, the Association seems to be leveraging its investment with NIH funding successfully and is "crowding-in" additional investment in its grantees from the United States' largest biomedical research funder.

Dollar Amount of NIH Funding Awarded to Association Grantees, 2014–2018

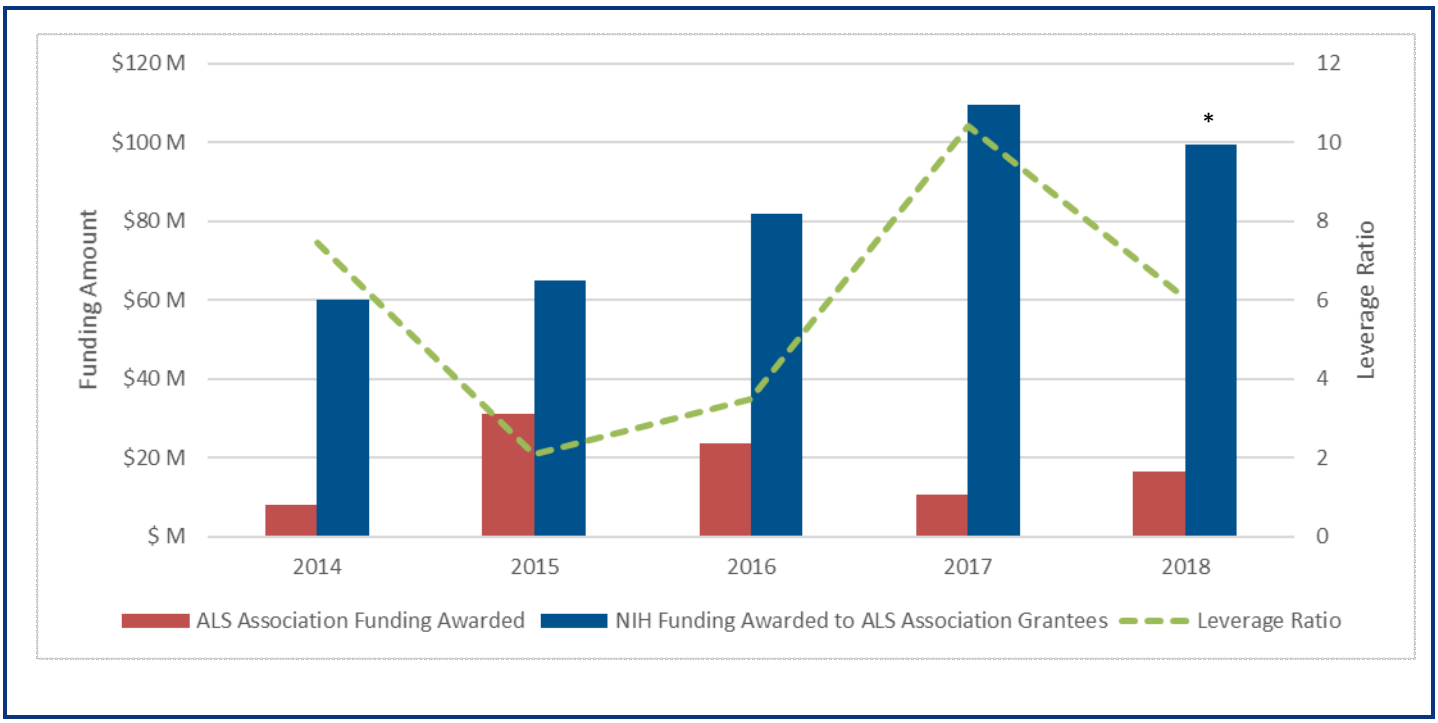
Figure 4 depicts the trend in total NIH funding awarded to Association grantees from 2014 through 2018. These data represent the sum of total NIH funds committed each year to Association grantees based on the award notice dates for the obligated funds and include funds from all NIH grant mechanisms. From 2014 through 2018, there is an obvious increase in the total amount of NIH funding committed to Association grantees, representing a compound annual growth rate (CAGR) of 13.4% over the entire period (and a 22.1% CAGR from 2014 through 2017). Despite the slight dip from 2017 through 2018, the overall trend seems to indicate that the NIH is increasing its stake in the grantees selected by the Association.

The ratio of NIH funding to Association funding awarded to grantees is also presented in Figure 4. The line representing this leverage ratio illustrates that, as a whole, the Association's grantees receive from the NIH a multiple of the amount received from the Association. This suggests that both the Association and its grantees effectively "leverage" dollars from the Association to raise additional funds from the NIH and use the two funding sources in combination to deepen and extend ALS research. The

leverage ratio is greater than six in each year except for 2015 and 2016, when the Association awarded an exceptionally large amount of funding from the Challenge, which naturally reduces the ratio of NIH to Association funding in the absence of a proportional, contemporaneous spike in NIH funding. Interestingly, following the Association's large investments in 2015 and 2016, the leverage ratio jumped in 2017 to its highest point (greater than 10) since the Challenge, which may indicate that the NIH responded by increasing its funding allocations because of a perceived multiplier on their investments in the Association's grantees.

The NIH has classified about $73.1 million of the funds presented in Figure 4 from 2014 through 2017 as specifically going to fund ALS. At the time these data were collected from NIH RePORTER in December 2018, none of the award records with an award notice year of 2018 had yet been classified by the NIH according to its Research, Condition, and Disease Categorization (RCDC).[2] Assuming that the average percentage of NIH funding awarded to Association grantees classified under "ALS" from 2014 through 2017 holds for the 2018 awards, the total amount of NIH funding awarded to Association grantees explicitly classified as "ALS" for the entire 2014 through 2018 period would be about $100 million.

Figure 4. The ALS Association and NIH Funds Awarded to ALS Association Grantees



** Data on 2018 NIH awards were incomplete within NIH RePORTER at the time of data collection.*

The awards not specifically designated as ALS research tend to be in related fields and topics. Careful analysis reveals the fact that the RCDCs of the grants not specifically categorized as "ALS" either list another category, often closely related to ALS, or provide no categorization data, even for NIH awards before 2018. A few of the most common categories of these NIH awards received by the Association's grantees, other than "ALS," are "neurosciences," "neurodegenerative," "genetics," "biotechnology," "brain disorders," "Alzheimer's disease," and "frontotemporal dementia." Considering the close relation of grantees' lines of research, much of the research they are pursuing holds realistic potential to yield benefits for ALS.

This analysis also approximates the amount of NIH funding awarded to Association grantees that could be considered "follow-on funding." Comparing the original award dates of the NIH awards and the date of grantees' first award from the Association reveals that $208.6 million of the total $415.9 million invested by the NIH in Association grantees from 2014 through 2018

[2] It cannot be confirmed, but the dip in NIH funding awarded to Association grantees from 2017 through 2018 could be caused by a delay in the appearance of some 2018 grant records in NIH RePORTER.

"followed on" the Association's initial investment. The primary observation that both funders are investing in these researchers indicates not only that these are likely top researchers but that these researchers are effective at leveraging funds from one source to generate follow-on funds from the other. In many cases, funds from the Association may be leading to results that assist in the successful procurement of resources from the NIH or vice versa.

Additionally, whatever the specific case may be regarding the original funding source that catalyzes the other, the combined funding amounts that Association grantees have received from both the Association and the NIH constitute a considerable increase in total funding for this group of researchers from 2014 through 2018. Not only do the Association grantees themselves have more resources with which to carry out their research agendas, which may directly or indirectly lead to major breakthroughs and discoveries, but the number of postdoctoral and graduate students who could be supported and benefit from such projects increases as well. Results from the survey analysis presented in Section 4 indicate that many grantees indeed used research funding from the Association to build the pipeline of human capital, knowledge, and talent in the field of ALS research. Data presented in Section 4, Table 3 indicate that 36% of grantees reported using their funding from the Association to provide support to a graduate student, and 31% used their funds to hire a postdoctoral researcher. (See Section 4 for further details on the survey methods and results.) Importantly, postdocs and graduate students represent the future generations of researchers who will investigate ALS topics.

Although the overall trends of total leveraged funding from the NIH are meaningful on their own, it is worth noting the distribution of these funds across the Association's grantees. Like most funding, it is not allocated uniformly. There are many reasons for this; in particular, age, experience level, and reputation are key factors in the amount of funds successfully raised from the NIH. Some senior researchers have earned reputations as productive top scientists and use their relatively abundant resources on many ongoing projects that produce results that may catalyze further grants. One hundred twenty-three, or slightly more than half, of the Association's 232 research grantees included in our analysis received funds from the NIH from 2014 through 2018. About 36% of the Association's grantees received more than $1 million, and approximately 10% received more than $10 million from the NIH over this period. Although this distribution is clearly skewed, it is important to recognize that large NIH center grants are included in these statistics. Many early-career researchers have funding from other sources like start-up packages from their institutions or career grants from the National Science Foundation and may be less likely to have received large NIH awards. Thus, even if some of the Association's grantees have not received a meaningful share of their funding from the NIH during this period, it does not necessarily imply that their funding needs are not being met by other sources.

Count of New NIH Awards Made to ALS Association Grantees, 2014–2018

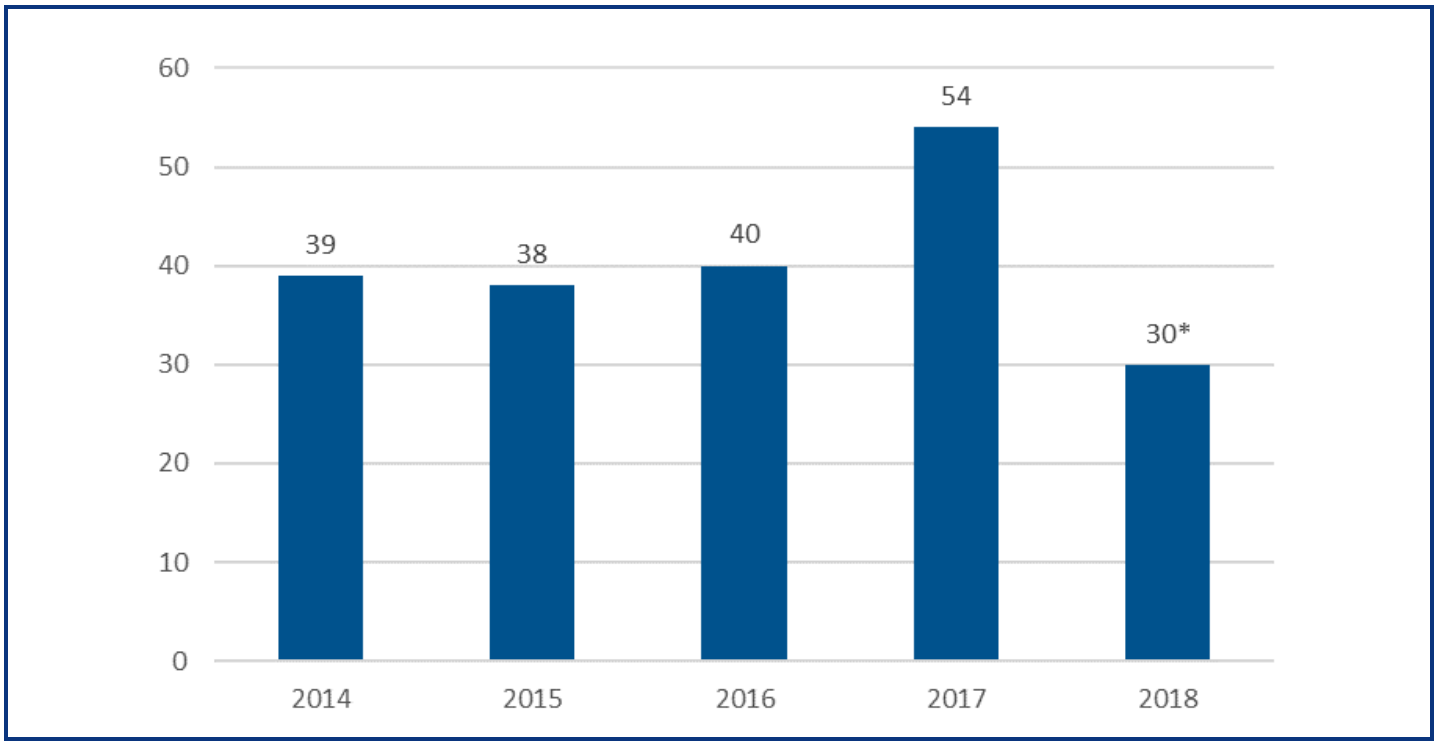
Figure 5 depicts the trend in the total number of new NIH awards made to grantees of the Association from 2014 through 2018. These data strictly represent new awards, based on the award notice date, and consider only the award notice date associated with the original record for multiyear grants. Multiyear grants were identified by a unique serial number that is assigned to grant records in the NIH RePORTER database. The general trend in the count of new NIH awards shows a marked increase of about 40% from 2014 and 2015 through 2017. The jump in 2017 is offset by a sharp dip in 2018, which might be the result of incomplete data from NIH RePORTER for 2018 at the time this analysis was conducted.

Because most NIH grants are multiyear awards, yearly fluctuations do not imply sudden, dramatic changes in the supply of funding provided by the NIH to the Association's grantees that year. Rather, considering the varying duration of NIH awards, these counts can provide a rough indication of the funds committed in future years. For example, funding from the new NIH grants awarded in 2017 will be spread out over future years, including 2018, where we observed a dip in new grants, and we can also infer that new NIH grants awarded in 2017 and 2018 will account for some of the funding distributed in 2019.

Despite the unpredictability of federal budgets, the pipeline of research dollars committed by the NIH to grantees of the Association appears generally strong for future years. However, the spike in the number of new NIH awards made to grantees of the Association in 2017 was followed by a dip in 2018 (although there is uncertainty about the extent of any potential decrease in 2018 due to the probable lack of complete NIH data) and should be monitored because either sustained decreases or erratic

funding flows would likely contribute to greater difficulties faced by Association grantees. As noted earlier, even a stable supply of funding from the NIH to the Association's grantees would constitute an increase in the combined amount of funding available to these researchers from these two key sources.

Figure 5. Count of New NIH Awards to ALS Grantees



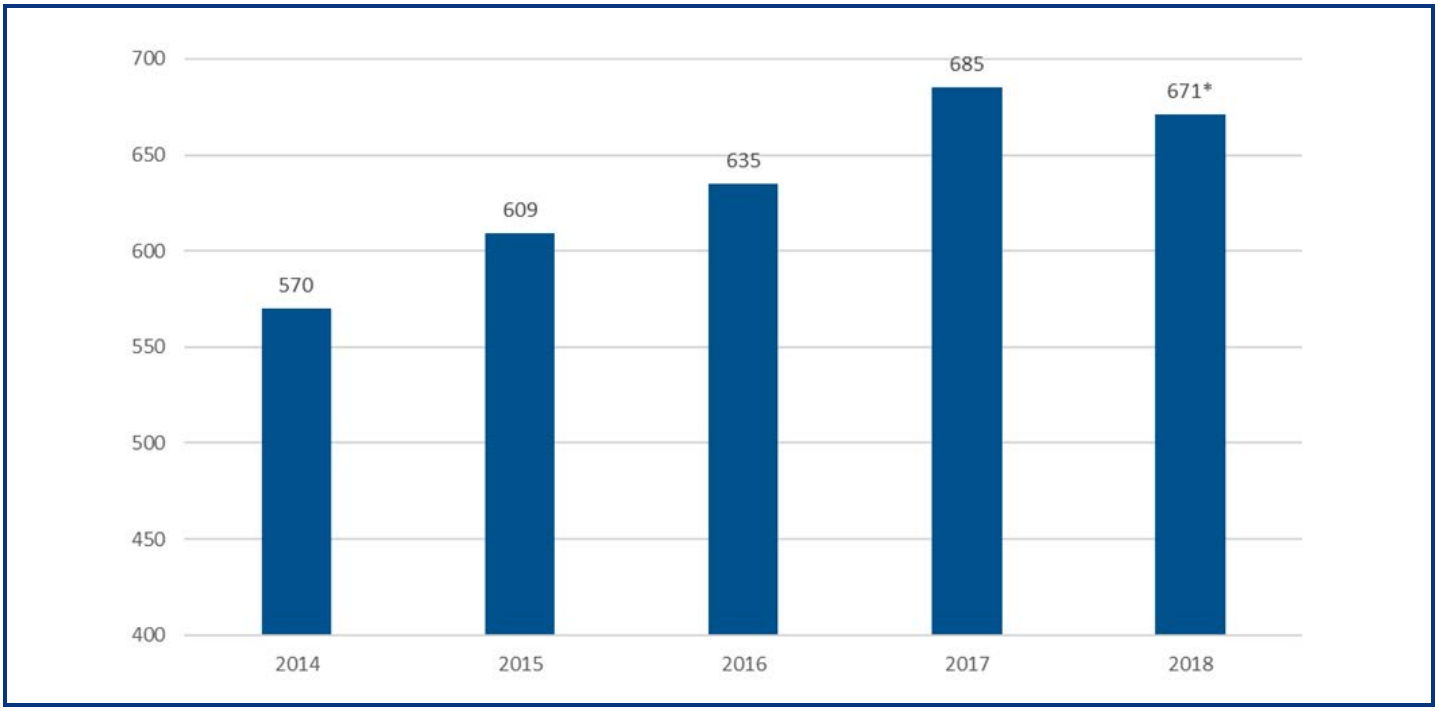
** Data on 2018 NIH awards were incomplete within NIH RePORTER at the time of data collection.*

Publication Output

The data in Figure 6 illustrate a 20% increase in scientific output measured by the number of journal articles published by Association grantees from 2014 through years 2017 and 2018. What seems like a slight decrease from 2017 to 2018 is likely due to the unfortunate timing of this analysis (January 2019), because Clarivate Analytics Web of Science typically does not completely finish indexing publications from the previous year until late February or early March. This does not diminish the point that there has been considerable total growth in scientific output from 2014 to more recent years. In particular, the impressive jump in the number of articles from 2015 to 2016 has far from receded back to earlier levels of output, and, in fact, the output per researcher has since then grown further.

The quality of scientific publications—defined by the ultimate usefulness of the scientific knowledge contained within the pages of a publication to improve human well-being through innovation—is difficult if not impossible to measure. Nonetheless, attempts to measure quality of science and potential for future impact remain an important consideration of scientometric analysis. Although we do not endeavor to investigate quality and its related dimensions in-depth within the body of literature published by Association grantees since 2014, by providing data on the quantity of this research that has appeared within a few well-known journals within the fields of science dealing with ALS, we aim to provide a signal of the relevance of grantees' publications and their present value as perceived by their peers. By the ambitious definition of quality imparted above, there is indeed great variation in the quality of published research, and it should be plainly acknowledged that quality may at times vary as greatly within journals as it does across them.

Figure 6. Count of Journal Articles Authored by Association Grantees



** Data on 2018 publications were incomplete within Clarivate Analytics Web of Science at the time of data collection.*

Table 1 presents the number of articles authored by Association grantees that appeared in a handful of select journals from 2014 through 2018. Most of the journals presented in Table 1 are cross-disciplinary and encompass a multitude of topics, most of them outside of ALS-specific research. These journals were selected, however, because of their reputations within the scientific community; many of these journals are perennially regarded as "high impact." Although the journal *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* may not garner as widespread esteem as *Nature*, for example, it is regarded as an important journal among those in the field of ALS research and a valuable resource of highly relevant knowledge.

From 2014 through 2018, Association grantees published 28 articles in *Nature* and 27 articles in *Science*, two of the top journals across all fields and disciplines of science. In addition, during this same time, Association grantees published 33 articles in *Nature Neuroscience* and 56 in *Neuron*—two more specialized but still very well-known journals—and a remarkable 146 articles in the eminently relevant *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*. As previously mentioned, the journal in which an article appears contains limited meaning as to whether the specific research will ultimately play a critical role in future innovations. However, the sheer volume of new data, new genes, clinical trials, methods, techniques, and other contributions to the knowledge base contained within this body of research suggests that the Association has contributed to the production of ALS science in such a way that may accelerate the arrival of better treatments, preventions, or even cures for ALS.

Table 1. Number of Articles in Select Journals Authored by Association Grantees, 2014–2018*

Journal	Number of Articles
Nature	28
Nature Neuroscience	33
Cell	25
Science	27
New England Journal of Medicine	10
Neuron	56
Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration	146
PLOS One	144

** Data on 2018 publications were incomplete within Clarivate Analytics Web of Science at the time of data collection.*

Even without the ability to conclusively attribute, in part or in whole, any given publication authored by an Association grantee to the fact that they have received an award from the Association, these data clearly reflect the caliber of scientists selected as grantees and the adeptness of the Association in identifying talent. By assuming some lags between the administration of Association grants and the publication of research by grantees, one may infer perhaps that a component of the sharp increase in the number of articles published from 2016 to 2017 is attributable to the Association. Although it is almost certainly true that some of the articles included in the counts for 2014 and 2015 are not attributable to the grants made by the Association, it is equally true that not enough time has passed to have the results published of many grants made within the last 2 or 3 years.

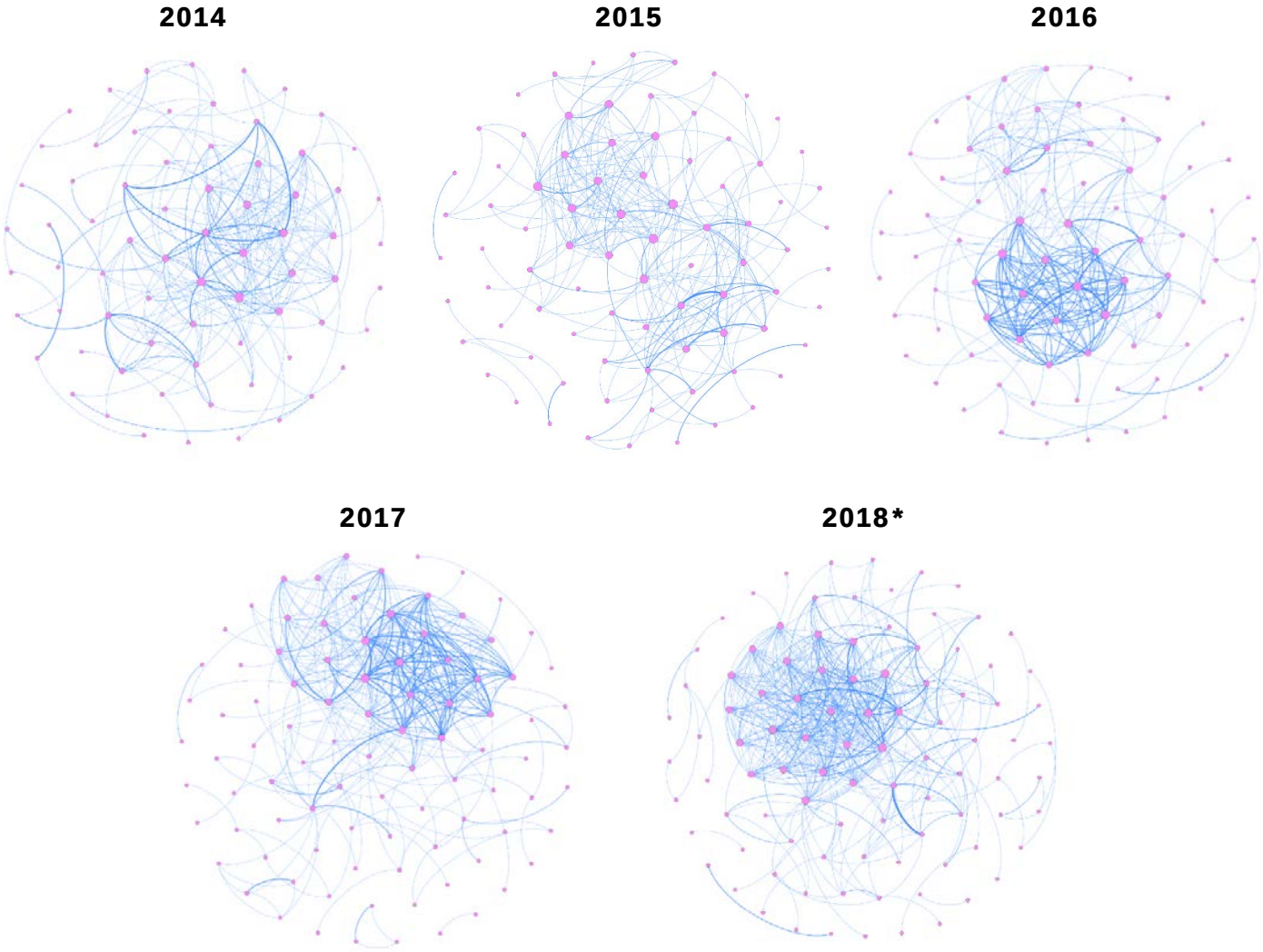
Collaboration Among Association Grantees Based on Co-authorship

Collaboration among Association grantees based on co-authorship is an important complement to the analysis of leveraged investment, the rawest of inputs, because collaboration represents the leveraging of ideas and sometimes resources like samples or instruments. We have seen already that the number of journal articles published annually by the Association's grantees is increasing, but an analysis of their co-authorship patterns may reveal how effectively and how fast the knowledge produced by grantees spreads, gets recombined, and evolves.

The transmission of knowledge is critical to scientific advancement because breakthroughs in knowledge are based on knowledge, methods, tools, and resources that exist. If researchers are disconnected from one another and their strands of research remain largely isolated, science may advance more slowly because intellectual capital is fragmented. However, when researchers frequently collaborate and share other rich interactions, these networks may serve as efficient markets for ideas, enabling new ones to emerge and spread more quickly and for the best ones to ultimately flourish. Moreover, it is not only ideas that may be enhanced but also samples, specimens, tools, and other research infrastructure that strong collaborative networks may produce superior iterations of.

Figure 7 depicts the annual change in the co-authorship network of Association grantees from 2014 through 2018. Changes in the network's structure over time provide a signal as to whether these researchers are leveraging one another's knowledge, samples, and other research tools and infrastructure and the extent to which this is increasing. The key features of the network to focus on in this analysis are its size and density. Because the network only includes grantees who co-authored an article with another grantee in a given publishing year, network size is defined by the number of co-authors, represented by "nodes," in the network. Density is defined by the number of unique co-authorship pairs in the network, depicted by the lines or "edges" that connect different grantees.

Figure 7. Annual Change in the Grantee Co-authorship Network, Years 2014–2018



** Data on 2018 publications were incomplete within Clarivate Analytics Web of Science at the time of data collection.*

It is important to make the distinction between the number of unique co-author pairs and total co-authorships. In the network diagram, there exists only one line (edge) for any unique co-author pair, but the number of co-authored publications between that pair is indicated by the thickness, or "weight," of the line connecting the two. The size of the nodes in the graph is scaled as well. The nodes, representing grantees, are scaled by the number of other unique grantees that she or he has co-authored articles within the given year.

Select articles reporting significant achievements in ALS research and acknowledging funding from the Association

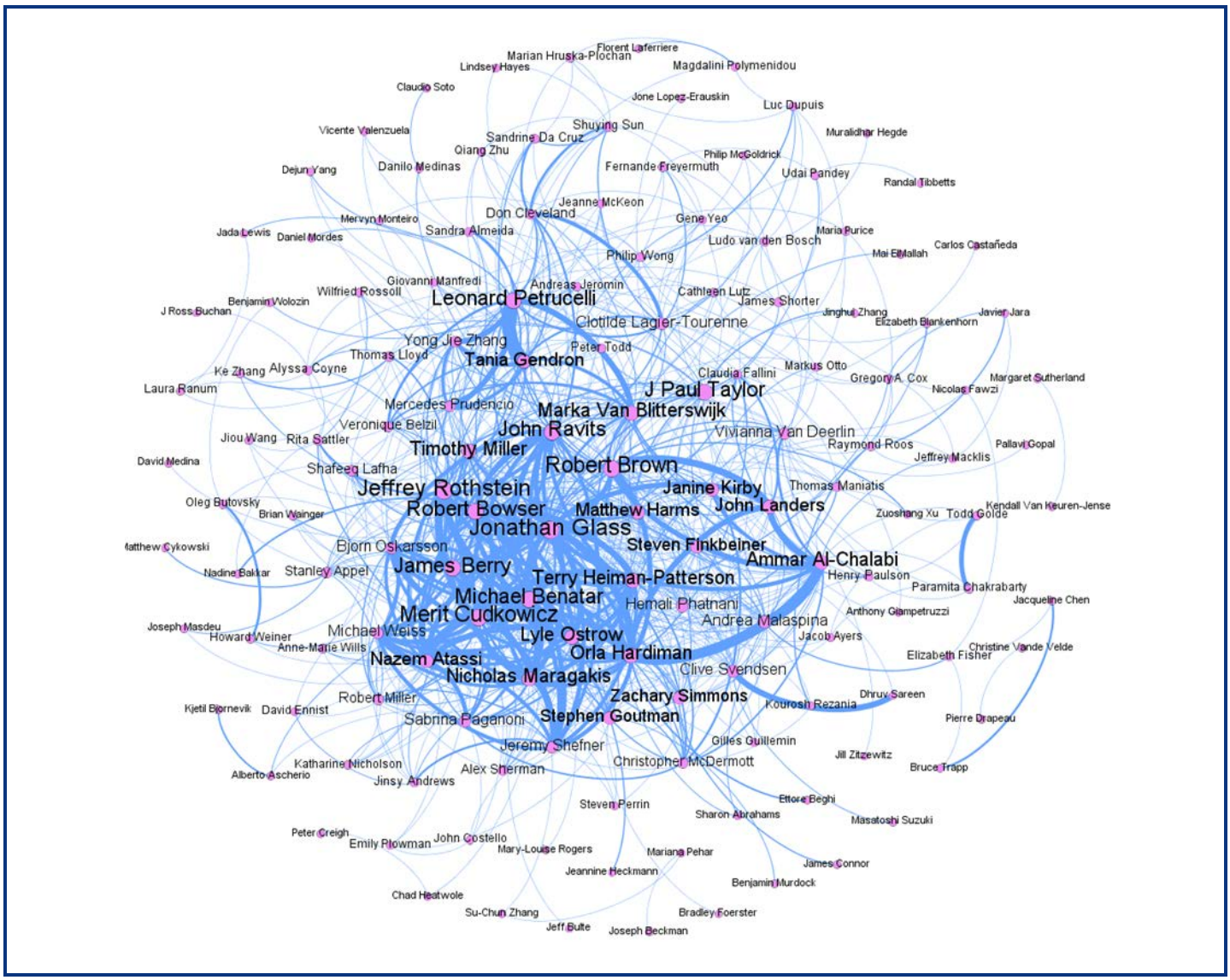
- "Antisense proline-arginine RAN dipeptides linked to C9ORF72-ALS/FTD form toxic nuclear aggregates that initiate in vitro and in vivo neuronal death" published in *NEURON* in 2014, which has been cited by 143 other publications (as of December 2018).
- "C9orf72 dipeptide repeats impair the assembly, dynamics, and function of membrane-less organelles" published in *CELL* in 2016, which has been cited by 118 other publications (as of December 2018).
- "Spt4 selectively regulates the expression of C9orf72 sense and antisense mutant transcripts" published in *SCIENCE* in 2016, which has been cited by 30 other publications (as of December 2018).
- "Poly(GP) proteins are a useful pharmacodynamic marker for C9ORF72-associated amyotrophic lateral sclerosis" published in *SCIENCE TRANSLATIONAL MEDICINE* in 2017, which has been cited by 23 other publications (as of December 2018).
- "TDP-43 pathology disrupts nuclear pore complexes and nucleocytoplasmic transport in ALS/FTD" published in *NATURE NEUROSCIENCE* in 2018, which has been cited by 20 other publications (as of December 2018).
- "Genome-wide analyses identify KIF5A as a novel ALS gene" published in *NEURON* in 2018, which has been cited by 9 other publications (as of December 2018).
- "Hot-spot KIF5A mutations cause familial ALS" published in *BRAIN* in 2018, which has been cited by 10 other publications (as of December 2018).
- "Human iPSC-derived endothelial cells and microengineered organ-chip enhance neuronal development" published in *STEM CELL REPORTS* in 2018, which has been cited by 2 other publications (as of December 2018).

The annual change in the Association grantee co-authorship network illustrates an unambiguous increase over time in both network size and network density. From 2014 through 2018, the network went from 71 grantees collaborating to form 229 unique co-author pairs to 96 grantees collaborating to form 471 unique co-author pairs. The number of co-author pairs more than doubled over this period. The largest annual increases in the number of unique co-author pairs occurred most recently in 2017 and again in 2018, constituting increases of about 42% and 32%, respectively, over the prior year. Over this period from 2014 through 2018, it appears that many of the original collaborations among grantees were maintained or had even grown, while clearly many new unique co-authorship pairs and research teams formed.

Considering the typical time interval from receipt of funds for research to the publication of a journal article containing the results of that research, it is not surprising to see signs of acceleration beginning in 2016. In 2016, the network shows a marked increase in the number of thick lines, representing a greater number of papers published by given pairs of grantees. Acceleration in collaboration among grantees strengthened in 2017, evidenced by pronounced increases in the number of nodes and unique pairs as well as the densification of clusters. The network's size conspicuously increases again in 2018 and also becomes strikingly more integrated. In addition to the 32% increase in the number of unique pairs mentioned previously, the number of larger nodes increases—indicating that more grantees have more unique co-authors—resulting in very short distances between most of the grantees and any other grantee in the network. The high number of direct connections and otherwise relatively short distances between grantees illustrate the point that knowledge, ideas, samples, and other research tools may be diffused more efficiently among grantees in 2018 versus in 2014.

Figure 8 depicts the grantee co-authorship network across the entire period 2014 through 2018. This diagram is constructed the same way, with edge weight scaled by the number of co-authored articles by a given pair and node size scaled by the number of co-authors a grantee has, but it also includes name labels. These name labels help identify the position of individual grantees within the network. Positioning of individual grantees in the network may enable their ideas, or those that they promote, to spread or become visible more quickly or may enable them to more easily form certain new collaborations.

Figure 8. 2014–2018 Grantee Co-authorship Network*

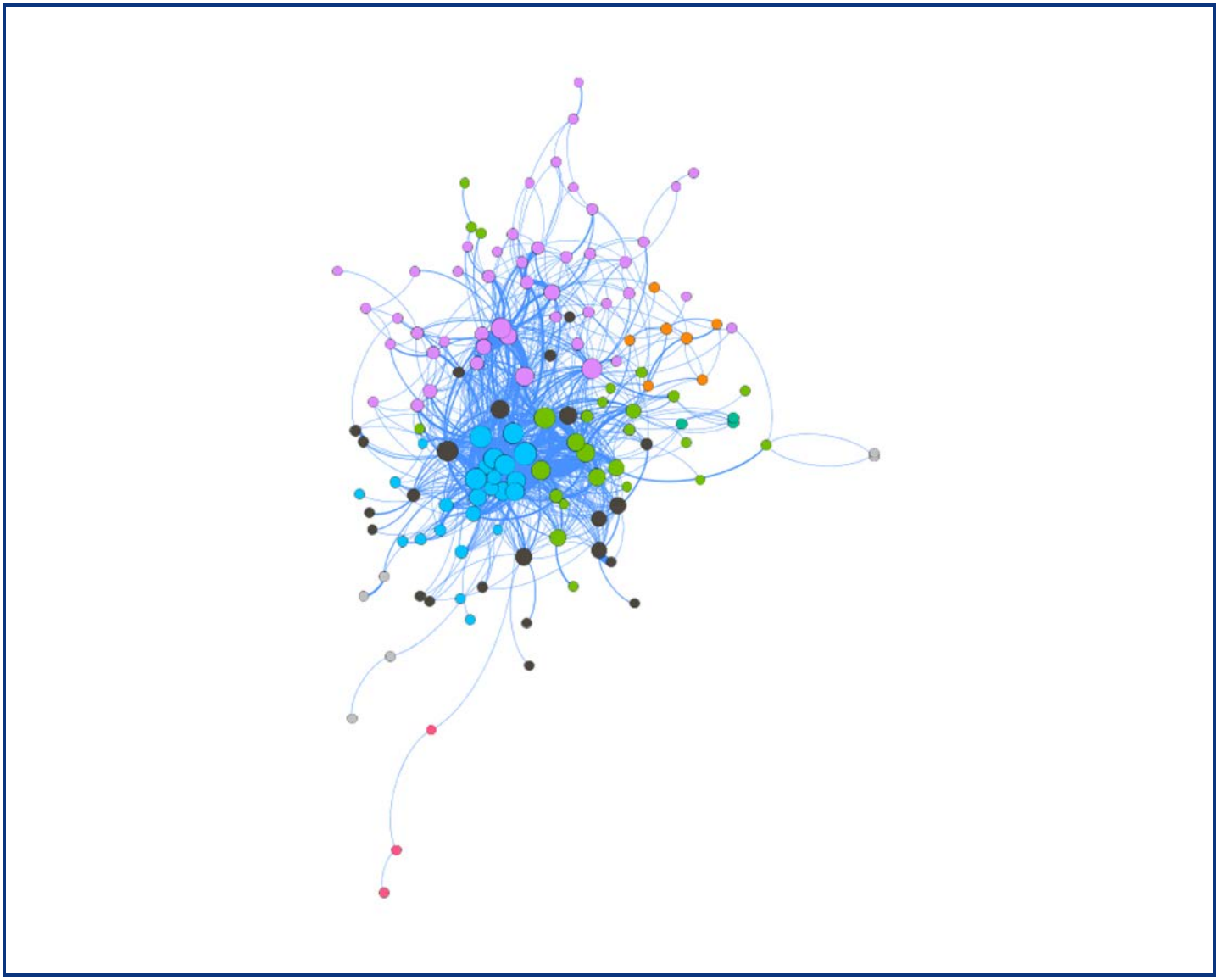


** Data on 2018 publications were incomplete within Clarivate Analytics Web of Science at the time of data collection.*

Because this network is comprehensive of all publications co-authored by grantees from 2014 through 2018, this diagram obviously is largest in terms of both the number of grantees represented and number of unique grantee co-author pairs. However, what is most important with respect to the analysis of the 2014 through 2018 diagram is the makeup of the grantee community and the situation of individual grantees within it. There is clearly a large, dense primary cluster directly involving many grantees. There is also a smaller secondary cluster apparently formed around Leonard Petrucelli. While distinct, there are still many co-author pairs that serve as integrators across the two clusters. Most grantees are directly connected to one or both of these clusters, and very few are not connected at least indirectly to them through another co-author.

The "communities" of co-authors are more formally segmented in Figure 9 with the help of an algorithm that spatially organizes and color codes the nodes by their immediate co-authors, the co-authors of their immediate co-authors, and so on, ultimately identifying communities based on relative proximity to other groups in the network. While the segmentation reveals multiple communities, which are relatively more integrated within themselves than across groups, most grantees belong to a community that is well connected to other important communities. These types of connections suggest that the knowledge and tools

Figure 9. 2014–2018 Grantee Co-authorship Communities*



** Data on 2018 publications were incomplete within Clarivate Analytics Web of Science at the time of data collection.*

generated by these communities are far from isolated and that, on the contrary, their work is almost certainly seen and leveraged by the other groups. These communities form the basis of intellectual exchange and the exchange of other resources and tools, which are necessary for conducting research that may lead to breakthroughs in the treatment of ALS. If the collaboration trends among researchers funded by the Association continue, the overall community will continue growing in size and density, becoming increasingly conducive to the acceleration of science dealing with ALS.

Funding Acknowledgements and Important Co-funders within the Ecosystem

Each year, beginning with 2014 as the base year, the number of journal articles that acknowledge the Association increased. The number of articles published in 2018 that acknowledged the Association was more than double (124% greater than) the number of 2014 articles that acknowledged the Association.

From the perspective of leveraging its investments, it is also worthwhile to analyze other funders within the ecosystem that are supporting the Association's grantees. Consistency in the acknowledgement of the NIH in publications may be relatively more reliable than acknowledgments of the Association because of guidelines that accompany NIH awards; however, despite these helpful guidelines, the acknowledgement data are still imperfect. Unsurprisingly, as the largest funder of health research in the

United States, the NIH is acknowledged in roughly half of all journal articles authored by the Association's grantees published from 2014 through 2018. This ratio is fairly constant across the 2014 through 2018 time period. Papers that do not acknowledge NIH support may have been primarily supported by foreign government agencies (particularly for grantees and research teams based outside the United States) or private philanthropies like the Association. As federal research budgets get stretched thinner by growth in the number of potential projects and awardees without a commensurate increase in the total spending, private philanthropies play an increasingly important role in funding both basic and applied research.

Although it was not possible to undertake a more detailed co-funding analysis within the time constraints of this project, RTI did identify several other funders besides NIH that appear to be most frequently acknowledged in publications alongside the Association. Among the top most frequently acknowledged co-funders (roughly in order beginning with the greatest number of co-funding incidents) are the Muscular Dystrophy Association, the Medical Research Council (United Kingdom), Target ALS, the ALS Therapy Alliance, the Mayo Clinic, the Motor Neurone Disease Association (United Kingdom), the U.S. Department of Defense, the Robert Packard Center for ALS Research at Johns Hopkins, Wellcome Trust (United Kingdom), and the National Multiple Sclerosis Society.

The names appearing on the list above underscore the increasing importance of foundations and private charities in scientific research. The full list of co-funders extends into the thousands and comprises many different types of entities such as U.S. federal agencies, foreign government agencies, U.S.- and non-U.S.-based foundations, biopharmaceutical companies, specialized research institutes, and universities. Beyond funders that are acknowledged alongside the Association, there is an even longer list of funders, independent of the Association, that are acknowledged within the publications that appeared between 2014 and 2018 authored by grantees. These funders are also relevant, not just because of the likely undercount of ALS Association-funded articles as previously noted, but because tangential projects and areas of research pursued by ALS Association grantees almost certainly interact to some extent with the research that is directly funded by the Association.

Additionally, one must recognize that researchers not only develop strategies involving the allocations of their time to different strands of research, but they also strategize about how to acquire the funding to pursue it. From this perspective, knowledge about the current topology and evolving dynamics of the funding ecosystem has strategic implications for the Association. Specifically, it may be advantageous to identify important current and future co-funders and to coordinate with them by building and maintaining strong relationships. Co-investing with funders who share overlapping interests with the Association mission may help maximize leveraging of research investments, particularly in cases where the other funder is also well networked (with co-funders besides the Association).

4. RESEARCH GRANTEE SURVEY

AIMS

In consultation with The ALS Association, RTI designed and fielded an online survey of the Association's research grantees to complement the analysis of secondary data (Section 3). The aims of the survey were to measure grantees' research accomplishments using the Association funding, as well as their perspectives on how this funding affected their progress. This section describes the survey methods and results.

METHODS

Survey Design

The study's main research questions drove the development of the grantee survey (see Section 1). The RTI team worked with the Association to outline key indicators relevant to each research question and develop survey items to measure those variables. Key considerations to reduce participant burden were a) keeping the survey to 15 minutes or less, b) using as many close-ended items as possible, and c) measuring variables that could not be otherwise measured using secondary data.

The survey included 15 questions related to participants' name and contact information, scientific focus, overall impact areas, research outputs, follow-on funding, and collaboration. Research output items measured both scientific contributions and support of early career professionals and infrastructure improvements. Follow-on funding items asked participants about their applications to external sources (e.g., NIH) for subsequent funding, if they won those awards, and the estimated award amounts. Collaboration items focused on new collaborations across a variety of disciplines as a result of the Association funding. Finally, two open-ended items at the end of the survey asked participants about their most significant accomplishment and for any remaining comments.

When answering the questions, we directed participants to think about funding they had received from the Association between 2014 and 2018 and to think about impacts of the funding received during this time. This time period served as a proxy for measuring the impact of the Challenge donations because the Challenge donations made up a large portion of the Association's funding streams after 2014.

Recruitment and Data Collection

The survey sample included lead investigators with valid email addresses who had received a research grant from the Association between 2014 and 2018. The Association provided contact information for their 237 grantees. In some instances, email addresses were missing or inactive (i.e., emails that "bounced back"), and in one case, the grantee had passed away. RTI worked with the Association to replace invalid email addresses with valid ones. In other instances, the database had multiple email contacts for a single grant. We retained all valid email addresses to facilitate recruitment rather than selecting one email address per grant. During recruitment, 14 email addresses bounced back, and we identified 9 new email addresses for grantees with missing or inactive email information. The final recruitment list included 226 email addresses.

RTI designed and hosted the online survey using SurveyGizmo and fielded the survey from December 2018 through January 2019. Recruitment of the Association's research grantees involved a series of invitation and reminder emails. The Association emailed a pre-invitation letter explaining that they were evaluating the impact of their grant programs and encouraging participants to respond to the online survey. RTI then emailed a formal invitation containing the survey link. The Association sent four reminder emails. The invitations and survey language indicated that participants had the option to enter a raffle to win up to $1,000 toward a conference registration fee. However, after data collection ended, the evaluation team was notified that the raffle would violate federal law prohibiting private lotteries. In response, RTI sent a letter to survey respondents who

had opted into the raffle explaining why the raffle was not permitted and offering a $20 Amazon gift card for each of those respondents in place of the raffle.

Data Cleaning and Analysis

We removed cases from the dataset if no survey questions were answered. Some participants started the survey but did not complete it and then took the survey a second time and completed it. In those instances, we deleted the partially completed record and retained the completed record to avoid counting responses for a single grantee twice.

We calculated descriptive statistics (counts, percentages, means, and standard deviations) for all closed-ended, quantitative variables. For ease of understanding, we rounded all percentages to the nearest whole number. We recoded the organizational affiliations that participants reported into four types of organizations (academic, other not-for-profit, for-profit, government) based on publicly available information on each institution. For open-ended items, we reviewed and summarized responses according to each of the main research questions.

RESULTS

Response Rate

In total, 124 grantees completed the survey between December 2018 and January 2019. One individual completed the survey before the deadline and then completed it again after the deadline; the analysis excludes this participant's second set of responses. Two respondents' email addresses did not match the final recruitment list. By comparing responses from these individuals to the secondary data, we determined that they each worked with a lead investigator from the recruitment list (both of whom had not responded to the survey). We deemed these to be valid responses. Thus, the final analytic sample included 53% of the Association's 236 grantees (this calculation excludes one grantee who had passed away).

Sample Characteristics

As shown in Table 2, most respondents (76%) reported academic organizations as their primary organizational affiliation. Fewer respondents named other not-for-profit (11%) or for-profit (4%) organizations, and only one respondent reported a government organization (1%).

Table 2. Respondents' Organizational Affiliations

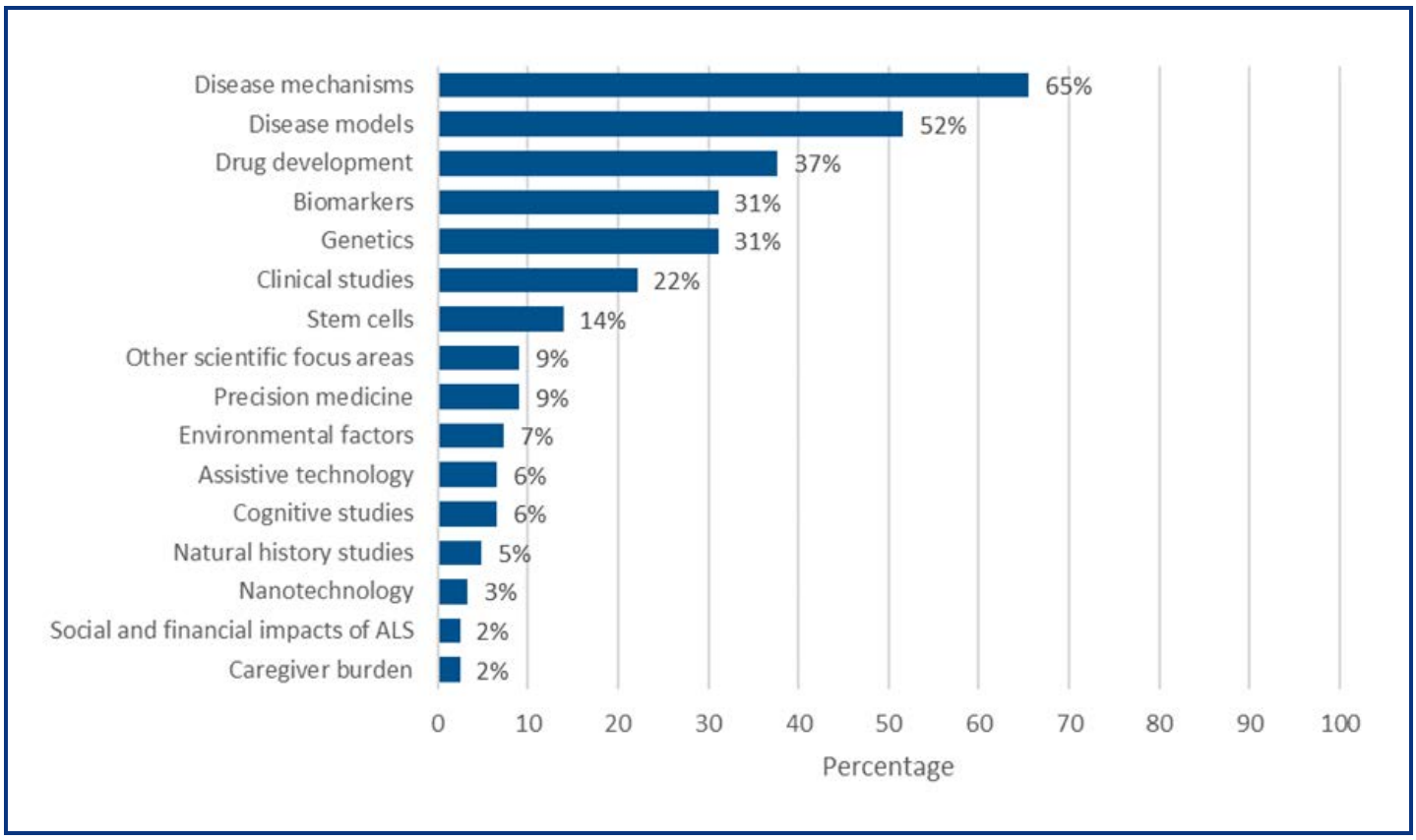
	Respondents n (%)
Academic	94 (76%)
Other not-for-profit	14 (11%)
For-profit	5 (4%)
Government	1 (1%)
No answer	10 (8%)

Note: N = 124

Because of rounding, percentages may not sum to 100%.

Respondents specified their scientific focus areas and could select multiple responses. Figure 10 presents the distribution of participants' reported focus areas. Nearly two-thirds of respondents focused on disease mechanisms (65%), followed by a focus on disease models (52%). **Notably, drug development (37%), biomarkers (31%), and genetics (31%) were also common focus areas among respondents.** Several respondents (9%) reported other areas of focus, such as imaging, chemical biology, molecular neuropathology, or virology.

Figure 10. Respondents' Scientific Focus Areas



Note: N = 124

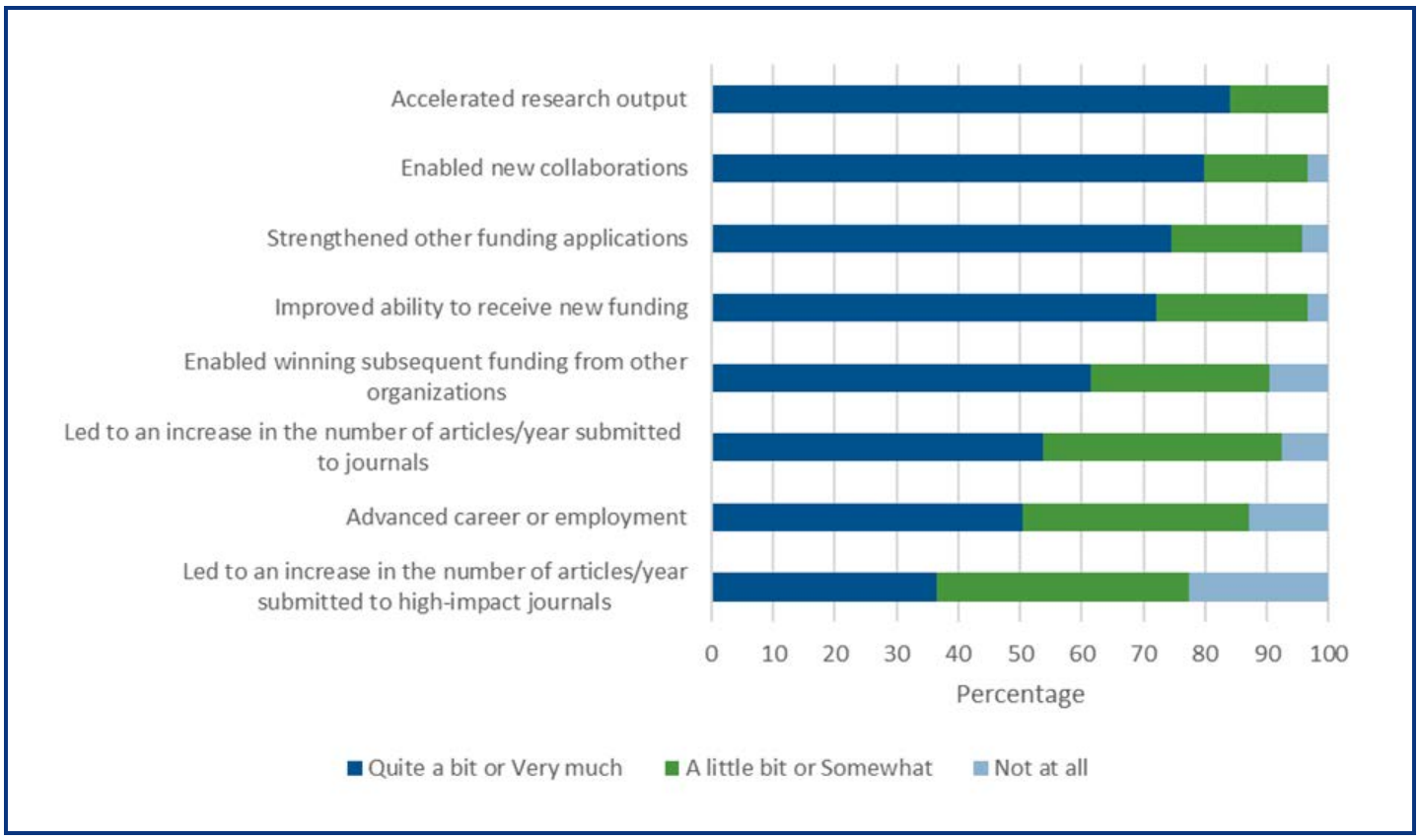
Respondents could select more than one option. Percentages may sum to more than 100%.

Research Output

The first main research question asked about the impacts of the Association funding on research outputs. Several survey items examined this research question including a measure of perceived overall impact on a variety of research areas. The survey instructed participants to consider any research grants that they received from the Association between 2014 and 2018 and then rate eight statements about the impact of those grants on their work using a 5-point response scale (1 = "Not at all," 2 = "A little bit," 3 = "Somewhat," 4 = "Quite a bit," 5 = "Very much").

Most participants reported that receiving an ALS Association research grant had accelerated their research output quite a bit or very much (84%). Almost 80% of respondents reported the Association grant funding helped them form a new collaboration quite a bit or very much. Furthermore, a majority of participants reported that funding by the Association strengthened their other funding applications (75%), improved their ability to receive new funding (72%), and enabled them to win subsequent funding from other organizations (61%). Over a third reported that the Association funding increased the number of articles they submitted to high-impact journals (37%). Figure 11 further illustrates participants' impact ratings.

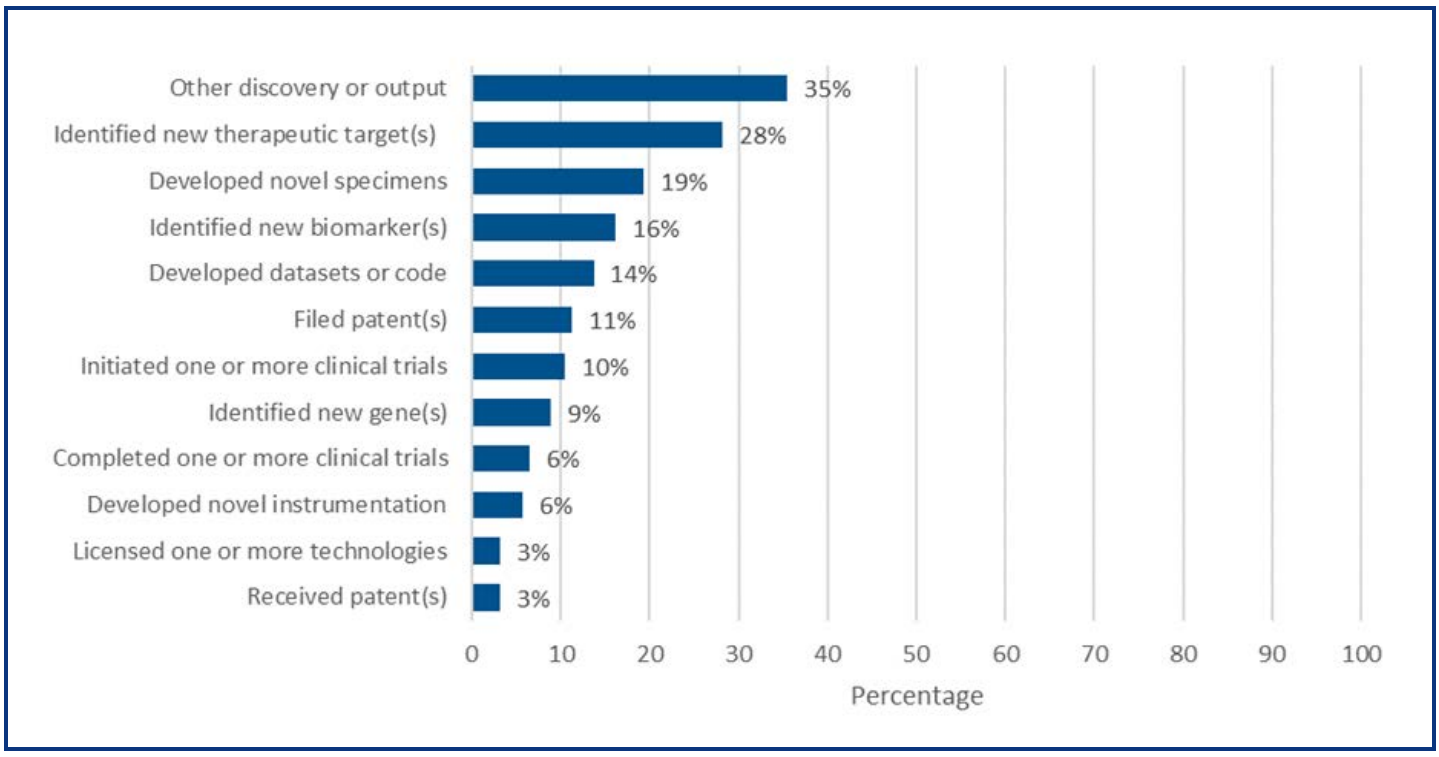
Figure 11. Impact Area Ratings



Note: N ranged from 116 to 121

In addition to perceived impact on research output, the survey measured actual outputs that resulted from the Association funding. Respondents identified whether their ALS Association-funded research led to various accomplishments, or "outputs," as shown in Figure 12. **Almost a third of respondents reported that their funding resulted in identification of new therapeutic targets (28%). Respondents also reported development of novel specimens (19%), identification of new biomarkers (16%), identification of new genes (9%), and initiation or completion of clinical trials (12%).** Although fewer respondents reported developing novel instrumentation (6%), receipt of patents (3%), or licensing technologies (3%), more than a third (35%) reported their funding affected other areas of discovery. **Some of the other discoveries participants described included "risk factors," "classification of ALS patients based on skin fibroblast phenotypes," and "speech-related activity in 'hand/arm' areas of motor cortex."**

Figure 12. Respondents Reporting Research Outputs Funded by the Association



Note: N = 124

Respondents could select more than one option. Percentages may sum to more than 100%.

In addition to research outputs, we measured other indicators of productivity and contributions to the ALS research field, including support of new researchers and acquisition of research equipment since 2014. Across the grantee sample, 37% used the Association funds to support graduate students for research, 32% reported hiring a postdoctoral researcher, and 15% reported purchasing laboratory instrumentation. Results suggested that some grantees did not use their funding to bring on new staff or instrumentation because 41% chose to skip this question. Table 3 summarizes these results.

Table 3. Respondents Reporting Other Research Productivity

	Respondents n (%)
Provided support to a graduate student for research	46 (37%)
Hired a postdoctoral researcher	39 (32%)
Purchased laboratory instrumentation	19 (15%)
No response	51 (41%)

Note: N = 124

Respondents could select more than one option. Percentages may sum to more than 100%.

Follow-On Funding

The second research question driving this survey and evaluation asked whether grantees have been able to leverage their Association funding into follow-on funding. The survey included measures on external funding applications and awards. Specifically, participants indicated whether the Association enabled them to apply for subsequent funding from a variety of other sources, and if so, they reported the total award amounts from each funding source. As shown in Table 4, participants most frequently reported applying for funding from philanthropic foundations other than the Association (41%), non-R01

Table 4. Amount of Subsequent Funding Received by Source

Source of Funding	Applied for Funding n (%)	Received Funding n (%)	Average $ Amount Awarded[a] Mean (SD)	Range of $ Amount Awarded[a]	Total $ Awarded across Respondents[a]
NIH—R01 grant(s)	29 (29%)	15 (15%)	$1,718,657 ($1,378,789)	$219,000–$5,235,000	$25,779,848
NIH—other than R01	36 (36%)	15 (15%)	$1,619,876 ($2,243,621)	$100,000–$7,000,000	$22,678,258
Another source	12 (12%)	7 (7%)	$3,037,143 ($7,483,960)	$10,000–$20,000,000	$21,260,003
Philanthropic foundation other than the Association	41 (41%)	32 (32%)	$564,727 $(674,156)	$50,000–$2,500,000	$18,071,259
Grantee's own institution	29 (29%)	22 (22%)	$507,773 ($1,266,558)	$11[b]–$5,500,000	$11,171,011
Another federal agency (DoD, VA, etc.)	24 (24%)	12 (12%)	$911,667 ($536,497)	$50,000–$2,000,000	$10,940,000
Other nonprofit entity	14 (14%)	8 (8%)	$1,219,375 ($2,037,243)	$5,000–$6,000,000	$9,755,000
Corporate or commercial entity	15 (15%)	9 (9%)	$432,778 ($777,967)	$100,000–$2,500,000	$3,895,000
No funding applications	8 (8%)	--	--	--	--

Note: N = 101

Respondents could select more than one source of funding. Percentages may sum to more than 100%.

[a] Amounts are based on respondents who reported receiving funding.

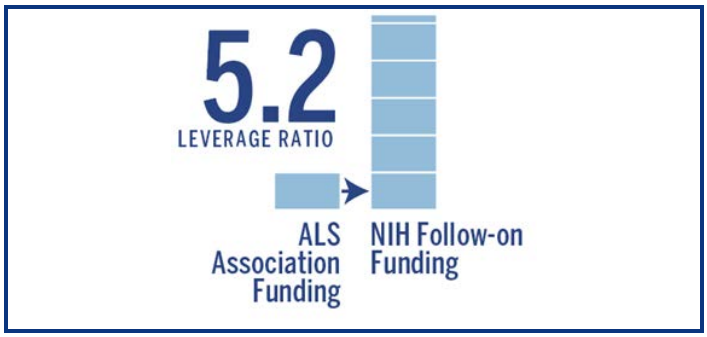
[b] This $11 amount from one participant's write-in response likely reflects a typo. The next highest amount reported was $4,000.

awards (36%) and the NIH for R01 awards (29%), and one's own institution (29%). Nearly one-third of grantees won the philanthropic foundation awards (32%), and nearly one-quarter won awards from their own institution (22%). The least reported of both applied for and received funding sources were other nonprofit entities and corporate or commercial entities. The highest award totals across sources included approximately $25.8 million in R01 awards and $22.7 million in non-R01 awards from the NIH. Additionally, nearly 7% of respondents specified receiving awards from another source (as a write-in response), including international sources, telethons, and private or state funding. These other awards totaled approximately $21.3 million. In total, those who responded to this question (101 out of 124 participants) reported $123.6 million in external awards that they applied for as a result of their ALS Association grant. A follow-up analysis comparing the survey data with the secondary data indicated that the Association had awarded $39,995,435 to these participants.

In an additional follow-up analysis, we compared participants' survey responses about NIH follow-on funding with these respondents' Association funding. For participants who reported that the Association enabled them to successfully apply for and receive NIH funding (n = 25), we summed their self-reported NIH dollar amounts, both R01 and non-R01, and calculated the ratio of NIH follow-on funding to their total amount of funding from the Association. This calculation yielded an average leverage ratio across the group. Results indicated a leverage ratio of 5.2 (Figure 13). Thus, for those grantees who reported that their award from the Association at least partially enabled a successful NIH application, they leveraged their funding from the Association into 5.2 times that amount in NIH follow-on funding.

Collaboration

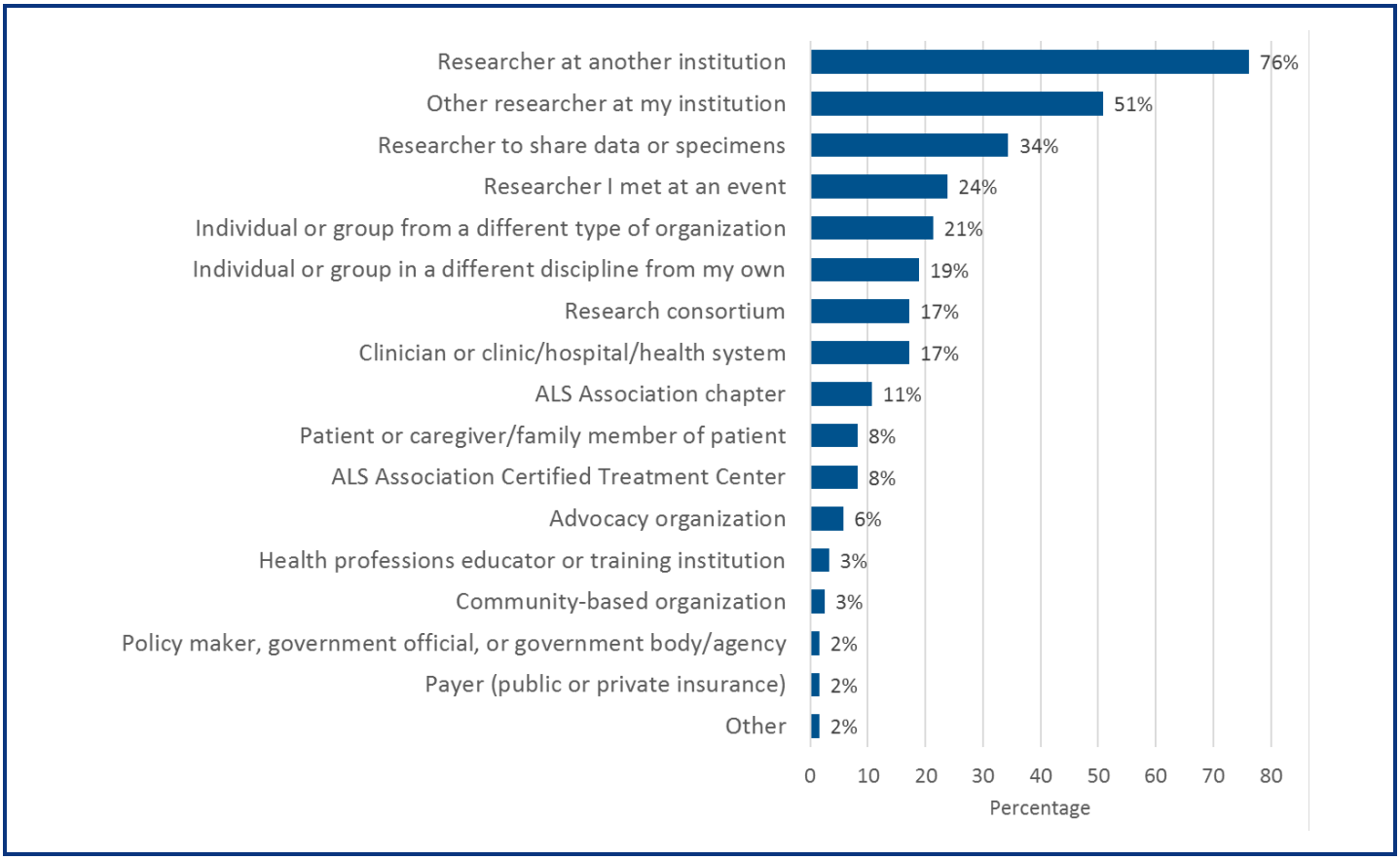
Figure 13. NIH Follow-On Funding Leverage Ratio



Note. This leverage ratio is based on the subset of Association researchers who reported on the grantee survey that their award from the Association enabled them to apply for and receive NIH funding (n = 25).

The final research question pertained to the Association's impact on collaborations. Survey participants reported new collaborations that they formed as a result of receiving an Association grant. Figure 14 shows these results. More than three-quarters of respondents reported new collaborations with researcher(s) at another institution (76%), and half of respondents also reported collaborating with other researcher(s) at their own institution (51%). **Notably, some grantees reported collaborations with clinical care sites (17%), certified treatment centers (8%), and patients (8%).** Fewer participants reported collaborating with health educators (3%), community-based organizations (3%), insurance payers (2%), or policy-related entities (2%). Figure 14 further summarizes these results. Beyond these, several participants (2%) reported other collaborations, including those with manufacturers of related technology, pharmaceutical companies, biotechnology companies, and venture capitalists.

Figure 14. Collaborations Formed after Receiving an Association Grant



Note: N = 124

Respondents could select more than one option. Percentages may sum to more than 100%.

Open-Ended Feedback

The end of the survey included two open-ended questions asking about participants' most significant accomplishment from work funded by their Association grant and for any additional comments. Most participants (n = 108; 87%) answered the question about their accomplishments, providing details on a vast array of scientific achievements from assistive technologies to "*using cultured adult motor neurons to study cellular mechanisms of ALS.*" **Approximately 18 participants mentioned gene research, 12 described therapeutics, and 9 highlighted clinical trials.**

In total, 58 participants provided valid additional comments (47%; n = 3 comments were not applicable, for example, "No" or "None"). Most expressed gratitude for the Association funding and thought this funding made their work possible; for example, "*Funding from [T]he ALS Association has been transformative to the way ALS genetics and genomics research is now conducted in the United States*" and "*The Association support has been critical to starting off the projects in my lab. The support for basic and biophysical science is key - not all disease foundations look upon this work highly so I appreciate [T]he ALS Associations efforts here and I hope they continue.*"

Across both questions, some participants provided information on work with clinics and patients. Table 5 presents examples of these responses and significant accomplishments pertaining to genes, therapeutics, and clinical trials. Note that this report does not present the complete set of significant accomplishments because most responses used highly technical language pertaining to ALS research methods, data collection, and results.

Table 5. Quotes on Discoveries and Care

Gene Targeting and Discovery	"Development and leadership of a large multinational consortium centered on ALS genetics and genomics that has transformed the landscape of ALS research."
	"Identified a new gene that causes ALS-like disease in a mouse model system and are now looking for connection to potential ALS patients."
	"I identified several genetic suppressor genes of C9ORF72 associated poly(GR) toxicity. 3 of them are involved in DNA damage repair process."
	"I have cloned the entire library of human chaperone genes and I am currently testing this library against ALS associated toxic proteins FUS and TDP43."
Therapeutics	"Preclinical testing of a new therapeutic approach to use antibodies against dipeptide repeat proteins in C9ORF72 ALS/FTD."
	"Developed a new drug discovery platform; identified potential leads; start exploring therapeutic development."
Clinical Trials	"We have been able to move forward with 3 clinical trials either initiated by [the Association] and fully funded by [the Association]."
	"I was able to initiate several clinical trials that would have not been possible without the support from [T]he ALS Association. While results are not available yet, a lot of data and samples have already been generated. I am hopeful that there will be positive results from these trials."
Patient Care	"[The Association] funding helped me and my students build important relationships with [the Association] and ALS patients that have helped us move our basic biophysics to more therapeutically focused work."
	"Constantly advancing translational science towards bringing therapeutic benefits to the ALS patients."
	"[The Association] has been critical support for clinic, translational and basic science programs"

Note: This table presents verbatim open-ended responses, including any misspellings.

Notably, in response to the open-ended questions, several participants (n = 13) mentioned that their grant projects were in the early stages, so they had not yet accomplished some or most of their research objectives. For example, one grantee wrote, "*The award is very recent (6 months), so most of the expected outcomes are anticipated in the next year or two. I'm sure I'll tick many*

more boxes by then!" In a follow-up analysis, we connected these responses to secondary data listing the first grant award year for each participant. Most of these participants (n = 7) received their first grant from the Association in 2018.

Limitations

This survey faced two limitations that likely led to conservative estimates of research outputs, follow-on funding, and collaborations. We introduced the first limitation in the open-ended results section, which pertains to funding year. Participants who received Association grants more recently, such as in 2017 or 2018, would not have had adequate time to accomplish most of their research aims, build noteworthy collaborations, or apply extensively for new funding as a result of those grants. In particular, had there been a longer delay between grant award date and the survey, the amount of subsequent funding that participants reported likely would have been larger. Furthermore, more time could have yielded additional research outputs and collaborations. After linking the survey and secondary data, we determined that 32% of survey participants received their first Association grant in 2017 or 2018.

A second limitation is that the final analytic sample did not include all researchers who received grants from the Association after 2014, so we cannot claim that the results reflect the full pool of these researchers. We considered the response rate of 53% to be acceptable given a short data collection period that overlapped with several major holidays. However, a larger sample would provide more robust estimates of grantees' perceptions of the Association's impact on their research, as well as how much follow-on funding and collaboration they think resulted from their Association grant. Furthermore, a larger sample facilitates subgroup analysis by grant year, for example, comparing results within earlier versus later grant years. Given the actual sample size, these subgroups were too small to provide reliable estimates.

Even while taking these limitations into consideration and the possibility for conservative estimates, the survey results continue to indicate that grantees have made strides in their research programs and, to a large extent, attribute their progress to the Association's funding.

5. KEY INFORMANT INTERVIEWS

AIMS

We interviewed key informants to help contextualize findings from the secondary data analysis and survey analysis. The interviews served to illustrate several individuals' perspectives on the impact of financial support from The ALS Association rather than to represent a comprehensive qualitative evaluation of the grant program.

METHODS

Recruitment

RTI consulted with the Association to identify key informants to interview, aiming to include researchers, care service providers, and advocates. To recruit interviewees, the Association sent a pre-invitation lead letter explaining the goal of the interviews and encouraging individuals to respond, and RTI then emailed prospective participants a formal invitation. We informed participants that we would use what we learned from the conversation to highlight their work in this report and that the Association may use the information to publicly promote their investments. Interviewees received a $200 incentive for their participation. Five individuals agreed to be interviewed for this project:

- **John E. Landers, PhD**, Associate Professor, Department of Neurology, University of Massachusetts Medical School
- **Fred M. DeGrandis, JD,** CEO of NorthCoast Healthcare Services, LLC; Member of National Board of Directors and Chair of Patient Access and Strategic Growth, Cancer Treatment Centers of America; Public Policy Chair of the National Board of Trustees of The ALS Association
- **Dexter Ang, BS,** CEO and Co-founder of Pison Technology
- **Jeffrey A. Cohen, MD,** Chair and Professor of Neurology, Geisel School of Medicine at Dartmouth, Dartmouth-Hitchcock Medical Center
- **Elijah W. Stommel, MD, PhD,** Professor of Neurology, Geisel School of Medicine at Dartmouth, Dartmouth-Hitchcock Medical Center

Data Collection

The interview guide, developed jointly by RTI and the Association, included questions on the following topics:

- the interviewee's work,
- their reactions to receiving funding from the Association,
- key accomplishments and successes supported by that funding,
- the impact of the funding on their work,
- how the funding benefited early-career professionals,
- how their work affects ALS patients and their families, and
- what they would like donors to know about their work.

An interviewer from RTI's evaluation team conducted these interviews by phone, and a notetaker joined the call to record relevant discussion points. We directed interviewees to provide their honest opinions and to try to explain their research in a way that someone outside their field could understand. Each interview took about 60 minutes. Before starting interviews, we obtained permission from interviewees to audio-record the session. RTI used the recordings to produce transcripts to fill any gaps in the notetaker's record of discussion and to translate interview data into testimonials with quotes.

Data Analysis

After conducting the full set of interviews, the evaluation team identified key takeaways, findings, and themes that emerged from the interview notes and transcripts. Through internal discussion, the team determined how the information from each interview could help contextualize different findings from the secondary data analysis and survey. More in-depth qualitative coding and analysis were outside the scope of the key informant interview phase.

IMPACT STORIES

For this report, we summarized the key findings from each interview as an "impact story." Each impact story focuses on the effect that the Association grants have made on each interviewee's organization. These impact stories describe collaborations, follow-on funding, patient care, and advocacy.

Key themes that emerged:

- New discoveries included new genes (including the recently published KIF5A gene), evidence for possible environmental causes of ALS, and development of new assistive technologies. Genetic discoveries are important because finding new genes helps researchers identify disease pathways so they can develop and test new drugs.
- Those involved in clinical care felt that Association grants had supported clinical improvements at treatment centers. These improvements included multidisciplinary care, care coordination, caregiver support, health navigation, and opportunities to join clinical trials.
- The Association grant program played a role in funding innovative and preliminary work. Several interviewees thought the Association had funded work that they would not have been able to get funded through the NIH, and the Association funding enabled them to collect the initial data needed to secure later funding from government agencies.
- Interviewees felt they supported a range of early-career professionals via Association funding. They believed that they had influenced the next generation of professionals to stay involved in the ALS field in multiple ways, such as going to medical school, writing subsequent ALS-related grants, and opening new ALS treatment centers.

ALS Association Grantees Work Together for a Common Cause through Project MinE

Before the Challenge, Project MinE USA was just an idea. Dr. John Landers, a professor at the University of Massachusetts (UMass) Medical School, and Dr. Jonathan Glass of Emory University had pitched the idea to the Association. Establishing a branch of Project MinE in the United States would allow them to be part of a worldwide consortium of groups working together to find genetic factors for ALS.

Dr. John Landers. Image provided by The ALS Association.

"If you understand what genes can contribute to the disease, you can start to figure out what are the mechanisms that cause ALS, and that's where you can start to think about therapeutic treatments," Landers said. "But to be frank, genetics is very expensive, and the budget wasn't really there to the level that we needed it."

After the Challenge occurred, that all changed.

"We got a call from the Association saying that 'We do now have the ability to contribute,'" he recounted. "As a result of that, we were very happy because that allowed us to be part of this larger consortium, but also to further just genetics in general. That is what the goal is, and without the Ice Bucket money, a lot of the things that we wanted to do would have been impossible."

By the second anniversary of the Challenge in 2016, the Project MinE USA had helped identify gene changes related to ALS in the *NEK1* gene. *NEK1* is responsible for DNA damage repair and other cell functions.

Just 2 years later, Landers and a team of 237 researchers from over 130 institutions published an article on a new ALS gene called *KIF5A* in the journal *Neuron*. The gene makes a protein that is the body's "cargo train" for transporting materials from cells in the spinal cord to the limbs. Some people with ALS have changes in this gene that cause a defect in proteins, which can lead to some of the issues seen in people with the disease.

"The three main areas where identifying genes will help us are, one, to identify these pathways and mechanisms going wrong in all ALS patients, not just familial ALS patients," he said. "The second area is to develop mouse models and other types of models we can study. If you're developing a new therapeutic, you're going to want to test it out in these animal models before you bring it to the clinic. The third thing is gene therapies. There's already several ongoing trials. It is amazing just the advances, both on the gene therapy side, but in combination with identifying what these genetic defects are."

He characterized the Project MinE group as a diverse community that contributes everything from patient DNA samples and genetic sequencing to expertise in bioinformatics and pathology.

"None of us are experts in everything. To have different groups working together towards a common cause is where the Association was tremendous," he said. "By having this worldwide consortium where we're all contributing to the pot and sharing our ideas, that's what's going to help us towards identifying more of those genes that are contributing to ALS."

ALS Funds Translate to Direct Patient Impact through Local Chapters

In the Cleveland, Ohio, area, support for the local chapter of the Association has reverberated throughout the community, generating public awareness, policy change, clinical research trials, economic growth, and resources for people living with ALS and their caregivers.

Cleveland resident Fred M. DeGrandis, who has more than 30 years of health care experience in hospitals and health systems, serves on the National Board of Trustees of the Association. He describes how the Association's support of his community's local chapter has translated into treatment opportunities and direct care to patients.

According to DeGrandis, the Cleveland-area Certified Treatment Center of Excellence uses Association funds to bring innovative clinical trials to the area's nationally recognized medical institutions, improve access to treatment and equipment, and coordinate in-home care and specialty services that improve quality of life for people with ALS. The Center receives an annual grant of about $25,000 from the Association. Association funds also allow local chapters to deploy ALS patient navigators, who are embedded in the health system, and to connect families with vital resources, health providers, and treatment opportunities.

Fred M. DeGrandis. Image provided by The ALS Association.

"For a patient, having access to research locally is very important," he said. "That importance is multi-faceted, as well. Research provides the ability to become a part of being a research project or a research endeavor. [It] provides hope to patients, which is utterly important when you're going through treatment for a serious medical condition."

DeGrandis became a local advocate for ALS policy, public outreach, and research to find a cure after his father passed away from the disease in 1997. In addition to organizing outreach events and serving as the Public Policy Chair for the Association, he has successfully advanced legislation in his home state to improve access to care for ALS families.

DeGrandis celebrates the Challenge for "broadening the circle" of the ALS community and spreading information about the importance of research investigating this complex disease to the public. He wants everyone who participated in the viral challenge to know their contributions accelerated the pace of ALS research.

"There's 'bubbling-up' of so many research projects that would never have occurred without this funding," he said. "Particularly the Ice Bucket funding. And there is hope in the ALS community that the resources will ultimately drive us toward prolonging life. Maybe making ALS a chronic disease instead of a fatal disease."

The ALS Association Assistive Technology Challenge Paves the Way for Helping People Living with ALS Communicate Better

Entrepreneur and MIT graduate Dexter Ang had officially founded his startup, Pison Technology, only 4 months before the Association's Assistive Technology Challenge. Reaching his goal of winning seed money from this competition in 2016 filled him with excitement and emotion.

From left to right, Kyle Conners, who contributed to testing the Pison assistive technology innovation, with Dexter Ang and David Cipoletta. Image provided by The ALS Association.

For years, starting with his mother having ALS, he'd hoped to help people living with ALS maintain their ability to communicate with loved ones even as their physical functioning declined. But he needed funding to kick-start his company and begin developing assistive technology faster. Now, he could.

"It was a catalyst for us to recognize that we were on to something bigger, and it was the first large amount of money for us as a startup," he said. "To be able to be a small company and receive a check for $100,000 was significant for us to be able to propel our technology research. Having the Association as an ally, financially as well corporally and publicly, was a very big boost to our level of confidence and stature as a company."

Pison's technology senses movement in the nerves and transfers those signals into computer commands such as mouse clicks. It means that even people who are no longer able to physically move can now use a computer to communicate. He illustrates the impact the technology can have on the daily lives of people with ALS by describing one person who uses the device:

"We have a person who cannot speak, he cannot move his body in any functional manner," he described. "He currently uses our technology to move a cursor on a computer screen. Our technology was easily able to be customized. It could differentiate his mouse clicks at 100% accuracy. He says that our technology is more reliable, faster, than any other method he had used. We already have the beginning of very substantial and concrete traction towards making impact in people's lives, and this person is using it on a daily basis. What we believe we're doing is one of those rare things where technology can help and add value without taking away anything. And we can do it soon and we can do it in a practical manner that can impact people in a very big manner."

As Ang and his team showed increasingly more early progress, the company gained traction. He said support from the Association helped them "gain credibility" with the National Science Foundation and the Department of Health and Human Services, which he said led to winning more small business grants.

"It's been very clear that seeing the Association as a partner, not just financially, but as a development partner for feedback as well as to deliver our technology to end users, that is a big part of our commercialization plan," he said. "That would not have existed without this close relationship."

His long-term goal is to expand the company so that his technology can help millions of people.

"So when people are thinking about, what did they fund with the Ice Bucket Challenge? They did not just fund something that moves the ball forward with ALS. They funded something that moved the ball forward with the entire technology development in the entire world that many stakeholders are interested in. So to be a part of a larger movement, this is something that everyone can feel proud of. This is just really the beginning," he said.

ALS Association–Certified Treatment Center Extends Life-Saving Care to Patients in Need

For people living with ALS, access to specialized care means support, hope, and a better quality of life. Dr. Jeffrey Cohen, neurologist and director of the Dartmouth-Hitchcock ALS Clinic in Lebanon, New Hampshire, describes how support from the Association and the Challenge has affected ALS patients in northern New England. The clinic is one of the Association's Certified Centers for Treatment Excellence.

"We're able to give the totality of services to the patient in one location," he said. "I think for the average practitioner, be it neurologist or non-neurologist, these patients really require a lot of time, expertise, and a multidisciplinary approach, which is not readily available. So, we fulfill that need."

Cohen said support from the Association allows the clinic to offer a range of care services that it otherwise would not be able to provide. ALS patients at the clinic get comprehensive care, meaning they can see specialists in neurology, sleep medicine, nutrition, physical therapy, palliative care, and occupational therapy in one place. Families and other caregivers can learn more about the disease and go to support groups. The clinic also houses an ALS Patient Services Representative who meets with every patient and makes home visits to see how the patient is doing in their home environment.

With the support of the Association, the clinic has made a difference in the lives of every patient seen at the clinic, according to Cohen.

"There was a person that couldn't afford the tube feedings for her G-tube [gastrostomy tube], and we were able to purchase the tube feedings for her," he said. "The dietician delivered them to her house and explained to her about the tube feedings. I mean, basically, it was her nutrition. She would have died of starvation otherwise."

He also noted the Association has given him and his colleagues the burst of support they needed to expand the clinic's services across the region. The group of providers established two more ALS clinics, one in Manchester, New Hampshire, and one in Brunswick, Maine.

Not only is the Dartmouth-Hitchcock ALS clinic making an impact on people living with ALS today, but it is also educating the next generation of medical trainees to give them the skills they need to care for ALS patients. For example, Dr. Jay Taylor, a former trainee at Cohen's clinic, now directs the new clinic in Maine.

Cohen has nothing but gratitude for those who have donated money to the Association and to the Challenge.

"You're definitely helping," he said. "More importantly than my life, you're making the life of my patients much better because you're supporting resources that would not normally be available and that are incredibly, sorely needed for the patients."

ALS Association Funds Support New Research into the Genetic and Environmental Causes of ALS

It's the classic chicken-and-egg conundrum: Researchers need funding to do research, but to get funding, they need to have already done research. Finding ways to get innovative work off the ground is the key to unscrambling this puzzle.

Dr. Elijah Stommel. Image provided by The ALS Association.

Neurologist and researcher Dr. Elijah Stommel of the Dartmouth-Hitchcock Medical Center describes how he used grant funding from the Association to launch a new program of research on the genetic and environmental causes of ALS. It's a unique program that the Center's director, Jeffrey Cohen, lauded as "much different from the usual research."

"[ALS] is a mysterious disease in that about 90% of it has no known cause," Stommel said. "Our work is concentrated on trying to understand these environmental influences and how they might trigger the disease. Families and the patients themselves are not only devastated, but they're also very vexed by the notion that nobody understands why they have the disease. They're very interested in knowing if there was something they might've been exposed to."

Stommel and his team set out to study how humans might be exposed to airborne toxins produced by blue-green micro-organisms called cyanobacteria that form in bodies of water. To study how those toxins might be linked to cases of ALS, they used funds from the Association to collect bacterial samples from the air. At the same time, they also surveyed people with ALS and measured the bacteria in their lungs.

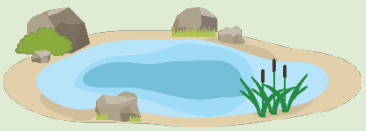
"We're trying to determine whether there is a clustering of ALS in association with any number of toxins," he explained. "If you live near a water body that has cyanobacteria in it, we've theorized, or hypothesized, that you would get a higher level of exposure to aerosolized cyanobacteria. And there is some evidence to show that ALS cases tend to be on the east side of the nearest water body in New England."

This initial work eventually led to funding from the Centers for Disease Control and Prevention (CDC), which allowed his research team to expand on their preliminary data. The researchers will conduct a large genome-wide association study of people with ALS and will look at the interaction between their genes and lifetime exposures to toxins. They will analyze blood samples, hair samples, urine samples, and even toenail samples to pinpoint biomarkers and toxins.

"None of this could've been initiated or started without the help of the Association. We certainly wouldn't have been able to get the funding from the CDC without preliminary data," he said. "The Association can be extremely helpful if you have a preliminary project that's unlikely to get funded by an organization like the NIH. [The Association] seems to be more willing to invest in high-risk, novel ideas. I'm very grateful to them for that help."

His hope is that by figuring how what toxins can contribute to ALS, we can work to mitigate exposure in the future. He is also positive that we are closer to finding a cure:

"I'm optimistic enough that I would tell ALS patients that are worried about their genetic makeup that in another 20, 30 years that there will likely be very good treatments for this disorder," he said. "That would be my opinion. But I think that should take away some of the fear that people have nowadays. There will be good treatments on the horizon."



6. DISCUSSION

An influx of donations after the Challenge in 2014 enabled The ALS Association to increase the amount of funding allocated to its global research programs and its clinical grant programs. Our evaluation analyzed these grant programs with the aim of identifying signals of their potential impact between 2014 and 2018. Overall, results from this evaluation suggest that grants awarded by the Association from 2014 through 2018 likely contributed to increases in research advancements, availability of ALS care, follow-on funding for research, collaboration among researchers, and advancement in ALS research careers. Here, we summarize key findings in these areas of potential impact.

KEY FINDINGS

Research advancements:

- Researchers we interviewed highlighted their publications on gene discoveries and possible environmental contributions to ALS. For example, in 2018, the Project MinE consortium published the results of a genome-wide analysis that identified a new ALS gene, KIF5A, and the Stommel lab published papers linking toenail mercury levels to ALS and papers on exposure to toxins associated with ALS. (Section 5)
- Survey respondents identified a range of research outcomes resulting from Association funding. One of the most common outcomes was new therapeutic targets. Participants also reported gene discovery, initiation or completion of one or more clinical trials, and identification of new biomarkers. (Section 4)
- The number of articles authored by the Association's grantees published annually in academic journals increased by roughly 20% since 2014. (Section 3)
- Numerous articles authored by the Association's grantees have been published in prestigious journals across all fields of science and have contributed an even greater wealth of articles to specialized journals that are eminently relevant to ALS. (Section 3)
- Most survey respondents felt that Association funding accelerated their research output. (Section 4)

Clinical care improvements:

- After the Challenge, the Association funded 29 new ALS CTCEs, 20 new RTCs, and 7 new affiliated clinics to increase availability of ALS care. (Section 2)
- Key informants described how clinical program grants had supported their clinics in offering more multidisciplinary, holistic services; expanding access to care with new treatment centers; and enabling them to work more closely with local Association chapters. Clinical improvements included caregiver support, nutrition and dietetics services, social services, home visits from a patient services representative, and health navigation. (Section 5)

Follow-on funding:

- The amount of NIH funding that the Association's grantees have received increased at a CAGR of about 22% from 2014 through 2017. (Section 3)
- From 2014 through 2018, the NIH awarded at least $415.9 million to the Association's grantees, of which at least $208.6 million could be considered "follow-on" funding. From 2014 through 2017, the NIH tagged $73.1 million as funding for ALS specifically (2018 data were not available for this latter estimate). (Section 3)
- Roughly half of publications authored by the Association's grantees acknowledged the NIH as a research sponsor. Additionally, hundreds of other funders were co-acknowledged alongside the Association, including other U.S. federal agencies, foreign government agencies, U.S.- and non-U.S.-based foundations, biopharmaceutical companies, specialized research institutes, and universities. (Section 3)
- Many survey respondents reported that their funding from the Association enabled them to apply subsequently for funding from other sources, including philanthropic organizations, the NIH, and their own institutions. Most respondents also thought the Association funding improved their ability to receive new funding. (Section 4)
- A theme emerged from key informant interviews, suggesting that the Association grant program played a role in funding

innovative and preliminary work. Several interviewees thought the Association had funded work that they would not have been able to get funded through the NIH, and the Association funding enabled them to collect the initial data needed to secure later funding from government agencies. (Section 5)

Collaboration:

- Network diagrams of grantee co-authorships suggest that an integrated, cohesive community of Association grantees developed from 2014 through 2018 from what previously appeared to be more distinct, smaller, and less densely connected communities. (Section 3)
- The total number of Association grantees who are co-authoring journal articles increased, as did the number of unique pairs of grantee co-authors and the overall number of publications co-authored by grantees. (Section 3)
- Most survey respondents felt that Association funding enabled new collaborations. The most commonly reported collaborations were with researchers at other institutions or at their own. Some also reported cross-disciplinary collaborations with clinicians, treatment centers and clinics, and patients. (Section 4)
- One notable example of collaboration from the key informant interviews was the support of Project MinE USA, a global consortium for ALS genetics research. (Section 5)

Career advancement:

- Among survey respondents, the impact of Association funding on career advancement received the second lowest ranking out of eight possible areas of impact. However, a possible explanation may be that many survey respondents may already be mid- or late-career professionals. About a third of survey respondents said they were able to support a graduate student or postdoctoral student with Association funding. (Section 4)
- Key informants described a number of early-career professionals they had supported with Association funding, from undergraduates, postbaccalaureate students, pre- and postdoctoral students, to seasoned clinicians and researchers. They felt that they had influenced the next generation of professionals to stay involved in the ALS field in multiple ways, such as going to medical school, writing subsequent ALS-related grants, and opening new ALS treatment centers. (Section 5)

SUMMARY OF EVALUATION APPROACHES

Collecting both secondary data and survey data strengthened the evaluation overall because each approach provided unique measurements of research accomplishments, collaborations, and follow-on funding among Association grantees. The secondary data reflected observable events or outcomes that were produced by actual behavior or actions (e.g., publication records and NIH funding records), while survey responses captured more subjective and expansive impacts than could be measured through the secondary analysis. One notable example pertains to actual and perceived impacts of Association funding on research outputs. Survey participants felt strongly that the Association accelerated their research output. Indeed, the secondary analysis of grantee publications showed not only increasing publications over time, but also acknowledgement of the Association in publications, suggesting that the Association funding helped accelerate these publications and/or the research leading up to them. Combined, the findings indicate objective and experiential impacts of the Association's funding programs.

Although most evaluation efforts focused on the Association's research grantees, the key informant interviews provided several snapshots of how the Association supports advocacy initiatives and access to care. Analyzing quantitative indicators of advocacy and care would be warranted in future evaluations.

In addition, conducting the grantee survey with the remaining set of nonrespondents would provide a more representative dataset and allow for subgroup analyses by funding year. Feilding this survey with the full sample of 2014 through 2018 grantees after a longer time lag could also provide valuable insights on how the perceived impact of Association funding changes as accomplishments amass.

Next steps are to share these findings with the Association Board to help inform future grant investments.

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