

**Department of Health and Human Services
Centers for Disease Control and Prevention
Agency for Toxic Substances and Disease Registry**

**National Amyotrophic Lateral Sclerosis (ALS) Registry Annual
Meeting**



**August 7-8, 2018
Summary Report**

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry.

2018 National ALS Registry Annual Meeting Executive Summary

The cause(s) of ALS (Amyotrophic Lateral Sclerosis) remain unknown for 90-95 percent of those diagnosed with the disease and there is still no cure.

The Agency for Toxic Substances and Disease Registry (ATSDR) established the National ALS Registry to determine how many people in the US are living with ALS, to describe the demographics of ALS patients, and most importantly to examine the risk factors for ALS. Although the Registry's primary purpose is to capture cases of ALS, the Registry does a lot more than just count cases. The Registry is also:

- Funding ALS research,
- Collecting specimens from Registry enrollees through the National ALS Biorepository,
- Connecting patients with researchers recruiting for ALS clinical trials or epidemiological studies,
- Obtaining and analyzing potential etiologic data from Registry enrollees through 17 different online risk factor modules such as occupational history, military history, residential history, history of traumatic brain injury and (TBI), and
- Providing data and biospecimens to scientists to further ALS research.

ATSDR held the National ALS Registry Annual Meeting in Atlanta on August 7-8, 2018. There were 51 attendees, including persons living with ALS, neurologists, researchers, representatives of national ALS organizations, representatives of pharmaceutical companies, Registry staff, and other ALS experts.

[Background, Methodology, and State of the Registry](#)

Because ALS is a non-notifiable condition, CDC does not receive reports from states of the occurrence of ALS, as it does for most communicable diseases. The novel methodology developed by ATSDR for identifying ALS cases uses data from national administrative databases (i.e., Medicare and the Veterans Administration) in addition to the information entered into the online Registry web portal by persons living with ALS.

Improvements and accomplishments during the last year:

- Published the third *Morbidity and Mortality Weekly Report (MMWR)* report on February 23
- Collected hundreds of additional biospecimens via the National ALS Biorepository
- Paired biospecimens with epidemiological and risk factor survey data already collected by the Registry
- Redesigned the Registry website with a responsive design, enabling access by hand held devices
- Published over one dozen peer-reviewed articles/abstracts from Registry staff and research partners
- Published a Notice of Funding Opportunity and funded 1 R01 and 4 new grants awarded in Fall 2018
- Initiated the development of a new Spanish Registry website
- Targeted 56 percent of Registry funding to supporting ALS research

- Created new digital assets including graphics, videos, and infographics
- Launched an outreach project with partners in selected states
- Implemented a Customer Satisfaction Survey that focuses on Registry enrollment to increase our understanding of how people are learning about the Registry and to

Research

The National ALS Registry released the third prevalence report in February 2018 for persons living with ALS in the US. ALS prevalence was estimated to be 5 cases/100,000 for 2014. The total case count was 15,927, including cases from the national databases and the Registry online portal. This is a slight increase over the previous report. ALS continues to be more common in whites, males, and persons 60-69 years of age. The lowest number of ALS cases was among persons 18-39 years of age and > 80 years of age. Males continue to have a higher prevalence than females across all data sources.

Data from the Registry indicate that completion of the risk factor surveys is steadily increasing. Persons with ALS completed over 76,000 risk factor surveys to date. They completed approximately 65,000 last year at this point. The Research Notification System has also proven to be quite successful, with approximately 95% of registered persons with ALS opting in to participate in research notifications. Over 35 institutions, including pharmaceutical companies, domestically and abroad, have used the Registry to recruit for their clinical trials and epidemiological studies.

National ALS Biorepository

The National ALS Registry now includes a Biorepository. People taking part in the Registry are eligible to participate in the National ALS Biorepository. From those interested, the Biorepository selected participants to be geographically representative of the US. Blood and urine specimens are collected in the person's home. The Registry can now pair biospecimens with epidemiological and risk factor survey data already collected by the Registry for use by scientists in their research. Registry participants may also donate tissues postmortem. Postmortem samples consist of brain, spinal cord, cerebrospinal fluid (CSF), bone, muscle, and skin. Persons with ALS can take part in the Registry and Biorepository even if they have donated specimens to other biorepositories and studies. Biospecimens have been collected from over 500 participants, including over 30 postmortem collections to-date. There are now thousands of aliquoted samples available for researchers to use that include bone, blood, brain tissue, cerebrospinal fluid (CSF), fingernails, and hair.

Registry Enrollment

This session included discussions on the Registry enrollment, demographics, and completion of the risk factor surveys. Registry enrollment increased rapidly during the first months immediately following the launch of the Registry in October 2010, then there was a slight uptick in enrollment in 2013 and 2014, probably due to the Ice Bucket Challenge, and there has been a slow decline since then. Approximately 40% of Registry participants are female and 60% are male. The percentage of ALS patients enrolled in the US by region is highest in the Midwest (31%) compared with only 17% in the Northeast. ATSDR is currently working on outreach activities with its partners to increase enrollment.

In addition to registering, persons with ALS are encouraged to take the risk factor surveys available on the Registry. The completion rate for the surveys is about 60% compared with 70%

to 80% for other national surveys including the NHIS – Household Module, NHANES – Conditional Exam, and the NIS – Landline Response Rates. The risk factor survey data provide information to researchers to assist in discovering other ALS risk factors and etiology, allows patients to tell their stories, and optionally link biospecimen data for more robust studies.

[Evaluating the Completeness of the National ALS Registry](#)

Evaluating the completeness of the National ALS Registry is important because ALS is not a reportable disease. Physicians and other health care providers are required to report diseases designated as reportable. Although no surveillance system is able to identify 100% of the cases, because ALS is not reportable, ATSDR uses non-traditional case ascertainment, making evaluation of the completeness of the Registry even more important. ATSDR used two different methods to evaluate the completeness of the Registry: state and metropolitan area surveillance data and capture-recapture methodology. The State/Metro Surveillance Project involved intense case ascertainment in three states (New Jersey, Florida, and Texas) and eight metropolitan areas (Atlanta, Baltimore, Chicago, Detroit, Las Vegas, Los Angeles, Philadelphia, and San Francisco). ATSDR compared patients identified by the state/metro surveillance project with those in the Registry. The findings showed that the Registry was more likely to miss people who were non-white, Hispanic, living in the Western US, not using Medicare for insurance, and less than 65 years of age.

Capture/Recapture methodology uses probability analysis to estimate the number of cases that might be missed. Both methods showed remarkably similar results. Both methods identified non-whites and those less than 65 years of age as under-represented in the Registry. Both methods identified Medicare as an important source for case identification. Men were found to be under-represented in the Registry using capture-recapture methodology, but not in the comparison of state and metropolitan surveillance data. The comparison of state and metropolitan area surveillance data identified Hispanics and those from Western states as under-represented, but this was not assessed using capture-recapture methodology.

ATSDR is working to increase outreach to populations shown to be under-represented in the Registry by creating a Registry website in Spanish and by placing articles in local papers that target African Americans and rural communities. ATSDR is also planning to use the estimate of underreporting from these methodologies to adjust future ALS prevalence estimates.

[Communication & Outreach](#)

One of the most important objectives of the meeting is to discuss the barriers, challenges, and successes the Registry has experienced and to receive recommendations on how to address these issues. Some of the issues were that the Registry could do a better job of communicating all that it is doing and the Registry website is difficult to navigate. ATSDR is currently working with its partners, the ALS Association, the Muscular Dystrophy Association, the Les Turner ALS Foundation, and with Brunet Garcia to address these challenges to increase awareness of the Registry and to improve registration and completion of the risk factor surveys.

Some of the ways the Registry is addressing these issues are as follows:

- ATSDR created a new award winning video titled “[Hope](#)” to show the value of the registry.
- All of the Registry materials, including [videos](#), social media, and [printed materials](#) are available for use by the partner organizations and others.

- ATSDR reorganized the Registry website to make it easier to navigate. They are continuing to find ways to improve the website and welcome feedback from everyone.
- The Registry team is also trying to reach people who are under-represented in the Registry. One of the partnerships they engaged this year was with BlackDoctors.org, which is a very popular health-related website primarily aimed at African American communities. They ran a well-received article to raise awareness about ALS and the Registry.
- ATSDR wrote and released this year for which they pay a minimal amount for placement, and then local journalists pick them up. As of July 2018, this generated 3672 news articles. Journalists continuously pickup these articles online.
- A collaboration with Medscape produced a very nice article targeting neurologists in rural areas.

[Under-Enrolled States Outreach Project Update](#)

The goals of the Under-Enrolled States Outreach Project are to focus on six states where enrollment in the Registry is less than expected and to identify health districts within those states, which could benefit from increased Registry outreach. The six states participating in this project are Hawaii, Mississippi, New York, West Virginia, Utah, and Wyoming. The Registry and the ALS Association and MDA are working collaboratively to compare data to identify the health districts in each state that are under-enrolled. The ALS Association and MDA developed and implemented outreach plans during July 1-December 31, 2018. ATSDR will review and assess the findings to determine the effectiveness of the project. If the project is effective in raising enrollment levels, the plan is to expand the project to other selected under-enrolled states.

[ALS Association](#)

The ALS Association works exclusively on ALS and is the largest national non-governmental funder of ALS research. They are supportive of the Registry, working with 39 chapters, two territories, and over 130 clinical partners nationwide. There are 62 Centers of Excellence, which also participate in research. The ALS Association promotes the Registry during their events, meetings and conferences, through social media, on their website, as well as also encouraging their chapters to promote the Registry.

The ALS Association is working closely with the Registry and has identified challenges and opportunities. Challenges include an ALS community that does not have the best impression about what the Registry is and may not have a clear understanding of why the Registry is important. They pointed out the need for the Registry to provide feedback to the ALS community on their research and other activities. There is also the challenge of under-counting. However, the work that the Registry is doing to improve understanding of the under-counting seems to be very important to identifying the solution, which will help in the allocation of resources. They also underscored the value of the Registry in supporting the type of research to address the very important question of why some people get ALS and others do not.

[Muscular Dystrophy Association](#)

The Muscular Dystrophy Association continues its efforts to improve and expand their ability to support the National ALS Registry. MDA supports research, support services, Care Centers, education, and the Resource Center. More than 12,000 individuals with ALS have access to nearly 50 designated MDA ALS Care Centers across the US and a Network of Care Centers at over 150 top institutions and affiliates. MDA promotes the National ALS Registry through social media, online publications, outreach phone calls, community events, MDA Care centers, the MDA website that houses information on the National ALS Registry, ALS support groups, the National Resource Center, educational conferences and seminars, and print materials.

Some of the highlights of MDA's 2018 National ALS Registry outreach efforts include an ATSDR breakout session and information booth during the MDA Clinical Conference in March 2018. They also incorporate MDA Engage Events on the ALS Registry into regional MDA Engage Events as far as data, information, and print materials. MDA is posting weekly Registry messages to the MDA national social media pages and monthly to MDA's local district level social media pages, and providing a link to the National ALS Registry on MDA.org.

[Les Turner ALS Foundation](#)

The Les Turner ALS Foundation provides comprehensive ALS care in Chicagoland through individualized care, local community support, and scientific research at the Les Turner ALS Center at Northwestern Medicine. The support services team works directly with persons living with ALS and their families and others. Their promotional efforts for the National ALS Registry and Biorepository include home and clinic visits, support groups, a National ALS Registry Associate, print newsletters, e-news and website, Annual Education Meeting, education for medical professionals, Annual Research Symposium on ALS and NeuroRepair, community education and expos, and social media.

A unique feature of the Les Turner ALS Foundation is the National ALS Registry Associate. She meets every person who presents to the clinic, provided they are willing to meet with her. She provides personal assistance for anyone who is interested in being in the Registry or who may need assistance with completing the risk factor modules. They have estimated that between her support and assistance at the clinic, the Turner Foundation is currently enrolling 80% of individuals they serve in the Registry.

[Brunet-Garcia](#)

Brunet-Garcia is working with the National ALS Registry on strengthening communications and outreach efforts. Their objectives are to raise awareness and engagement of the Registry, provide value to persons with ALS with simpler access to updates from the ALS Registry and stakeholders, and to coordinate efforts of partners and others to promote the Registry and support persons with ALS.

Brunet-Garcia has developed improved messaging and branding including articles, testimonial quotes, social media, fact sheets, and posters. ATSDR shares all of the materials with the partners. Brunet-Garcia also created marketing materials to show the value of the Registry including fact sheets and a new retractable display for use at conferences and other events.

They are also working with the Registry and the partners to assess feedback to ensure the best products in terms of content and design.

Update from Pharma

[Cytokinetics, Inc.](#)

Cytokinetics, Inc. is working on developing drugs for muscles. Cytokinetics targets compounds that bind to the proteins that make up the sarcomere, which is the fundamental contractile unit of the muscle. They presented an update on their clinical trials in ALS for *tirasemtiv* and *reldesemtiv*, compounds that target troponin, one of the fundamental proteins that make up the contractile unit of the muscle. The compounds are known as fast skeletal muscle troponin activators (FSTAs). Cytokinetics presented the methodology and results of the Phase 3 clinical trial of *tirasemtiv*. Unfortunately, patients did not tolerate *tirasemtiv* well, resulting in dose reductions and discontinuations of the drug. Therefore, Cytokinetics discontinued the development of *tirasemtiv*. However, because patients who tolerated the drug and received benefit, Cytokinetics is continuing to make *tirasemtiv* available to the patients in the trial whose physicians deem that they are benefitting.

Cytokinetics also described their clinical trial with *reldesemtiv*, a similar compound to *tirasemtiv*, but with a completely different chemical structure, which does not have the side effects seen with *tirasemtiv*. *Reldesemtiv* has greater pharmacodynamic effect at lower plasma concentrations, was designed to minimize crossing of the blood brain barrier (BBB), has no known drug-drug interaction with riluzole that *tirasemtiv* did, and has demonstrated tolerability in healthy subjects.

Cytokinetics used the National ALS Registry's notification tool for both clinical trials and reported that the tool works very well and recommends its use for all studies.

[Mitsubishi Tanabe Pharma America](#)

Mitsubishi Tanabe Pharma America reported on the Edaravone Biomarker Study they hope to implement by the end of 2018. Mitsubishi Tanabe introduced Edaravone, a drug that slows the loss of physical function, approximately one year before this meeting. Since then, the number of patients placed on the drug has increased to over 3000. However, many payers placed restrictions on access to Edaravone and many questions were raised about which patient populations were appropriate to receive the drug and what the optimal timing was to initiate therapy, in addition to questions about the clinical development program. In the first Phase 3 trial, the drug did not meet its primary endpoint.

A second Phase 3 trial used an enrichment strategy gleaned from the first trial. This examined a population that was high functioning, but rapidly progressing. In the second trial, the drug did meet its primary endpoint.

However, there are questions remaining that Mitsubishi Tanabe hopes this biomarker study will begin to answer regarding the drug's mechanism of action, identification of a quantifiable biologic measure for the effects of Edaravone on ALS, help in determining the feasibility and validity of specific biomarkers in patients undergoing Edaravone therapy, and provide guidance

regarding more frequent dosing at higher strengths. Mitsubishi Tanabe may release the findings of the biomarker study as early as June 2019.

Mitsubishi Tanabe Pharma America is also using the National ALS Registry notification system to recruit participants for this study.

[NEALS Update](#)

The Northeast ALS Consortium (NEALS) functions as an international academic research consortium, a contracted research organization, and a resource for the ALS community at large. NEALS' mission is to translate scientific advances into new treatments for people with ALS and MND as rapidly as possible. Members are working on therapeutic developmental drugs for ALS, advocacy, and other activities, which further ALS care.

NEALS provides resources for the ALS research community including training site managers, coordinators, evaluators, and site and project PIs. NEALS has also created the Pooled Resource Open-Access ALS Clinical Trials Database (PRO-ACT), a repository of data from placebo and treatment patients. There also is the NeuroBANK, which is a powerful natural history database. NEALS also maintains a Biorepository/Living Library and coordinates monthly webinars for persons living with ALS, caregivers, and the ALS community.

The number of NEALS research trials and persons participating in the trials were presented by year from 1999 through 2017, which show the dramatic increase in NEALS-associated research studies.

The National ALS Registry is working with NEALS to assist in recruiting patients for their clinical trials and studies through the Registry's Research Notification System and serves on their committee for recruitment.

[ATSDR-Funded Research Update](#)

ATSDR provides funding to support ALS research studies to help the ALS community learn more about the disease and to help prioritize new risk factor modules for the Registry. Principle investigators presented updates of nine ATSDR-funded studies on environmental and genetic risk factors.

[Persons Living with ALS Perspective and Next Steps](#)

These sessions provided critically important feedback from the ALS patient community on the value of the Registry, the components that are going well, and components that need to do better. Meeting participants also shared their observations and insights regarding the top priorities for the Registry and the Biorepository for the coming year.

National ALS Registry Action Items for 2018/19:

The National ALS Registry is not just an ATSDR initiative. We recognize that the success of the Registry depends on the collaboration of all the stakeholders. During the coming year we will continue to work collaboratively with the partner organizations and other stakeholders to achieve the following:

1. Send semiannual newsletter to inform ALS community of Registry activities on new research, research results, biorepository, ATSDR-funded studies, risk factor surveys
2. Redesign Registry website to make information for patients and caregivers more engaging and easier to find
3. Analyze data to determine activity that improves enrollment in the Registry, e.g., social media, promotional material, clinical staff suggestions
4. Increase researcher awareness of data and specimen availability
5. Provide enrollment statistics at smaller level than state e.g., health district
6. Provide an estimate of ALS prevalence that adjusts for under-ascertainment
7. Analyze risk factor survey completeness by year to look for improvements, e.g., how many enrolled, how many surveys were completed
8. Track status of recommendations from the annual meeting and provide an update at 6 months and present progress at the next annual meeting
9. Focus messaging about completion of surveys where data is most needed
10. Discuss research opportunities with representatives of pharmaceutical companies

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Acronyms Used in this Document

| Acronym | Expansion |
|----------------|--|
| AAC | Augmentative/Alternative Communication |
| AAN | American Academy of Neurology |
| ADS | Associate Director of Science |
| AE | Adverse Event |
| ALS | Amyotrophic Lateral Sclerosis |
| ALS COSMOS | ALS Multicenter Cohort Study of Oxidative Stress |
| ALSA | Amyotrophic Lateral Sclerosis Association |
| ALS-CBS | ALS Cognitive Behavioral Screen |
| ALS-CBS-CG | ALS Cognitive Behavioral Subscale Caregiver Portion |
| ALSFRS | ALS Functional Rating Scale |
| ALSFRS-R | Revised ALS Functional Rating Scale |
| AQS | Air Quality System |
| ARREST ALS | ATSDR Risk Factors Epidemiologic Studies in ALS |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| BAL | Bronchoalveolar Lavage |
| BBB | Blood-Brain Barrier |
| BFR | Brominated Flame Retardant |
| BMAA | Beta-Methylamino-L-Alanine |
| BMI | Body Mass Index |
| BORIM | Board of Registration in Medicine |
| BPA | Bisphenol A |
| BRFSS | Behavioral Risk Factor Surveillance System |
| CALS | Caregivers of ALS |
| CATI | Computer-Assisted-Telephone Interview |
| CDC | Centers for Disease Control and Prevention |
| CDC WONDER | CDC Wide-ranging ONline Data for Epidemiologic Research |
| CMAQ | Community Multi-Scale Air Quality Model |
| CME | Continuing Medical Education |
| CMS | Centers for Medicare and Medicaid Services |
| CNS | Central Nervous System |
| CNS-LS | Center for Neurologic Study-Lability Scale |
| COD | Cause of Death |
| COI | Conflict of Interest |
| COPD | Chronic Obstructive Pulmonary Disease |
| COWAT | Controlled Oral Word Association Test |
| CRaTe | Clinical Research in ALS and Related Disorders for Therapeutic Development |
| CRLI | Clinical Research Learning Institute |
| CRO | Clinical Research Organization |
| CSF | Cerebrospinal Fluid |
| CUMC | Columbia University Medical Center |
| DNA | Deoxyribonucleic Acid |
| DoD | Department of Defense |
| DTHHS | Division of Toxicology and Human Health Sciences |
| DUA | Data Use Agreement |
| EHR | Electronic Health Record |
| EHSB | Environmental Health Surveillance Branch |
| ELISA | Enzyme-Linked Immunosorbent Assay |
| EPA | Environmental Protection Agency |
| EPHT | Environmental Public Health Tracking |

| | |
|----------------|---|
| ERPO | Extramural Research Program Office |
| ERS | Environmental Risk Score |
| EV | Extracellular Vesicle |
| FBI-ALS | Frontal Behavioral Inventory |
| FDA | Food and Drug Administration |
| FFQ | Food Frequency Questionnaire |
| FFS | Fee-For-Service |
| FSTA | Fast Skeletal Muscle Troponin Activator |
| FTD | Frontotemporal Dementia |
| FVC | Forced Vital Capacity |
| GLM | Generalized Linear Models |
| GUID | Globally Unique Identifier |
| HAPs | Hazardous Air Pollutants |
| HHD | Hand Held Dynamometry |
| HHS | (United States Department of) Health and Human Services |
| HMDB | Human Metabolome Database |
| HMO | Health Maintenance Organization |
| HSP | Hereditary Spastic Paraplegia |
| ICD | International Classification of Diseases |
| ICP-MS | Inductively Coupled Plasma Mass Spectrometry |
| iPSC | Induced Pluripotent Stem Cells |
| IRB | Institutional Review Board |
| IT | Information Technology |
| MDA | Muscular Dystrophy Association |
| MDC | Multidisciplinary Clinics |
| MDPH | Massachusetts Department of Public Health |
| MGH | Massachusetts General Hospital |
| miRNA | microRNA |
| mtDNA or mDNA | Mitochondrial DNA |
| MMSE | Mini-Mental State Examination |
| MMWR | <i>Morbidity and Mortality Weekly Report</i> |
| MNA | Massachusetts Neurologic Association |
| MND | Motor Neuron Degeneration |
| MND | Motor Neuron Disease |
| MNDA | Motor Neuron Disease Association |
| MOH | Ministry of Health |
| MOVR™ Data Hub | neuroMuscular ObserVational Research Data Hub |
| MTA | Material Transfer Agreement |
| MTPA | Mitsubishi Tanabe Pharma America |
| MTPC | Mitsubishi Tanabe Pharma Corporation |
| NATA | National Air Toxics Assessment |
| NBB | NeuroBioBank |
| NCEH | National Center for Environmental Health |
| NDI | National Death Index |
| NEALS | Northeast Amyotrophic Lateral Sclerosis Consortium |
| NHANES | National Health and Nutrition Examination Survey |
| NIH | National Institutes of Health |
| NIV | Non-Invasive Ventilation |
| NMD | Neuromuscular Diseases |
| NOFO | Notice of Funding Opportunity |
| NPL | National Priority List |
| ODH | Ohio Department of Health |
| OHRP | Office for Human Research Protections |

| | |
|--------------------------|--|
| OMB | Office of Management and Budget |
| OS | Oxidative Stress |
| PALS | Persons with Amyotrophic Lateral Sclerosis |
| PCP | Primary Care Physician |
| PCR | Polymerase Chain Reaction |
| PI | Principal Investigator |
| PII | Personally Identifiable Information |
| PLS | Primary Lateral Sclerosis |
| PLS-DA | Partial Least Squares Regression-Discrimination Analysis |
| PM | Particulate Matter |
| PMA | Progressive Muscular Atrophy |
| Polychlorinated Biphenyl | PCB |
| POPs | Persistent Organic Pollutants |
| PRO-ACT | Pooled Resource Open-Access ALS Clinical Trials Database |
| qPCR | Quantitative PCR |
| RDCRN | Rare Disease Clinical Research Network |
| RFA | Request for Applications |
| RN | Registered Nurse |
| RNA | Ribonucleic Acid |
| RNS | Reactive Nitrogen Species |
| ROS | Reactive Oxygen Species |
| SAB | Scientific Advisory Board |
| SAE | Serious Adverse Events |
| SES | Socioeconomic Status |
| SMA | Spinal Muscular Atrophy |
| SME | Subject Matter Expert |
| SNP | Single Nucleotide Polymorphism |
| SOD-1 | Superoxide Dismutase 1 |
| SOP | Standard Operating Procedure |
| SPO | Scientific Program Official |
| SSN | Social Security Number |
| SVC | Slow Vital Capacity |
| T3DB | The Toxin and Toxin Target Database |
| TB | Tuberculosis |
| TBI | Traumatic Brain Injury |
| TEAE | Treatment-Emergent Adverse Event |
| TICS | Telephone Interview for Cognitive Status |
| TIV | Tracheotomy with Invasive Ventilation |
| UK | United Kingdom |
| VA | (United States Department of) Veterans Affairs |
| VITALITY-ALS | Ventilatory Investigation of <i>Tirasemtiv</i> and Assessments of Longitudinal Indices after Treatment for a Year in ALS |
| WALS | Western ALS Study Group |
| WGS | Whole Genome Sequence |
| WVFT | Written Verbal Fluency Test |

Centers for Disease Control and Prevention (CDC) Agency for Toxic Substances and Disease Registry (ATSDR) Annual Amyotrophic Lateral Sclerosis (ALS) Surveillance Meeting

Minutes of the Meeting August 7-8, 2018

Welcome and Introductions

**Robert Kingon, MPA, Facilitator
Carter Consulting, Inc.**

Mr. Robert Kingon called the meeting to order at 8:32 AM, observing that this marked the 13th annual meeting and his 10th meeting serving as facilitator. He explained that the meeting would be streamed live and that it was a requirement by the department for participants to sign the release form included in their meeting packets. He described ground rules for the meeting, reviewed housekeeping items, and led participants in a round of introductions. A participant roster is appended to the end of this document.

Opening Remarks

**Patrick Breysse, PhD
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry**

Dr. Breysse welcomed everyone. He emphasized that the field of environmental health is very diverse and widespread, but that ALS is one of the most important areas the National Center for Environmental Health (NCEH) and the Agency for Toxic Substances and Disease Registry (ATSDR) are exploring. He said it was his pleasure to be there and that he was happy about and proud of the work being done by the National ALS Registry. He expressed appreciation for all of the clinicians, researchers, and especially persons with ALS for attending the Annual National ALS Registry Meeting. Having them all together allows for feedback that helps ATSDR shape the National ALS Registry. He also expressed appreciation for those taking the time to view the meeting through the online link. He stressed that everyone's feedback is invaluable, given that registries such as this only work when there is an interplay between scientists, non-profit organizations, and affected individuals. It cannot be emphasized enough that success depends upon the collaboration among all of the stakeholders.

The National ALS Registry is a groundbreaking effort. Those efforts help scientists to work toward a cure for ALS, something that everyone would like to imagine in their lifetimes. The Registry is making real progress, publishing its third report on ALS prevalence in February 2018 and is working on the fourth report schedule for fall publication. He noted that meeting participants would hear a high-level presentation of the third report. They also are excited about the National ALS Biorepository. The Biorepository is fully operational and patient specimen collections are ongoing, both in-home and postmortem. These samples are being paired with risk factors and survey data, which makes the Biorepository a unique resource for investigating ALS. In addition to specimens, there are ongoing analyses. Dr. Breysse indicated that highlights of the research being conducted with persons living with ALS and ATSDR's external partners,

as well as updates from ATSDR's funded researchers across the country. In the fall of 2018, ATSDR anticipates funding four additional new grants. Also during this meeting, recent research publications would be highlighted that focus on topics such as ALS mortality, disease progression, the State and Metro Surveillance projects, capture-recapture, and risk factors. ATSDR would like feedback on these and other topics as they move forward. ATSDR's partners, the ALS Association (ALSA), Muscular Dystrophy Association (MDA), and Les Turner ALS Foundation planned to provide updates of their Registry outreach activities. The Registry's Communications Team also planned to discuss ways to increase awareness. The Registry's Research Notification System has been extremely well-received by Registry enrollees and researchers. To date, over 35 institutions have used it for clinical trials and epidemiological studies. Over 95% of the Registry enrollees have opted in to receive notifications from the Registry about ALS research for which they are eligible. They also will hear from persons with ALS and their perspectives on living with ALS and the importance of the Registry. There also would be presentations about the new initiatives and ATSDR's progress on the Registry.

In closing, Dr. Breyse invited participants as the leading experts on ALS to help ATSDR continue to shape the National ALS Registry to be the best it can be. He stressed that everyone should feel free to provide their thoughts throughout the meeting and beyond, as this was not a one-time event. He welcomed everyone to Atlanta and offered them best wishes for a productive meeting.

Overview of the National ALS Registry

**D. Kevin Horton, DrPH, MSPH
Chief, Environmental Health Surveillance Branch
Division of Toxicology and Human Health Sciences
Agency for Toxic Substances and Disease Registry**

Dr. Horton welcomed everyone and thanked them for their attendance and taking time out of their busy schedules to attend. This is the 13th annual meeting, which is hard to believe. He thought a lot of good progress has been made in those 13 years and emphasized that the Registry is the product of the people in the room and their respective organizations. One of the theme's that would be repeated often is that ATSDR has not and cannot do this alone. They need everyone in the room to help promote the Registry. While they have been doing a good job of this, there is room for improvement.

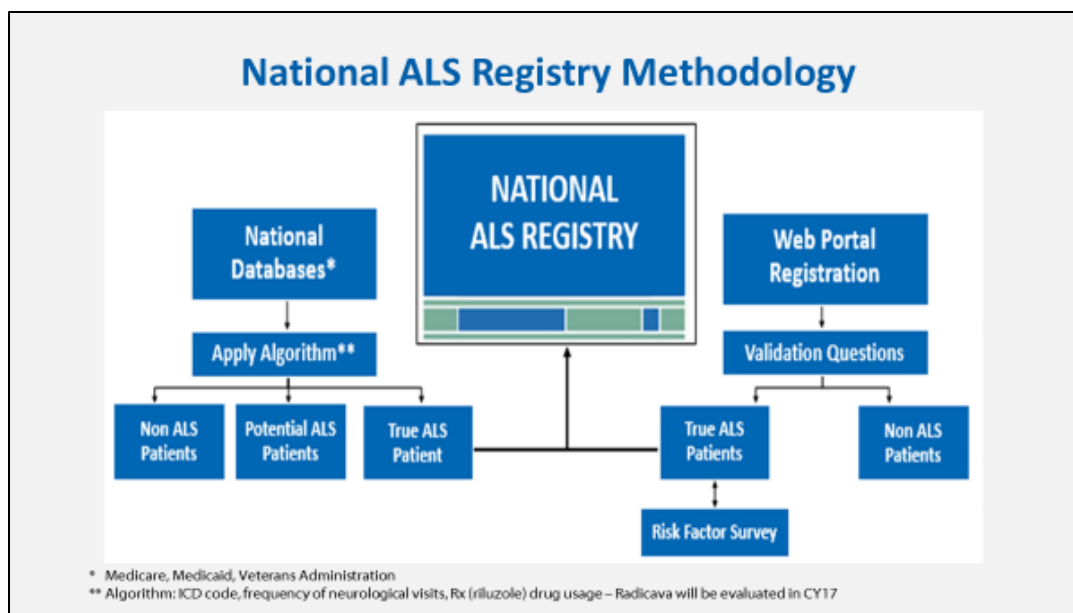
While Dr. Horton apologized to those who had heard his presentation previously, he pointed out that there were attendees who were new to the Registry and may not know how it operates, who the partners are, et cetera. He explained that ATSDR is one of several agencies under the Department of Health and Human Services (HHS). ATSDR's focus is largely on environmental health in terms of how the environment and toxic substances can impact human health. As part of HHS, ATSDR is the sister agency of the Centers for Disease Control and Prevention (CDC). Dr. Redfield, CDC's Director, also is the Administrator of ATSDR. ATSDR is co-located with CDC in Chamblee, Georgia.

In terms of the background and methodology of the National ALS Registry, the [US ALS Registry Act \(Public Law 110-373\)](#) was passed in October 2008. ALS organizations and persons with ALS (PALS) are directly responsible for the passing of this Act, which allowed ATSDR to set out on a path to create a population-based registry for the US. The purpose of the Registry is to describe the incidence, prevalence, mortality, demographics, and risk factors for ALS. There are

many speculations and hypotheses for what causes ALS. Through the risk factor survey modules, the Registry tries to pinpoint some of the possible factors they should be examining.

It is important to realize that, like thousands of other non-communicable diseases, ALS is non-notifiable. That means that CDC is not notified by state health departments, laboratories, physicians, or neurologists about new or existing cases of ALS. In the surveillance world, there are about 100 notifiable diseases at CDC. About 95% of these are infectious diseases. The other 5% are non-communicable diseases. The fact that ALS does not have reportable disease status made ATSDR's job very challenging when this law was passed in terms of how to realistically go about capturing every single newly diagnosed case of ALS in the country. Dr. Horton clarified that he was not necessarily advocating that ALS become a reportable disease, although it would make their lives much easier if it were. The argument is that if ALS is made a notifiable disease, why not make Parkinson's, Alzheimer's, and thousands of other diseases notifiable? While this sounds good, it places a huge burden on state and local health departments to begin collecting these data and notifying CDC. This is not up to CDC. It is largely a state-based decision. Massachusetts is the only state in which ALS is a reportable disease.

In the absence of reportable disease status, ATSDR had to develop a novel approach to identify newly diagnosed ALS cases. After conducting a multi-year pilot that tested various case-finding methodologies, ATSDR finally launched the National ALS Registry in 2010. Congress passed the act in 2008, but it took a couple of years to develop a methodology that ATSDR believes captures most of the ALS cases around the country. They know they are still missing some cases due to private insurance. The Registry takes a two-pronged approach to identify cases of ALS as depicted in the following graphic:



An algorithm was created during the pilot-testing phase for identifying ALS cases from large national databases from federal agencies such as Medicaid/Medicare and the Veteran's Administration (VA). This comprises millions upon millions of people and records. When applied to these national datasets, the algorithm separates people into three categories: Non-ALS Patients, Potential ALS Patients, and True ALS Patients. True ALS Patients are automatically added to the Registry. The algorithm is comprised of several elements such as the International

Classification of Diseases (ICD)-9 code used to identify disease and for billing purposes. ALS has a specific ICD code, but that alone cannot be relied upon due to the miscoding that occurs on a fairly wide scale basis. For that reason, it was necessary to fold in a couple of additional elements into the algorithm such as the frequency of a patient's visits to his or her neurologist. Many people typically visit their neurologist quarterly or four times per year, which is a good indication that the person probably has some type of neurological condition such as ALS. In addition, prescription drug usage is assessed. Before the introduction of Radicava[®], Rilutek[®] (riluzole) was the only drug used to treat ALS. If someone is taking riluzole, it is a pretty good indication that they have ALS. Radicava[®] will be evaluated for inclusion in the algorithm in order to start picking up patients who are taking this drug. This will not occur until ATSDR receives the calendar year 2017 data.

While the ALS Act primarily set out for ATSDR to capture cases of ALS, the Registry does a lot more than just count cases. ATSDR also is funding research and collecting biospecimens through the National ALS Biorepository. There is also the Research Notification Request mechanism. The Registry is now being used to help principal investigators (PIs) recruit patients for clinical trials or epidemiological studies. Also, there are now 17 risk factor modules within the Registry that collect information about military history, history of traumatic brain injury (TBI), occupational status, et cetera. It cannot be emphasized enough how critical ATSDR's partners are in encouraging patients to enroll and complete the risk factor modules. ATSDR cannot do this alone in a vacuum.

In terms of accomplishments and activities since the last meeting, ATSDR published the third *Morbidity and Mortality Weekly Report (MMWR)* report on February 23, 2018. This report covered calendar year 2014. They are diligently working on the fourth report covering calendar year 2015, which is scheduled for release in Fall 2018. Additionally, hundreds of biospecimens have been collected via the National ALS Biorepository, which addresses one aspect of the research arm of the Registry. There have been over 500 participants and over 30 postmortem collections to-date. There are now thousands of aliquoted samples available for researchers to use that include bone, blood, brain tissue, cerebrospinal fluid (CSF), fingernails, hair, et cetera. Biospecimens can be paired with epidemiological and risk factor survey data already collected by the Registry. For example, they could tell a researcher that a particular blood sample is from a 50-year old plumber who lives in Idaho and had early-onset ALS. This is a very rich source of data, which ATSDR wants external researchers to use to advance the science of ALS. ATSDR also has disseminated additional data and biospecimens via the new online Registry platform. ATSDR has approved and disseminated de-identified data and biospecimens to 6 investigators to-date, and has funded additional research projects. They published a Notice of Funding Opportunity (NOFO) and funded 1 R01 and 4 new grants to be awarded in Fall 2018. The details will be posted on the ATSDR website, via social media, and through their partners when the awards become official.

Efforts also have been made to improve communications and outreach to help with Registry enrollment, promotion, and to test the completeness of the Registry. A newly redesigned website with a responsive design was launched, new digital assets were created (e.g., videos, infographics), and an outreach project with partners was launched in select states. ATSDR knows the Registry, like many public health surveillance systems, is not 100% complete and that consideration must be given to how to reach out to the populations who are not necessarily represented such as minority populations or populations who do not usually go to ALS referral clinics.

In addition, a Customer Satisfaction Survey was launched recently that focuses on Registry enrollment. The purpose of this survey is to help improve the overall Registry web portal experience. This survey will help to determine where people are coming in, how they found out about the registry, et cetera. If they find that there is a gap in one area or another, perhaps they need to improve promotion and outreach to try to get more people to come into the Registry. Sample questions include:

- How did you hear about the Registry (e.g., neurologist, internet, ALSA, MDA, Les Turner)?
- How often do you visit the Registry website?
- Which Registry resources do you find most useful (e.g., clinic locator, continuing education module)?
- What other languages (aside from Spanish) should we consider implementing?
- What parts of the website can be improved (e.g., research info, clinical trial info)?

There is continuous recruitment for ALS clinical trials and epidemiological studies through the Registry. Over 35 institutions domestically and abroad have used the notification mechanism for their particular studies, including pharmaceutical companies.

The ATSDR team also tries to get out and about throughout the country and the world to promote the Registry through ALS patient symposiums, presenting at scientific conferences or medical meetings, et cetera. This helps ATSDR promote the Registry, the work being done, and the findings from the Registry and partners ATSDR supports. Last year, they attended the following 12 conferences and ALS patient symposiums with platform, panel, or poster presentations:

- Louisiana/Mississippi ALS Symposium August 10th, 2017; New Orleans, Louisiana
- 17th Annual Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS) Meeting, October 3-5, 2017; Clearwater Beach, Florida
- ALS Symposium and Kanas University Grand Rounds, October 19-20, 2017; Kansas City, Kansas
- 2017 Georgia ALS Educational Symposium, Savannah October 21, 2017; Savannah, Georgia
- 28th International Symposium on ALS/MND, December 8-10, 2017; Boston, Massachusetts
- 4th Annual Clinical Research in ALS and Related Disorders for Therapeutic Development (CreATe) Consortium Meeting, February 5-6, 2018; Miami, Florida
- MDA Clinical Conference, March 12-1, 2018; Washington, DC
- ALS Association Fly In, March 20, 2018; Washington, DC
- American Academy of Neurology (AAN), April 23-27, 2018; Los Angeles, California
- ALS Association Advocacy Day, May 14, 2018; Washington, DC
- ALS Research Symposium, June 8, 2018; Seattle, Washington
- Atlanta ALS Educational Symposium, July 28, 2018; Atlanta, Georgia

They also have been very active publishing ATSDR findings from the Registry, as well as findings from partners ATSDR either has funded or has helped recruit for. Over one dozen peer-reviewed publications/abstracts have been published within the past year from Registry staff and research partners:

- Kuczmarski T, Stommel E, Riley K, et al. Medical history of chemotherapy or immunosuppressive drug treatment reduces risk of amyotrophic lateral sclerosis (ALS). *J Neurology*, 2017.

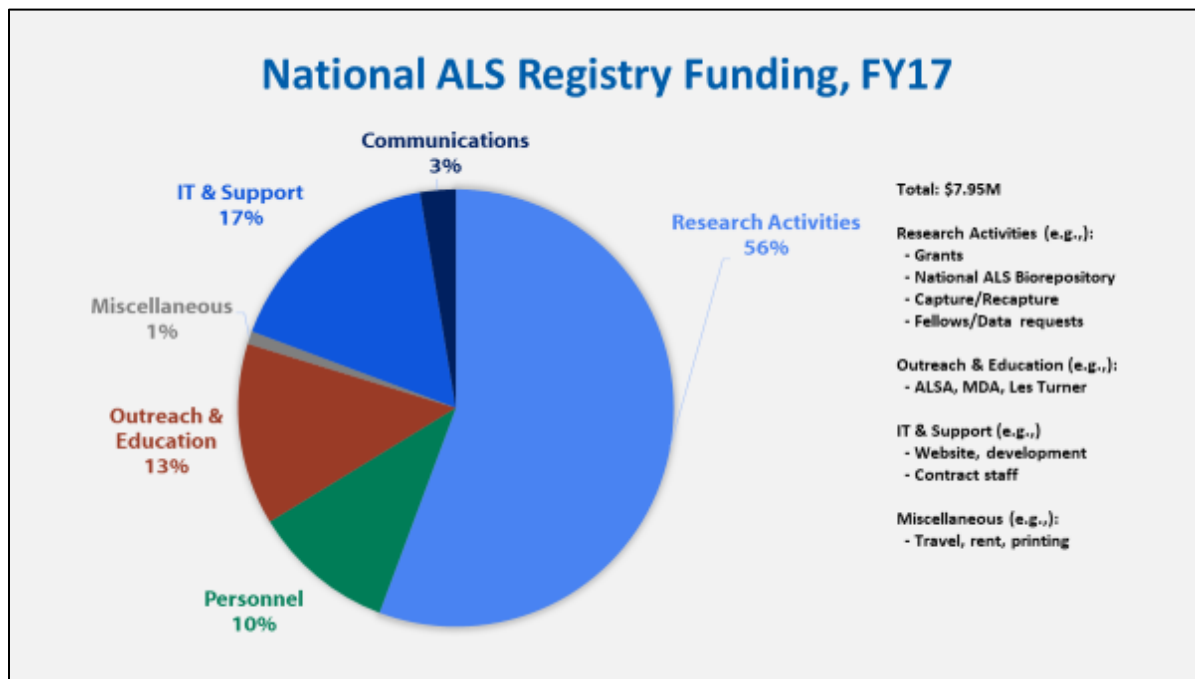
- ❑ Andrew A, Caller T, Tandan E, et al. Environmental and Occupational Exposures and Amyotrophic Lateral Sclerosis in New England. *Neurodegenerative Disease*.
- ❑ Parkin Kullmann JA & Pamphlett R. Does the index-to-ring finger length ratio (2D:4D) differ in amyotrophic lateral sclerosis (ALS)? Results from an international online case–control study. *BMJ Open*.
- ❑ Laliberte R. The Power of Many: Data from patient registries help advance research and improve care. *Neurology Now*.
- ❑ Kaye W, Wagner L, Wu R, Mehta P. Evaluating the completeness of the National ALS Registry, United States. *ALS/FTD*.
- ❑ Brown C. Non-Familial ALS: A tangled web. *Nature*.
- ❑ Mehta P, Horton DK, Kasarskis EJ, et al. CDC Grand Rounds: National Amyotrophic Lateral Sclerosis (ALS) Registry Impact, Challenges, and Future Directions. *MMWR*.
- ❑ Horton et al. A spatial analysis of amyotrophic lateral sclerosis (ALS) cases in the United States and their proximity to multidisciplinary ALS clinics, 2013. *ALS/FTD*.
- ❑ Wagner KN, Nagaraja HN, Allain DC, Quick A, Kolb SJ, Roggenbuck J. Patients with sporadic and familial amyotrophic lateral sclerosis found value in genetic testing. *Mol Genet Genomic Med*.
- ❑ Huang Z, Zhang H, Boss J, Goutman SA, Mukherjee B, Dinov ID, et al. Complete hazard ranking to analyze right-censored data: An ALS survival study. *PLoS Comput Biology*.
- ❑ Mehta P, Kaye W, Raymond J, et al. Prevalence of Amyotrophic Lateral Sclerosis — United States, 2014. *MMWR*.
- ❑ Harrison D, Mehta P, van Es M, Stommel E, Drory V, Nefussy B, van den Berg L, Crayle J, & Bedlack R. “ALS reversals”: demographics, disease characteristics, treatments, and comorbidities. *ALS/FTD*.
- ❑ Larson T, Kaye W, Mehta P, Horton D. K. Amyotrophic Lateral Sclerosis Mortality in the United States, 2011–2014. *Neuroepidemiology*.

There are many additional articles available at no cost through the ATSDR website, given that ATSDR tries to purchase the publication rights as soon as an article is published in order to make all of these publications open-access.

As mentioned earlier, the NOFO to “Identify, Analyze, and Evaluate Potential Risk Factors for Amyotrophic Lateral Sclerosis (ALS)” was published. It is anticipated that 4 awards will be funded pending the availability of funds. Each award is expected to be approximately \$400,000. In addition, ATSDR is launching a new Spanish Registry website and other languages are being assessed. There is a possibility that in the future, other languages will be incorporated into the website. New materials are being developed to increase awareness (e.g., clinic posters, videos, infographics). ATSDR is analyzing results from state outreach projects for possible national rollout. The fourth national prevalence report is currently in development. ATSDR is implementing a new GovDelivery email system to determine effectiveness of emails. One

problem they are having is that when they send out emails to people who have enrolled through the online portal, they do not know whether the emails are opened and read. The new email system will allow them to know whether an email has been opened and read. National outreach activities to increase awareness and enrollment are ongoing.

In terms of funding, Dr. Horton shared FY17 figures as they were able to provide complete information on that fiscal year. FY18 figures are anticipated to be similar and he will share that information as well once it is complete:



In summary, the National ALS Registry is the only population-based ALS registry for the US. ATSDR is doing its very best to fulfill the Congressional mandate to determine the incidence, prevalence, demographics, and risk-factors for ALS. ATSDR is facilitating research by analyzing thousands of risk-factor surveys to help determine etiology, collecting nationally-representative biospecimens to enhance external research, assisting in recruitment for clinical trials and epidemiologic studies, providing epidemiological data and biospecimens to researchers, and funding external research on ALS risk factors and etiology. Continuous enhancement efforts are made by engaging with partners to promote enrollment (e.g., ALSA, MDA, Les Turner); increasing visibility and usability (e.g., new website, Spanish language, videos); and improving case-ascertainment gaps (e.g., via cap/recap, w/in minority populations). Dr. Horton emphasized again that it is not just an ATSDR initiative. This is a multi-partner initiative. It cannot be done by ATSDR alone. They need everyone's help to demonstrate the importance of the Registry.

Discussion Points

Dr. Benatar requested a status implementation of the Globally Unique Identifier (GUID) and how linked the data potentially are.

Dr. Horton replied that the issue with the GUID is that it is not necessarily a unique identifier. They have found that different institutions are using different GUIDs. The National Institutes of Health (NIH) uses one GUID, while Massachusetts General uses another. ATSDR has implemented two GUIDs in an effort to have “keys that will fit multiple doors.” When someone enrolls in the Registry through the online portal, they are given the option to generate two different GUIDs. People are taking part in this, but unfortunately it is somewhat confusing to an end-user.

Dr. Mehta added that the GUID was implemented in January 2017. Previous enrollees can opt into the system as well. It is contingent upon how someone enters his or her name. Thus far, ATSDR has received no requests from researchers for GUID-coded data.

Dr. Kaye added that the GUID is dependent upon the computer in which the information is generated. NIH is using one server, while NEALS is using a different server. They generate different numbers. ATSDR has the fields that everyone is collecting and those are being kept, so they could generate a third GUID if necessary.

Dr. Benatar clarified that even if there are multiple systems, they are unique. They are just not global.

Overview of National ALS Registry Research Initiatives

Paul Mehta, MD
National ALS Registry Principal Investigator
Environmental Health Surveillance Branch
Division of Toxicology and Human Health Sciences
Agency for Toxic Substances and Disease Registry

During this presentation, Dr. Mehta reported on research areas of the Registry, the third and fourth reports on national ALS prevalence, Registry surveys, the notification mechanism for connecting persons with ALS (PALS) and researchers, notable registry publications, funding research, the new Request for Applications (RFA) on Grants.gov, future research initiatives, and Continuing Medical Education (CME) credits. He emphasized that with the Registry, ATSDR does much more than just count ALS cases. It also supports research, epidemiology, and the National ALS Biorepository. The Registry also collects survey data and includes a Research Notification Mechanism to connect PALS and researchers. Almost 60% of funding is allocated to external ALS research focused on etiology, risk factors, et cetera.

As mentioned earlier, the third prevalence report was published on February 22, 2018 in the *MMWR* and covers calendar year 2014. In 2014, prevalence was estimated to be 5 cases/100,000. Including national databases and the portal, the case count was 15,927. ALS continues to be more common in whites, males, and persons 60-69 years of age. That is unchanged from the first two reports. The lowest number of ALS cases was among persons 18-39 years of age and > 80 years of age. Males continue to have a higher prevalence than females across all data sources. The initial observations are that this is unchanged from 2013, prevalence is currently holding steady, and the demographics of the disease have not changed. More data are needed to estimate national prevalence trends. The fourth report is scheduled to be published in Fall 2018 and will cover calendar year 2015. With the fourth report, ICD-10 utilization began on October 1, 2015. Staff are examining how implementation of ICD-10 versus ICD-9 may impact the algorithm.

There currently are 17 risk factor surveys, which are in the process of being analyzed. Completion of the risk factor surveys is steadily increasing. Over 76,000 risk factor surveys have been completed to date. Approximately 65,000 had been completed last year at this point. This table provides a breakdown of the surveys available, their release dates, and the number completed as of August 1, 2018:

| Survey (n=17) | Release Date | No. Completed |
|--|----------------|---------------|
| Demographics | October, 2010 | 8414 |
| Occupational history | October, 2010 | 7660 |
| Military history | October, 2010 | 7507 |
| Smoking and alcohol history | October, 2010 | 7381 |
| Physical activity | October, 2010 | 7097 |
| Family history of neuro. diseases | October, 2010 | 6915 |
| Disease progression (ALSFRS) | October, 2010 | 6942 |
| Clinical data (e.g., devices used, body onset) | November, 2013 | 2796 |
| Open-ended etiological questions | November, 2013 | 2559 |
| Lifetime residential history | May, 2014 | 3011 |
| Lifetime occupational history | May, 2014 | 2982 |
| Residential pesticide use | May, 2014 | 2786 |
| Hobbies with toxicant exposures | August, 2014 | 2531 |
| Caffeine consumption | August, 2014 | 2384 |
| Reproductive history (women) | August, 2014 | 1316 |
| Health insurance status | December, 2014 | 2081 |
| Head and neck injuries | December, 2014 | 2053 |
| Total (as of 8/1/2018) | --- | 76,415 |

ATSDR continuously receives questions/suggestions about adding, changing, or modifying the risk factor surveys. The risk factor surveys were adapted and reviewed by Dr. Lorene Nelson's group at Stanford University. In order to add a risk factor survey, they must take one down due to potential burden. The Office of Management and Budget (OMB) permits 90 minutes. Consideration is being given to updating the Physical Activity Survey 5 with the next OMB submission. This survey currently measures oxidative stress, but may be revised to assess TBI and sports. However, existing data will be evaluated before making any changes to Survey 5. Ongoing analyses include the following:

- Reproductive History and ALS: ATSDR
- Disease Progression (Survey 7, ALSFRS): ATSDR
- Health Status and Clinical Module (Surveys 15 and 17): ATSDR/Bjorn Oskarsson, MD
- Open-Ended Questions on ALS Causes (Survey 16): ATSDR
- Physical Activity (Survey 5): ATSDR

The preliminary results for Surveys 1-6 have been published, and the following future analyses are planned:

- Exposure Matrix Development and Analysis:
 - Occupational History (brief)
 - Residential History
 - Lifetime Occupational History
 - Home Pesticide Use
 - Hobbies

- ❑ Caffeine Consumption
- ❑ Head & Neck Injuries, possibly combined with surveys:
 - Occupational history-brief
 - Military history
 - Lifetime Occupational History

Dr. Mehta emphasized that these data are available for researchers to request, and encouraged them to submit their ideas to ATSDR for consideration. Many of the surveys require cross-referencing with other surveys and cannot be examined alone.

The Research Notification System has taken off, with approximately 95% of Registry PALS opting in to participate in research. The Registry links PALS with scientists who are recruiting for research (e.g., clinical trials, studies). Domestic and international researchers are using the tool for recruitment purposes, with over 35 institutions having used the system thus far. Following are some of the clinical trials:

- ❑ Amylyx Pharmaceutical, Inc (Paganoni): CENTAUR-ALS, AMX0035 slows disease progression and muscle weakness
- ❑ Cytokinetics, Inc (Rudnicki): Fortitute-ALS (CK2127107), newest clinical trial, and ARREST ALS (Tirasemtiv) completed
- ❑ Flex Pharmaceuticals (Oskarsson): FLX-787, evaluate decrease in muscle cramps
- ❑ Barrow Neurological Institute (Ladha): determine whether tocilizumab (Actemra™) is safe and tolerable
- ❑ Neuraltus Pharmaceuticals, Inc (Block): NP001, Phase II, helps to slow down ALS by reducing inflammation
- ❑ University of Washington – Davis (Weiss): mexiletine calms over-excited nerves and brain cells, slowing disease progression
- ❑ Carolinas Neuromuscular Center (Brooks): evaluating the safety tolerability and clinical endpoint responsiveness of Ibudilast, MN 166

A new clinical trial application was received the previous week from Orion Pharmaceuticals that proposes to examine the effects of ODM-109 (oral levosimendan) on respiratory function in patients with ALS. This is a Phase III, randomized, double-blind, placebo-controlled, parallel-group, multi-center study. Approximately 450 PALS from 70 to 80 centers across the US would be enrolled in the study. The objective is to confirm whether levosimendan can significantly improve respiratory function measured by supine slow vital capacity (SVC). Enrollees will include males and females with a diagnosis of ALS with disease duration from symptom onset of 12-48 months. The Principal Investigator (PI) is Merit Cudkowicz, MD/MGH.

The following are some of the notifications using the Registry for epidemiological/risk factor studies:

- ❑ ALS Association (Bruijn): IMPACT-ALS, Investigating and Measuring Patient And Caregiver Trends about ALS

- ❑ Columbia University (Mitsumoto): ARREST ALS study, examine the relationship between oxidative stress (OS) and ALS as well as combined exposures on development of ALS, including environmental, occupational, lifestyle, dietary, and psychological risk factors.
- ❑ Massachusetts General Hospital (Nicholson): Microbiome assessment, role of gut microbiota in the development of diseases such as ALS, linked to inflammation.
- ❑ Barrow Neurological Institute (Shefner): ALS testing at home, travel requirement may prevent participation in studies, ALS patients will evaluate their own function at home.

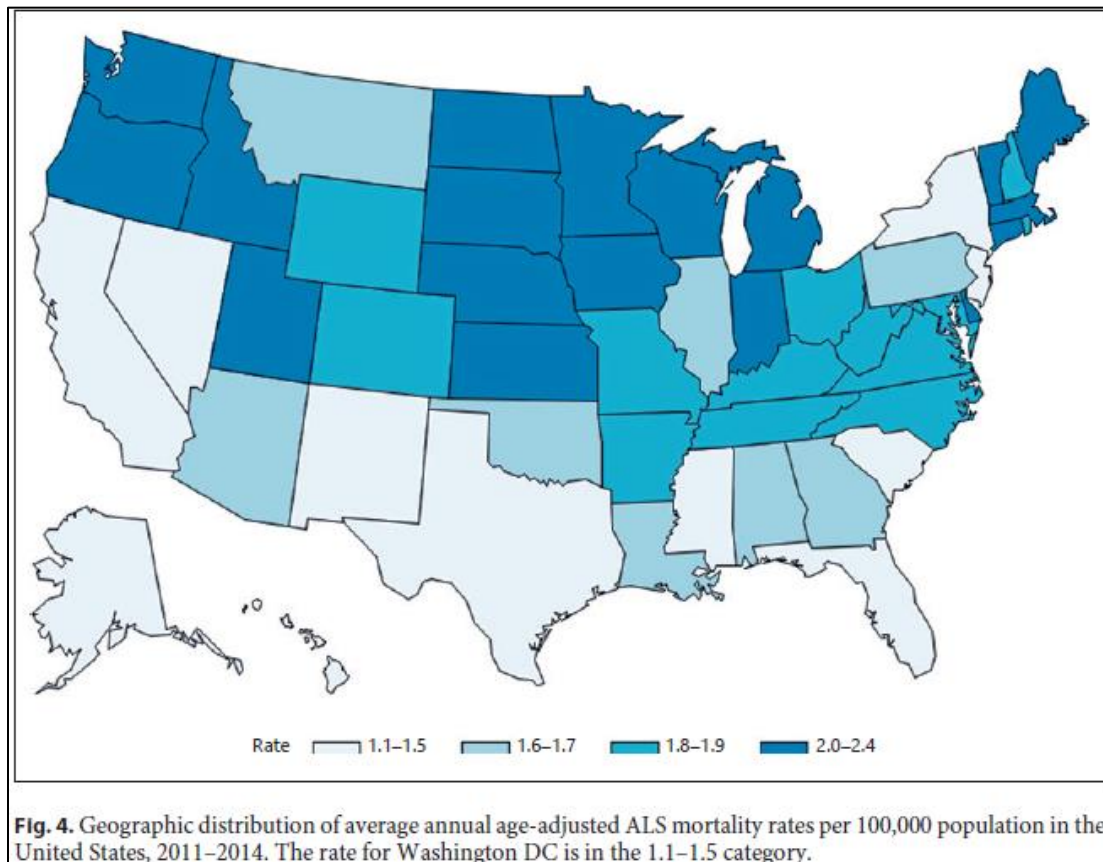
One advantage of this recruitment mechanism is user-friendliness for researchers. ATSDR works closely with researchers to answer any questions and address any potential issues before the proposed research is submitted to the committee for review. CDC Institutional Review Board (IRB) approval is not needed. IRB approval by the applicant's institution is adequate. Search criteria can be based upon a number of variables: age, sex, time since diagnosis, state, region, national. For multi-site clinical trials, single IRB approval is satisfactory versus 40 to 50 approvals. Protocols are preferred but not necessary. ATSDR understands that some of the pharmaceutical companies do not want to provide their full protocol on a particular drug due to the proprietary nature of some of the information. If the FDA has approved a formulation, CDC accepts that. The approval process typically takes less than 4 weeks. The research committee is comprised of neurologists and patients. Dr. Mehta encouraged those interested in joining the committee to let ATSDR know.

ATSDR published over a dozen peer-reviewed publications and abstracts. As mentioned earlier, the Registry pays for open-access whenever possible. Abstracts have been presented at AAN, NEALS, and the International ALS/MND Symposium. Some notable publications include the following:

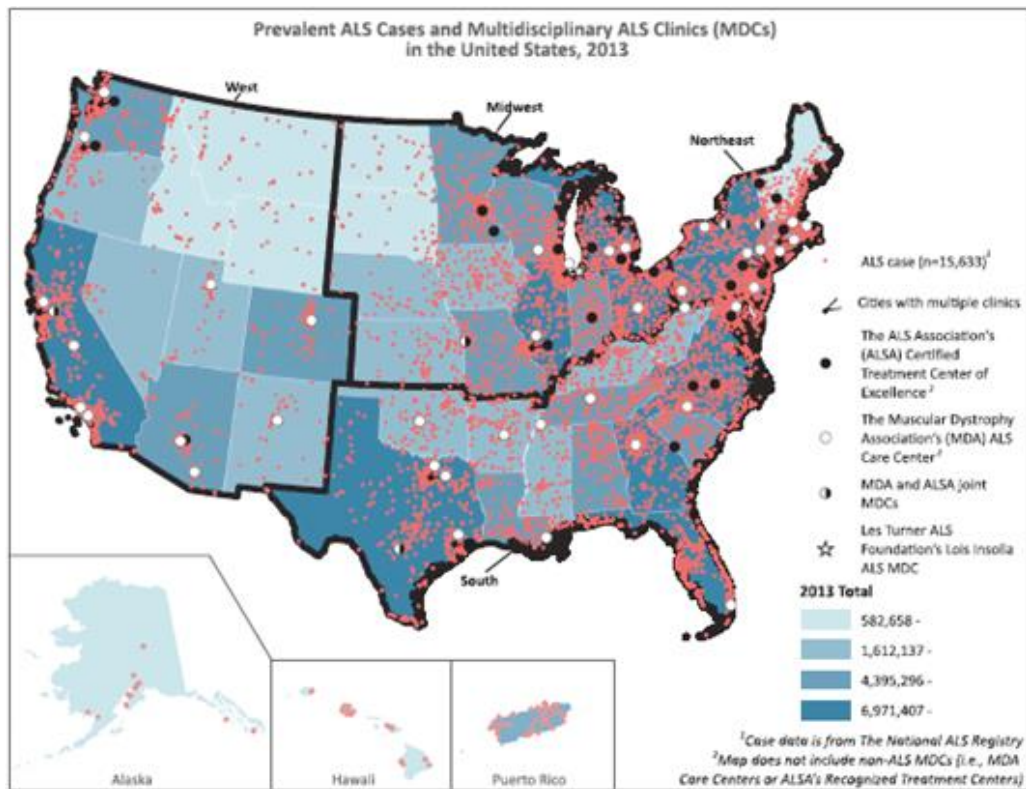
- ❑ Larson et al: Amyotrophic Lateral Sclerosis Mortality in the United States, 2011–2014.
- ❑ Horton et al: A spatial analysis of amyotrophic lateral sclerosis (ALS) cases in the United States and their proximity to multidisciplinary ALS clinics, 2013.
- ❑ Kaye et al: Evaluating the completeness of the National ALS Registry, United States.
- ❑ Harrison et al: “ALS reversals”: demographics, disease characteristics, treatments, and co-morbidities. (External collaboration with Duke Medical School, Richard Bedlack, MD, PhD)
- ❑ (In development): ALS among Patients with a Medicare Advantage Prescription Drug Plan; Prevalence, Survival and Patient Characteristics (Humana collaboration)

Amyotrophic Lateral Sclerosis Mortality in the United States, 2011–2014 by Larson et al was recently published. Mortality was analyzed previously by another researcher, and ATSDR felt that the calculation of mortality was somewhat over-stated. The reason for this is that when the analysis was performed, other motor neuron diseases (MNDs) were included. The recently published Larson et al study is much more specific. Based on this study, approximately 30,804 deaths were found in US coded as G12.2, ICD-10. Of these, about 21% (6476) were excluded from this analysis as they were deemed to be other MND or neurological disorders, including: 5039 progressive supranuclear palsy; 558 bulbar palsy; 331 primary lateral sclerosis; 80 progressive muscular atrophy; 351 non-specific term for MND; and 117 with some other cause. After exclusions, there were 24,328 ALS deaths. The overall age-adjusted mortality rate was

1.70 (95% CI 1.68–1.72). Males were 2.09 (95% CI 2.05–2.12), females 1.37 (95% CI 1.35–1.40), whites 1.84, blacks 1.03, and other 0.70. This paper provides increased sensitivity versus previous publications on ALS mortality. This map from the paper depicts the geographic regions where mortality was found to be higher:



A spatial analysis of amyotrophic lateral sclerosis (ALS) cases in the United States and their proximity to multidisciplinary ALS clinics, 2013 by Horton et al showed that about 45% of persons with ALS lived more than 50 miles from the closest multidisciplinary clinics (MDC), while 24.6% lived more than 100 miles from an MDC. The West had the furthest case-to-MDC proximity average, with approximately 600 miles being the furthest distance. There was no statistical difference in case-to-MDC by sex. By race, African Americans lived closer to MDCs at the 0-25 mile range. By age, those ≥ 80 years of age lived within 0-50 miles of an MDC. This map shows the location of the MDCs:



The importance of this paper is that it is known that access to care is very important with ALS in terms of adequate care, survival, and so forth. As shown on the map, there are large swaths of areas where there are no clinics.

As mentioned, ATSDR is funding extramural research to learn more about ALS etiology and risk factors. The information gleaned from these studies also will help ATSDR prioritize topics for future risk factor surveys and research initiatives. To date, 13 research studies have been funded. The newest R01 to be funded is from PI Evelyn Talbott, DrPH at the University of Pittsburgh and Co-PI Angela Malek, PhD at the Medical University of South Carolina. This is the first ATSDR-funded study to utilize specimens from the National ALS Biorepository. The objective of the study is to examine serum/plasma levels of ambient air environmental toxicants in combination with data on environmental and occupational exposures from interview data in relation to ALS risk. This study will include controls as well. All 13 funded studies are outlined in the following table:

| Study Name | Institution | Investigator | ATSDR Funding Period |
|---|------------------------------------|---|-----------------------------------|
| Identification and Characterization of Potential Environmental Risk Factors for ALS Using the ATSDR ALS Registry Cases and a Control Population | The University of Pittsburgh | Evelyn O. Talbott, DrPH | September, 2017 – September, 2020 |
| ALS Risk in Latin Americans: A population based case control comparative study with 3 European population based cohorts | Trinity College – Dublin, Ireland | Orla Hardiman, MD, PhD | September, 2016 – September, 2018 |
| A Population-Based Ohio ALS Repository and a Case-Control Study of ALS Risk Factors | Dartmouth College | Elijah Stommel, MD, PhD | September, 2016 – September, 2018 |
| Environmental risk factors and gene-environment interactions in ALS risk and progression | University of Miami | Michael Benatar, MD, PhD Marc Weisskopf, PhD | September, 2016 – September, 2018 |
| Case-Control Studies Nested in National ALS Registry to Evaluate Environmental Risks | Columbia University Medical Center | Hiroshi Mitsumoto, MD, DSc | September, 2015 – August, 2018 |
| Antecedent Medical Conditions and Medications: Associations with the Risk and Prognosis ALS | Stanford University | Lorene Nelson, PhD | September, 2015 – September, 2018 |
| Prospective study of biomarkers and risk factors for ALS incidence and progression | Harvard School of Public Health | Alberto Ascherio, MD, DrPH | July, 2014 – June, 2015 |
| Analysis of environmental risk factors for ALS using the National ALS Registry and the State-Based Comprehensive Surveillance Projects Database | Dartmouth College | Elijah W. Stommel, MD, PhD | July, 2014 – June, 2016 |
| Identification and Validation of ALS Environmental Risk Factors | University of Michigan | Eva Feldman, MD, PhD | August, 2013 – August, 2017 |
| A Prospective Comprehensive Epidemiologic Study in a Large Cohort in The National ALS Registry: A Step to Identify ALS Risk Factors | Columbia University Medical Center | Hiroshi Mitsumoto, MD, DSc | August, 2013 – August, 2017 |
| Epidemiology of ALS | Harvard University | Marc Weisskopf, PhD, ScD | July, 2012 – June, 2013 |
| Gene-environment Interactions in ALS | Northwestern University | Teepu Siddique, MD | July, 2012 – June, 2013 |
| Large-Scale Genome-Wide Association Study of ALS | National Institutes of Health | Bryan Traynor, MD, PhD | July, 2012 – June, 2013 |

In terms of grants to be funded in FY19, a NOFO titled *TS18-001: Identify, Analyze, and Evaluate Potential Risk Factors for Amyotrophic Lateral Sclerosis (ALS)* was published this year. The objective of the announcement/funding is to identify potential risk factors for ALS in humans that are potentially associated with or contribute to the etiology, progression, and pathophysiology of ALS in humans. The areas of interest for this line of research include: environmental and occupational, military service, infectious agents and viruses, nutritional intake, physical and sports activities, pharmaceutical use, and traumatic injuries. ATSDR anticipates funding 1 to 4 awards of \$400,000 per year for 3 years subject to funds. Funding is managed through a peer-review process completely external to EHSB. They will be told in September who the grantees will be. There are plans to fund an additional NOFO in FY19, although the topic areas have not yet been decided, it is anticipated to be similar to what was published in TS18-001.

ATSDR also has CMEs available for providers through its [Amyotrophic Lateral Sclerosis \(ALS\) Continuing Education Module](#). This course provides 1.5 contact hours of free continuing education.

Discussion Points

Regarding geographic distribution, Dr. Thakur noted that there are problems with identifying PALS and including them in the Registry if they are not engaged in treatment. He asked whether it could be that people who live further away from a treatment center are more likely to be under-counted, such that the estimates are low for the groups who are further away. He observed that when a surveillance system is run, there is a count of the people who actually are in a registry, but there is also the possibility for an estimate. The reports featured the count, but he wondered whether they discussed the estimate. Bringing together the estimate of missing cases and the count provides an estimated national or regional prevalence.

Dr. Mehta replied that for 2013, the prevalence was still about 5/100,000. The Registry is a surveillance system and cannot capture all of the cases. Certainly, the cases in rural areas may go to their primary care physician (PCP) or a neurologist once, get a diagnosis of ALS, and never go to a neurologist again. It is difficult to say, but it probably is a slight undercount. There are likely to be individuals in rural areas who have not been counted because they have not joined the Registry or were not captured by Medicare or the VA system. In terms of the potential to make an estimate, Dr. Mehta noted that there is a system called capture-recapture that examines the estimated number of missing cases. There is a way to use that methodology for a particular year to estimate the number of missing cases, which are residing with private payers. However, it will still only be an estimate. With ATSDR's data collection methods and algorithm, they feel pretty confident that they are capturing the bulk of ALS cases in the US. He indicated that Dr. Kaye would be presenting on the completeness of the Registry later in the day.

Regarding the annual reports, Dr. Finger said he still thought one thing that is misleading that had been brought up in previous years, is that the patients are referred to as "definite ALS." The way that it is most commonly used in the ALS community has a very different connotation than the way it is used specifically by the Registry. He suggested that the word "definite" should be changed or at least placed in quotes so that people are not misled to think that the undercount is due to definite versus probable. In terms of capture-recapture, he did not think they could estimate that they are missing 10% when by the best estimate over 40% are missing. Related to that, they talk about how hard it is to reach out to minorities and how much of the marketing efforts are to reach out to minorities and people in difficult areas, but simultaneously they are reporting prevalence numbers with no caveat saying that this is a white, educated disease. He did not think they could continue to say that there are not any minorities when they know that they are not being captured. This makes the outreach efforts harder. This has to do with how the statistics are framed. As Dr. Horton said, they will never be able to capture everyone. A \$1 million marketing budget in a country with 325 million people will never capture it. The statistical technique must reflect that. In the paper on the 2014 data, possible undercounting is not mentioned until the second to last paragraph. There is no reference to the fact that a study has been completed that says the possible undercounting is 40%, which implies that the prevalence rates are off by more than 60%, (In the completeness paper, of the 4,767 identified patients, only 2,720 were in the registry) and he wondered why that paper was not cited.

Dr. Mehta acknowledged that they must do a better job with the outreach efforts clarified that Dr. Finger was referring to the completeness paper.

Dr. Kaye indicated that the completeness paper was not cited because the 2014 paper was published before the completeness paper was published. A paper cannot be cited until it is published.

Dr. Bradley asked whether people who register answer any questions regarding whether they have had neck surgery, given that there is some evidence that neck surgery worsens ALS. If not, it would be interesting to capture whether individuals with ALS who register themselves had neck surgery. He also asked whether there is a way within the Registry to ask which cases have died.

Dr. Mehta replied that the cases are evaluated through the National Death Index (NDI) in order to get a cause of death (COD). The underlying condition may be ALS, but the COD might have been respiratory failure. None of the surveys ask about previous surgeries. They do ask about muscle cramps in the Clinical Onset Survey, but nothing specific about surgery. This potentially could be captured in Survey 16, which is the survey that asks people to talk about what they

think causes their ALS. However, that is a qualitative survey. The Registry can be queried to ask which cases have passed away. They estimate prevalence based on cumulative prevalence, so they cross-reference NDI every calendar year. Those cases who have died are removed as a case the subsequent year.

Dr. Kaye added that they are collecting data about neck injuries, but not on any type of surgery. The survey that collects information about neck injuries has been up for about a year.

Ms. Balas expressed concern regarding the geography of the centers shown from 2013 in terms of targeting and focusing their efforts. Since 2014, the ALS Association has doubled the number of certified treatment centers with which they work.

Dr. Horton indicated that this analysis could be done with 2014 and 2015 data.

Dr. Mehta added that in the paper, they do specify that these are only for 2013. This paper is unique in that they had co-authors from the ALS Association, Les Turner Foundation, and MDA. This was a group effort because they did not want to publish something without a say from all of the other partners as well.

Dr. Brooks asked whether the proportion of military cases each year was staying the same, increasing, or decreasing. When ALS became a VA benefit, there was a large increase in the VA Registry, so he wondered if they were assessing that type of micro environment issue as well.

Dr. Kaye replied that the cases are steady. They come in through the VA and maybe through the portal or Medicare as well.

Dr. Mehta added that they are not currently assessing the VA's Registry for ALS at this time, but it is an area they could pursue.

Dr. Thakur said he thought it would be helpful to hear a quick overview of what was meant by "cumulative prevalence" and specifically what is being counted and if, for example, survivability increased how that could affect cumulative prevalence.

Dr. Kaye indicated that "cumulative prevalence" means that someone does not have to qualify as a case in every given year. If someone is identified in Medicare in 2012 as a case, they remain a case until ATSDR receives a report from the NDI that they have passed away, and then they are taken out. Because the algorithm is based on using medical services, it is known that as people become sicker, they use less services. They may not be seen by a neurologist and may no longer take riluzole. They would not come up as a case, not because they were not a case, but because of the way the algorithm identifies people.

Dr. Tessaro said that he is a veteran and has talked to the ALS team at ATSDR, who think the number of veterans with ALS is significantly under-represented.

Update on the National ALS Biorepository

Laurie Wagner, MPH
Biorepository Coordinator
McKing Consulting Corporation

Wendy E. Kaye, PhD
Senior Scientist
McKing Consulting Corporation

Ms. Wagner presented a brief history and update on the National ALS Biorepository. A pilot study was conducted from September 2012 through September 2015. The first collections began in 2013. For the pilot study, 330 Registry participants were enrolled who provided blood, urine, hair, and nails. Specimens were collected in-home on two occasions approximately six months apart. Participants were recruited to be geographically representative of the US, with at least one person being recruited from every state by the end of the pilot study. In addition, 30 Registry participants were enrolled to donate tissues postmortem. All postmortem participants also took part in the in-home blood collections. There were changes after the pilot study. Persons with ALS can sign up to learn more about the Biorepository when they join the National ALS Registry. Specimens are collected only one time, and hair and nails are not being collected at this time. However, if researchers are interested in hair and/or nails, they can be added back. Saliva is collected from those who cannot donate blood and from a sample of persons interested in the Biorepository. Researchers can request specimens as well as data to go along with the specimens.

Here is a screenshot of the page that has been added to the ALS Registry where existing and new participants can sign up to express their interest in the Biorepository:

National ALS Biorepository Participant Interest

Research is an important part of the National ALS Registry. Specimens are needed for much of this research. The National ALS Biorepository is a new part of the National ALS Registry. If you are interested in learning more about the Biorepository, please check the "I Agree" box. A sample of interested PALS will get information packets.

I Agree

I would like to learn more about donating biospecimens to the National ALS Biorepository

I would like to learn more about donating postmortem tissues to the National ALS Biorepository

I would like to learn more about donating both biospecimens and postmortem tissues to the National ALS Biorepository

Please provide your mailing address and phone number. This information will be used to make sure we ask PALS from all over the US to take part. We will also use this information to contact you if you are selected.

Address:

City:

State:

Zip:

Phone: (ex:7701234567)

In terms of the process, ALS patients enrolled in the National ALS Registry can sign up to learn more about the biorepository. New enrollees can agree to receive more information about the Biorepository during registration. Previously enrolled participants in the Registry can update

their accounts to receive more information. The Biorepository staff receives a list of enrollees interested in the Biorepository on a monthly basis. Enrollees are selected to receive more information about the Biorepository based on their geographic location in order to ensure that there is nationwide representation. Selected enrollees are then mailed packets. Potential participants are called by a Biorepository Coordinator approximately one week after the package is mailed to answer any questions they have, go over and sign the consent form if interested, and schedule an appointment to give blood or mail in a saliva kit.

The role of the Biorepository coordinator is to make an appointment for a phlebotomist to visit the participant and coordinate the collection between the phlebotomist and the participant. Once the appointment is set up, the phlebotomist will go to the participant's home to collect specimens using the kit that was mailed to the home in advance and ship the specimens to the laboratory for next day delivery. Once received, the specimens are processed as follows:

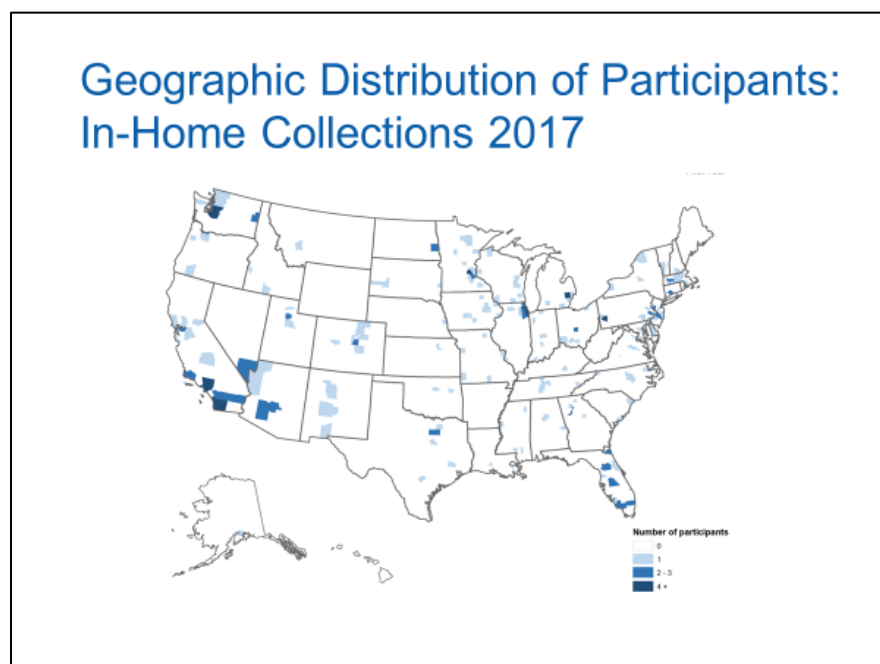
Blood Specimens

- Plasma is made into 0.5 ml aliquots
- Serum is made into 0.5 ml aliquots
- Metals free blood is made into 1.8 ml aliquots
- Deoxyribonucleic acid (DNA) is extracted from the Buffy Coat and made into 2 µg aliquots
- Ribonucleic acid (RNA) extracted and made into 2 µg aliquots

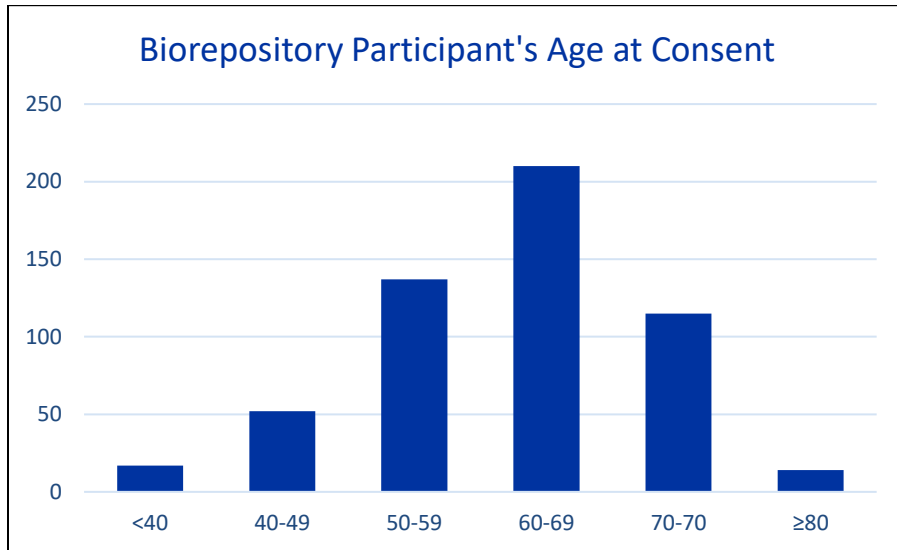
Urine Specimens

- Special aliquot for mercury analysis
- Urine made into 1.8 ml aliquots

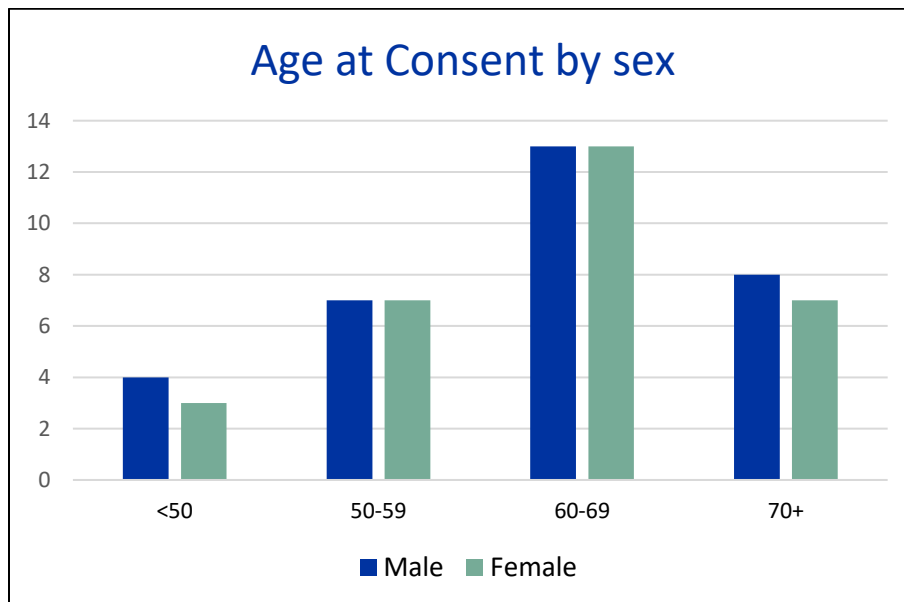
From January 4, 2017 through July 31, 2018, there were 487 participants who consented to the in-home blood and urine specimen collection, 110 who consented for saliva collection only, and 33 who consented to postmortem. Thus far, 449 in-home blood and urine specimens, 89 saliva only, and 14 post-mortem specimens have been collected. This 2017 map shows all of the areas from which specimens were collected, which includes nearly every state:



Consented participants are 63% male and live in 48 states, District of Columbia, and Puerto Rico. Participant ages at the time of consent are shown in the following chart:



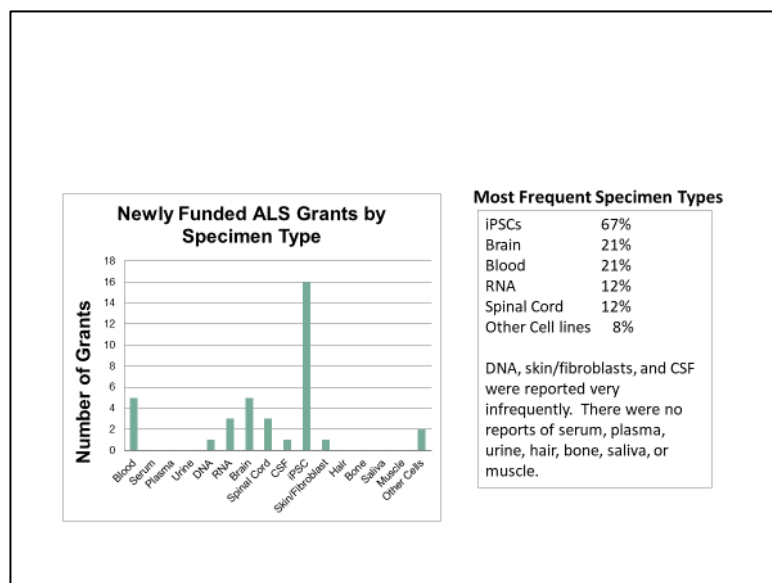
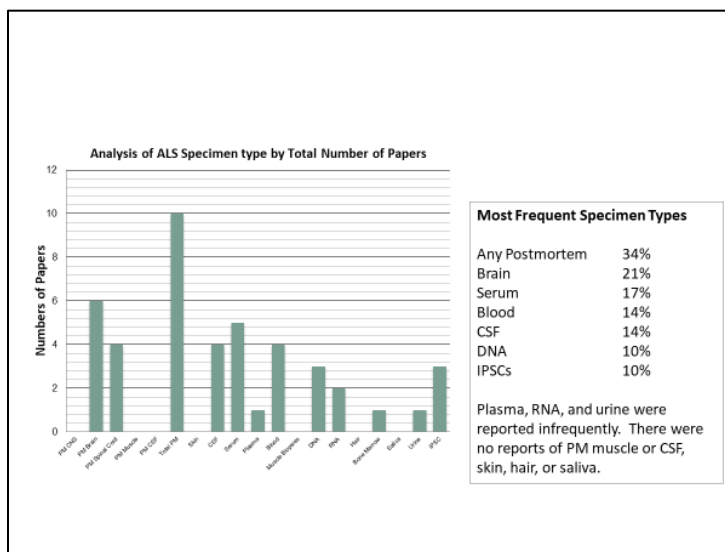
Postmortem samples consist of brain, spinal cord, cerebrospinal fluid (CSF), bone, muscle, and skin. Once received, brain and spinal cord are fixed and frozen, CSF is spun and frozen, bone is stored in formalin, muscle is stored in paraffin blocks, and skin is made into fibroblast lines. To date, 35 participants have donated postmortem samples including brain, spinal cord, CSF, bone, muscle, and skin. Of the consented participants, 5 withdrew and did not donate and 22 continue to be followed. This includes a few people who were in the pilot project. Postmortem participant ages at the time of consent are shown for males and females in the following table:



Dr. Kaye presented information regarding sample use. McKing Consulting Corporation is responsible for evaluating specimen demand. Multiple approaches are utilized to do so, including:

- ❑ Evaluation of historical use of specimens from persons with ALS in the literature
- ❑ Review of the literature to identify pressing questions in ALS research
- ❑ Review of specimen types used in currently funded research
- ❑ Interviews with experts in the field and staff at biorepositories that collect and distribute samples from persons with ALS for research purposes

Based on an analysis of the literature, 172 newly funded grants in 2017 or in 2018 were identified. Of these, 24 papers qualified and may have indicated use of multiple sample types. Induced pluripotent stem cells (iPSC), brain, and blood are the most frequently used samples. Historical use of specimens from persons with ALS and use of specimens from persons with ALS in funded ALS grants are depicted in the following two charts:



Dr. Kaye indicated that they are doing a small pilot study extracting cells from the blood and will immortalize and freeze them, so they will be available to turn into iPSCs. This seemed to be something that investigators were using a lot in research, so they are trying to add that to the biorepository.

McKing Consulting Corporation also is responsible for material distribution. Researchers can request samples for their ALS Research, for which the application process is outlined on the Registry website. Researchers must submit a research application form, cover letter, full protocol, and sample request form(s). The application and all supporting documentation are submitted online. A completed application goes through multiple reviews, including a laboratory review to verify specimens and quantities are available and if the approach is reasonable and a scientific review through an ATSDR review committee. After approval from ATSDR, the researcher signs a Material Transfer Agreement (MTA), pays a nominal fee to have the specimens pulled and shipped (there is no cost to researchers for collection of the specimens), McKing selects the appropriate samples, and the laboratory ships the samples to the investigator. The selection process can be complicated. All of the DNA from the pilot project has been run, so if researchers are looking for specific mutations and another group of people matched to them by age or area of the country, the process will take longer. Researcher requests received are shown in the following table:

| Description of Project | Group Conducting Analysis | Sample Types Requested |
|--|---|---|
| Metals analysis | CDC/ATSDR | Whole blood, serum, urine |
| Genomic analysis | NIH/ATSDR | DNA |
| Mitochondrial DNA and Micro RNAs in Amyotrophic Lateral Sclerosis | Columbia School of Public Health | Whole blood, plasma, brain, spinal cord |
| Role of FUS protein in inflammation and neurodegenerative disease | Icahn School of Medicine at Mount Sinai | Whole Blood, RNA, Cells |
| ALS risk, exposure sources, and effects on the unfolded protein response pathway | Dartmouth College | Nails |
| Targeting Ataxin-2 in Amyotrophic lateral sclerosis | University of Utah | Cells |

The take-home message is that the National ALS Registry now includes a Biorepository that is integrated into the Registry. Only people taking part in the Registry are eligible to participate in the Biorepository. From those interested, participants are selected to be geographically representative. Participants can make their samples more valuable by completing Registry risk factor surveys. Researchers can request samples for their studies. PALS can take part in the Registry and Biorepository even if they have donated specimens to other biorepositories and studies.

Discussion Points

Dr. Thakur said it was remarkable to him to see how generous people are in that they are willing to participate in multiple studies and repositories. However, he wondered about the efficiency in that and if with the GUIDs it is possible to link the survey completed in the ALS Registry with other repository data in order to virtually assemble a larger sample than if ATSDR collected it themselves.

Dr. Kaye indicated that the idea of being able to generate the GUID was that the ALS Registry might have data that others do not have, and they would be able to acquire that information. A researcher could apply to the Registry, indicate what they would like to do, and explain their protocol. Some clinical trials do not provide blood to outside researchers, but if someone is a part of the ALS Registry project, outside researchers could acquire their blood.

Given that Dr. Traynor is genotyping all of the samples, Dr. Brooks asked whether there was hope that the future use of these samples could allow for collaboration with Dr. Traynor to obtain the genome data on the samples to compare with whatever biomarker people are studying.

Dr. Kaye responded that they already have provided data that way to people who wanted only certain mutations.

Dr. Mehta added that they are looking at whole genome sequencing (WGS) as well. It costs roughly about \$400,000 to perform WGS on the 600 to 700 samples they have. It is pricy, but they are discussing with Dr. Traynor having his laboratory perform WGS on those samples.

Dr. Pentz asked whether they are getting sufficient postmortem samples using a voluntary system.

Dr. Kaye replied that they are and, in fact, are full. This is somewhat complicated in that the way the contract was written, they can only do 10 people per year. They consented up to a certain number. Once someone is consented, their samples will be collected regardless. Consideration must be given to whether there are better ways to do this. There are more people who would be interested in donating if it was available. Some physicians may be doing this on their own, the ALS Biorepository is the only national ongoing effort to do this. Everyone else has closed down due to the expense.

Dr. Bowser asked where the samples are processed and if there are any effects from the shipping, and if they are making fibroblast lines with the skin they are collecting postmortem.

Dr. Kaye indicated that the samples are shipped overnight to the laboratory in Rockville, Maryland. The containers have temperature loggers and cooling packs, and they have assessed the temperature data. In the pilot project, there were a couple of issues. During one summer, there were heat waves in Texas and a couple of samples were fried. They also have tested the hemoglobin in the samples as a marker of cell lysis, which suggests that they are doing okay in general. The skin cells are expanded immediately and then frozen.

Dr. Mehta added that they currently have 35 postmortem collections. The cost per patient is approximately \$30,000. Because it is extremely cost-prohibitive, they can do only so much given their budget.

Speaking from the perspective of persons living with ALS, Ms. Backman commended Dr. Kaye and Ms. Wagner for the Biorepository. The Les Turner ALS Foundation Biorepository was collecting about 8 to 10 postmortem samples per year, comprised primarily of brain and spinal cord samples, which they had run for about 20 years. When they were no longer able to continue to fund that at the end of 2016, they were delighted that the persons with ALS they work with around the Chicagoland area had another opportunity to donate. They have found in speaking with the over 200 families they work with at any point in time, this is a tremendous opportunity for them. They feel very strongly that this is something they can do to contribute to the greater science. In fact, they have talked to Dr. Kaye many times about finding a way to fund more of these collections because people want to sign up and contribute.

Dr. Gubitza added that the NIH NeuroBioBank (NBB) is also open for business for ALS tissue and there are also contributions to that through CReATe.

Dr. Kaye indicated that if people call them but they are full, they do try to direct them somewhere. For example, if they are a veteran, they direct them to the VA. Because they know the tissue is so valuable, they try to make it happen if someone expresses an interest.

Increasing Registry Enrollment

Registry Enrollment Update

Jaime Raymond, MPH
Epidemiologist, Environmental Health Surveillance Branch
Division of Toxicology and Human Health Sciences
Agency for Toxic Substances and Disease Registry

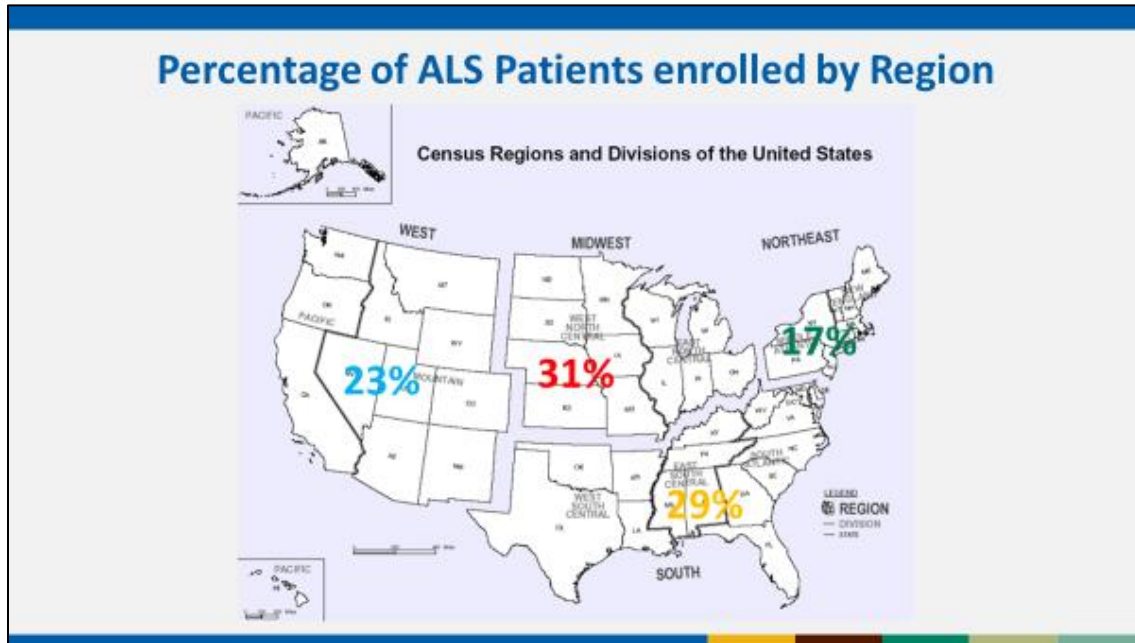
Ms. Raymond discussed the web portal data portion of the National ALS Registry, the demographic information broken down by time and region, the completeness of the surveys, and a comparison of the Registry survey rates to other federal surveys. In terms of the data that comes into the ALS Registry, administrative datasets and web portal data from the ALS Registry website are used. The algorithm that Dr. Horton discussed earlier is applied. During this session, Ms. Raymond discussed the survey data portion of the Registry website.

First, the survey data are assessed by gender over time. The percentages remain about 40% for females and 60% for males enrolled. The largest difference was in 2010 when there were 38% females and 62% males. This is what would be expected since ALS affects males more than females. In terms of the number of patients, Ms. Raymond clarified that due to OMB stipulations there was no y-axis because she cannot share the actual numbers. The largest proportion enrolled was in 2010, which was only 2.5 months. That was great enthusiasm at the beginning of the Registry. There was a slight uptick in 2013 and 2014, probably due to the Ice Bucket Challenge, and there has been a slow decline since then. ATSDR is currently working on outreach activities with partners to increase enrollment.

Looking at the number of patients enrolled by month from the beginning of the Registry through early June 2018, it is difficult to determine whether October really is the highest month or if half of these came from October 2010. However, it is good to see the enthusiasm again. Broken down over a 7-year span from January 1, 2011 through the end of 2017, once the first three months of the Registry are removed, a little more stability over time is observed for the

enrollment. January, May, and August have been the three most enrolled months over the past 7 years. May is National ALS Awareness Month.

This map shows the percentage of ALS patients enrolled by region, which shows that almost one-third of enrollees are from the Midwest while only 17% come from the Northeast:



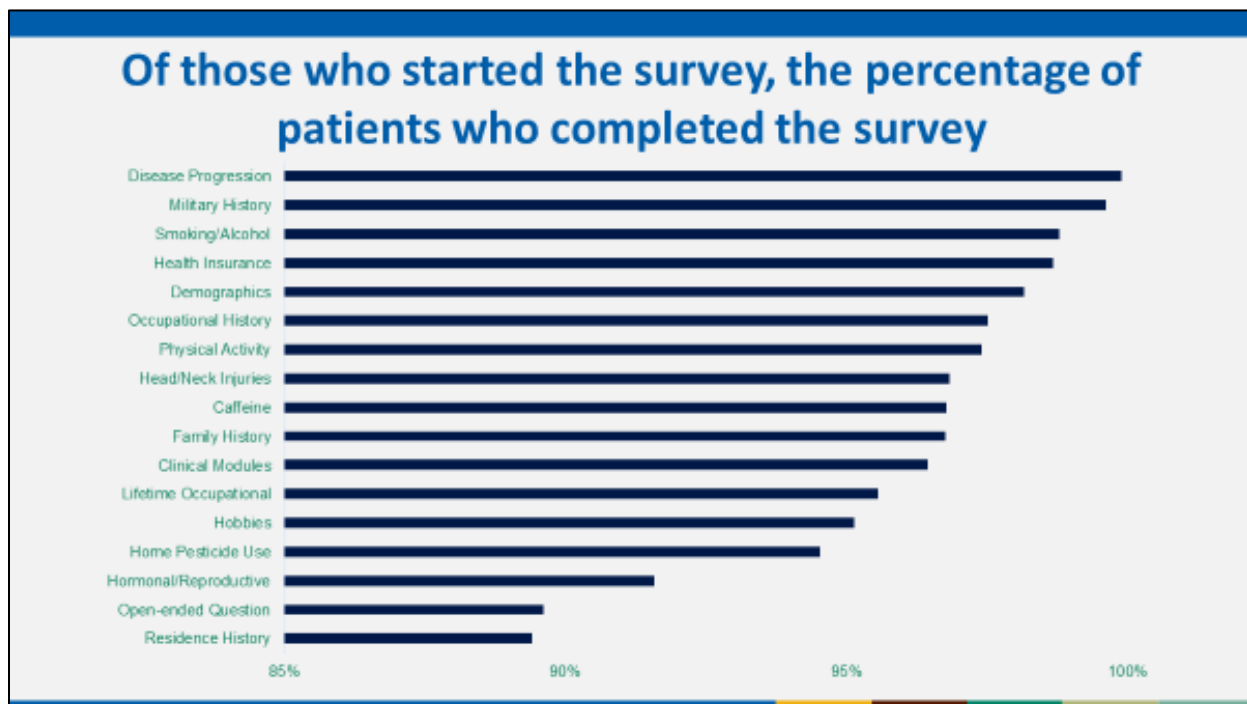
Here is a table that looks similar to what Dr. Mehta presented earlier. For this one, Ms. Raymond asked everyone to pay particular attention to the release dates:

| Survey (n=17) | Release Date | No. Completed |
|--|----------------|---------------|
| Demographics | October, 2010 | 8288 |
| Occupational history | October, 2010 | 7456 |
| Military history | October, 2010 | 7398 |
| Smoking and alcohol history | October, 2010 | 7275 |
| Physical activity | October, 2010 | 6995 |
| Family history of neuro. diseases | October, 2010 | 6819 |
| Disease progression (ALSFRS) | October, 2010 | 6847 |
| Clinical data (e.g., devices used, body onset) | November, 2013 | 2736 |
| Open-ended etiological questions | November, 2013 | 2508 |
| Lifetime residential history | May, 2014 | 2926 |
| Lifetime occupational history | May, 2014 | 2900 |
| Residential pesticide use | May, 2014 | 2714 |
| Hobbies with toxicant exposures | August, 2014 | 2461 |
| Caffeine consumption | August, 2014 | 2318 |
| Reproductive history (women) | August, 2014 | 1282 |
| Health insurance status | December, 2014 | 2016 |
| Head and neck injuries | December, 2014 | 1987 |
| Total (as of 6/4/2018) | --- | 75,016 |

The first 7 surveys were released at the launch of the Registry in October 2010. Three years later, 2 more surveys were released. The remainder of the surveys were completed and released throughout 2014.

In terms of the percentage of the risk factor surveys completed by patients, about 5% of patients have completed all 17 surveys and about 5% have completed just one survey. About 20% have completed 7 surveys, which for the most part were the first 7 though not all were the first 7. Almost 40% of those who have enrolled in the Registry have not completed 1 survey. The first 7 surveys were released in October 2010 and have the greatest chance of being completed. The Demographic Survey was completed by about 60% of those enrolled from the start of the Registry until early June 2018 and the Disease Progression Survey has been completed by just under 50% of enrollees. For the next 2 surveys that were released in December 2013, the number of patients enrolled from December 2013 through early June 2018 was used as the denominator even though some could have enrolled before that and returned to take the survey later. About 96% of patients who enrolled after December 2012 completed the Clinical Module, while about 86% completed the Open-Ended Survey. The Open-Ended Survey is qualitative, which would be difficult for people to complete making some people not want to do so, making an 86% completion rate pretty good. The next group of surveys was released in 2014 and showed completion of Residence History, Lifetime Occupational History, and Home Pesticide use ranging from about 24% to 21%. All three of these surveys are complex, especially the Residence History, and could be difficult to get through for some patients. Moving to the last 2 groups of surveys that were released in August and December of 2014, Head/Neck Injuries and Health Insurance are slightly lower but were released in December and were about 12%. Hormonal and Reproductive History is almost at 25%, but the denominator for that was only females.

This chart shows the percentage of patients who completed the surveys they started:



About 99% of the people who started the Disease Progression Survey completed it. Just under 90% of the Open-Ended Survey and Residence History Survey were completed if patients started them even though these can be difficult, time-consuming, and complex.

Ms. Raymond found an HHS document that discussed response rates in the survey, so she compared the Registry's Demographic Survey, which is the highest response survey, to these other surveys. Not all of them were web-based surveys. Some were telephone or in-person, so they cannot be completely compared, but this provides an idea of where they stand. The ALS Registry's completion rate is about 60% compared to 70% to 80% for the other national surveys, so the Registry is close.

In terms of how the Registry is doing, age and sex distribution look similar to what would be expected from ALS patients in general. The Demographic Survey has the highest completion rate of ALS registrants at 61%, which is slightly lower than other federal surveys. On average, each registrant is taking approximately 5 surveys out of 17 total.

The next steps are to continue to promote enrollment in the Registry and to remind patients that there also are risk factor surveys to take. These risk factor survey data are important because they provide information to approved researchers for their research projects, assist in discovering other ALS risk factors and etiology, allow patients to tell their stories, and optionally link biospecimen data for more robust studies.

Discussion Points

Dr. Bradley suggested that it would be very good to increase the percentage of survey completions, and to link the notification about the surveys when patients first register with the results that have come out from the surveys to show the registrants what actually can come out of this.

Dr. Sorenson asked for clarification regarding the 96% who had completed the Clinical Modules Survey.

Ms. Raymond replied that this could be slightly misleading. The denominator is those enrolled from December 2013 until early June 2018. People who enrolled in 2010 could have gone back and taken the survey, but she did not want to assume that everyone went back or was still living who had enrolled in October 2010.

Dr. Weisskopf asked when the ALS Functional Rating Scale (ALSFRS) is being completed, and if they had any sense of how many people are completing these each time they are received.

Ms. Raymond said she did not look at how many repeats were done for the ALSFRS. She just looked at whether someone had completed it at least one time.

Dr. Kaye added that the ALSFRS can be completed 3 times in the first year and then 2 times each year after that. Enrollees receive it 3 months after the first time they take it to identify people who are fast progressors, and then they get on the 6-month and yearly timeframe. She has seen people with as many as 7 or 8 completed, which falls into line with everything else. There are takers and non-takers. The people who are takers are very religious about completing these.

Dr. Finger observed that the surveys are fulfilling very different purposes. For example, it seems like capturing demographics would always be important. However, for some of the other surveys it seems like the purpose is to build a sample for epidemiologists to study. From a patient's perspective, it looks intimidating when there is a big list. For a lot of these studies, having 2000 responses provides plenty of data in order to move forward. It seems to him that more thought should be given to what these surveys are trying to accomplish, when that goal is achieved, and when to move on.

Ms. Balas recalled that during the 2017 annual meeting, a considerable amount of time was spent talking about patient surveys and completion rates. She noted that most of the information provided during this session was aggregate data over the past 5 years or so. She wondered whether they could provide year over year data to determine whether survey completion rates are actually improving through all of the outreach efforts.

Dr. Kaye replied there have been discussions about ways they might look into that. ATSDR cannot use pop-ups and other items because they are not 508-compliant. They have been discussing the idea of having a thermometer like national campaigns use. A participant's thermometer would fill as they completed surveys, which would offer a visual of their progress.

Dr. Gubitza said she liked Dr. Finger's suggestion that for some surveys, they do not need 15,000 data points. Perhaps there are already very valuable data from 2000 patients. Perhaps there could be a thermometer for a survey that shows a goal that needs to be reached to complete a dataset. They would need feedback from epidemiologists about what type of numbers would be needed for different surveys, and every year they would probably need to determine what things have changed.

Dr. Finger noted that finding out what numbers would be needed for valid power also should be determined when consideration is given to adding new surveys. No one goes into this thinking they need 100%.

Ms. Balas added that with respect to thermometers, pop-ups, and smiley faces, one of the things that they hear a lot is that it is not intimidating. It is a matter of time. It is not clear that they explain the value-add for someone to spend their time completing numerous surveys. She was not sure that a thermometer would be the motivating factor for someone to complete all 17 surveys. They have to figure out what the motivating factors are and how to communicate them to people.

Dr. Bradley emphasized that showing the results would be beneficial.

Dr. Mehta indicated that they want to implement newsletters in the future to have more active interaction with the patient population, giving them information about outstanding surveys, areas in which ATSDR needs help, and so forth.

Evaluating the Completeness of the National ALS Registry

Wendy E. Kaye, PhD
Senior Scientist
McKing Consulting Corporation

Dr. Kaye indicated that in addition to her talk, she would be presenting some of Dr. Lorene Nelson's data on capture-recapture as well, given that she was unable to attend.

In terms of why it is important to evaluate the completeness of the National ALS Registry, ALS is not a reportable condition as mentioned earlier. The National ALS Registry uses a unique methodology to identify cases. A validated algorithm is applied to large administrative health datasets. This is followed by self-identification after validation using screening questions that were developed by the VA and shown to be 93% accurate. ATSDR used two different methods for evaluating completeness, state and metropolitan area surveillance data and capture-recapture methodology.

The State/Metro Surveillance Project involved intense case ascertainment. States and metropolitan areas were selected to over-represent minority populations. Selected states included New Jersey, Florida, and Texas. Eight metropolitan areas outside of those states were selected. Metropolitan areas had to have at least 1.5 million population. Metropolitan areas include Atlanta, Baltimore, Chicago, Detroit, Las Vegas, Los Angeles, Philadelphia, and San Francisco. Those states were selected to over-represent minority populations, because they wanted to be able to make some estimates of ALS prevalence and incidence within subgroups. In order to do that, it was necessary to pick areas where there were likely to be more cases identified because of the underlying demographics of the population.

Providers in these areas who see ALS patients were identified and called. In the larger metropolitan areas, the providers were more specialized in that they saw only patients with multiple sclerosis (MS), epilepsy, or ALS. However, in more rural areas general neurologists saw whomever presented but might see only one case of ALS every few years. In each metropolitan area, a comprehensive, up-to-date list was prepared of practicing neurologists to contact, identified ALS specialists, and then removed sub-specialties unlikely to see ALS patients (e.g., pediatric neurologists). Providers were contacted through a combination of mailings, phone calls, faxes, and office visits. A case reporting form was completed for each case. A subset of cases was selected for more detailed information, which went blinded to Dr. Sorenson who rated their El Escorial criteria. The agreement between what was reported by the neurologists and Dr. Sorenson's determination was assessed.

The State/Metro Surveillance Project identified 5883 cases of ALS in the 3 states and 8 metropolitan areas. Of these, 1116 died before the National ALS Registry started and 4767 cases were eligible for comparison. Cases were collected from January 1, 2009 through December 31, 2011 in order to ensure that they were comparing apples-to-apples. If someone was a case in 2009 and passed away, they could not have been reported by the physician in 2011. There are important differences between the National ALS Registry and the State/Metro ALS Surveillance Project, which are identified in the following table:

| Factor | National ALS Registry | State/Metro Surveillance |
|--------------------|---|---|
| Case Ascertainment | Existing national claims data and self-registration | Health care providers |
| Time Frame | Ongoing | January 1, 2009-December 31, 2011 |
| Data Collected | Case identification, risk factor data | Case identification, medical records verification |
| Purpose | Calculate national rates | Evaluate completeness of the National ALS Registry. |

As noted earlier, a paper was recently published that provided these data. Cases were compared that were identified by the two different methodologies. The cases identified by the State/Metro surveillance project had to be alive on October 19, 2010 (the date the Registry launched). The time period of comparison for both projects was October 19, 2010 through December 31, 2011. Cases were matched using a combination of information including partial Social Security Number (SSN), name, date of birth, and sex. The distribution of cases that did and did not match were compared.

In the comparison of demographic characteristics for matched and unmatched cases, there was a significant difference based on age, race, ethnicity, and area of the country in which the case was identified, but not on sex. The area was broken into 3 general areas of the South (Texas, Florida, Atlanta), West (Los Angeles, San Francisco, Las Vegas), and North (New Jersey, Baltimore, Philadelphia, Detroit, and Chicago). Then they looked at issues related to El Escorial diagnosis criteria and insurance for matched/unmatched cases at the time the case was reported. That information would have come only from the surveillance system, because that is not obviously in claims data which includes only the ICD-9 code. There was a difference based on El Escorial criteria and whether someone had Medicare as their insurance. Those with Medicare were much more likely to be found. There was no difference in the VA data and those that the Registry reported. In summary, the Registry was more likely to miss people who were non-white, Hispanic, living in the Western US, not using Medicare for insurance, and less than 65 years of age.

On the flip side, Dr. Lorene Nelson has been working on capture-recapture analysis. Dr. Kaye reported on the same time period that Dr. Nelson used for the 2010-2011 data. She is currently working on an analysis of the 2014 data.

Capture-recapture analyses was designed for wildlife biologists to try to figure out how many fish are in the lake. For example, ten fish are captured, tagged, and tossed back in the lake. One month later, 10 fish are pulled out and are checked for tags. A lot of fancy mathematical equations are used to estimate the number of fish based on the number recaptured with tags. This is a probability analysis.

In terms of ALS, the objective is to estimate the number of cases that are being missed. Simple algebraic methods can be used to estimate the number of missing cases when there are only two sources, but requires heavy assumptions because the probability of being “captured” in one source may be associated positively or negatively with being captured by other sources. Within a given source, the probability of “capture” may not be the same across individuals in that there

might be variations by age, sex, race, and/or other demographics. A method called log-linear modeling allows for conducting statistical analyses to estimate the number of missing cases (undercount) even when assumptions are violated.

The goals of capture-recapture are to: 1) estimate the degree of undercount to correct the ALS prevalence estimates for the number of cases that are not ascertained using a combination of case finding methods; 2) determine whether the degree of undercount varies according to age, sex, race, or geographic distribution; 3) develop insight into whether certain individuals are likely to be systematically under-ascertained by the Registry; and 4) determine whether additional case finding methods are needed, and/or whether currently used case finding methods might be duplicative.

In 2010-2011, the first time period for which the analysis was done, overall undercounting appeared to be about 20%. That varies significantly by different characteristics. Medicare and the web portal are the most important case-finding methods. Together, they identify 94% of all cases. Capture-recapture methods estimate the proportion of ALS cases missed by the combination of federal data sources and the web portal to be approximately 27%. The degree of undercounting differed according to sex, age, race. The percentage of undercount is greater for men (31%) than women (21%), greater for younger (34%) than older (21%), and greater for nonwhites (43%) than whites (24%).

Both methods identified non-whites and those less than 65 years of age as under-represented in the Registry. Both methods identified Medicare as an important source for case identification. Men were found to be under-represented in the Registry using capture-recapture methodology, but not in the comparison of state and metropolitan surveillance data. The comparison of state and metropolitan area surveillance data identified Hispanics and those from Western states as under-represented, but this was not assessed using capture-recapture methodology.

In conclusion, both methods showed remarkably similar results. ATSDR is working to increase outreach to populations shown to be under-represented in the Registry by creating a Registry website in Spanish and by placing articles in local papers that target African Americans and rural communities. Once the capture-recapture analysis is completed for the 2014 time period, that information could be used to get another estimate of ALS prevalence. That information probably could be used as well on the 2015 data by the different categories that are underestimated. While that could be reported as well, it is important to remember that this is still just an estimate and is a different way of calculating the estimate. The truth is probably somewhere in between, because one estimate is being adjusted with another estimate to provide the top and bottom and a more complete picture.

Discussion Points

Dr. Bradley requested clarification regarding whether the areas from the Registry and high-intensity surveys were coterminous, and whether it is possible to separate race by back correcting for the under-representation to determine the frequency among African Americans.

Dr. Kaye said that the areas were identical and that it is possible to separate race, though not 100%. The State/Metro Surveillance System data cannot be used to correct, because that is not the way it was designed. The capture-recapture statistical analysis must be used to make that adjustment. That analysis has white and non-white, but not Hispanic. The other issue when adjusting with the capture-recapture information, some of the granularity would be lost in terms of prevalence by subgroup. They could get this from the Registry but may not have the numbers

to do the corrections at that level to roll it up. The Registry reports include white, African American, Asian, Other.

Dr. Thakur observed that currently there is the number 5/100,000 and he thought Dr. Kaye was saying that they wanted to use this method to say that the estimated prevalence is going to be 6 with a confidence interval and that would be the number.

Dr. Kaye clarified that they would give a second number and say that it is between A and B.

Dr. Mehta added that for that particular analysis, the data were from 2010-2011 where the prevalence was 3.9/100,000. For 2014, it is 5/100,000. For 2015, it is going to change as well. Throughout the years, they continue to do a better job of capturing the cases of ALS. For 2010-2011, they are missing an estimated 27% of cases. The estimated number missing will most likely be a much lower number for 2014 when capture-recapture is completed.

Dr. Kaye pointed out that they cannot use the under-reporting from 2010-2011 to adjust 2014 because the methods have changed slightly. The algorithm has been tweaked slightly and they have gotten another dataset from the Centers for Medicare and Medicaid Services (CMS) that includes hospice information. There are some things that should have increased case ascertainment. Once the capture-recapture analysis is completed for 2014, they will be able to adjust 2014 and probably would feel fairly comfortable using that.

Dr. Finger recalled that Dr. Kaye noted that the two studies were quite similar and that the adjustment factor for capture-recapture was about 25%. Given that in the completeness study they were able to find 58% of patients, that would suggest an adjustment factor of over 70%. He was not sure whether these were telling them the same thing. Secondly, the paper that was discussed earlier about mortality found that slightly higher than 6000 patients per year were dying. Assuming that on average, the mean is about 4 years survival, 4×6000 is 24,000. That is consistent with dividing by the adjustment factor from the completeness paper. He did not see how these papers were telling them the same thing.

Dr. Kaye clarified that the completeness paper cannot be used to do the adjustment because of the sample that was selected. It was just to do a comparison between A and B and not to get the degree of under-reporting within the entire registry.

Dr. Finger emphasized that although Texas, Florida, Atlanta, and California are different from the nation, they provide an enormous sample with which to control for different demographics.

Dr. Kaye agreed that they are significantly different, especially racially. Los Angeles is 39% born outside the US. There is ethnically a difference. They wanted to be able to look at different racial groups. There is a paper that looks at the incidence among non-whites. Somewhere between 600 to 700 cases were non-white in that small area, which is a huge number. Because of the way the sample was selected and the fact that it was not designed to try to determine a number of under-estimation but to evaluate the demographics of those who are under-represented, they cannot say that because they matched 60% and did not match 40% that the whole country is under-represented by 40%.

Dr. Finger said perhaps he was confused by the title of the paper, "Evaluating the completeness of the Registry" and that it finds that the registry is 58% complete.

Dr. Kaye pointed out that because the Registry relies a lot on self-reporting, the question regards whether there are groups that are not represented because they are not in the Medicare

or VA datasets ATSDR gets, so the only way to find them was for them to self-report. The idea was to be able to target outreach to identify those groups and get more people to self-register, not just to increase the representativeness but also to reach people to complete surveys as well because those groups may be very different from the people currently completing surveys. The current population is close to 95% Caucasian.

Dr. Mehta added that with the completeness paper, they also over-sampled in those areas with the higher minority populations. If they went to Minnesota, chances are that the completeness would be much higher because that portion of the population is in the Registry as compared to an area such as Florida or California. California is an area they want to work on to increase enrollment. So, completeness was done in areas where the minority population was over-weighted.

Dr. Kaye noted that the paper that was published on the pilot project, Minnesota was one of the sub-populations. They basically tested that same methodology. They were given a file that said, "We think these people might have ALS. They came from Medicare or the VA. You have your own clinics. We want you all to match them up to see who is and is not there. Then we're going to figure out which of the characteristics are very predictive." They were going to find all of the people identified through Medicare and the VA. However, the number they could identify and verify that way in South Carolina was much lower. It does vary by area and probably has something to do with the racial distribution, age distribution, how people pay for their healthcare, and the uninsured.

Dr. Brooks pointed out that one of the successes of this program has been to identify the complexities of identifying patients in different parts of the country with a rare neurological disease. He thought they should say more about that and was in strong agreement with Dr. Finger in this regard, because it has incredible policy implications for the longevity and survival of the Registry in terms of how they identify what they have found out and how these techniques can be improved and be helpful for other diseases moving forward.

Dr. Kaye said that as an aside, she and Ms. Wagner are working with the National MS Society and they are using similar methodology with administrative datasets to calculate a case count, with the idea that others may be able to tweak these methodologies with the help of clinicians to get prevalence estimates for diseases that do not have them now.

Massachusetts ALS Registry Update

Alicia Fraser DSc
Director, Massachusetts ALS Registry
Massachusetts Department of Public Health

Dr. Fraser indicated that in terms of the Massachusetts Registry methods, ALS is designated as a reportable disease by Massachusetts state regulations. This helps them to have a near complete collection of ALS case reports for the state. Reports of patients treated or evaluated for ALS are submitted annually to the Massachusetts Department of Public Health (MDPH) by hospitals, ALS clinics, and neurologists. Medical records are obtained and abstracted by a nurse who works for the registry for all patients reported. Eligible cases are reviewed by consulting ALS specialists to confirm diagnosis based on El Escorial criteria and determine dates of onset and diagnosis. Onset is defined as the date when a patient first experiences weakness as reported in the medical record. Date of diagnosis is defined as the date when ALS

is first mentioned as a possible diagnosis or when a patient is referred to an ALS clinic. This is done for consistency. The eligibility criterion is simply that the person must be a resident of Massachusetts. They do receive reports on patients who are not Massachusetts residents because people from Rhode Island, New Hampshire, and other bordering states do travel to Massachusetts to take advantage of the multi-disciplinary clinics in the area. The MDPH Registry of Vital Records and the National Death Index (NDI) are used to confirm any deaths. This allows them to correctly identify a prevalence count.

These are the current variables that are available in the Massachusetts Registry database:

| Clinical and Demographic Information | |
|---|--|
| • Sex | • Familial History (yes/no) |
| • Race | • Genetic Mutation |
| • Hispanic Ethnicity | • Primary and Secondary Clinical Diagnoses |
| • Country of Birth | • Site of onset of progressive weakness |
| • Usual Occupation | • Upper and lower motor neuron symptoms |
| • Military Veteran (<i>collected 2010 onward</i>) | • EMG study results |
| • Date of Birth | |
| • Address at time of diagnosis | |

During this session, Dr. Fraser presented data from 2008-2012. They do have two additional years of data that are ready to be analyzed. Unfortunately, she was unable to present these data because the reports just came in at the end of the fiscal year and it will take a couple of months to perform the analyses. Based on the five years of data from 2008-2012, they are seeing an annual average age-adjusted prevalence of ALS of 5.6/100,000 and an incidence of 2.3/100,000. While prevalence appears to be increasing, they do not see a concurrent increase in incidence. This is believed to be an artifact of the registry having started in 2007 and the registry missing some patients who were diagnosed in earlier years who had not been reported to the Massachusetts ALS Registry. When the two additional years of data are analyzed, they can confirm that. Dr. Fraser expects the prevalence rates to be around 5.6/100,000 range and does not think there is an increase in prevalence.

The distribution of El Escorial categories among the present cases are 237 Definite, 352 Probable, 201 Laboratory-Supported Probable, 221 Suspected, and 47 Possible. The medical records continue to be evaluated for the suspected and probable cases each year for three years. If the patient has not progressed to a clear diagnosis of ALS at that time, it is considered not ALS.

In terms of the difference between males and females, the incidence of ALS increased with age until approximately 80 years, with the highest rate occurring in those aged 70-79 years. Incidence is approximately 12.5/100,000 in males 70-79 years of age and about 10/100,000 for females. More diagnoses are seen among men than women. The crude ratio is about 1.2 as opposed to the 1.5 the National ALS Registry is seeing. An age-adjustment is done on that

because it is known that women tend to live longer such that there is a higher proportion of women in the older age category. The age-adjusted ratio is 1.4, which is very similar.

Moving on to some diagnostic and clinical surveillance data pertaining to site of onset of weakness by age, limb onset of weakness is the majority in the age groups diagnosed under the age of 80. As age increases, bulbar onset increases as well in addition to generalized, respiratory, and truncal weakness onset. Looking at site of onset of weakness by sex, limb weakness is the most common onset site for both males and females. Bulbar weakness, the second most common onset site, is more frequent in females. They were interested in how this might interact with the increase in bulbar onset with increasing age and knowing that females tend to be diagnosed at an older age. They found that females are about 5 years older at age of onset compared to males, but the median time to diagnosis is the same at about 11 months between males and females.

Because they are often asked about completeness of reporting, an evaluation was done using death certification data from the Massachusetts Registry of Vital Statistics. They looked at patients reported to them only through a Vital Statistics death record, which was 7% of patients reported between 2008-2012. They consider those 7% to be patients who were possibly missed through normal reporting. After doing the verification, they found that 70% of those reported to them through the Vital Statistics death certificate only were deemed not to be ALS. The coding for ALS is a broader category on the death certificate and includes a lot of other non-diseases. Among those that were possible ALS, there were only 25 cases that were verified as being definite, probable, suspected, possible, or late-stage. Late-stage patients are those who are identified through hospice for whom they were unable to get access to medical records previously to confirm the diagnosis, but for whom their physicians are very clear are ALS. They want to include these patients in the registry, so they added the late-stage category. Among all of those, only 25 were missing out of 839 reported in the normal way from hospitals, clinics, and neurologists. That is about 3%, which was very reassuring that they are doing a good job with a very high completion of reporting. Of those 25, about half (N=14) were diagnosed before 2008.

In terms of outreach and awareness activities, in December 2017, similar data were presented during the Motor Neuron Disease Association (MNDA) Symposium in Boston. In March 2018, the Massachusetts ALS Registry had an exhibit at the Massachusetts Neurologic Association (MNA) annual meeting. Part of the reason for that was to try to spread awareness of the Massachusetts ALS Registry to make sure that physicians are reporting, and to let them know that they are there as a resource for research activities. An ALS signs and symptoms brochure was developed in partnership with NEALS, the ALS Association, and their ALS physician consultants. Dr. Fraser shared a draft of the brochure and described it, which will be mailed to all of the neurologists in the state. She pointed out that the brochure includes information about the National ALS Registry, and encourages physicians to let their patients know about the Registry and to let them know that they need to actively register to participate in the National ALS Registry. They wanted to make sure that physicians and patients understand that there are two distinct registries, one of which occurs automatically without the patients needing to register and the other that requires active patient enrollment.

In terms of next steps, the Massachusetts ALS Registry received its first application for data access to research environmental factors associated with ALS. That application has been reviewed by their IRB and is close to being approved. They are preparing a manuscript for publication on ALS occurrence in Massachusetts for 2008-2014. Unfortunately, their amazing ALS Coordinator had to move due to family reasons so they are currently working to fill that position, which is going to delay manuscript preparation somewhat. Though they were hoping to

have it published by the end of the Summer, it may be the end of the year before it is ready for publication. Plans are underway to provide access to aggregate ALS Registry data on the [Environmental Public Health Tracking](#) (EPHT) portal, which is a CDC-funded website that provides interactive maps and charts on a lot of health and environmental-related data. Anyone can use this website to look up the prevalence and incidence of ALS in Massachusetts over the years by male/female, et cetera. As they obtain more data, they will be able to add more graphic layers that will make it possible to look by county or community. With regard to current data collection activities, the physician consultants just completed review and verification of 2015 ALS patients. Medical records are being obtained and abstracted for patients reported in 2016. Final 2017 patient reports are arriving from hospitals, clinics, and neurologists.

Discussion Points

Dr. Mehta indicated that they are working with the MDPH and submitted an IRB application to access personally identifiable information (PII) data from them to compare to the National ALS Registry as an ongoing process and collaboration with MDPH.

Mr. Tessaro asked what the driving force was in Massachusetts to have ALS become a reportable disease (person, government agency, private organization), and what percentage of ALS patients have been misdiagnosed before they get to the definite ALS diagnosis.

Dr. Fraser replied that the way that ALS became reportable in Massachusetts was two-fold. First, there was a community concern among residents in a particular area of Massachusetts. Some residents contacted MDPH because they felt that there was a perceived higher incidence of ALS as well as some other associated diseases in their region. MDPH commonly investigates community concerns and if there is enough evidence, they will conduct a larger study. For this particular issue, they conducted a pretty big study looking at the incidence of ALS. In that case, they did not find that there was any geographic excess. Concurrently to that, ATSDR was funding pilot projects in different states to look at ALS surveillance. MDPH received a grant from ATSDR to develop some methods to look at surveillance. It is a lot of work and the best way to do this is not intuitive right away. Initially, their verification forms for physicians were 10 pages long. Part of the pilot focused on evaluating the best methods for running a registry. Those two things collided until, with the grant from ATSDR, they were able to develop some strong methods. There was a lot of citizen and community pressure on the legislature to fund a registry and have ALS be a reportable disease, so community advocacy played a large role. In addition, Former Massachusetts Governor Cellucci was diagnosed with ALS, so there was additional support because of him and people's familiarity with and appreciation of him. The Massachusetts ALS Registry was officially started by the legislature, and all of their funding now is through the state budget. It was listed as a reportable disease in the same section as other infectious diseases. Dr. Fraser said she would add the percentage of misdiagnosed cases to the list of topics to evaluate in the future. A large portion of the reports they receive are deemed not eligible either because they are out of state or they are found to be not ALS. To be able to identify those who were misdiagnosed with ALS may be somewhat trickier, because some patients are reported to them because they have a similar diagnostic code to ALS but have not actually been misdiagnosed.

Dr. Bradley thought this was a wonderful and tremendously strong study because ALS is a reportable disease in Massachusetts. He said he would like to hear a discussion between Dr. Kaye and Ms. Fraser about the differences in the incidence rates they found of 2.3 and the National ALS Registry of 1.7 and whether they thought there was a regional reason for this, or if it was an ascertainment problem.

Dr. Kaye responded that the National ALS Registry does not measure incidence. It measures prevalence and the prevalence rates are very similar. The incidence rate from the State/Metro Surveillance project probably has some downward pressure because of the over-representation of minorities in the underlying demographics. In that project, the incidence was about 2/100,000 in whites, 1/100,000 in African Americans, and even less than 1/100,000 in Asians and Hispanics. Some data out of England found that Africans in England had a rate of about 1/100,000.

Dr. Fraser responded that their rates are not great in terms of race and ethnicity right now. Among what they have, their cases are 90% non-Hispanic whites, 3% Hispanic, 3% black or African American, 3% unknown, and 1% Asian. Based on Census data, there are 72% non-Hispanic whites, so there is a disparity. The more data they get, the more closely they will be able to look at this. They have been working on enhancing the collection of race and ethnicity data over the past couple of years. They are able to get some of this from death certificates and the NDI, so retrospectively they can add to their data. It does appear that they are not seeing a representative proportion of cases among populations of color. With the knowledge of how complete their data are, it does appear that the incidence is lower.

Dr. Horton asked what the consequence would be for a healthcare provider who does not want to report cases to MDPH.

Dr. Fraser indicated that they have only experienced this a couple of times. One physician said that they do not believe in reporting in general. There are just some people who do not like to report anything to the government. Massachusetts does not have a mechanism for fines. In that case, they did not pursue it further. This was a physician in a rural area who had one case for whom MDPH was trying to acquire additional medical records to confirm the diagnosis. They had medical records from several hospitals. The physician contacted their patient, which was unfortunate because there was no need to do that. The patient then got upset, so they did not want to pursue it. What they could have done if they wanted to would have been to file a complaint with the Board of Registration in Medicine (BORIM), because it is a legal requirement for physicians to report.

Communication & Outreach

Agency for Toxic Substances and Disease Registry

Janine Cory, MPH
Associate Director of Communication
Division of Toxicology and Human Health Sciences
Agency for Toxic Substances and Disease Registry

Ms. Cory discussed some of the barriers, challenges, and successes they have had. They attended last year's meeting and heard the feedback about the website being difficult to navigate and other issues. They have addressed some of these issues and have tried to think a little bit "outside the box."

They created a video titled "[Hope](#)" to show the value of the registry. The video won a Hermes Creative Award and a Telly Award. The video cost \$4 for captioning. They were up against a lot of large companies with big budgets. She thanked those in the room who appeared in the video and reminded everyone that everything they make can be placed on partners' websites,

repurposed, et cetera. They know that dissemination happens and information is shared at a very local level.

They also heard loud and clear that the website was difficult to navigate and tried to make it better. They tried to make this easier to think about by the audience. Ms. Cory encouraged everyone to look at the redesigned site and provide feedback. They did some informal testing with the website to ensure that the usability is there. They made it and know what they are looking for, but they do not know how everybody is trying to get information. Hopefully, the new organization is an improvement from last year.

They also have been thinking about how to reach people who are not already committed to ALS who do not know about it to try to get into some of the communities that may not have high awareness. One of the partnerships they engaged in this year was with BlackDoctors.org, which is a very popular health-related website primarily aimed at African American communities. After ATSDR worked with them, they were kind enough to run a nice article that has been getting a lot of traction. This is one way they are thinking about how to use some of the newer media to get to the general public to raise awareness versus finding out how to get people into the Registry.

To try to get into more of the free local community newspapers, they wrote some MAT releases. These are pre-written articles by people at CDC for which they pay a minimal amount for placement, and then local journalists pick them up. This reaches a very different audience. Mr. Tessaro has permitted them to use his picture for everything. Since they do not control where the articles come up in the newspapers, they have come up next to some questionable items. As of July 2018, this generated 3672 news articles and these get picked up continuously online.

They also have been giving thought to clinicians. The clinicians in the room are very dedicated to ALS, but what about neurologists in rural areas who are not near a big center and only rarely see patients? ATSDR had a very nice editorial collaboration with Medscape, which is one of the top ways to reach clinicians. The article had a digital banner at the top as well. This was a very nice article written by Dr. Mehta that gave a very generic overview of ALS, which they tried to target to general neurologists and PCPs thinking more about raising awareness of the registry rather than specific recruitment.

They are trying to understand whether they are getting the message about the Registry to the right people, and if they are showing value. Those could be two very different things. It is important to understand that awareness does not equal enrollment. While everyone in the room is aware of the need for people who make monetary and public health decisions to understand the Registry and its value, that is very different from thinking about clinicians and patients. Equally important to acknowledging what they can do, is to acknowledge what they cannot do. They are thinking about ways to clearly demonstrate this. Hence the video. They keep telling people if they join the Registry it helps promote research and provide a better understanding of ALS, but it is not clear whether this message has been taken in a concrete way to show value to patients and their clinicians. That is one of the things that is a goal for educational materials that are being produced.

Some of that is about raising awareness and getting the Registry “on the radar” so to speak, and that is a little different from enrollment which is showing the clinician what the value is. It is known that for everything from vaccines to blood pressure medication, the clinician influence is the strongest predictor of patient health and behavior. They need to show the clinician that there can be value for the patient, the patient’s diagnosis, and predictors of future treatments. There

can be value for the patient as well from a mental health aspect of feeling like contributing, and they need to express this to clinicians and show that there is value on an individual level. Consideration needs to be given to how to package that and drive home the importance at an individual and societal level. That is also about awareness. They are letting people know about the Registry, which is a different expectation from enrolling. That may be a multi-step process and is something that maybe they need to start with awareness, get to education, and then move toward enrollment.

Working with partners is also important. It is known that some places are doing really well and every patient they see is a patient who is going to enroll in the Registry. Consideration must be given to how to tap into and replicate that model and think about other factors. Is what works in Minnesota going to work in an urban area in Atlanta? There may be other factors. It is not clear that they always know how this information disseminates down. How does it work on a one-to-one level if someone is diagnosed and in a clinic? What is being expressed about the Registry? How is the value being shown? How are our partners emphasizing and promoting it rather than saying, "Hey, by the way, there is the Registry and it's really great and it helps us all"? How does that work? This is usually a "show and tell" of all of the great things they have done. But to make the afternoon a working meeting, they must accept that there are some things they can and cannot do and that is why they look to partners for help. This is a work in progress, so it is important to hear from PALS, researchers, and clinicians about if/how the tools are used and if not, why not, and what could be done better.

Discussion Points

Dr. Finger said he just went on the site and clicked Mr. Tessaro's picture "For Persons With ALS" and it directed him to an FAQ that is pretty bland and dated. For example, it talks about the 2014 released report on the early data. In terms of value for the patients, there should be something flashy that spells out the value of why this is a great research project and emphasizing that it is the ALS patients' registry.

Dr. Mehta noted that this information has been submitted to the information technology (IT) folks and is just waiting for the change to be approved through the system.

Ms. Cory said that they could certainly make it more engaging and put the value in lights to explain why it is important for persons with ALS.

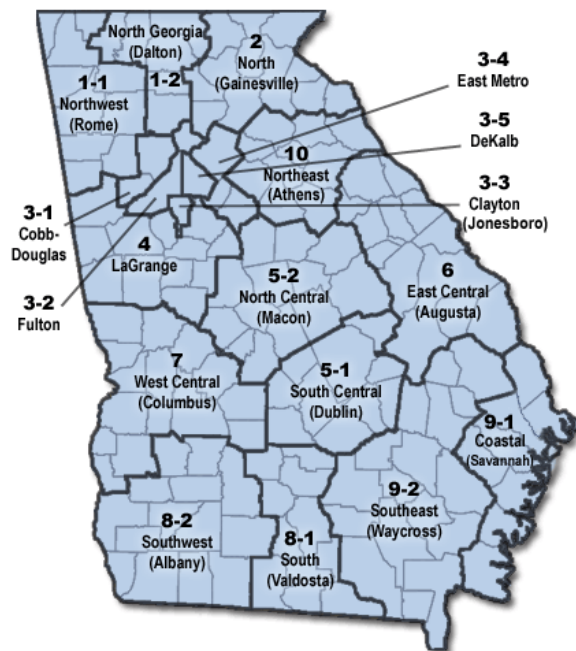
Dr. Mehta noted that clicking just below Mr. Tessaro's photograph on "For Persons With ALS" links to general information and resources.

Under-Enrolled States Outreach Project Update

Reshma Punjani, MPH
Orise Fellow
Agency for Toxic Substances and Disease Registry

Ms. Punjani reviewed the previously conducted Georgia Pilot Project; provided an update on the Under-Enrolled States Outreach Project, including a review of the objectives, methods, and available data; discussed strategies to increase Registry enrollment through partner and chapter collaboration; provided ALS Association and MDA updates, and discussed the next steps for this project.

The Georgia Pilot Project was conducted in 2015 as the first state outreach project. This was done because Georgia was classified as an under-enrolled state compared to what was expected enrollment. The primary objective was to help target outreach activities for the Registry by increasing awareness and enrollment. Areas smaller than a state were identified. Through this project, it was possible to identify health districts that were under-enrolled, which helps ATSDR's partners know where their outreach should be targeted. Due to Office of Management and Budget (OMB) restrictions, this could not be done by city, but using districts allows for a more targeted approach. Another objective was to provide a qualitative assessment of the Registry enrollment and test the data collection methods using this Georgia data. Georgia's 159 counties are divided into health districts. Looking at the following map, Health District 3 (Metropolitan Atlanta) is doing the best:



Under-enrolled districts include: District 1 (Northwest, borders Alabama and Tennessee), District 6 (East Central, which includes Augusta), District 7 (West Central, includes Columbus to the Alabama border), and District 9 (Southeast, South of Augusta by the Florida border).

After receiving the results of this project, the Georgia ALS Association chapter implemented a couple of strategies. The first was in the ALS clinics where Registry information was provided in new patient packets at ALS clinics, which led to patients being aware of what the Registry is and then hopefully enrolling in the Registry. Tablets were made available to assist in enrolling patients. There was outreach to support groups by having peer speakers discuss the purpose and ease of the Registry. This peer-to-peer interaction was successful. There was more outreach during the Annual Chapter events, including the ALS Educational Symposium and the Walk to Defeat ALS. In addition, there was an ALS Association Chapter follow-up. By focusing on existing patients, they found that there was an increase in enrollment. Registry enrollment increased following implementation of each of these outreach strategies, which moved Georgia from being an under-enrolled state to a not under-enrolled state.

The current project being conducted is the Under-Enrolled States Outreach Project. The goals of this project are to focus on six under-enrolled states and identify health districts within those states which could benefit from increased Registry outreach. The data being used include the

self-enrollment data for patients into the National ALS Registry. When patients enroll in the Registry, it is done by city. Those cities were geocoded into counties, which were then grouped into existing health districts. Census data for 2010 also were used. In addition, ATSDR had registration numbers from the ALS Association, MDA, and Les Turner by county as a comparison.

In terms of the methods for this project, the first step was to identify under-enrolled states in the US. For this pilot project, six states were used: Hawaii, Mississippi, New York, West Virginia, Utah, and Wyoming. Counties from those states were categorized into health districts, and then the number of people in the Registry per health district was compared to the number of cases expected. The number of expected cases of ALS for each state was determined by multiplying the number of persons in the state using the Census data by the US prevalence rate, which resulted in the number of expected ALS cases per state. This also was compared to the Registry enrollment data received from the ALS Association, MDA, and Les Turner. The health districts identified as being under-enrolled are shown below their respective states:

| | |
|--|--|
| <ul style="list-style-type: none"> <input type="checkbox"/> Hawaii <ul style="list-style-type: none"> ➤ Maui district <input type="checkbox"/> Mississippi <ul style="list-style-type: none"> ➤ District 9 <input type="checkbox"/> New York <ul style="list-style-type: none"> ➤ Capital Area ➤ Central <input type="checkbox"/> West Virginia <ul style="list-style-type: none"> ➤ District 3 | <ul style="list-style-type: none"> <input type="checkbox"/> Utah <ul style="list-style-type: none"> ➤ Bear River ➤ Central ➤ Salt Lake Valley ➤ TriCounty ➤ Utah ➤ Wasatch ➤ Weber-Morgan <input type="checkbox"/> Wyoming <ul style="list-style-type: none"> ➤ Region 2 |
|--|--|

After the health districts were identified, ATSDR worked with the ALS Association and MDA to develop outreach plans. The first component of the outreach plan is a phone script. The Partners worked together to create a phone script template that could be used during periodic outreach calls to ALS patients served by their local chapters and clinics. The phone script serves as a great resource because it provides both partners a template to help them provide the same information to all patients. The next part of the plan was social media outreach. ATSDR provided a Registry Master Table that includes pre-approved messages for Facebook and Twitter, as well as approved graphics for promoting the Registry. The local chapters and clinics could use this resource to promote the Registry and increase awareness. The third part of the outreach plan is partner-specific events. This outreach will run from July 1-December 31, 2018. During this time period, there are probably multiple events that the local chapters and clinics are hosting. Having these events increases the awareness of the Registry, given that local representatives are able to distribute information to patients about what the Registry is, what it does, and how to get involved.

Prior to launching the project on July 1, 2018, staff training needed to be completed. For the ALS Association the training webinar was completed and six chapters were involved. For those who were not able to join the live webinar feed, it was recorded to be available online. One-on-one follow-up calls were made to local chapter representatives. They wanted to establish the target numbers in the under-enrolled districts to have a plan regarding how to do the calls and social media outreach. The calls and social media outreach have begun and will continue until the end of December. In terms of challenges and opportunities that have arisen during the

outreach, concerns have been expressed about the call length and follow-up. Although this is a phone script that should take about 3 to 5 minutes, a patient on the phone may have follow-up questions and/or other needs. Since this is a challenge, patients may have to be referred to someone who can provide them with more information. Another issue that has been addressed is that in some of the small rural chapters, there is an issue with phone, internet, and manpower availability. Another challenge that has arisen is a potential overlap with MDA. However, although the partners are using a similar script, there are places in the script for both partner agencies to include information about specific local events. A patient may be contacted twice, but at least both organizations are able to provide information on local events that are occurring. In October, there will be a consultation with ALS Association clinics. These outreach efforts will be addressed during that meeting as well.

In terms of MDA, all Care & Clinical Services staff in these states were trained on this project and tools were rolled out in June. In July, the offices placed their outreach plans together for the project and some of the calls began in the 6 markets. Each family will receive at least two outreach calls about the Registry during the 6-month project period, but no more than two calls during that timeframe. For August, MDA plans to have outreach to the Care Centers as part of the strategic approach. All 6 markets will be sharing their social media messages and promoting the Registry at their events.

In terms of next steps, outreach to the under-enrolled districts will continue through December 31, 2018. Both partner agencies will report their outreach numbers (calls and social media) to ATSDR on a monthly basis. ATSDR will review and assess these data at the end of the six-month project period to determine the effectiveness of increased outreach to under-enrolled districts compared to the same time period in 2017.

Discussion Points

Dr. Factor-Litvak asked how the 6 areas were identified that had under-enrollment.

Ms. Punjani indicated that every month, data are distributed that categorize the states in three tiers. When this outreach project was started, ATSDR picked the 6 states that were the most under-enrolled. Of course, this changes from month-to-month. Next year, there could be different states.

Dr. Kaye added that they look at the percentage of reporting for the entire country, and then individually put the states into three tiers: 1) doing as well as the national average, 2) doing below the national average, or 3) doing above the national average. The states below the national average were considered to be under-enrolled, tiered those, and picked 6.

Dr. Horton clarified that they are looking at enrollment only, not survey completion rates.

Dr. Finger asked how different the under-enrollment numbers are from the information from the administrative data. He emphasized that this has implications for who they need to be reaching out to. The end goal for reaching out to those people depends upon whether they are showing up in other ways in the data.

Ms. Punjani indicated that she has looked at only the data available through the self-enrollment mechanism.

Thinking about all of the things they have looked at, Dr. Kaye did not believe they had looked at the number of people enrolled by state compared to what they think it should be based on population. However, they could do this if they have not. They do know that people who choose Medicare Advantage for their healthcare, which is the health maintenance organization (HMO) option, rather than a fee-for-service option (FFS), do not show up in the administrative data ATSDR receives. Part C cannot be used because it just says, "I paid \$400 per month for X to use Kaiser" and no diagnosis data are associated with that. Kaiser has a very large footprint in California, so one might hypothesize that there is under-enrollment in California because they are missing the HMO population. Consideration is being given to how to get people in California to join the Registry and determine whether there is another dataset that they do not know about.

Muscular Dystrophy Association

Robin Geiger, DNP, FNP, NP-C
Vice President, Care & Clinical Services
Muscular Dystrophy Association

Dr. Geiger shared MDA's efforts for heightened awareness of the ALS Registry. MDA's strength lies in support of continued efforts toward innovation and science, which includes research, support, services, Care Centers, education, and the Resource Center. The continuous efforts to improve and expand the ability to support the National ALS Registry shows MDA's commitment, strength, innovation, and care.

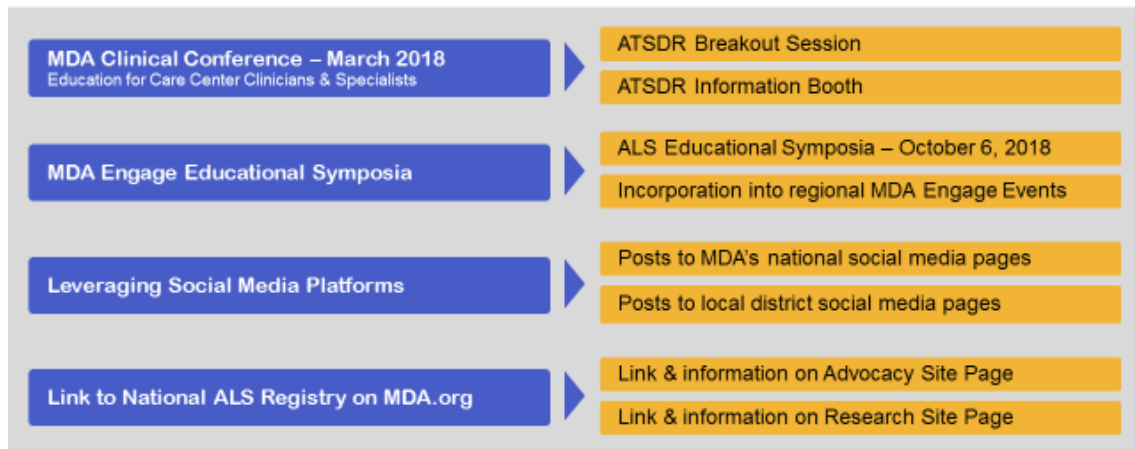
By strengthening its internal presence in its Care Centers, MDA is able to get a ground's eye view of needed practices and programs from direct staff collaborating with Care Center Directors, contributing to research through the MDA's strong research team, and reinventing the MDA Resource Center into more of a resource hub to align with increased support services and providing families and patients, including hospitals, with external networks for strong support.

MDA has been leading and innovating for over 65 years by taking a global perspective across neuromuscular diseases to uncover breakthroughs and strong efforts to accelerate treatments and cures. Over the last 5 years, MDA has spent nearly \$29 million on ALS research. In 2017, MDA supported over 49 ALS grants, with a total commitment of over \$12 million. MDA's Conference Series brings together the world's top researchers and clinicians to share ideas and updates.

MDA continues to provide care across clinical trials in the US and Puerto Rico. More than 12,000 individuals with ALS have access to MDA ALS Care Centers across the US. There are nearly 50 designated MDA ALS Care Centers across the US and a Network of Care Centers at over 150 top institutions and affiliates. MDA's MOVR™ (neuroMuscular ObserVational Research) Data Hub also will accelerate research and optimize clinical care.

MDA promotes the National ALS Registry through social media platforms, online publications, outreach phone calls, community gathering and events, MDA Care centers, the MDA website that houses information on the National ALS Registry, ALS support groups, the National Resource Center, educational conferences and seminars, and print materials. Through social media, MDA is able to post pre-approved weekly and monthly information on the National ALS Registry.

National ALS Registry Outreach Efforts 2018 Highlights



MDA | 7

In terms of highlights of MDA's 2018 National ALS Registry outreach efforts, during the MDA Clinical Conference in March 2018, there was an ATSDR breakout session and information booth. The MDA Engage Educational Symposia for ALS will be held October 6, 2018 in Houston, Texas. MDA continues to incorporate MDA Engage Events on the ALS Registry into regional MDA Engage Events as far as data, information, print materials, and ensuring that MDA is a strong supporter of education and information awareness of the ALS Registry. MDA leverages its social media platforms as well by posting weekly to the MDA national social media pages, and monthly to MDA's local district level social media pages. This is pre-approved information that they can share readily through social media. They also provide a link to the National ALS Registry on MDA.org. That link information can be found on the Advocacy and Research Site pages. National ALS Registry materials are included in MDA's ALS Newly Diagnosed Binder and MDA Welcome/Registration Folders for ALS Families, distributed at MDA Care Centers by Care Specialists and Care Center Team Members, and promoted in MDA publications. The National ALS Registry is promoted in MDA publications, including Quest Magazine that is published quarterly, blog entries, and local district-level newsletters. The Registry is promoted by trained MDA staff members, including Resource Specialists from MDA's National Resource Center and through strategic outreach phone calls and face-to-face connections with MDA's local Care & Clinical Services Specialists and Field Team Members. MDA also has implemented strategies for documenting outreach and disseminates a document summarizing the results through external collaborations. They also identify and document reported barriers.

As noted earlier, MDA is collaborating with ATSDR on the Under-Enrolled Health Districts project. In addition to routine outreach conducted across the country, MDA is implementing a targeted strategy aimed at increasing National ALS Registry enrollment in areas identified by the ATSDR as being under-represented. MDA uses this information strategically to implement their best efforts through their Care Clinics and administrative abilities and connections in hospitals and institutions to increase the under-enrolled health districts. MDA is increasing its efforts through direct outreach by phone calls, posting monthly pre-approved announcements on Facebook, appropriately and strategically calling patients who are identified in the MDA District Offices, and families living with ALS will be invited to attend MDA's national ALS Engaged Symposia in October 2018 in Houston, Texas. In addition, they continue their

discussions and never assume that enough information has been disseminated with regard to the ALS Registry. This is done by continuing support groups, meetings, educational events, community gatherings, and meetings with the Care Center Teams and Affiliates. In March when they held the MDA Clinical Conference, they started a pilot project with MDA Care Center Directors to strengthen outreach for all neuromuscular diseases and highlight ALS. MDA looks forward to continuing to collaborate with its external partners to strengthen the ALS Registry.

Discussion Points

Mr. Tessaro observed that just as Dr. Finger mentioned about the ALS Registry site not having any blinking lights, the MDA site does not really do anything even after one links to the ALS page. There is nothing to grab a person or family member who might be interested. There is more about the MDA Registry than there is about the National ALS Registry. He asked whether they had plans to apply the advice that had been given to make the National ALS Registry link bigger, bolder, and a stronger part of the MDA website.

Dr. Geiger said that she did note Mr. Tessaro's suggestion. MDA has plans to increase its grassroots efforts, which includes heightening the page. They are looking at the MDA website in total and evaluating the effectiveness of the page to capture users' attention and that there are appropriate links for information.

Dr. Haidet-Phillips added that a lot of the disease-specific web pages need a lot of work on the MDA website. ALS is one of them and they are evaluating how they can strengthen that, particularly the research site.

Dr. Brooks noted that at the trench-level, they find the MDA Registry very helpful because they can send people to enter that registry and present it as a best practice type of registry for which the patient does not have to do anything. At the same time, during the second day of a patient's clinic visit, they attach the information with respect to the National ALS Registry and highlight how they can join.

Dr. Horton requested additional information about the MDA's ALS Newly Diagnosed Binder Toolkit and where it is being distributed. In terms of the 12,000 people mentioned as having access to the Care Clinics, he asked how that number was derived.

Dr. Geiger replied that MDA created a packet of information for newly diagnosed patients so that they would have a manual of support networks and services available to them. Information about the National ALS Registry is in that binder. The binder is being distributed through the MDA Care Centers throughout the country. The 12,000 people mentioned as having access to the Care Clinics is the number of ALS patients registered with MDA and seen at a Care Center.

Dr. Brooks indicated that each MDA Care Center has to give a diagnostic sheet, which is where MDA gets their data.

Dr. Finger asked how quickly they are getting feedback following outreach efforts from the Registry regarding increased enrollment.

Dr. Geiger replied that it depends upon the type of feedback. While the feedback might be readily available, it is evaluated over time so it may take a couple of months before all of the feedback is quantified.

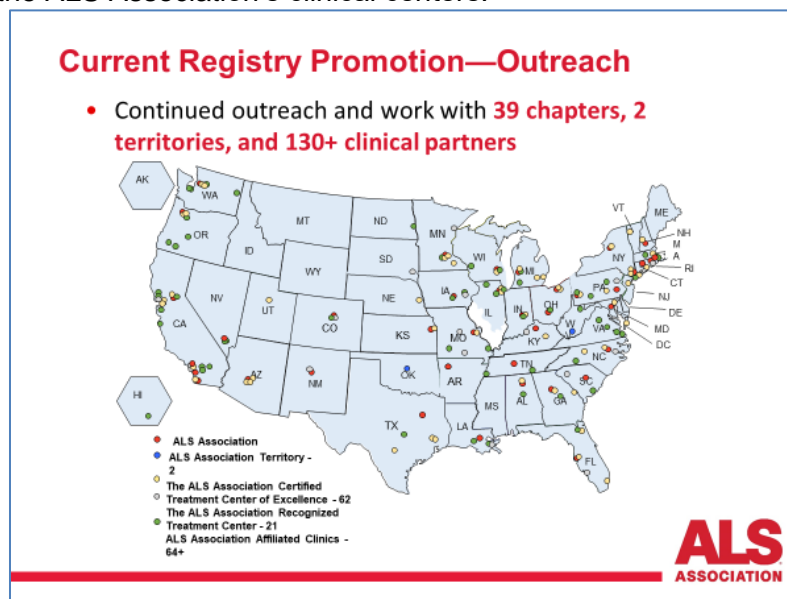
Dr. Mehta added that ATSDR provides a monthly report to MDA and the ALS Association on under-performing states, categorized by Tiers 1, 2, 3. The report also includes information on the National ALS Biorepository regarding areas where they would like to see increased collections. At this point, the report is only at the state level. If the health district project is successful, ATSDR hopes to roll that out nationally.

ALS Association

Neil Thakur, PhD
Executive Vice President, Missions Strategy
ALS Association

Dr. Thakur indicated that the mission of the ALS Association is to discover treatments and a cure for ALS and to serve, advocate for, and empower people affected by ALS to live their lives to the fullest. The ALS Association is the only national nonprofit organization exclusively fighting ALS on every front, and is the largest non-government funder of ALS research. The Registry is very important to the ALS Association. While there had been a lot of discussion about the importance of the Registry in promoting research, the Registry is also important for an accurate count or solid estimate of the people with ALS in the ALS Association's discussions regarding public policies because counts are important in terms of allocating resources. The ALS Association is also excited about the idea that they might be getting health district-level counts from the Registry as well, because that can help them figure out how to allocate clinical resources. The Registry is an important component of everything the ALS Association does, and they are excited about all of the changes ATSDR is making.

This is a map of the ALS Association's clinical centers:



They certify a variety of centers around the country to provide the best care possible, and the centers have to meet certain treatment standards. There are 62 Centers of Excellence, which also participate in research. Another 20 or so recognized treatment centers do not participate in research but do meet the same standards for multi-disciplinary care.

In addition to the care services component, they have people working with people with ALS. Clinics are providing services to people with ALS, so there are a lot of direct one-on-one relationships. In addition, they have a number of fundraising and promotion activities. They talk about the National ALS Registry during their events, such as walks. They promote the Registry through social media and the ALS Association website, and they encourage their chapters to promote information from CDC/ATSDR as well. The Care Services Staff work with the chapters. The chapters train clinicians on how to talk about the Registry for people with ALS and encourage their enrollment.

In addition, the ALS Association has been talking a lot about the Registry in their meetings and conferences. In December 2017, they had a meeting in which they talked about best practices for the Registry and for enrollment. For example, they discussed ways to improve enrollment. One of the recommendations was to help people understand the benefit of the Registry. The ALS Association has been shifting its communications to emphasize that if people enroll in the Registry, researchers who are recruiting for a clinical trial can contact them if they select that option. In addition, they send out reminders to encourage people to complete their surveys and they have volunteers to assist with enrollment.

They had a meeting in March that people attended from around the country to talk primarily about policy issues, but they also discussed the Registry and showed some of the videos. They discussed better ways to help their chapters get information and materials they need to support recruitment. This is part of an ongoing refinement process of how they engage people in the Registry, by having these conversations.

The ALS Association's national conference was held in May. This conference is attended by people with ALS, families, and advocates together from across the country. This year, there were over 400 attendees. Two CDC Registry videos were shown during the conference opening: "Why the ALS Registry is Important" and "ALS Research Counts on You." The ALS Association engaged people with ALS from the conference to create their own promotional video. The conference also was used as a pilot for a Biorepository sample collection. Folks from the ATSDR team attended to collect materials for the Biorepository. Demand exceeded the number of available sample kits. The ALS Association found this to be a very successful event, and everyone there seemed to enjoy the opportunity to participate and donate their specimens.

The ALS Association is also involved in the Under-Enrolled States Project. They have 6 chapters involved to correspond to the 6 areas that have not been meeting their targets. They already have been talking to their chapters, have conducted a training webinar, and have started their phone calls. They have Care Services staff who already have a connection with people who have ALS. They do not know who is/is not enrolled in the Registry, so they are making calls to their patients to find out if they are enrolled and if not, whether they would like to be enrolled. They are working through the scripts and putting out social media reminders targeting the under-counted areas. They are in the early stages, but will refine as the project matures.

In July, they had an FDA Drug Development Workshop, during which they discussed clinical trial design. This provided a forum for members of the ALS community to have their voices heard. They heard from people with ALS, caregivers, physicians, researchers, statisticians, and others. The caregiver perspective opened new avenues of improvement for trials. Senior leadership from the FDA were present. There were panels on clinical trial design, patient experience, and drug development. They expect to see more clinical trials in the ALS space in the future. The Registry remains an important recruiting tool and an opportunity for some

targeted recruiting as well. If people are registered, they have their identifier that is connecting them to other data sources that are maintained in other places. If researchers need to recruit a certain number of people with certain characteristics, that combination of Registry linked to other resources can be used to target people more precisely who might be good fits for that trial. The researchers can reach out to them if they volunteered to be contacted. This is one opportunity where the Registry can grow more as the Registry data gets integrated with other scientific resources. The efficiency of this opportunity is another potential selling point for people who want to participate in the Registry. They can be targeted in a way that is more effective and more tailored toward them.

As mentioned earlier, the ALS Association's large clinical conference will be convened in October in Texas. The ALS Clinic Directors will be invited for a session specifically to talk about the Registry and generate new ideas for how to make Registry recruitment more efficient and participation in the surveys more complete.

In terms of the challenges and opportunities, one of the challenges is that the ALS community does not have the best impression about what the Registry is and they may not have a clear understanding of why the Registry is important. Another challenge is the issue of under-counting. While everyone is aware of this, perhaps they did not quite understand the magnitude of this. It seems like with the work that Dr. Kaye has been doing, there is a solution to this. To Dr. Thakur, this seems like a huge step forward. To say that an estimate is more robust than the actual count sounds a little paradoxical, but in this case is actually correct because it seems to be more accurate to use for meaningful things like determining how resources should be allocated.

There is value in the Registry in supporting research. It is not clear why some people get ALS and others do not. A certain type of data is needed to get at that very difficult question, and the Registry is a fundamental component of that because it cannot be done through typical clinical trials in an efficient way. He had not heard a lot of discussion about this. ATSDR has been working hard to make sure these data are interoperable with other ALS data resources through the use of universal identifiers. However, there has been poor uptake so no one has been asking for this data to be linked with other data resources. That is a concern and they must figure out why. Part of it perhaps is that there are things going on within the Registry, how data are accessible, or how scientists are made aware of the data resources that are there. Also, other resources need to be interoperating with the Registry. The whole community needs to be more thoughtful about how they track the research that comes out of these datasets, and how to get credit when they make the effort to share their data, make it interoperable, and make it useable. A simple way to do that is for all ALS data sources to have digital object identifiers (DOIs) so they are easier to track and automate the tracking that comes out of that.

Dr. Kaye and her team have been working on differential under-reporting as well. It is important for care providers to recognize where the under-reporting is in the Registry and what that means in terms of under-servicing these communities as well. Dr. Thakur thinks there is a link and that they need to keep talking about this as well. That is another value of the Registry.

All of this comes together and it is nice to have a great count, but all of this needs to be used to drive operations, research, and action. That is the feedback loop people were talking about earlier in the day, and that needs to be made clear back to the community. That is ultimately what will help with enrollment and the completion of all of these surveys and the hard work it takes to fill them all out.

Discussion Points

Dr. Brooks said that one of the difficulties he saw as a clinician is that they are having to open clinics for ALS patients, there are long waits for ALS patients to get into clinics, there is under-diagnosis in ALS in the US, and a delay in the diagnosis and getting people in for treatments. One of the potential problems is the core ALS syndrome rather than the surround. Most of the ALS clinics deal with the surround. In the paper they published about classification, they talked about the issue with ICD-10 and upcoming ICD-11 and the classification of ALS. That is one of the problems they are facing with the Registry and the reality of the patients. There is ALS, ALS Plus, Atypical ALS, et cetera. The Registry mechanics must come to grips with the classification difficulties. At the patient level, they are seeing more of these patients coming through. It is not clear why they are not represented in the numbers. If more people are out there who are being treated and living longer, the prevalence will go up. The question is, when will that happen?

Dr. Finger sees the value on the research and patient side with regard to the trial notification. It is important from the patient side, it is important to convey the need to be all-encompassing. They do not want patients waiting around for trial notification if only a quarter of trials are using this system. This raised the question for the ALS Association regarding whether they are encouraging use of the Registry notification system when they are sponsoring trials.

Dr. Thakur said he believes they are and on their web page they have a broader listing of trials. There is a push-pull approach. People can go onto the Registry and click that they want to be contacted, and if people with ALS want to contact people who are running a trial, the information is posted on the ALS Association web page. There also is a contact to an actual human being who supports all of this. The ALS Association supports her time and she works out of NEALS. Her phone number is listed as well. Both approaches are needed.

Ms. Balas added that the ALS Association encourages people to use the Trial Notification. Many researchers are still unaware of it. They have not gone as far as to mandate that. It has been more of an education about other tools they have available through their sponsorship of trials.

Dr. Mehta emphasized that they would love for more pharmaceutical companies to come to ATSDR to use the notification resource for their trials. A lot of it is by word-of-mouth.

Les Turner ALS Foundation

Andrea Pauls Backman, MBA
Executive Director
Les Turner ALS Foundation

Cara Gallagher, MA, LPC
National ALS Registry Associate
Les Turner ALS Foundation

Ms. Backman indicated that the Les Turner ALS Foundation is the leader in comprehensive ALS care in Chicagoland. Unlike the national organizations, they are a regional, Chicago-based organization. They have been doing this work since 1977. They provide individualized care, local community support, and hope through scientific research at the Les Turner ALS Center at Northwestern Medicine. The mission is “to provide the most comprehensive care and support to people living with ALS and their families in Chicagoland, so they can confidently navigate the disease and advance scientific research for the prevention, treatment, and cure of ALS.” When they revised their mission statement this year, they wanted to reflect that they are partners with the ALS community in the work that they do. They are not there to mandate or tell people what

they should or should not do. They really are there to help people navigate their way through this disease, because it is quite a journey.

In terms of the Les Turner ALS Foundation's Impact on ALS research, care, and support, nearly \$70 million has been raised to support ALS since 1977 to support the foundation's mission. Much like the national organizations, their programs are in the same types of categories. Over half (55%) of the funding is allocated to the Les Turner ALS Center at Northwestern Medicine, which encompasses four research laboratories and the Lois Insolia ALS Clinic that has been there since 1986. About 39% is allocated to support services because it directly impacts how they do their education outreach about the National ALS Registry, and 6% supports education.

With respect to support services, the Les Turner ALS Foundation provides a personalized approach to treatment and care, preparing people living with ALS to navigate their difficult journey and supporting them each step of the way. The Support Services Team works very much on a one-to-one basis with each person living with ALS. They tell them from the moment they are diagnosed that the team is with them through every step of the journey, and they mean that. They also work directly with people's families, employers, neighbors, et cetera. The Les Turner ALS Foundation is part of the community, and they are part of the Les Turner family. The Support Services Team currently has 8 team members comprised of RNs, social workers, and professional counselors all of whom work directly with people with ALS and their families. The types of services that team provides include the following:

- Home and community services
- Augmentative communications services
- Equipment, respite and transportation grants
- Support group meetings
- National ALS Registry Associate and support

While this is very similar to how the national organizations structure their information, the difference is that because the Les Turner ALS Foundation is local and is intertwined so deeply in the community, they have individual nurses who will meet someone in their home every 6 weeks for 3 to 4 hours. They know their family, their dog, their children, and they walk through every aspect of the disease with them. They are able to coordinate people's needs directly with the Lois Insolia ALS Clinic, because they share all of the notes from the field with the clinic and the clinic notes are shared with the team so there is complete continuity of care.

The following is a list of the Les Turner ALS Foundation's promotional efforts for the National ALS Registry and Biorepository:

- Home and Clinic Visits
- Support Groups
- National ALS Registry Associate
- Print Newsletters
- E-news and Website
- Annual Education Meeting
- Education for Medical Professionals
- Annual Research Symposium on ALS and NeuroRepair
- Community Education and Expos
- Social Media: Facebook, Twitter, and LinkedIn

The home and clinic visits are a very important part of what they do. When there are Support Service Coordinators in the home, Cara Gallagher, the National ALS Registry Associate is

there. She meets every person who presents to the clinic, provided they are willing to meet with her. There are certain situations in which clinic visits may not be appropriate, especially for someone who is brand new in their diagnosis. Mass outreach efforts through the office include print newsletters, e-news, and a website.

Ms. Gallagher said that she came to the Les Turner ALS Foundation about two years ago and was asked to be their National ALS Registry Associate. That job entails providing education to the individuals being served as well as the community, and also providing personal assistance for anyone who is interested in being in the Registry or who may need assistance with completing the modules and changing passwords, as well as those who originally registered before the Biorepository was part of the Registry. They have estimated that between her support and being at the clinic, 80% of individuals served by the Les Turner Foundation are currently enrolled in the National ALS Registry.

Many people have requested her assistance after enrolling in the Registry, and they report that after looking at the modules they have no interest in doing it on their own. They will call her and request assistance because either they do not have the ability to complete the modules, or do not want to try to do them on their own. She will go to someone's home or whatever facility they are in to help them complete the modules, with very little problem. It is usually about a 2-hour process from start to finish. When they finish with all of the modules, people often say that it was not nearly as daunting as it appeared that it was going to be. They try to make it as pleasant an experience as possible for them. Sometimes people will go through the modules and read the questions and maybe feel like they do not really understand what they are being asked and what the appropriate answers are. A lot of that comes from the surveys regarding pesticides, herbicides, exercise, et cetera. Ms. Gallagher's direct involvement ensures that the modules are being completed from start to finish so the frustration factor goes away, and that all of the questions are being answered more consistently.

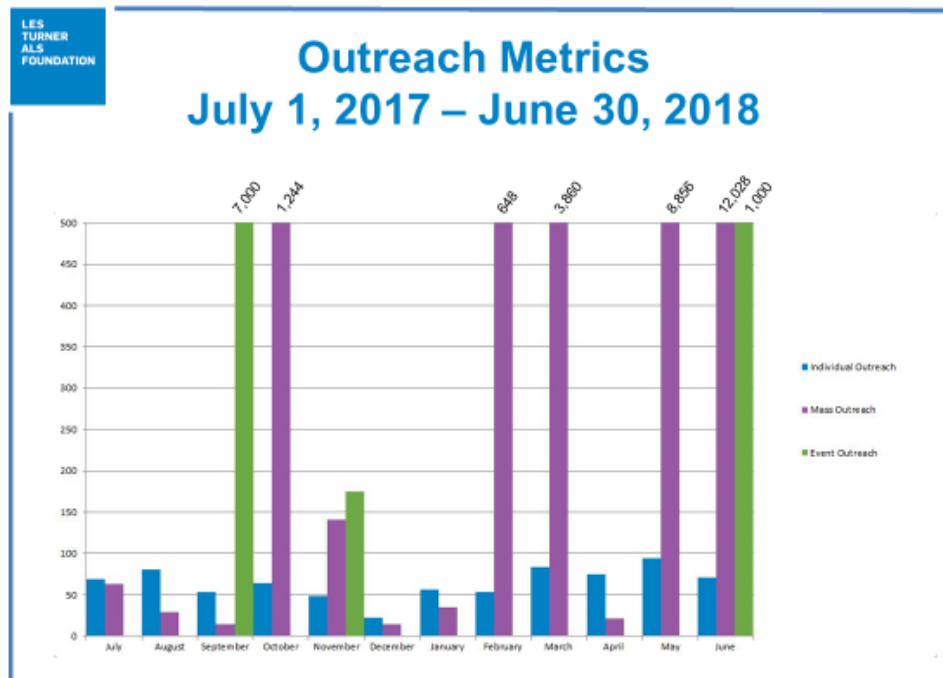
In addition to the individuals they already have registered, she assists approximately 25% of new patients with their registration and completion of the modules as well. Her involvement at the clinic twice a week has provided her an opportunity to meet with patients while they are waiting for their doctors. They can register right there at the clinic, which is a great way to get people started. Sometimes people will say that they want to try to complete the modules themselves at home, but she usually reaches out in a week or two to set up a time to go to their home to help them complete the modules. It is nice because she is getting feedback directly from the people who are registering about how they feel and what their experience has been.

Ms. Backman went over some examples of the Les Turner Foundation's promotion on a general basis, as well as some metrics to show how effective those promotional efforts have been. They have an e-newsletter that goes out on a monthly basis, in which they talk about the Registry. They have a prominent National ALS Registry and Biorepository space on their website. They do collect metrics in terms of how many landings they are getting on this website and how that may have changed over time. They convene several conferences such as the Les Turner Symposium on ALS and NeuroRepair Symposium, which is done every November. Clinicians and patients attend this symposium, so they are able to speak to both audiences about the Registry. They hold an annual educational seminar, *ALS News You Can Use*, which was held last spring and will be held again next October.

With the increased digital assets they have gotten from the Registry that they are able to share on Facebook and Twitter, they have noticed a significant uptick in the sharing of this information and the interest level. Approximately 6000 to 7000 people participate in the annual ALS Walk for

Life, where they talk about the Registry as well. In terms of outreach to medical professionals, the Les Turner Foundation has really increased this area of their outreach over the last year. They have sent 125 individually signed letters to local neurologists to educate them about and assist them with the Registry and the Biorepository. The Les Turner ALS Center at Northwestern Medicine will host an ALS clinical conference for medical professionals in September 2018. This is geared toward doctors, nurses, and occupational therapists, all of whom will be able to get CMEs for this day-long conference.

The outreach metrics are depicted in the follow chart:



There is individual outreach such as Ms. Gallagher meeting with people in clinic and in their homes and talking to them on the phone. There also is mass outreach, which includes the website, e-newsletter, et cetera. In addition, there are events such as education conferences, symposia, clinical conferences, walks, et cetera. When they do have something to share, the bars literally go off of the chart. Over time, there are a variety of ways to reach out to people. Most important is that the purple bar is showing significant increase in outreach because of the quality and frequency of the new digital assets they have received, so they are looking forward to receiving more of those.

Ms. Gallagher talked about feedback from people living with ALS. Regarding the Registry, they have found that many people do not have internet access or who do not have updated equipment. So, it is very challenging for them to be able to get onto the Registry and complete the process. They have taken that challenge away by having her take her own laptop and a hotspot. Even if someone has internet, 9 out of 10 times they do not know their password. Other people have been registered for a long period of time and may have received help at the very beginning when the Registry started, but they do not remember their user name and password. More than likely, their password has expired. She is able to contact support to get passwords reset and get people moving. The caregivers are truly appreciative for her having the one-on-one time to come out to do this with their family members. They find that it is a great time to sit

and enjoy the conversation about where people lived, where they got married, how long they lived in each house, which child was born in which house, et cetera. Some people have moved over 40 times, so this can be somewhat overwhelming. The caregivers also like the fact that it is 2 hours of time they can take for themselves to run to the grocery store, take a shower, or make a phone call. People seem to be very comfortable with the 2-hour timeframe that it typically takes to complete the modules.

The Registry and Biorepository give people a sense of hope. They also feel that the disease is getting more attention than ever before, which likely will lead to a cure or treatment. Their desire to make a difference in their lives and the lives of others is a driving factor for people to participate in the Registry and Biorepository. When they are discussing the Registry, there is a motivational component because people know that if they qualify for a clinical trial that they may be making a difference for a future generation. There seems to be a very strong feeling that making a difference adds value to their lives. It is a great opportunity for people and it is a selling point that while someone may not be going to work anymore or doing the things that made them feel fulfilled, completing the Registry and potentially being able to participate in trials gives people hope and to feel that it is useful to participate. A lot of times people go through the surveys and realize they have to give some thought to their lifestyle choices and the potential causes of disease, so some interesting statements have come out of this. In terms of the Biorepository, registration is easy. Unfortunately, they met their capacity so a lot of people who were hoping to participate were not able to make donations. In short, they are hopeful that in October they will be able to participate and feel like they are making an impact.

Discussion Points

Dr. Horton said it was great to hear this feedback. He asked how they choose to go to a person's home, and if it is a sample that is selected.

Ms. Gallagher responded that she offers her assistance to any person who is not enrolled in the Registry who they meet through the clinic or who is being served through the Les Turner Foundation. She will follow up with people who say they want to try it on their own to see if they have done it. She will go through all of the modules with them as well.

Dr. Mehta emphasized that the hands-on concierge approach of helping persons with ALS and their caregivers enroll makes a major difference. It is certainly a model to be considered in other areas as well.

Ms. Backman thought that raised a good point. In terms of people they are not capturing in this Registry, if 25% of people just based on their sample are calling Ms. Gallagher because they need personal assistance, does that mean they are potentially losing 25% of people at the outset? If that number is extrapolated, it is a sizeable number.

Mr. Kingon requested additional information about Mr. Les Turner.

Ms. Backman indicated that Les Turner was a business man outside of Chicago, Illinois who was diagnosed in 1976. He was in his 30s and was married with 3 young boys. He and his family did not know where to turn, so they gathered in his living room. They brought together people, including his brother-in-law and sister-in-law, Harvey and Bonny Gaffen, who started the Les Turner Foundation. Ms. Backman said she was proud to report that the Gaffens are still involved in the foundation and still serve on the board. It is very fortunate that they had a need and created a solution.

Brunet-García

Francie Lefkowitz
Account Executive
Brunet-García

Anna Jaffee
Senior Account Manager
Brunet-García

Ms. Lefkowitz noted that Brunet-García has been working with the National ALS Registry on communication and outreach for the last three years, and said it was great to see all of the assets and materials they have created used by the partners. During this session, she focused on the efforts and findings from the previous year.

This year, they began with the following primary objectives to help guide their research and the strategies that they are using:

- Raise awareness and engagement of National ALS Registry among persons living with ALS, their family members and caregivers, as well as ALS clinicians and researchers
- Provide value to persons with ALS with simpler access to updates from the ALS Registry and stakeholders
- Coordinate efforts of partners and other stakeholders to promote the Registry and support persons living with ALS

They spent a lot of time at the beginning of the year trying to figure out what would guide their strategies. They spent a lot of time reviewing the current materials (brochures, fact sheets, and digital assets like social media and the website content). They also spent a lot of time talking to partners to gain information on what people living with ALS were saying, which helped determine what to focus on and led to the actual efforts and strategies.

They worked on messaging and branding. This includes a CDC feature article, testimonial quotes, social media, fact sheets, and posters. Over the years, materials have been created, but new information arises over time. For example, the Biorepository launched in the last year, so it was not included in the original materials. Print, electronic, and social media materials must be updated and made consistent as time goes on. For social media, they developed static and animated graphics and updated posts. Once this was completed, they worked with the partners to share the materials with them to make sure to expand the reach beyond CDC/ATSDR. They also wanted to make sure that when people visit the website, they can quickly find what they need and are not spending too much time clicking around. They reviewed the website for user experience and consistency.

Marketing materials were also created. One of these is an 8.5 x 11 one-page fact sheet that describes the research funded by the Registry. This can be viewed online, and people will be able to order it online soon. This was created to demonstrate the value of the Registry and show that it does more than count cases. The fact sheet includes two quotes from patients and one from a researcher, along with a photograph of Ed Tessaro. It is great to put a face to a name, which is something they have heard from patients and plan to implement more as time goes on. Another piece that was updated this year was the retractable banner to ensure that the content matches the messaging and values and that the look is updated. This item can be used at events, conferences, and in clinics.

Posters are being created as well, but are still in development. Brunet-García worked with the Registry and the ALS Association on these posters. There were two separate versions of the poster. They conducted testing and collected feedback on the design and content, speaking with a few persons living with ALS and care coordinators to learn what would be the best in terms of design and content. One of the versions did not have a photograph, and they found that people resonated more with a photograph and that it grabbed and kept their attention better. Therefore, they have decided to move forward with the poster that includes the photograph. They also learned that the URL needs to be bigger and that because some people do not have computers or Wi-Fi, they need a telephone number, which was added. In addition, they learned about the placement of the information. They are also talking to Care Coordinators and Clinic Coordinators to find out where the materials should go and what is feasible. Ms. Lefkowitz invited feedback on these materials, given that they have not yet been finalized.

The coming year will be used to update print materials with new messaging and branding, determine strategies to increase awareness and enrollment in under-enrolled populations, and revise the website to help with usability.

Discussion Points

Ms. Backman asked when the revised print materials are anticipated to be finished, and what the anticipated launch data is for new digital materials.

Ms. Lefkowitz replied that the print materials will probably be completed in stages, because it could be a lot to do at once. The first piece will be the new patient one-pager, which is currently a tri-fold brochure. Taking into account updating and clearance, she anticipated that this may be ready by February 2019. They will keep the partners updated on this. In addition to the new patient one-pager, they probably will update the infographics that are online and used a lot in the new patient binders. After that, they will complete the researcher and provider materials. Those will probably be ready around Spring. The digital pieces also will have to go through clearance, which they hope to complete sooner because they know these are requested a lot. Hopefully, these will be ready by late Fall.

In terms of the effort to drive more people to the Registry, Mr. Tessaro asked what they had learned in the last couple of years that they should not do.

Ms. Lefkowitz replied that one thing they learned was that they should try to stay away from the more scientific/clinical discussions and focus more on the value of the Registry. The Les Turner Foundation talked about how patients like to hear how they are able to help future generations, and that they want to feel like they are part of something. They also learned that people who have computer and internet access do go online a lot to look for information, so they need to make sure that information can be found easily online. Another thing they should all talk about more is the peer-to-peer conversations. Clinicians and patients are more likely to respond when they hear others talking about it in-person. They have received a lot of positive feedback about

Ed Tessaro's picture, which they have used on about 5 items this year. She invited others to share photographs as well.

Open Panel Discussion

Moderator: Ms. Janine Cory, ATSDR

Panelists: Ms. Reshma Punjani, ATSDR

Dr. Geiger, MDA

Dr. Neil Thakur, ALS Association

Ms. Backman and Ms. Gallagher, Les Turner Foundation

Ms. Lefkowitz and Ms. Anna Jaffee, Brunet-García

Ms. Cory noted that they began to formulate some ideas about what works following each presentation, and emphasized that Mr. Tessaro's question about what does not work is equally valuable to consider. She opened the floor for discussion about what does and does not work that might be helpful to share.

Discussion Points

Dr. Benatar wondered what mechanisms are in place to identify which interventions actually do work, as opposed to informal anecdotes, impressions, or a general sense. It would be good to know as they target different interventions that there is a strategy to measure those.

Ms. Cory reminded everyone that earlier she pointed out that awareness does not equal registration. If the ultimate goal is registration, the metrics are in place to determine state achievements and for some states, regional success.

Dr. Benatar agreed that they have metrics to assess the end product of enrollment, but he asked whether they can track what led to the conversion from awareness to registration (e.g., an activity on social media, the way materials were presented in the clinic, et cetera).

Ms. Cory said she thought this was a valid question and is one of the suggestions they have heard and would like to look at. Some of the workers on the ground said, "I did x, y, and z but I don't know if that led to enrollment." In theory, it is probably multi-factorial based.

Dr. Mehta said that based on a lot of what they have seen internally, all of the clinics and chapters are different. Some promote the Registry more than others. A lot of this is driven by the clinic director and neurologists at the clinic if it is in their protocol or checklist to inform/educate about the Registry and how persons with ALS can participate in the research.

Dr. Benatar stressed that this sounds like informal impressions rather than having a mechanism in place. It seemed to him that this may have been an oversight that perhaps should be put in place going forward so that they can track when someone enrolls what the hook was that led them to enrollment. Then they could track this from a real metrics perspective in order to better understand where to invest time, energy, and resources for future enrollments.

Dr. Horton said one thing they plan to use is the customer service survey that was put online recently. It is tracking how people heard about the Registry along with other questions. This will give them some impression about where people came from and how they heard about the Registry in the first place.

Dr. Finger pointed out that this has been discussed for a couple of years in a row. It seems like most websites will know if someone got there from Facebook or Twitter, so he wondered whether the Registry website records any of those data.

Dr. Mehta replied that they are not permitted to record those data because of IRB concerns, because it could be assumed that they are tracking individuals coming from a particular area. Ms. Cory added that they can set up an evaluation mechanism that would look at that, but they cannot do it from the government website. An evaluation intervention at a specific site could collect data about what drove someone to the Registry.

Dr. Finger pointed out that when ads are purchased on Facebook or Twitter, very detailed information is provided on engagement. He asked whether ATSDR could speak to what type of ads on Facebook or Twitter have led to worthwhile engagement.

Dr. Mehta indicated that they are in discussions before the next fiscal year begins about having some sort of outreach such as placing information in Google, Twitter, and Facebook ads for ALS in order to have greater outreach online.

Dr. Finger emphasized that the number one frustration among patients is continuing to have the same discussions year after year. For example, Becky Kidd spoke repeatedly last year about the importance of measuring and Dr. Benatar just emphasized the importance of data over anecdote. The response is always, "Perhaps next year." That is not good enough. They should not ask patients to be involved, ask for input, and then respond multiple years later that something could be done possibly in the future. This is "baby stuff." Understanding Facebook and Twitter responses is not something that should wait to be understood in 2019. They should all be embarrassed that this was not done 5 years ago. They have to do better.

Dr. Brooks said that one of the epidemiological observations is that more married people use riluzole than unmarried people. With that in mind, he asked whether they had any data on the marital status of people who complete multiple versus few modules, what the marital status is of people who enter different parts of the country, et cetera. This is something they should be able to figure out by the next day. Or perhaps they could assess the correlation of riluzole use and the number of forms completed.

Dr. Kaye replied that marital status should be in Module 1, the demographic module, so they could assess whether there is a correlation between marital status and the number of surveys completed. The one fallacy is that there already is a correlation between someone completing at least one survey. That is, if someone has completed one survey, the probability that they have completed 5 or more is 85%. Riluzole use is in Module 17. There may be a lot of people who completed the information on marital status who did not complete the information on riluzole because there was a 2- to 3-year lag between Modules 1 and 17. While riluzole use could get someone identified, they do not have marital status on those who come in through administrative data. They have marital status only on those who complete surveys. Ms. Raymond and Dr. Oskarsson are looking at Module 17 and already have the data out, so they could look at that.

Dr. Benatar said he was thinking about engagement of the research community and using the tremendous resource that has been generated through the Registry, and it occurred to him that it would be helpful for people to have a sense of the alignment of the different data sources. For example, they could report the number of people who have registered through the portal, the number for whom they have complete environmental exposure questionnaires, the number for

whom they have WGS data, the subset in which they have cross-sectional longitudinal biospecimens, et cetera. Understanding where those subsets are and how they connect is critical as people are thinking about research questions. Seeing the numbers in isolation is not helpful. There needs to be a mechanism for people who wish to tap into and use the resources to understand what resources are available and where the intersection points are.

Dr. Mehta said they have discussed having something available similar to what is provided for the Biorepository showcasing exactly what is available for researchers to request.

Ms. Balas underscored Dr. Finger's point and indicated that the ALS Association chapters feel a similar frustration. She and Dr. Mehta have had multiple conversations regarding how to encourage chapters to have the same level of enthusiasm about recruitment. They do not necessarily have good data to direct people on how to improve their outreach or support the efforts they have made that have been a value-add. She agreed that those analytics would be very useful to organizations like the ALS Association and MDA to target not only where to target efforts, but also what to do.

Ms. Cory said she thought part of the issue was that they have not tried to codify what works. That is the next step. As far as getting the analytics from digital media buys is absolutely possible. They did not make those buys this year. However, it is absolutely mandatory for the future that if they purchase they should examine the deeper analytics.

Dr. Finger said he thought the onus also was on the sponsors. Many of the Registry postings he sees are coming from the national partner sites, which he assumed was part of their contract. Therefore, they also should be looking at the metrics and provide feedback to ATSDR and Brunet-García about which of these lead to engagement. This is not complicated. It is just a matter of people taking it more seriously. The purpose of this information is to improve all of this.

Dr. Thakur agreed that they need metrics and pointed out that if metrics are focused on a specific campaign, once that campaign ends they need to translate that moving forward. A more comprehensive set of measures is needed. He thought the same should be done for the scientific community in terms of having some goals or at least some measures about how many people they want using these data and thinking about a way to shift that usage over time in order to achieve better use of this resource. This goes back to the fundamental point about why there is a Registry and thinking about how to close the loop. It is not just about getting people enrolled. It also is about getting the information out and then letting everyone recognize what the value is. He thought the discussion throughout the day about the value of the Registry had been somewhat fuzzy. He hoped they could talk about this more concretely on the second day of the meeting. When that is crisp in their own minds, perhaps they can convey it better to the community more crisply as well.

Mr. Baker stated that often times when The ALS Association posts information about the registry, they receive very negative feedback from patients. He asked Dr. Finger what could be done from a patient's perspective to change this.

Dr. Finger said he thought that as more papers are published looking at risk factors, that will help greatly. The frustration comes from lobbying on Capitol Hill, getting the legislation passed, and 6 years later having a report published that said there are 12,000 patients that no one took seriously. No one thought that was anywhere near accurate or honest in the way it was presented. The additional years were similar. He thinks eventually papers will be published that provide valuable insight, which will illustrate the value of the Registry in showing the risk factors that are important and will inform clinic use. They must do a much better job telling that story,

which is not as visible as it could be at times. Looking back at the video from last year and what Becky Kidd said repeatedly, he was not sure they had made progress on that. As a patient, there is absolutely nothing more frustrating than when the years go by without progress. In the meantime, he has seen way too many of his friends not make it through the year.

Dr. Bradley observed that Dr. Finger raised optimistic views of what they might get out of the Registry if they wait long enough in terms of the epidemiology—where the cases are, what they are exposed to, et cetera. The problem with the Registry is that it does not have any controls. He thought they should ask Dr. Kaye whether she could do what Dr. Finger was asking without there being controls and, therefore, to ask Dr. Finger whether he could drive a funding program to see if they could get the Registry to also have a control analysis.

Dr. Finger pointed out that every question requires a different set of controls (e.g., a family member, someone from the local area who does not have the disease, someone with the same occupation from a different area, et cetera). That gets into expensive mission creep where perhaps having better ways of matching would be beneficial.

Dr. Bradley said the whole point of having controls is just what Dr. Finger is saying. That means having controls across the board, not making subgroups.

Dr. Oskarsson said he thought that trying to understand what brought people to the Registry is greatly important, but even if they have really good campaigns, they may not see that much of a bump. They had the Ice Bucket Challenge during the Registry and they saw only a small bump, but that was a hugely successful campaign that drove people toward the Registry. Any other effort likely will not be that helpful.

Dr. Brooks pointed out that the epidemiological equivalent of a single arm study is the presence of conjugal ALS in the Registry. He asked how many cases of conjugal ALS are in the Registry.

Dr. Kaye responded that she did not think there were any. She knew of one incident that was reported as a possible cluster in Alaska that Dr. Sorenson helped them with about 20 years ago. Neither of them actually had ALS.

Dr. Mehta added that even if there is a matching last name, there is no way to determine whether it is a spouse husband and wife team.

Dr. Kaye said when they were trying to de-duplicate, they likely would have found them if they had the same last name and were at the same address. They probably would have been removed because they would have been thought to be a duplicate.

Dr. Sorenson said that only would be true if it was concurrent. They had a case where one spouse was diagnosed with ALS 20 years earlier, and later the spouse developed it.

Dr. Mehta observed that spouses having ALS concurrently would be of interest, which is probably much rarer than one spouse having it 10 to 15 years later.

Dr Factor-Litvak said she thought the issue of controls was incredibly important. Anytime they write grant proposals, even with case series, reviewers do not like them very much. Even a higher level point is to gain representativeness in the Registry from patients from under-served areas, from under-represented groups, minority groups, et cetera. That should be of paramount importance. Epidemiologists can think about how to get controls for the Registry without having

them enroll in the Registry. They have brainstormed and some of them have come up with some ideas or not. The issue of representativeness, especially for risk factor epidemiology for a highly complex disease where there are likely multiple genetic and environmental things that have to come together for the disease to develop and likely different ones in different people, is really very important. That needs to be a prime focus of getting more participants enrolled in the Registry.

Dr. Bradley asked Dr. Andrew to comment on this, because they have put into the Ohio ALS Registry a population control group analysis that they must have done on a very small budget. They have something on the order of 230 control patients who all completed questionnaires, and a proportion of those have provided biological samples of nails and saliva. This is not an enormously expensive study. This is a mailout done through a Registry that has millions of the normal population.

Dr. Andrew agreed that a more concerted effort to try to get controls would not be prohibitively expensive if it were done to try to get a nationally representative sample that is balanced with the national representation the ALS Registry has already greatly achieved in terms of distribution. Rather than focus state-by-state, it would seem like a national effort could be made.

Dr. Mehta emphasized that the Registry has added to the body of science regarding what potentially causes ALS. Right now they have no idea. Some papers may say a particular heavy metal is or is not a risk factor for ALS. ATSDR funds Dartmouth. They fund Dr. Bradley to look at cyanobacteria as a potential risk factor for ALS. ATSDR is adding to the body of science, but they are a small team. They do what they can with what they have. They try to publish research papers as fast as they can on the risk factor surveys, potential collaborations they have, et cetera. They are not the only ALS entity. There are the NIH, FDA, ALS Association, MDA, and Les Turner as well. Nobody wants to hear this, especially with this crazy disease where the lifespan is so short. They would love to be able to definitively say what causes ALS, but thus far no one has been able to pinpoint a particular cause of sporadic ALS. They must step back and realize that causation and correlation are two different things. ATSDR is simply trying to add to the body of science for ALS, just like Drs. Benatar, Brooks, Goutman, and others are. The frustration in the community among patients is because they wonder why more is not being done, but it is important to realize that they do what they can with what they have and they are working with partners to do more. ATSDR receives a very small amount of funding to run the Registry, and they do a lot with what they have and can demonstrate with research that has been funded and papers that have been published.

Dr. Benatar empathized that the science is never moving fast enough for someone who has the disease unfortunately. He wondered whether there was an opportunity in terms of outreach, education, public relations, et cetera to do more with the scientific work that is being done and published to feature it as part of an awareness campaign. When a paper is published, perhaps it could be featured in some way to explain the result and how it helped move the science forward in this mass action way and promote that as part of a public education campaign. That could serve the long-term goals of the Registry well. Even if this has been done, perhaps there is an opportunity to do more.

Dr. Mehta agreed that they could highlight all of the research/papers that have been done so far in a clear format would be helpful. As mentioned earlier, they buy open access to the papers they publish so that people can read them. However, they do not translate the papers into a readable format for a caregiver who may not understand what a scientific paper says. He agreed that they could do a much better job of translating and disseminating the findings.

Ms. Cory added that some of the resources she showed in her talk were all in-house efforts. The MAT article was \$3000. Some of the things they would like to do are of their price range, but that is where they rely on partners to use their connection, word-of-mouth, and community access. She agreed that translating the research into more digestible success stories would be helpful.

Dr. Haidet-Phillips suggested that in the Tweets and Facebook posts that ATSDR creates about the Registry, perhaps they could add a link to an article and one sentence about what they found—something translated that the lay public could understand. This could tie together what is coming out of patients enrolling in the Registry. When MDA funds research, they ask the researcher to write a brief 2-sentence summary to provide an synopsis of what was done.

Dr. Gubitza added that the communication piece is very important at NIH, so they do press releases. At the end of July, the National Institute of Neurological Disorders and Stroke (NINDS) did a press release on an NINDS-funded study on ALS. There was a scientific publication in a scientific journal that their communications team summarized in approachable language. The media will take up a press release if it rises to a story they want to feature. That has been quite effective.

Ms. Balas said she was thinking that while a tweet and so forth are very useful, one of the highest traffic areas of the ALS Association's social media is their blog and blog posts. This is always surprising to her. They have someone on their staff whose job she used to say is to translate the research to English. That English is very well-received. That is a very easy lift of the ALS Registry to put this type of information on their blog to create some type of relatable material. That would need to come from ATSDR because if the ALS Association does the translation from research to English, then it would have to go back to ATSDR for clearance and approval which is a time delay. The chapters rely on the blog from the national office to put out research material. They do not do their own. They often put tweets and such out into the atmosphere and they get re-tweeted by the chapters as well.

Dr. Mehta added that if they translated an article that has been published into layman's language to show what ATSDR has contributed to the body of science behind ALS, that would be a way to highlight a particular area.

Dr. Bradley expressed appreciation for everything that ATSDR and the Registry does, especially on a very small budget. Ultimately, it is Congress that will give more money to CDC. That political aspect is clearly very important. They should leave the meeting with a renewed effort into trying to bring more emphasis on trying to bring the political message to bear.

Dr. Thakur said while it may sound a little circular, the main justification for the Registry is the size of the population that the Registry has documented. That is why he is so focused on the number and making sure that it is correct. They said that the Registry estimates that it is 5/100,000, but they think it is higher. People seem to be receiving that argument very well. They also have had some discussion with the OMB about the Registry. They have emphasized the points, including that it is not known why some people get ALS and others do not. They emphasize that the Registry is the only way to broadly ascertain what the environmental risks might be because this area is under-invested in overall. All of the other places they talk about ALS and funding for ALS, they draw back to the Registry and the numbers from the Registry as evidence for all of the other arguments. All of their policy discussions drive from that estimated number of how many people there are with ALS. It also drives from the fact that what really causes ALS remains unknown. Part of his concern from this discussion was that he heard Dr.

Mehta talking about how they have to analyze the data and that it cannot work if it is only his team or the investigators funded directly by CDC/ATSDR, but he also was concerned about the idea that they cannot use the Registry data without finding controls to match. If that is true, they need to find a different methodology. Why would they spend money finding controls if they do not think something is a risk, but how do they know it is a risk if until they do some work? They get stuck where they cannot get started, because they have defined things in a certain way. He was not clear whether that was actually happening, but that was the implication he was drawing from the conversation.

Dr. Geiger agreed that it was not just about awareness, but also it regards their effectiveness with that awareness. They are sharing as much as they can as far as education, research, and data. But they have to make sure that MDA and the ALS Association also share their own data analytics with the National ALS Registry so they can identify what they are doing right and where they are stalling in terms of outreach. MDA is evaluating where they are putting their dollars and how effective they are in terms of outreach with their Care Center Clinic Directors, getting grassroots feedback from the people who are there with the patients, to determine whether it is working.

Regarding Dr. Thakur's point about policy, Ms. Balas indicated that they recently have had some communication with OMB. Being a proactive resource and trying to have the communication is critical. One of the things Dr. Thakur brought up is the economic value of the Registry in terms of creating jobs and other opportunities in the US within the science space. When they think about how they communicate with whichever administration currently is sitting on Pennsylvania Avenue, it is important not only to leverage the scientific value but also how it is economically beneficial. They should continue to weave that into the conversation, and that is something that she had not heard during the last couple of years during this meeting.

Ms. Cory asked whether anyone else had ever used that angle or perspective when speaking about the Registry.

Dr. Mehta stressed that while he thought it would be great to have controls, inherently registries do not have controls. For example, cancer and birth defects registries have no controls. Controls are extremely expensive. A few years ago, consideration was given to adding controls to the Registry, but the cost was estimated to be about \$1000 per control, which is extremely cost-prohibitive.

Dr. Kaye seconded Dr. Finger's comment that every study needs different controls depending upon the research question. There would need to be multiple controls per person (neighborhood, family, occupational, et cetera). Dr. Talbott's study is a good example. She is getting samples from the Biorepository and she has all of the cases, but her study is pulling its own controls. They will identify the controls and draw their samples, but they do not have to get the cases as well. They are only having to do half of the work, which is how they need to think.

Dr. Mehta added that they are providing over 300 samples to Dr. Talbott, but she is getting only about 30 controls.

Dr. Talbott said the issue is making sure they have good survey data.

Dr. Brooks pointed out that while they are all in the ALS space, CDC/ATSDR also has registries in NMD, other neurological diseases, birth defects, et cetera. From the point of view of lobbying, perhaps they should lobby through something like the American Brain Foundation or the AAN.

There is overlap with the techniques and tools of the MS Society. That all should be brought together in terms of a lobbying effort to maintain this Registry and show its value added to these other potential goals they want to achieve.

Ms. Cory said they have been talking about how people understand cancer registries and that is something they need to make a parallel argument for how data are really used. That relates to telling the story of the successes.

Dr. Horton acknowledged that it is very clear that not every clinic director promotes the Registry, or at least puts literature into a patient's hand. Some groups like Dr. Brooks' group are fantastic, but some clinic directors do not even mention the Registry. That obviously has to change. The same is true with chapters. Some chapters do a really good job of promoting the Registry, while it is not clear that other chapters even understand what it is ATSDR is doing. Consideration must be given to how to ensure that chapters and clinic directors are at the same level, that they are providing the same message, and that the patients are hearing the same message that it is important for people to enroll in the Registry. ATSDR has agreements with the national MDA and ALS Association, but they do not have one-on-one agreements with each chapter. They have to rely on the national groups to make that happen so that all chapters and all clinic directors are delivering the same, consistent message. ATSDR knows they are missing data. They hear that, recognize that, and have done papers on it. But, they also have their ears open to be being told how they can find these people. They are doing the best they can to try to find minority populations, people on private pay, et cetera. They want to hear ideas about how they could approach finding these people.

Dr. Stommel said he thought it would be instructive to look historically at other diseases. ALS is an incredibly complicated set of diseases and is poorly understood at this point. But, looking back at HIV/AIDS and some forms of cancer that have been largely cured at this point, they could examine the approach and amount of money that went into it. Perhaps they could invite input from people from the cancer registry or those who historically were involved in getting to the bottom of HIV/AIDS to see how they surmounted some of the financial aspects that probably seemed unsurmountable early on. The fact that ALS is a relatively rare disease compared to cancer makes it less popular in terms of getting financing, but there are some precedents that could be examined more carefully.

Dr. Mehta replied that ATSDR is all about looking at what has been done and leveraging resources where they can. They do not want to go down a road if someone else has gone down it and learned lessons. Cancer and HIV/AIDS have reportable disease status, but ALS does not. While they can learn from cancer and HIV/AIDS, it is important to keep in mind that ALS does not have the luxury of being a notifiable disease. This is why they took the novel approach they did in trying to capture these cases. Where they can leverage information and lessons learned from other groups, they will.

Dr. Stommel pointed out that there are others who have tremendous financial resources who "think outside of the box" such as Elon Musk and other very rich people, who perhaps they should try to approach or invite to a meeting.

Dr. Mehta indicated that they have had conversations with IBM Watson representatives about looking at the risk factor surveys. They are open to recommendations.

Dr. Benatar noted that they have tried different ways in their clinic to raise awareness about the Registry. They work with the ALS Association chapter representative in the clinic. They think about when the best time is to talk to people about the Registry. The only feedback they get in terms of knowing whether anything they are doing or changing is good or bad is when they see

the reports that Mr. Hicks sends out that show whether they are an under-performing state. That is a macro-level view of whether anything they are trying is impactful. That is where his comment was coming from about having metrics and being able to track efforts. The best leverage is with the people who are already engaged, want to do things, and are able and willing but do not know whether what they are doing is having the impact they would like. It would be tremendously helpful if ATSDR could think of ways to empower them to know whether what they are doing is working. They know they cannot enroll a large segment of their population because of language. That will change if the Registry becomes available in Spanish as well.

Dr. Horton agreed that metrics are good and that they cannot change something if they do not measure it. However, it is not necessary to do a study to know that the more you promote something the better. If there are clinic directors or chapters that are not even giving out the literature to let people know about it, a study is not needed for that. He said he understood what Dr. Benatar was saying, but also the more people who can spread the word about the Registry, especially clinic directors or neurologists, the better. People seem to trust their neurologists or a medical professional. Having them at least provide literature on the Registry would be better.

Dr. Benatar emphasized that the rub is that at the moment, clinic directors lack the resources to provide the care that patients need. They do not have enough time in their multi-specialty clinics for every patient to see every allied health professional they need to see. In order to run and maintain clinics, they have to raise philanthropy of hundreds of thousands of dollars every year to provide a clinical service. So, when they tell someone that part of their responsibility is to talk about the National ALS Registry, they want that to be as cost-effective and efficient an intervention as possible because unfortunately, they do not have the luxury of doing everything. They want to be able to do the things that have the highest impact. Having the metrics helps them do that, and can help lower the barrier for people to be able to have these conversations and promote the Registry while also giving them the tools, feedback, encouragement, and ways in which they can make this “ask” in the most effective way. The reality on the ground is that clinics struggle to keep the doors open to provide the services, never mind the research Registry ad and other things that they drop on top of it.

Dr. Horton said he understood and appreciated that. From his own personal view, he would be happy if just their literature was tucked into whatever is given to the patients when they are first diagnosed. A lot of neurologists provide some type of package. If a physician does not have time to discuss the Registry, at least the patient would have something to read in their folder once they are home. That is pretty easy, would go a long way, and does not need metrics.

Dr. Kaye reported that consistently since they began, Minnesota breaks the curve on the number enrolled in the Registry compared with what would be expected. She asked Dr. Sorenson to speak about why. Is it because people in Minnesota are more compliant, are more likely to join things, or something else?

Dr. Sorenson said they do a lot of what Ms. Gallagher does in Chicago. They introduce the concepts of the Registry in the clinic, and their nurse goes over the educational information that is included in the packet that people are given. What really makes a difference is that the chapter in Minneapolis will register the patient over the phone. Nearly all patients in Minnesota register with the chapter. They do not go over the modules with the patients, so he doubted that their questionnaire data is as strong as enrollment, but they do get them set up and enrolled. It is that personal connection that makes the difference—taking the burden away from the patient and having someone else help them with it is key. It is true in Minnesota that if he tells a patient

they should do something, they do it. He emphasized that placing the burden of registration on the patient will result in losing a lot of them. Patients are truly overwhelmed with all of the things that are happening on a daily basis, and this is just one more thing that from a patient perspective may not have the highest priority.

Dr. Mehta indicated that Texas is very difficult. It is large and diverse. They would love to make a greater impact in that state. A lot is driven by the director- or neurologist-level as well. Case-in-point, they were giving a talk in Seattle to the ALS Association's Evergreen Chapter and were told that the chapter is also responsible for Alaska and parts of Montana and they said their effort is to make sure these people know about the Registry and provide assistance. It is different for each chapter and each clinic, and there needs to be more uniformity.

End of the Day Wrap-Up

Robert Kingon, MPA, Facilitator
Carter Consulting, Inc.

Mr. Kingon referred participants to their packets for a list of nearby restaurants, reminded them that they would reconvene at 8:30 the next morning, and officially adjourned the meeting for the day.

August 8, 2018

Update from Pharma

Cytokinetics, Inc

Sarah Kulke, MD
Senior Medical Director
Medical Affairs
Cytokinetics, Inc

Dr. Kulke presented updates on Cytokinetics' clinical trials in ALS. Cytokinetics develops drugs for muscles. Specifically, Cytokinetics targets compounds that bind to the proteins that make up the sarcomere, which is the fundamental contractile unit of the muscle. The fundamental proteins that make up the contractile unit are the myosin and myosin heads, actin, troponin, and tropomyosin. *Tirasemtiv* and *reldesemtiv* both target troponin and are known as fast skeletal muscle troponin activators (FSTAs). Dr. Kulke shared a video of the muscle contracting, which showed the myocin heads binding to and pulling causing the actin to come together. That is what makes muscles contract.

The Ventilatory Investigation of Tirasemtiv and Assessments of Longitudinal Indices after Treatment for a Year in ALS (VITALITY-ALS) study was Cytokinetics' Phase 3 clinical trial. They reported these results in December of 2017. This was a study of *tirasemtiv* in ALS. There were 4 dosing groups: Placebo, 250 mg/day, 375 mg/day, 500 mg/day. Unfortunately, *tirasemtiv* was not well-tolerated and dose reductions and discontinuations were common. There was a nice dose response in terms of down-titration and discontinuations from treatment. Because many people dropped out of the study, they were left without the power to demonstrate a difference statistically between the drug and placebo. There was no statistical difference in slow vital capacity (SVC), the primary outcome variable, between *tirasemtiv* and placebo. It may be that the down-titrations and discontinuations led to this result. There are other reasons that this could have happened, such as the thinking that the hypothesis was wrong to begin with.

However, the adverse events (AEs) that led to discontinuation were thought to be related to an off-target effect in the central nervous system (CNS) having to do with GABA receptors such that people had a lot of dizziness. There was also some weight loss, insomnia, and fatigue. Serious adverse events (SAEs) were similar between the two dosing groups, and it was really these AEs related to dizziness that led to the discontinuations. However, among the patients who were able to tolerate and stay on *tirasemtiv*, there was a hint of biological activity. That led them to believe that potentially the mechanism of action may actually have merit. They were able to discern a difference in SVC in patients who were on the highest dose (500 mg/day) and stayed on it. Some activity could be seen among patients who stayed on any dose for at least 20 weeks also.

In conclusion, VITALITY-ALS did not meet its primary or secondary endpoints, possibly due to poor tolerability of the drug. In patients who remained on *tirasemtiv*, there is evidence of an effect on SVC, with the highest effect in patients on 500 mg daily. Fast skeletal muscle troponin activation remains a viable therapeutic strategy worthy of further study in patients with ALS. *Tirasemtiv* was discontinued in terms of its development. However, because patients who tolerated the drug and received benefit, Cytokinetics is continuing to make *tirasemtiv* available

to the patients in the trial whose physicians deem that they are benefitting. Through the FDA's Expanded Access program, they are transferring patients from the extension trial, the Ventilatory Investigations in Global Open-label Research in ALS (VIGOR-ALS), into a managed access program for as long as they feel they are receiving benefits.

The next compound is *reldesemtiv*, which has the same mechanism of action in that it binds to troponin and is a FSTA. However, its chemical structure is completely different. It was designed and optimized to not have the side-effect profile seen with *tirasemtiv*.

A study that Cytokinetics commonly conducts with its FSTAs is for a healthy individual to sit in a chair with their foot strapped to a plate. The fibular nerve is stimulated, which causes the foot to dorsiflex and they measure the force on the plate from stimulation of that nerve. The volunteers in this case were then given *reldesemtiv* and the force generated was measured over a series of different stimulation frequencies. At very similar concentrations in both cases there was a nice dose response with greater force produced with greater concentration in healthy volunteers with *reldesemtiv* and *tirasemtiv*. Of interest to Cytokinetics is that *reldesemtiv* appears to have a stronger response at a similar dose range, so there is evidence that it may be more potent. It may have a better side effect profile and may be more potent than *tirasemtiv*.

The FORTITUDE-ALS is now ongoing and is recruiting across the US. There are some centers in Europe, Canada, and Australia as well. There are four therapeutic groups: Placebo, 150 mg, 300 mg, and 450 mg. These patients are similar to the patients enrolled in VITALITY-ALS. About 450 patients will be enrolled with a diagnosis of ALS for ≤ 24 months. They have to have SVC greater than 60%, and the primary outcome is change in SVC from baseline to Week 12 in percent predicted SVC. Secondary outcomes include muscle strength, change from baseline to Visit Week 12 in the ALS Functional Rating Scale–Revised (ALSFRS-R), incidence and severity of treatment-emergent adverse events (TEAEs), and pharmacokinetics. There also are some interesting exploratory outcomes that have not been tested before in ALS trials, including:

- Fine motor skills assessed on iPad app during clinic visits
- Voice recording assessed on an app on a patient device weekly at home and on iPad at clinic visits
- Weekly home SVC testing
- Health Economics Outcome Measures: when a patient is prescribed and agrees to use:
 - Manual or power wheelchair
 - Augmentative/Alternative Communication (AAC)
 - Feeding tube
 - NIV
- Central review of flow volume loop by pulmonologist

In summary, *reldesemtiv* and *tirasemtiv* are both FSTAs, but *reldesemtiv* is derived from a different and unrelated chemical structure. It has greater pharmacodynamic effect at lower plasma concentrations, was designed to minimize crossing of the blood brain barrier (BBB), has no known drug-drug interaction with riluzole that *tirasemtiv* did, and has demonstrated tolerability in healthy subjects.

Discussion Points

Dr. Finger observed that in moving *tirasemtiv* from Phase 2 to Phase 3, Cytokinetics changed the primary endpoint SVC to a secondary endpoint, and requested further information about why this was done.

Dr. Kulke clarified that for *reldesemtiv*, SVC is the primary endpoint.

Dr. Stommel noted that from a physiological standpoint, this type of medication would be more like a turbo charge for an engine. It is not going to slow down neurodegeneration. He asked whether consideration has been given to *reldesemtiv* being used for athletics.

Dr. Kulke confirmed that *reldesemtiv* is not designed to impact the nerve. It is designed to improve muscle function. The FDA is concerned about *reldesemtiv* being used for athletics. Cytokinetics is very cautious to emphasize that they are focused on diseases that impact individuals with poor muscle function, weakness, and degeneration. Cytokinetics is partnered with Astellas on *reldesemtiv*. Astellas is conducting two other studies, one of which is a clinical trial in the frail and elderly. When people get older, they experience muscle wasting sarcopenia. Muscle wasting also occurs with chronic obstructive pulmonary disease (COPD). Right now *reldesemtiv* is being studied for ALS, spinal muscular atrophy (SMA), COPD, and frailty. Cytokinetics recently reported their Phase 2 results for SMA at Cure SMA. This study showed a significant improvement in 6-minute walk time with *reldesemtiv* in patients with SMA.

Dr. Brooks asked whether Cytokinetics used the CDC research notification tool.

Dr. Kulke said they used the notification tool for both VITALITY-ALS and FORTITUDE-ALS, and that it had been great. She is a big proponent of that tool and thinks that everyone should use that system for all of their studies. It works very well. She always gets a big bump in the number of people reaching out after they do that.

Mr. Tessaro asked whether the Phase 2 study gave them a signal about dosage tolerance, and if it was unusual to find that in a Phase 3 report.

Dr. Kulke replied that the Phase 2 study did give them a signal. When they saw that in Phase 2, they implemented some adjustments that they thought would handle it. They believed that over time people became more tolerant of *tirasemtiv*, so they did a two-week run in which everyone received *tirasemtiv*, which they hoped would cause those who were not tolerating it to drop out of the study so that they would be left with only patients who tolerated it. That is not what happened. People continued to withdraw throughout the study. Unfortunately, *tirasemtiv* is not a good fit.

Mitsubishi Tanabe Pharma America

Stephen Apple, MD
Scientific Affairs Team
Mitsubishi Tanabe Pharma America

Dr. Apple reported on a biomarker study that Mitsubishi Tanabe Pharma America hopes to implement by the end of 2018, the Edaravone Biomarker Study. In terms of why they are planning this study, a lot of this comes from questions they heard from patients and providers. They are hoping that this biomarker study will begin to start answering some of these questions.

Last year, their Vice President of Medical Affairs, Dr. Jean Hubble, spoke during the Annual National ALS Registry Meeting about the clinical information surrounding at that time their newly introduced compound, edaravone. For many, that was the first time they were introduced to both the safety and efficacy of that drug. Literally this time last year, the first patient in the US went on edaravone. Since that time, over 3000 patients have been placed on edaravone.

This year also has been quite challenging. Although several ALS treaters immediately adopted edaravone as part of their paradigm for treating their ALS patients, many payers placed restrictions on access to this drug. These restrictions were only to patients who could meet the criteria for the Phase 3 pivotal trial rather than the broader indication the FDA had given it. In addition, many ALS treaters had questions about which patient populations were appropriate to be offered this drug and what the optimal timing was to initiate therapy. There also were questions surrounding Mitsubishi Tanabe Pharma America's clinical development program. In the first Phase 3 trial, the data numerically favored edaravone. However, the drug did not meet its primary endpoint, which was changed in the ALSFRS-R.

This surprised the Japanese investigators and the Mitsubishi Tanabe Research Consortium greatly, because this compound had really shown promise in its pre-clinical studies. Rather than abandoning an ALS indication, a post-hoc analysis was performed and identified a population that would show an effect within a short 6-month period of time. They then ran a second Phase 3 trial using an enrichment strategy they gleaned from the first trial. This examined a population that was high-functioning, but rapidly progressing. In the second trial, the drug did meet its primary endpoint. Mitsubishi Tanabe's Development Group did not see this as a failure of the drug in the first trial, but rather a failure in the clinical trial design. They did not believe that this was a biologic issue that meant only a subset of ALS patients could benefit from this drug. They believed it could be circulated for a wide ALS population.

That was met with a lot of skepticism and a lot of additional questions. Compounding that is that the US ALS community had no real-world experience with the drug prior to its availability, given that all of the clinical trials were conducted solely in Japan. Dr. Apple emphasized that he was not going to spend any time talking about the safety, efficacy, or generalizability of the drug to a larger audience. Instead, he wanted to set some context that there are a lot of questions. The FDA label's mechanism of action has one word "unknown." The Clinical Development Group believes that the drug has utility in oxidative stress. This comes from the fact that in a Phase 2 trial patients who had high levels of 3-nitrotyrosine (3-NT), a non-specific biomarker for oxidative stress, had 3-NT levels that were almost non-existent after undergoing 6 months of therapy with 60 mg of edaravone.

This raised questions about how to elucidate the mechanism of action. What about patients and ALS treaters? This drug is not a cure for ALS. It does not reverse the disease, nor does it arrest it. Simply, it slows the loss of physical function. Patients will still progress albeit at a slower pace. They will still feel the effects of their disease, so they have questions about how they will know it is working. Therefore, there are a lot of questions Mitsubishi Tanabe hopes that this biomarker study will begin to answer. There are four things they are looking to accomplish with this study, which are to:

- Elucidate the mechanism of action or at least get pointed in the right direction where further research can assist them
- Identify a quantifiable biologic measure for the effects of edaravone on ALS, or a leading indicator of the ALSFRS-R

- ❑ Assist researchers and clinicians in determining the feasibility and validity of specific biomarkers in patients undergoing edaravone therapy
- ❑ Find guidance that can be utilized to inform Mitsubishi Tanabe's Phase 4 post-marketing commitment with the FDA, specifically regarding more frequent dosing at higher strengths

The plan is to conduct a prospective study among 200 commercially insured adult patients treated with edaravone at approximately 25-30 sites. They want to do this in the real-world so that it crosses all care settings. It does not matter if the patient is being infused at the hospital, a standalone infusion center, a doctor's office, or at home. They want to make this as easy as possible for the patients and the sites. Biomarkers will be assessed at enrollment, baseline, and 24 weeks. Biomarkers for oxidative stress, inflammation, and neuronal injury/death will be evaluated. Efficacy (changes in ALSFRS-R and ALSAQ-40 scores, respiratory function) and safety also will be assessed. If all goes well, interim findings are expected as early as the second quarter of 2019. The findings will help establish the use of biomarkers to assess the effect of edaravone in ALS. The data generated will help define the real-world safety and efficacy of edaravone, supplementing clinical trial observations.

This trial design will follow the same design that all of Mitsubishi Tanabe's ALS studies have. This will be a 6-month trial with 6 cycles. The first cycle will be 14 days on drug, followed by a 14-day drug holiday. The second through the sixth cycle will be 10 of 14 days on drug, followed by a 14-day drug holiday. They have learned over the last year with these 3000 patients that as far as the time from getting a prescription to the time that their benefits are actually approved can take from 5 to 12 weeks, depending upon the insurance company. Therefore, they proposed that the patients act as their own controls. Once they are given a prescription, they will have their biofluids taken (blood and urine) and clinical assessments done. The next time will be at the time of infusion, then at the end of active drug, and then again at the end of the drug holiday. Mitsubishi Tanabe is also in talks with multiple agencies, including CDC, about being able to utilize their biorepositories in order to correlate comparators for natural history of the disease against these patients.

The clinical assessments will include the ALSFRS-R, King's Staging, forced vital capacity (FVC)/SVC, ALSQ40, hand held dynamometry (HHD) (sub-study), Vitals/body mass index (BMI), Origent model inputs, and Appel Scale (Sub-study). They also will be looking to correlate slow versus fast progressors and FVC against machine learning such as the Origent modeling. The broad categories of biomarkers they will be examining include: oxidative stress, inflammation, neuronal injury, and death. In terms of timing, they have spent the last year with a large steering committee of experts looking at what specific biomarkers would be appropriate for this study. They have engaged their Clinical Research Organizations (CROs), have finalized their protocol, and will be engaging with a central IRB. Hopefully toward the end of this year, site selection will begin. If all goes well, the first patient will be enrolled by the end of the year. They are realistic that if they do not get that patient in at least two weeks before Thanksgiving, because of the holidays, it is going to be January before the first patient is enrolled. There are several assessment points for preliminary data throughout 2019, and they expect to have the last data point collected by the second quarter of 2020 if all goes well. Shortly after that, final analyses and subsequent publications are anticipated.

Discussion Points

Dr. Brooks observed that they had talked the day before about how to get patients to enroll in the Registry and complete the modules. He wondered if there was a way to use the fact that there are no natural history data to convince payers that a drug might be useful, not only for the

subgroups who are picked for a clinical trial, but in the whole group. Dr. Bastings' report regarding FDA approval looked at all of the clinical trials and concluded that the directionality of the effect of edaravone was the same, it just was not statistically significant. He wondered if they could try to get patients engaged in the Registry by providing more longitudinal data so that there is a natural history to take to the FDA and payers to show how a subgroup of patients may be the leading group to demonstrate that a drug is working, but that it does not mean it will work only in that group.

Dr. Apple said they hope for this as well and it is part of what they have been working on. Because there was no experience with the drug prior to it being available, a lot of what they have had to do this year is talk to key opinion leaders and experts in the ALS treating community about the safety and efficacy of this drug. They have had to look at it beyond the inclusion criteria for the clinical trial to a more generalizable audience. That is why they are hoping that this biomarker study answers a lot of those questions. Mitsubishi Tanabe is aware that there are lingering questions and wants to be able to answer them as definitively as possible. However, they are realistic in that some of these questions may not be answered with this trial but will raise more questions and more avenues where research is necessary.

Dr. Feldman indicated that there are a lot of historical and fairly good data from Japan, because edaravone has been on the market since 2001 or 2002 for acute ischemic stroke and is continuously used. The recommendations for stroke are to give 30 mg BID for 14 days for ischemic stroke, which is 60 mg a day and is the routine dose in the study. It is not given past 14 days because of potential renal failure and significant kidney issues. Therefore, she wondered whether Dr. Apple had seen those SAEs reported and whether he thought there was an ethnic difference such that Asians may be more susceptible to the potential renal negative effects of this drug than other ethnic groups.

Dr. Apple responded that this was a question he delved into quite a bit with their pharmacovigilance and drug safety individuals, especially as they were getting ready to submit for the FDA label. What they found was that in the ALS trials, there was nothing to indicate any type of renal issue. It was only in the stroke trials that they saw this, and a lot of that was based on the protocol surrounding the trial, not the 14 days. The FDA looked at a conglomerate of 3 Phase 3 trials (J16, J18, J19) and found nothing that would suggest any type of renal injury.

Mr. Tessaro observed that the study make-up included very few slow and long progressors and asked Dr. Apple's take on the efficacy of the drug for long and slow progressing ALS patients.

Dr. Apple replied that the first trial, which did not meet statistical significance, was made up of a preponderance of slow progressors. In a short 6-month timeframe, the drug did not show effect. It was numerically favored, but did not meet statistical significance. The reason they went to a population made up of fast progressors was because that clinical trial for ethical reasons was only 6 months and they needed to be able to show that effect. They do believe that it has effect with slow and fast progressors, but they utilized that fast progressing population to show that effect in 6 months. That brought on a lot of skepticism by the ALS treating community and payers, because they perceived that it only works in a subset of ALS patients. They hope with this biomarker study they will be able to put that to rest and can show generalizability. Dr. Oskarsson asked whether this was one of the additional studies the FDA mandated, and when they anticipate having results.

Dr. Apple replied that the mandated study is the assessment of more frequent and higher doses. They are hoping that the biomarker study can inform them of optimal dosing to move

forward in the Phase 4 post-marketing studies. This includes toxicology and hepatic issues, as well as dosing. They are finalizing with the FDA now, so they believe they will have more information in October on the finalized protocol that they can talk about.

NEALS Update

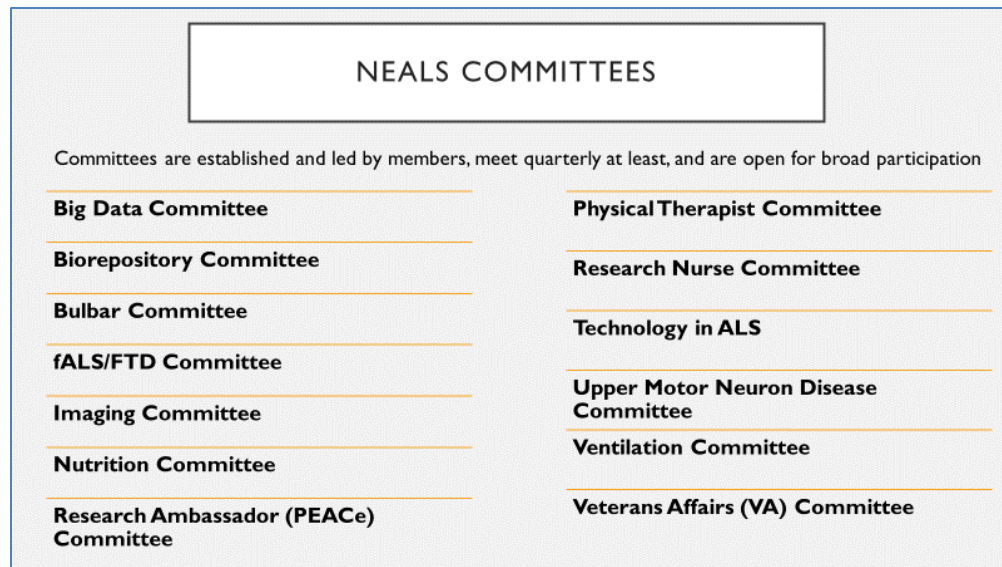
Björn Oskarsson, MD
Director ALS and MDA Clinics
Mayo Clinic, Jacksonville

Dr. Oskarsson clarified that he is not a member of the Executive Committee for the Northeast ALS Consortium (NEALS), but has been a member of NEALS for over 10 years, and that he was presenting on behalf of Dr. James Berry who was unable to attend.

For those who are not familiar with NEALS, Dr. Oskarsson explained that NEALS functions as an international academic research consortium, a contracted research organization, and a resource for the ALS community at large. NEALS' mission is to translate scientific advances into new treatments for people with ALS and MND as rapidly as possible. The NEALS consortium is committed to the principles of open scientific communication, peer review, full and open disclosure of potential conflicts of interest (COI), and democratic governance of its organization and activities.

NEALS was formed in Boston in 1995 and is currently run by an Executive Committee comprised of 12 members with a depth of experience and a unique perspective. The Executive Committee includes clinical investigators, evaluators, coordinators, and scientific experts. The current Chair is Dr. Jonathan Glass, who is based in Atlanta. NEALS also has a Scientific Advisory Board (SAB) that provides a forum for investigators and industry to vet new ideas for drugs, technologies, and trials. The SAB ensures the scientific rigor of the projects. Dr. Bowser sits on the SAB.

NEALS has two full-time employees who take care of many of the day-to-day practical aspects of running the organization (e.g., assisting the Co-Chairs with initiatives/communications, planning meetings, tracking member committee activity, organizing trainings, overseeing finances, helping coordinate the biorepository, overseeing social media, planning/executing webinar series, onboarding new chairs). There are two main Coordination Centers, Massachusetts General Hospital (MGH) and Barrow Neurological Institute. The organization grew out of the Northeast, but has spread across the US and now includes sites in Canada, Israel, India, and Australia. The greatest resource of the organization is its members. Member investigators are participating in many different aspects of therapeutic developmental drugs for ALS, advocacy, and other types of activities for the furtherment of ALS care in the world. Much of the work being done on any given issue in NEALS is done through the following committees:



One of the aims of NEALS is to provide resources for the ALS research community. That includes training site managers, coordinators, evaluators, and site and project PIs. One of the greatest achievements of NEALS has been the creation of the Pooled Resource Open-Access ALS Clinical Trials Database (PRO-ACT). This is a marvelous repository of data from placebo and treatment patients. There also is the NeuroBANK, which is a powerful natural history database with a wealth of information. It utilizes GUIDs, which are compatible with the National ALS Registry.

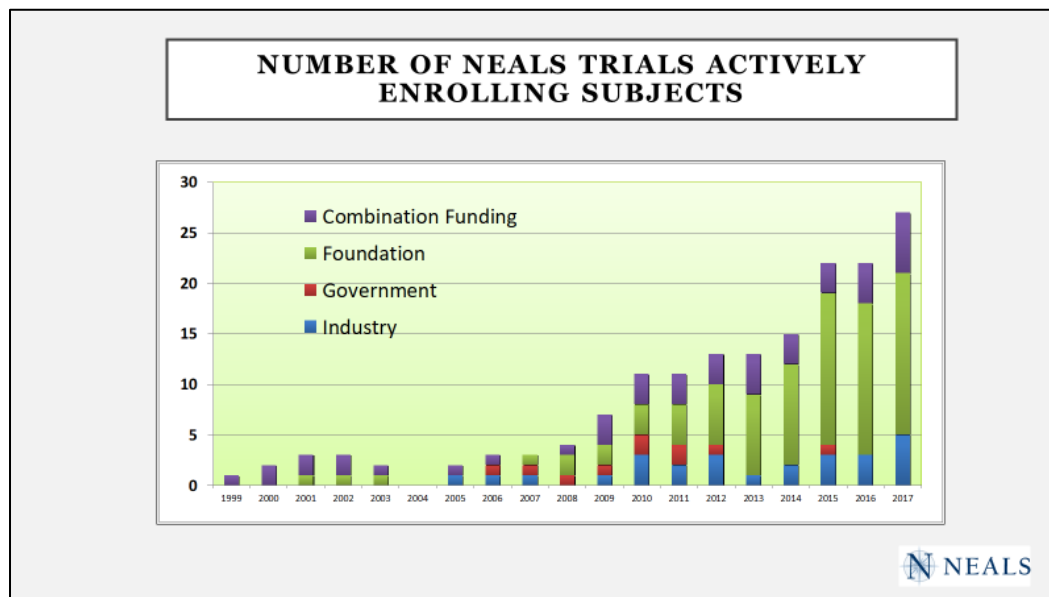
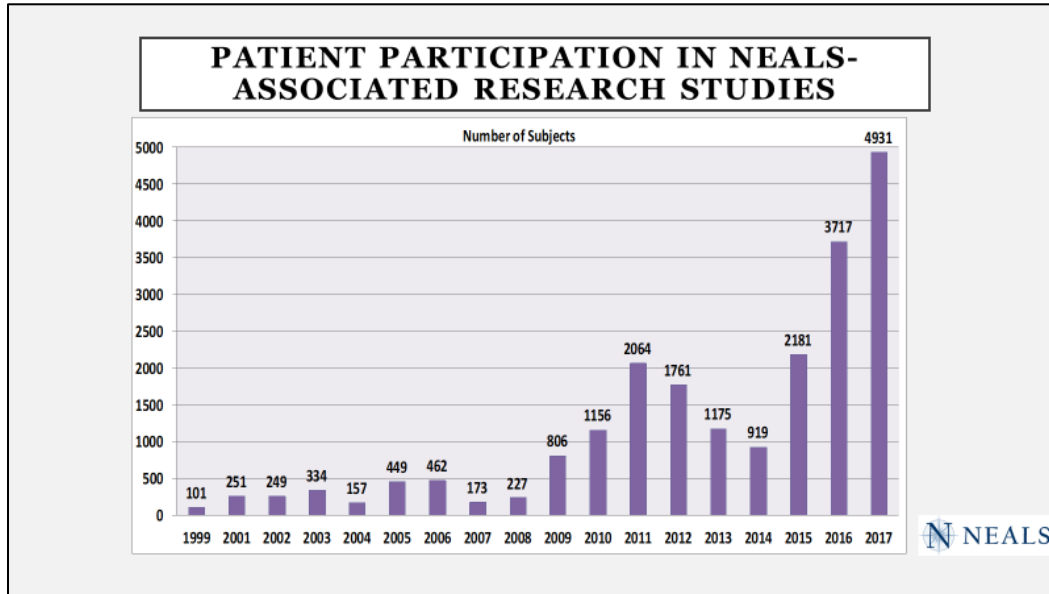
NEALS also has a Biorepository/Living Library, which is located in both Coordination Centers. The team who runs this includes Dr. Berry and Dr. Bowser. Specimens are computer-organized, can be assessed by tablet, and can be requested easily. Bar code scanners are used to collect and track the samples. From October 2017 through June 2018, there have been 29 shipments of samples to 15 laboratories. This has resulted in multiple publications to date, along with multiple analyses, reports, and manuscripts in process.

The challenges for the NEALS Biorepository include covering the costs. While it is currently operating under a 2-year grant from Project ALS to support the biorepository, future grant funding is unclear. MGH philanthropy supports some of the biorepository and acts as bridge funding between grants. NEALS has charges per sample for industry (\$100/CSF, \$50/blood). The biorepository's utility is sometimes difficult to see. In order to raise awareness among patients and investigators, NEALS plans to start asking parties who receive samples for permission to state that NEALS has shared with them and for a brief public statement about their work, or a generic statement saying they are working on ALS research. This will allow NEALS to advertise its sharing activity more effectively. The samples are disseminated from where they are stored at Barrow or MGH, which is where Material Transfer Agreements (MTAs) originate. Typically, there are no issues with this, other than it can take time. They are working on this. They have completed MTAs with industry and academia, and have different agreements for each.

Another aspect of NEALS is its efforts to engage with PALS. To do so, NEALS coordinates monthly webinars for PALS, Caregivers of ALS (CALs), and the broader ALS community. All webinars are recorded and are available on the NEALS website. There have been 17 webinars since September 2016 with over 2600 participants. The average number of attendees for a live

session is 153, while the average number of recording views is 166. The NEALS Clinical Research Learning Institute (CRLI) is funded by The ALS Association and is led by Richard Bedlack. The goal of CRLI is to empower PALS and CALS to be research advocates in the ALS community. Over 250 PALS and CALS have completed the CRLI training to become Research Ambassadors. There were 13 ambassadors at CRLI training in Sacramento, California in 2017 and 24 ambassadors at CRLI training at the NEALS meeting in 2017.

The number of subjects involved in NEALS trials and the number of NEALS trials actively enrolling subjects are shown in the following two tables:



In summary, the primary ongoing funders for NEALS include Packard Center, ALS Therapy Alliance, ALS Association, MDA, and ALS Hope Foundation. NEALS investigators play active roles in improving clinical trial start-up efficiencies, training of patient advocates for clinical research, expanding participation, and generation of experienced investigators globally for expansion of ALS clinical trials.

Dr. Oskarsson also mentioned the Western ALS Study Group (WALS), which is another ALS trials organization. It is somewhat older than NEALS, started in the Western US a couple of years before NEALS. Today, it has spread throughout the country but there are many fewer sites. They still conduct some trials, but not as many as NEALS. It serves as more of a discussion forum among investigators and industry.

Discussion Points

Ms. Backman observed that NEALS also has a biorepository and is looking to make that information available to researchers just as the National ALS Biorepository is. She asked what they could tell their patient population with respect to sampling, what they are looking for, and how easy it is to handle enrollment and collection.

Dr. Bowser replied that most of the NEALS Biorepository collection studies are driven by individuals and PIs and what funding is available for those. As opposed to the National ALS Biorepository, which has a funding mechanism and collects samples from patients throughout the country. The studies that have provided samples to NEALS for the biorepository efforts have either been samples collected in clinical trials that are then donated to the biorepository for use for research purposes, or a number of specific studies that are collecting samples for research purposes for various hypothesis-driven types of science that have been spearheaded by individual PIs who have their own 25-30 sites that are collecting samples under specific guidelines and for specific reasons. Individuals cannot just be referred to provide samples. It is driven by individual studies.

Regarding the effort to track the papers and work that results from NEALS sharing samples, Dr. Thakur asked whether they give people electronic identifiers so that this can be done in an automated way such that they can acknowledge receiving specific samples with electronic tags in order to harvest information automatically. Something like a research resource identifier that is used for cell lines.

Dr. Bowser replied that while they have not done that, individual PIs often request a couple of hundred samples. They cannot give them 200 GUIDs for them to put in their acknowledgement section. It is challenging to provide samples to investigators around the world and want them to acknowledge utilization. They have to follow-up multiple times a year to remind the researchers that they should do this, and still they often do not so it is hard to track. NEALS also needs to do a better job of finding investigators who are willing to share the data that has arisen from the use of the samples in order to create a better data repository of the samples, and then allow other investigators to utilize that information. This would be a tremendous resource going forward. They have been talking about this for a while and want to try to initiate it. Instead of tracking via the GUID numbers, which has its own challenges, perhaps they can collect data back from individual investigators to create a living resource of research data.

Dr Thakur agreed that GUIDs are not the right tool, but from the ALS Association perspective, there needs to be a way to track the impacts of their investment in a comprehensive way. He said he would like to talk to Dr. Bowser further about this.

Dr. Bowser indicated that they have the data on how many samples that are sent to each individual investigator. They just have not released that information to anyone.

Dr. Finger asked Dr. Bowser to talk about the complementarity or supplementarity between the ALS Biorepository and the NEALS Biorepository and the strengths of each.

Dr. Bowser replied that they were created somewhat independently and for separate purposes. The NEALS Biorepository is driven by other clinical trials and other clinical research studies that are collecting samples. Therefore, the population of patients are those who are presenting to clinics and participating in the trials. The ALS Biorepository is a national effort that allows people in other areas who typically cannot participate in clinical trials or do not have the ability to go to some of the major neuromuscular clinics to participate in these research efforts and provide samples. They are complementary in that regard and should be able to build off of one another. It is a great example of trying to build a better national resource and ability for PALS to participate regardless of where they live.

Dr. Wright, the Scientific Program Official (SPO) working with Dr. Mehta and his team on the extramural research portfolio, indicated that a term and condition of CDC/ATSDR awards is to develop robust data management and data sharing plans.

Dr. Mehta emphasized that the National ALS Registry is complementary and is not in competition with NEALS. They all want the same thing. The National ALS Registry also looks at genetics, biomarkers, and so forth. They have a similar mechanism of disseminating samples to researchers.

Dr. Kaye asked whether NEALS requires the investigators who get their specimens to do an annual renewal/update similar to an IRB renewal. The National ALS Registry has a required annual update on specimens that asks questions such as: *Have you presented anywhere? Have you published a paper? What do you think you might use in the future?* They had to get the form approved by OMB, so it is official. Since it asks about future sample use, it is advantageous for people to complete the form because then they know what to be collecting. It is a way for researchers to get a plug in for what they might need in the future.

Dr. Bowser responded that they do not, but they ask investigators how they have used the samples. They are just happy to get a response, but they do not require the investigators to reapply or renew anything. They have queried at their meetings about these types of things. Because their repository is driven by PIs, collections, and clinical trials it is difficult to predict what will be needed.

Dr. Mehta indicated that ATSDR is also a member of NEALS and serves on their committee for recruitment.

Persons Living with ALS Perspective on the Registry

Robert Kingon, MPA, Facilitator Carter Consulting, Inc.

Mr. Kingon indicated that this session would offer an opportunity to hear from attendees who are persons living with ALS about their perspective on the National ALS Registry.

Dr. Stephen Finger

Dr. Finger said that when he was diagnosed a little over 5 years ago and his doctor told him about everything that was going on, one of the things he did was present the flyer on the Registry. As someone who spent his career looking at data, it was surprising to Dr. Finger that something had not been done in the past. It was very apparent what the value was in terms of patients being able to provide samples and capturing information from patients to try to get a better handle on how many patients have this disease, who is getting it, whether they have similar backgrounds, et cetera. He has been very encouraged by seeing some of the papers that were to be presented in the afternoon utilizing these data to examine a variety of questions. When he went home that first day, he was overwhelmed. Many patients are overwhelmed, but there are a lot of patients who want to do something. When he and his wife got home and a day later were flipping through the packet, having the Registry for them to actively sit down and do made them feel like they were contributing and fighting. Most of the time, people with ALS do not get that opportunity to feel like they are in the fight. When he was in South Carolina and got a notification that he could participate in the pilot for the Biorepository, he jumped at the opportunity. Given this disease, the fact that someone was going to come out to his house to collect the samples was incredibly reassuring. It showed that researchers were recognizing the reality of the disease. He was not getting a notification saying, "If your wife is willing to take off of work for two days and drive you across the country, you can participate." They recognized the situation and offered to have someone come to their home. He really appreciated that and sees the value in this project.

He also sees the difficulties. Having an \$8 or \$10 million budget every year to cover this huge country is not sufficient. This is not a notifiable disease, so it is hard to track down these patients. He thinks that perhaps they use that less as a reason and more as an excuse sometimes. Over \$80 million has been invested in this project. Compared to what the MDA and ALS Association contribute to research each year, \$8 million is a huge amount. This is a big project. It is imperative for everyone involved, not just those at CDC or who are working fulltime as contractors, to make sure they are doing this the best they can. A lot of times, his frustration comes from the fact that looking at the summaries of this meeting year-after-year, many of the conversations about how to do better are exactly the same. They can do better. This is a difficult problem, but there are simple ways to do better. They talk about counting cases. Looking back to when this Registry was going online, the State/Metro studies were funded for millions of dollars to evaluate the completeness of the Registry. This is not some error in the title of a paper released last year. The purpose of those studies was to evaluate the completeness of the Registry. They need to leverage those to truly understand the completeness. They oversample minority populations; however, given the demographics of the states in that study, it is silly to say, "You don't have enough old white men in Florida in order to provide a good estimate of the number of cases being tracked." Looking at the aggregated State/Metro studies that essentially went door-to-door finding patients, still over 70% of the patients they found were white. They

have the demographic data, so there is no excuse not to use pretty basic stat techniques to use these multi-million dollar studies to get a good handle on the counts.

It also is imperative that the partners provide better information and more encouragement per se about the number of patients they are seeing relative to the counts that are being reported in the official documents. MDA in their limited number of clinics is seeing 12,000 patients a year. The ALS Association states in all of their marketing materials that they interact with over 19,000 patients per year. Neither of them is touching everyone, so somewhere there is a disconnect. They have to do better. It is imperative for the partners to point out if reports are flawed and how they can do better. The partners are helping when talking about under-represented states. Those were selected because ATSDR went to its partners to understand how many patients they think are in each state. Why is that data not shared more broadly? Why is that data not just informing these efforts, but also informing how they think about prevalence or incidence. Obviously, counts are not going to be the major or sole focus of this project. Getting a count is very important, as they heard from the ALS Association or patients when they go to Capitol Hill. Those are very important numbers not just for requesting \$10 million a year for the Registry, but also asking for \$10 million a year for the DoD and NIH funding. These are important issues and they can do better.

Beyond that, Dr. Finger thinks there is huge value from having this nationwide, eventually somewhat representative or somewhat unrepresentative, sample of patients. Enrollment is a big thing. They are only going to be able to enroll a certain number of people a year with a \$1 million marketing budget; however, they should make sure if they only have \$1 million they are doing their best. Again, the frustration comes from talking about tangible ways to improve and then having the same discussion the following year. They can do better. They can get so distracted thinking that enrollment is the ultimate goal. The ultimate goal is generating data that can be used for studies. That is going to come from the surveys. In terms of the presentation on surveys, most of what was discussed was about a 4- or 10-year time period. If this is an annual meeting, they need to focus on how they are doing. Did they do better than last year and, if so, why? Did we get value from encouraging a patient to sit down and fill out a survey that has been stuck on that page in very static form for the past 6 years?

They have new surveys. If additional responses to existing surveys are not providing value, they must recognize the burden put on patients and remove them. Each survey has the potential for turning off a patient from completing other surveys. At last year's meeting, Dr. Finger talked about how he had filled out a couple of surveys in the past. But, he got to one that was so frustrating that he stopped. He did not just stop for that one. He stopped for good, because he did not see the value. Last year, suggestions were made about ways to improve how the surveys are posted on the website. The first day of this year's meeting, they had the same discussion. If they truly think improving the response rates to these surveys is important, they have to do something—not do something maybe by 2024, but do something this year. They talk about the website and get people to go to the website. If they click on "For ALS Patients," there are broken links. Yet, they know this is who is most important in terms of improving this project. When he brought that up earlier, the response was that it is in the works and that page will be updated eventually, but the government takes time. Then 15 minutes later, he was told that with one email, IT was able to fix that. There are reasons why being a government agency slows down the process and makes it more difficult. They must recognize when the reason things are not doing well is because of that and differentiate that from when that is a convenient excuse for sloppy work. Again, this project has huge value. It has huge value given the devastating nature of this disease. It has huge value in providing an outlet for patients. It has huge value for providing these data in useable ways for researchers so they can start by doing analyses

instead of starting by doing surveys. But they must be doing their best to maximize its usefulness. This disease does not allow them the latitude for anything else.

Alan Alderman

Mr. Alderman said that he was glad to have this opportunity. As he looked around the room, he saw many people who were far smarter and far more educated than he is. He was diagnosed with ALS nearly 17 years ago. He said like many people, he was frustrated by the lack of speed. While Dr. Finger said that the goals of the ALS Registry is to gather data, he would argue that gathering data is a secondary goal. The primary goal is to find a cure for this horrible disease. His personal goal is to put everyone one of them out of a job, and he will not stop until that happens. There are a lot of things that can be improved on, which have been discussed. However, they are also doing a lot of things right. In the years that he has been coming to this meeting, he has seen an improved website. It is much more user-friendly and easier than the old one. The password was once a problem, but now they can go 60 days. It used to take about 48 hours to have the password reset. Now it is a matter of clicking on a link and responding to an email. He thanked Dr. Horton, Dr. Mehta, and everyone at ATSDR for all they have done for those living with ALS.

Another frustration is that he lives in a state that is always at the bottom of enrollment. There is always under-enrollment. He knows that when a new patient is diagnosed and they are given their information binder, there is information about the Registry in that binder. He knows that the ALS Association and MDA representatives are at his clinic talking to people about the Registry. He has his iPad and will go into a patient's room and if they are not enrolled he says, "Hey, let's enroll you right now." He wants to learn what they can do not to be on the bottom. The day before when they were talking about websites, only one of the 3 partners had a direct link to the Registry on their home page. In his opinion, that is shameful. They have to go out and engage patients and let them know that the Registry is important and make it easy for them. Every partner should have a banner with a direct link to the Registry on their home page. Only 8 of the 63 ALS Association chapters have a direct link on their home page to the Registry. They need to change that. The Registry website must be accessible to all patients. Those are simple changes. He agrees that they can do a lot better getting patients enrolled in the under-enrolled states. They lack the knowledge about the Registry. Many of his patients have said that they went in and filled out a survey, but they do not see any feedback. There needs to be more feedback to patients about how the Registry is being used. He loves that they receive notification of clinical trials. That is an improvement from even 2 or 3 years ago. But, patients still need more feedback about how information patients provide is being used. He recalled hearing something the day before about perhaps sending a monthly newsletter to everyone enrolled in the Registry to share updates and ask them to spread the word and share that with their fellow ALS patients. To him, that would be very beneficial.

Mr. Alderman thanked everyone for all that they do for those living with ALS. This is a horrible disease. Like Dr. Finger, he has seen far too many of his dear friends die of this disease. There was a three-week period not too long ago when he attended 7 funerals of friends who had this disease. They need to understand the urgency and approach all of their jobs with that sense of urgency. Together they will find a cure. It is going to take a while, and it is going to take a lot of effort. When they have done it, they will gather together but will sit around the table and have a party, dance, and celebrate all the hard work that they have done.

Dr. Horton indicated that later this year, Mr. Alderman is going to be rowing across the ocean 3000 miles in 50 days all in the name of raising awareness for ALS. Dr. Horton told him that

there probably are not too many abled-bodies who could do something like that. This speaks volumes about the passion that people have for trying to cure this disease or at least raise awareness. That is very commendable. He noted that Mr. Alderman had some flyers to share with those interested in more information about that.

Ed Tessaro

Mr. Tessaro said he had three important ideas: 1) gratitude, 2) selling and marketing plans in clinics all over the country, and 3) website promotion. He acknowledged that there are very clear challenges on the latter two, but first he talked about being grateful. He has been attending these meetings for about 8 years. The nature of his community, ALS patients, is that they tend to go inward and not challenge themselves and do what they used to do as able-bodied people. That is a big mistake from a psychology and physical standpoint. What everyone brings every year to Atlanta in their papers, presentations, and authenticity is something that he carries to every ALS family he spends time with—dozens of people every month. This is something he and his wife take great pleasure in doing. They are grateful for his own slow progression and the things that he had nothing to do with except that was the luck of the draw. He is grateful for being so close to the Emory ALS Clinic and to have been in Dr. Glass's and Dr. Feldman's Phase 2 stem cell trials in 2011. He also is happy for the MDA and ALS Association relationship he has. He enjoys raising money for those groups, primarily MDA. It goes far beyond that. His community is so well-established that he can find a safe harbor anytime he wants one. He is also thankful for the pharmaceutical community. He began edaravone in February. While he had no results to report, he was aware of how fast FDA approved that drug. A few years ago, it would have been impossible to anticipate so fast a track. The new drug treatments under study right now, 20- to 25-fold, are 5 times more than when he was diagnosed 10 years ago. His gratitude is what he gets up every morning with and he took everything they had given during this meeting as a reason for optimism.

Second, the clinics do a great job selling the Registry. He listened to what was said about some clinics not even mentioning the Registry or its benefits. He knows why that might be true, because when someone walks in being devastated by a gut punch like this kind of diagnosis, it is not a time to get all processy about forms. But, there is a way to do it. He said he wanted to personally volunteer with Paul and Peter to advocate for what they want clinics to do. They have great people who do not have enough time to get to all of the folks on a given day. But with himself and others, they should be able to put a deliverable into a clinic's hand and sell it in a way that someone can take as a given that if they walk into an ALS clinic, they are going to walk out with what Dr. Rick Bedlack does at Duke. There is no reason that should not happen. He knows it is heavy lifting and clinics do not have enough time in the day, but he thinks they can challenge that. Third, in terms of website development, he recalled what Dr. Brooks said about "blinking red lights" as a metaphor for how strong the Registry message ought to be on the website of everybody. Anybody who has an ALS page has to have blinking red lights. He did not think they were doing that enough right now. When people are doing good jobs, they have to be proud of it and brag about what good jobs people are doing. What works and what doesn't? Are we touting what works with the same energy and enthusiasm that they should? Mr. Tessaro ended with gratitude and thanked everyone again for what each of them bring to this meeting, because he carries it with him in his heart every day.

ATSDR-Funded Research Update

Identification and Characterization of Potential Environmental Risk Factors for ALS Using the ATSDR ALS Registry Cases and a Control Population

Evelyn O. Talbott, DrPH
Professor of Epidemiology
University of Pittsburgh

In terms of how she got there and why she is conducting ALS research, Dr. Talbott said that she is an Environmental Epidemiologist at the University of Pittsburgh. She studies various environmental issues, such as cancer clusters and disease clusters, and has done that for many years. In 2003, a friend of hers became President of the Western Pennsylvania ALS Association in Pittsburgh after her husband was diagnosed with ALS.

Dr. Talbott wrote a small project with her and then met Dr. Bowser in 2005 and she had a student, Angela Malek, who is now her Co-Investigator. Dr. Malek conducted one of the early case-control studies looking at environmental toxicants. In addition, Dr. Talbott's husband is a neurologist and he would come home in the evening and talk about his patients and referring them to the ALS center. She has been living for a long time with the knowledge of this disease, how important it is, and how urgent it is to find out all they can. She found this group to be amazing in their dedication and passion in studying the disease, and was very honored to be there.

During this session, Dr. Talbott presented a progress report on the study "Identification and Characterization of Potential Environmental Risk Factors for ALS Using ATSDR ALS Registry Cases and a Control Population." They are 9 months in to this study that was funded by ATSDR. The goal of this study is to examine environmental and occupational risk factors for ALS by conducting a case-control study of cases from the ATSDR ALS National Registry and to try to identify a population-based group of matched controls.

This is a table from a chapter they wrote a couple of years ago looking at some of the investigated risk factors for ALS, with the most recent potential risk being air pollution:

| Risk Factor | Classification of Risk |
|---|-------------------------------|
| Certain metals (e.g. lead, mercury) ²⁻¹⁹ | Increased risk |
| Military service ^{20,21} | Increased risk |
| Genetic factors | Increased risk |
| Pesticides and insecticides ^{16,22,23} | Increased risk |
| Physical activity, some sports (e.g. soccer, football) ²⁴⁻²⁶ | Possible increased risk |
| Head injuries/trauma ^{25,27-31} | Equivocal support |
| Smoking ^{32,33} | Increased risk |
| Solvent exposure ^{9,10} | Possible increased risk |
| Air pollution ³⁴ | Possible increased risk |

¹ Talbott EO, Malek AM, Lacomis D. The epidemiology of amyotrophic lateral sclerosis. *Handb Clin Neurol* 2016; 138: 225-38

The Environmental Protection Agency (EPA) conducts a survey every three years called National Air Toxics Assessment (NATA), which assesses the levels across the country of 187 air toxicants, 35 of which fall into the neurotoxicant chemic group. These are suspected neurologic air toxicants:

| Chemical Group | | |
|---------------------|----------------------------------|--------------------------------|
| Metals | Aromatic Solvents | Chlorinated Solvents |
| Arsenic | Benzene | 1,1,1-trichloroethane |
| Cadmium | Ethyl benzene | 1,1,2,2-tetrachloroethane |
| Lead | Styrene | Carbon disulfide |
| Manganese | Toluene | Carbon tetrachloride |
| Mercury | Xylene | Chloroform |
| Nickel | 2,4-dinitrotoluene | Cresols and Cresylic acid |
| Selenium | Other HAPs* | Ethylene oxide |
| Pesticides | Acylamide | Hexane |
| Ethylene dibromide | Allyl chloride | Methyl chloride |
| Ethylene dichloride | Cyanide compounds | Methylene chloride |
| Hexachlorobenzene | Hexachloroethane | Perchloroethylene |
| | Hydrazine | Trichloroethylene |
| | Polychlorinated biphenyls (PCBs) | Vinyl chloride |
| | | *HAPS=Hazardous Air Pollutants |

These data exist at the Census tract level and have been very carefully modeled. Dr. Talbott and others have used these data in studies such as for childhood autism. It is an average over a Census tract, but there are many hazardous waste sites and chemistry-related industries that do exude a fair amount of pollution. For example, they have the Clairton Coke Works in Pittsburgh that always throws off their particulate matter 2.5 (PM_{2.5}) and benzene because it is the world's largest coke oven. The 13,000 people who live around this coke oven have very high exposures to PM 2.5 and benzene.

In terms of the literature and the importance of posting this information, a Danish case-control study was conducted/published by Selene *et al.* This study, which enrolled 926 ALS cases and 2662 general population controls, estimated residential exposures of the participants to six measures of air pollution. For all six measures, estimated exposures were higher for ALS cases than for controls. The size of the effects were similar or higher than those for smoking in other studies. The weakness of this study was that the use of monitors for the land use regression were based only on 2009 [EHP, 2017]. Drs. Mehta, Kaye, Raymond *et al.* reported on ALS Registry findings on the 2014 prevalence of ALS in the US. A total of 15,927 persons were identified as having definite ALS across three national databases (Medicare, VA Health Administration, and Veterans Benefits Administration) and through web portal registration for 2014. They determined that the prevalence of 5/100,000 is similar to the previous year (2013) and appears to be greater in the Midwest and Northeast compared to the South and West. This, as they point out, is most likely due to population diversity [MMWR, 2018]. Dr. Talbott thinks the ALS Registry is a very worthwhile endeavor because now they are able to chart yearly whether prevalence is increasing/decreasing in various parts of the country.

The design proposed for "Identification and Characterization of Potential Environmental Risk Factors for ALS Using ATSDR ALS Registry Cases and a Control Population" is a matched case-control study with cases comprised of PALS from the Pilot National ALS Registry and Biorepository, 2011-2015 (n=330), and controls comprised of individuals without ALS matched

on age (+1 year), gender, and geographic area, identified from targeted consumer marketing database lists (n~330).

They are using two things that they hope are going to work reasonably well hand-in-glove. The first is a survey of demographics, occupational history, residential history, pesticide use, hobbies, and personal risk factors. For cases, the ATSDR ALS Registry survey self-administered on-line will be used. For controls, a computer-assisted-telephone interview (CATI) will be used that is comprised of the same questions and format as the CDC ALS Registry survey. The second is that they will attempt to compare these with blood analyses for persistent organic pollutants (POPs). The cases will come from the ATSDR ALS Biorepository Pilot Study from the biospecimen study component results of analyses of blood samples for pesticides and other chemicals conducted by CDC, which are soon to be underway. The controls will receive a home/office visit for a blood draw. Those most likely will be a home visit, because it makes it easier for the person to complete and the team to control the methodology of how the blood will be taken and shipped. Specimens will be sent to the same laboratory in British Columbia that is used for the measurement of the ALS Biorepository case samples.

The specific aims of the study are as follows:

- ❑ Specific Aim 1a: Evaluate self-reported environmental/occupational exposure to metals, pesticides, and solvents for ALS cases and controls as independent risk factors for ALS
- ❑ Specific Aim 1b: Download, link, and examine exposure to Ambient Air Pollution: Fine Particulate Matter (PM_{2.5}) and Ozone using EPA downscale modeled data:
 - Daily ambient 24-hour average PM_{2.5} (µg/m³) and 8-hour maximum ozone (O₃) (ppb) linked to residence using a downscaling modeling approach from EPA Air Quality System (AQS) for 2002-2012. Bayesian space-time modeling to combine air monitoring data and gridded numerical output from the Community Multi-Scale Air Quality Model (CMAQ) to produce point level daily air pollution predictions.
 - Person-specific exposure estimates will be developed based on residential history obtained from the ALS Registry survey (city/town and state on all locations where the case/control lived for ≥6 months). If Census tract is not available, we will modify our approach to develop estimated exposures at the most resolute geographic level available.
 - Average yearly exposures over time will be estimated. Average weighted exposure estimates for each participant will be computed for the full-time period (2002-2012) (till year of diagnosis for case-control match).
- ❑ Specific Aim 1c: Download, link and examine Ambient Air Toxics: EPA National-Scale Air Toxics Assessment (NATA) Data:
 - Residential addresses of cases and controls will be linked to NATA concentration data of 35 suspected neurotoxicant hazardous air pollutants (HAPs) for the years 1996, 1999, 2002, 2005, and 2011.
 - Historical exposure at different time periods will be constructed by assigning the residence at the time of each NATA assessment to that year's HAPs for the geographic area. For intervening years, the data will be interpolated (e.g., 1999-2001), etc.
- ❑ Specific Aim 2: Measure exposures to solvents and pesticides in samples (n=309 cases, n=309 controls) with a battery of tests using blood concentrations of persistent environmental pollutants (pesticides and solvents) in cases and controls:

- To capture earlier years of exposure, we will focus on levels of neurotoxins known to have long (>7 years) half-life exposures.
 - There has been only one study to date of pesticides in serum by Su *et al.* (*JAMA Neurol.* 2016) (n=101 cases, n=110 controls).
- **Specific Aim 3:** Among ALS cases, examine the functional relationship between environmental toxicants in human biological samples and key biological pathways and common genes associated with the development of ALS:
- DNA for ALS cases will be used to test for genes not yet covered by the NeuroChip along with the DNA test results, and participant test results for heavy metals and POCs.
 - Within ALS cases examine the most common mutations as a group as well as the prevalence of the C9ORF72 repeat expansion and describe the distribution of their characteristics and environmental exposures of interest.

In terms of progress during Year 1, they had to get IRB approval and complete an MTA and data use agreement (DUA). Data have been obtained from the National ALS Registry survey dataset on cases and checked for completeness. They have started the control sampling methods and protocol. They have developed recruitment materials, a brochure, a website, a CATI survey, scripts, and completed a pilot of the survey. They hope to commence interviews by September 2018. PM_{2.5} and ozone EPA downscale data have been downloaded, as well as EPA NATA data for the US. The blood draw protocol and service agreement have been completed for control specimens, and they are using the same group that Drs. Mehta and Kaye used for the ALS Biorepository. They have begun to develop a sampling frame for control identification via a vendor, MSG, which makes lists available for both cell and land lines by geographic region, age, and gender. They have 63 ALS cases mapped and matched to 945 potential controls (15 controls per case). Survey instruments from ATSDR/ALS have been programmed into their [Qualtrics Survey System](#). They have trained 10 interviewers and commenced with internal piloting. As a method of incentive remuneration, they have initiated the WePay card system. Recruitment materials (e.g., telephone scripts, ALS research website, pre-notification letters and a brochure) have been developed.

Among the surveys needed from the ALS Pilot Biorepository Participants for the cases (n=330), the degree of completion is shown in the following table:

| Survey # | Survey Description | N | Percent |
|----------|---|-----|---------|
| 1 | Background Information (demographic data) | 280 | 84.8 |
| 2 | Occupation | 268 | 81.2 |
| 3 | Military History | 266 | 80.6 |
| 4 | Smoking | 263 | 79.7 |
| 8 | Residence History | 93 | 28.2 |
| 9 | Occupational History (specific exposures) | 94 | 28.5 |
| 10 | Home Pesticide Use | 93 | 28.2 |
| 11 | Hobbies | 67 | 20.3 |

Among the surveys needed, 8-11 were added later so they do not have high completion rates. There are reasonable data for residential history on 93 people. Going forward, they will start with these 93 people, but they would like to know if it is possible to tap into the newer people who are signing on to augment the sample size with some newer data. For the study to be credible, they do need good residential history because they are linking it to all of the other databases that relate to pesticides, solvents, and environmental exposures. Dr. Talbott said that while she understands that the Registry is hypothesis-generating, to look at the possibility of causation and putative factors, there have to be controls. The pesticide question is best answered with a control population.

Discussion Points

Putting aside any environmental factors like lack of phone service or the absence of a caretaker to help the person with ALS on the phone, Mr. Baker asked what is preventing them from using CATI to try to increase the number of responses from PALS.

Dr. Kaye indicated that the primary reason is cost. It costs hundreds of dollars per person to put somebody on the phone for those kinds of surveys.

Dr. Factor-Litvak added that they have done telephone interviewing with PALS in the ALS Multicenter Cohort Study of Oxidative Stress (ALS COSMOS) and the ATSDR Risk Factors Epidemiologic Studies in ALS (ARREST ALS), as well as with the controls in ARREST ALS. They generally can do this. It requires very dedicated interviewers as well as a caregiver in the home to help the patient with questions they cannot answer.

Dr. Talbott agreed that it could cost hundreds of dollars. They are using CATI for which they will be charged \$55, but that is the university.

Dr. Thakur observed that this raised an interesting point about trade-offs within the program. If more money is spent on survey collection, that means there is less money for the Biorepository. That may or may not be a reasonable trade-off, but it is worth thinking about.

Dr. Goutman asked what their projected response rate is for controls in terms of the number of people they will need to contact to recruit 1 control participant.

Dr. Talbott replied that while they do not know, they have estimates from the National Health and Nutrition Examination Survey (NHANES) and the Behavioral Risk Factor Surveillance System (BRFSS). The Behavioral Community Health Survey Department has a dedicated interviewing component to it, so they are highly trained and skilled. They are hoping that the response will be between 60% and 70%, but they really do not know. They are offering an incentive that is dependent upon signing on for both parts of the study (survey and phlebotomy). They are sending people a pre-paid Visa card at the completion of the study, which they hope will help. They have a combination of land-line and cell phone numbers, which is crucial to getting people on the phone. They hope that due to the Ice Bucket Challenge and other ALS efforts that have been going on since 2009, everyone knows that ALS is an important condition to study. They are going to appeal to this group of people who will be largely 60 to 70 years of age to “step up to the plate” and get involved.

Dr. Brooks asked whether their organic assays will pick up phthalates, which he asked because he wondered if they were measuring the right things. One of the epidemiological key points for ALS is a higher rate of hypothyroidism, which is related to phthalate toxicity. Phthalates are

present in jet fuel, so the Air Force is assessing phthalate levels in the air bases in terms of exposures.

Dr. Factor-Litvak indicated that phthalates cannot be well-measured in blood because the assays are not good and they are subject to contamination. Measuring the metabolites of phthalates in urine is the way to do a phthalate analysis. She noted that perchlorate is in jet fuel, while phthalates are in plastics. Consideration must be given to the toxicokinetics of the actual contents. Phthalates have a very short half-life of hours to maybe a day at most, and perchlorates have a relatively short half-life as well. Both are associated in some but not all studies with hypothyroidism. Thinking about non-persistent contaminants like perchlorate, phthalates, bisphenol A (BPA), and other phenyls is one issue because only recent exposure can be measured. To measure long-term exposure, polychlorinated biphenyl (PCBs), certain of the chlorinated pesticides, and brominated flame retardants (BFRs) are persistent and are sequestered in fat. Cumulative exposure can be measured for these throughout a longer period.

Identification and Characterization of Potential Environmental Risk Factors for ALS Using the ATSDR ALS Registry Cases and a Control Population

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Dr. Bradley provided a broad overview of “A Population-Based Ohio ALS Repository and a Case-Control Study of ALS Risk Factors” funded by ATSDR. Ohio is in many ways an epicenter of some of the environmental risk factors that relate to ALS. This state has had an enormous amount of industrial activity, a very large agricultural industry, and large cyanobacteria blooms that affect Lake Erie and many of the other lakes in the region. It also has a network of quite large medical centers that deal with ALS. They thought that Ohio would be a very useful place to extend the State and Metropolitan Surveillance Program that the National ALS Registry had in operation earlier, and to offer this possibility of being able to do essentially the same in Ohio and to combine it with a case-control study of environmental factors as risk factors.

They submitted a grant application to the National ALS Registry with 3 specific aims, which was designed to be a 3-year study in which patients would be collected over 2.5 years and obtain IRB approvals for extending this to the various centers over the whole of Ohio. They initially intended to just look at the North two-thirds of Ohio, because they developed this collaboration with the Cleveland Clinic and Dr. Erik Pioro, as this was where the main drainage of patients from the Northern parts of Ohio presented. Unfortunately, they did not get funding for that first year. However, they were lucky enough to get funding after that first year, but only for a 2-year period. The specific aims of the study are to:

- ❑ Assess ALS incidence by developing the Ohio ALS Repository, a comprehensive, population-based ALS registry for newly diagnosed residents of northern/central Ohio. In order to have enough ALS patients, the study was extended to the whole of Ohio. At the start of the study, Ohio had a population of about 10 million and the latest Census says it is about 12 million. They projected for a 2-year period over the whole of Ohio that they would recruit about 314 patients based on an incidence of about 2/100,000.

- ❑ Identify ALS risk factors by comparing questionnaire data on exposure to environmental toxins and toxicants between ALS patients and controls, which Dr. Stommel and colleagues have been doing for several years in Northern New England, and to look in a case-control fashion at those risk factors.
- ❑ Perform geospatial analyses of potential residential environmental exposures to a variety of toxin and toxicant sources in relation to the risk of developing ALS.

In terms of progress to date, they were able to set up all of the IRB permissions in the Cleveland Clinic, the networking collaborations with all of the MDA and ALS Association chapters in Ohio, and the plans for all outreach activities before the funding started. What they were not able to get set up before the funding was the network of IRB permissions in all of the other medical centers in Ohio. This has proved to be a very difficult problem, given that they have to deal with the individual IRBs in each of these institutions. They have only recently come on board, with approval now for virtually every one of the medical centers they need to work with in Ohio. The only one they have had absolutely no ability to get into is the VA, but they are still trying to work on that one because it is likely to be a significant source of ALS patients.

Primarily what they have to report as of August 1, 2018 are the patients who have come through the Cleveland Clinic. The criterion for inclusion is patients who were diagnosed between October 1, 2016 through September 30, 2018. Thus far, they have recorded 152 patients with ALS with the requirement that they have definite or probable ALS. That is an incidence at this moment of approximately 50% of what they think the frequency of the disease should be in that population. About 265 patients who went through the Cleveland Clinic did not qualify because they either were from out of state or were diagnosed before October 2016. Thus far, 85 questionnaires have been collected from the 152 patients, which is about 50%. Among the random population controls, 217 have completed questionnaires. This has been an interesting and relatively cheap activity, with 2000 invitations mailed out to invite people to complete questionnaires. From that, they received the 217 questionnaires. Among the 69 clinic controls, 24 questionnaires have been completed.

Of course, they need to get the cases from the remainder of Ohio. The plan is to have a trained RN to visit 20+ neuromuscular centers between March 2019 and May 2019. She will record all of the ALS patients in the centers, with the hope of getting a better ascertainment of the frequency. It is anticipated that they will have another 80 to 120 additional cases coming out of the other medical centers in Columbus, Cincinnati, and others. They look forward after the end of this study to being able to obtain annual ALS patient deaths in Ohio (2016-2021) from the NDI Plus Service to compare with this Ohio ALS Registry count. They also have been collecting biosamples. To date, blood samples have been collected from 36 ALS patients and 7 clinic controls. Toenails have been collected from 59 ALS patients and 18 clinic controls.

With regard to Specific Aim 2, they have collected the environmental pollution sources from a tremendously intense database that they think is going to be very useful for this and future studies. This is an enormous database. The number of sites that can release environmental pollutants include landfills, municipal incinerators, National Priority List (NPL) sites, et cetera. From this, an Ohio population-based case-control analyses have been completed and have been reported or are in the process of reporting that a number of solvents, lead, and pesticides have an increased risk ratio in these case-control studies. Occupations involving construction, manufacturing, mechanical, military, or painting have an increased odds ratio. Waterskiing, which results in exposure to cyanobacteria, has an increased odds ratio. Interestingly enough,

they published a paper recently showing that prior chemotherapy is a protective agent. However, the reason is not yet known.

Regarding Specific Aim 3, databases of sources of environmental pollutants in Ohio have been completed for individual sites of pollution (n=2551), individual chemicals recorded in those sites (n=282,502); total number of chemicals (N=~ 10,000/site); and cyanobacteria compound metrics for all lakes >8 hectares in Ohio, including Lake Erie and Grand Lake St. Marys. The GIS exposure case-control analysis of Ohio is pending completion of collection of all Ohio ALS cases. Completion of the GIS component is dependent upon funding support, which they are currently seeking. The projected start date for the GIS analysis is June 2019.

Discussion Points

Dr. Brooks observed that Ohio is indeed a great laboratory. Dr. Ralph Buncher looked at pesticide use many years ago, so he suggested bringing Dr. Buncher out of retirement to assist on this study. Dr. Buncher's first pass at this was that there was no relationship between the use of pesticides at the county-level. Dr. Bradley at al are looking at a different level, which will be very important.

Dr. Bradley replied that they are expecting to be able to do this on a countywide basis or finer for pesticides. That type of analysis is actually better-designed for not only the state, but also for national evaluations. They do plan a national evaluation of that.

Dr. Feldman asked whether there is a central database for the sources of environmental pollutants in Ohio described for Specific Aim 3 that is an umbrella for the multiple databases.

Dr. Bradley replied that those analyses are all from Northern New England, which is a single database. They plan to amalgamate both the Ohio study, the Northern New England study, and a database they have collected for Florida. They intend to roll that all together into a single database.

Dr. Wright said ATSDR shares his pain with the administrative burden of IRBs and those processes. The Common Rule is going into effect probably within the year. If she understands correctly, there are a lot of changes afoot for extramural research, including whether surveillance research is considered research under the Office for Human Research Protections (OHRP) as well as management of IRBs of record, which is the Cleveland Clinic for this study.

Dr. Kaye requested additional information about what Dr. Bradley plans to do with the NDI data, because she did not think that what they proposed is permitted.

Dr. Andrew replied that they planned to use this to try to validate the incidence rate that they have compared to the expected number of deaths in the NDI.

Dr. Kaye explained that the NDI would not give them people based on cause of death. A list of names has to be provided to the NDI, which they will run to indicate what was on their death certificate. They do not go the opposite direction. They might be able to obtain the data from the Ohio Department of Health (ODH), after going through their review process and IRB.

Dr. Bradley said his concept was that they would simply look at the number of deaths in approximately their timeframe to see how that correlates.

Dr. Kaye said she did not think NDI would tell them how many people died of ALS.

Dr. Weisskopf indicated that this information could be obtained from the CDC Wide-ranging ONline Data for Epidemiologic Research (CDC WONDER). From NDI, Dr. Bradley should be able to get the overall mortality rate for his region for a given time.

Dr. Finger thought what Dr. Bradley has done reinforces the importance of the central ALS Biorepository, given all of the difficulties in collecting the data. Given all of this effort, he asked how these data would be shared with the National ALS Registry. If it cannot be shared, he wondered what the Registry was trying to accomplish with this funding in terms of whether it is about funding additional registries or trying to leverage what the National ALS Registry is doing.

Dr. Bradley indicated that one of the things they initially discussed with the Registry regarded how they could provide to the Registry the cases they found in that time window and compare them to the cases enrolled with the Registry during that same time frame. They came to the recognition that unfortunately, the Registry could not provide the investigators with the names because of the OMB and other problems. However, the investigators could provide the names or at least some identifier characteristics that would allow cross-correlation. They have not thought this through yet, but have to begin to think about it. In terms of questionnaires and samples that will be collected in Ohio, there is a possibility of at least sharing all of the questionnaire data.

Toenail Mercury Levels and ALS Risk

Angeline S. Andrew, PhD
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Dartmouth College

Dr. Andrew reported on some of the mercury work that she and her colleagues have done in New Hampshire and Vermont that motivated their request for nail samples from the National ALS Biorepository. For the Northern New England case-control study, questionnaires were used that were collected between 2009 through 2015 to look at self-reported metal exposures. Lead has been shown in many other studies to be a primary risk factor. However, mercury which was a primary hypothesis, did not show any self-reported risk based on occupational- or hobby-related self-reported exposure. The literature on occupational studies of mercury exposure and ALS are fairly inconsistent. Some show no relationship at all¹, while others show an increased risk associated with occupational exposure² [Gresham, 1986 and Moriwaka, 1986; and ² Provinciali, 1990, Praline, 2007]. There are numerous case studies of individuals with ALS that have been directly related to mercury toxicity that actually show various remarkable symptoms of ALS and a compelling relationship. Some animal studies of methylated mercury, an organic form of mercury, do show accumulation of mercury in the large spinal motor neurons and the loss of these neurons subsequently [Su, 1997].

That information led them to hypothesize that perhaps it is the form of mercury that is critical. The form of mercury most people are familiar with is the silver liquid elemental form mercury like that in a thermometer. This form of mercury is not well-absorbed through the skin, although the vapor is quite toxic so it is not to be taken lightly. There also are inorganic mercury compounds, specifically methylmercury, which is the form that is found in fish tissue and it persists in fish despite cooking and is 95% absorbed in the GI tract and binds to proteins, specifically cysteine [Mergler, 2007].

Dr. Andrew and her colleagues proposed to use toenails as a biomarker of exposure to mercury based on some prior studies in cancer, because the toenails reflect an integrated exposure over about 6 to 9 months and are not highly variable based on what was eaten the day before for example [Bergomi, 2002]. The high sulfur and keratin content of the toenails binds mercury and they can reflect methylmercury exposure, and are highly correlated with brain mercury level in several autopsy studies [Bjorkman, 2007].

For a study in 2014 after Dr. Andrew joined the group, they started collecting toenail clippings, but did not see strong relationships between either age or gender and toenail collection. They sent the toenails to the Trace Metals Core at Dartmouth, which is run by Dr. Brian Jackson. He washed the toenails, acid digested them, and ran them through an inductively coupled plasma mass spectrometry (ICP-MS) to measure multiple metals, including mercury. He found a significantly higher level of mercury in the ALS cases compared to the controls with a 2.5-fold odds ratio or increased risk of ALS associated with the mercury exposure above the median. These results are adjusted for age and gender.

After that finding, they went on to test the hypothesis that perhaps the source of the mercury in the toenails would be methylmercury based on fish consumption. It is well-known that methylmercury is bioaccumulated, biomagnified in fact, through the food chain and would be present mostly in higher trophic levels of fish. They used a US market database of fish fillet mean methylmercury concentrations¹ to assign a methylmercury amount to the food frequency questionnaire-based reported fish consumption for each of the patients and controls in their database and found a significant relationship [Karimi, 2012]. The toenail mercury level that they measured was highly correlated with having an annual estimated mercury content from fish based on the questionnaire in the upper 75th percentile. Therefore, it seems that there is a relationship between the toenail mercury and fish consumption. Dr. Andrew emphasized that they looked at overall fish consumption in relation to ALS and there is evidently no relationship. Therefore, she was not saying that fish is the problem. She was saying the high trophic level of fish is a source of methylmercury.

Prior literature had shown a relationship in a Wisconsin study between eating a large amount of freshwater Lake Michigan fish and ALS risk. They speculated in their discussion that the reasons for that relationship could include PCBs, cyanobacterial toxins, or methylmercury¹. That is some of the only literature supporting a relationship between methylmercury from fish and ALS. Again, over fish consumption is not a risk factor. In fact, the dietary studies that were conducted in prospective cohorts of omega 3 polyunsaturated fatty acids, of which fish is a good source, do show a protective effect. Choosing the species of fish is important² [Fitzgerald, 2014; Sienko, 1990].

In summary, they found a relationship between toenail levels of mercury and an increased risk of ALS, and that those toenail levels were related to a high trophic level fish consumption. Now they plan to see if they find a similar relationship between nail levels of mercury and ALS in a larger cohort using nail samples from the National ALS Biorepository. They also are interested in conducting a study of nails from a prospectively followed cohort in which the nails would be measured at baseline and people would be followed over time.

Discussion Points

Dr. Weisskopf pointed out that one thing that must be considered for someone who has ALS is whether the excretory mechanism in the metabolism are changing, or even if toenail production is changing. It would be interesting to know whether that might affect the structure of the toenail.

If it slows down potentially, there might be accumulation over different time periods, which would need to be taken into account. When they are thinking of biomarkers, it is worth knowing what happens typically in an ALS patient with the production of whatever that biosample is.

Dr. Stommel indicated that changes in keratin occur in ALS patients, and ALS patients are generally less likely to develop decubitus ulcers because of the type of collagen that they have.

Dr. Andrew indicated that they measured a set of 12 metals, and she did perform an analysis of those to see if they are all off because there is some odd keratin in there, but they were not.

Dr. Brooks said that if he was studying toenails in people with syphilis and found that they had increased arsenic, he would not necessarily say that syphilis is caused by arsenic because it was being treated by arsenic. One of the controls for this has to be the incidence of fungal infection, whether every toe was examined, an assessment of whether there was any known fungal infection, et cetera. In strokes, the sweat changes on one side versus the other. They see seborrheic dermatitis in ALS and other neurological conditions as well.

Dr. Andrew agreed that with any biomarkers, they need to be very careful about what they are measuring and that there are not artifacts. They do measure multiple nails. They have the big and little toes, so they do have the pooled sample of multiple toes. The National ALS Biorepository sample will be fingernails, which should have the equivalent concentrations of methylmercury accumulation. They are traditionally less used for mercury studies because of the occupational external contamination issue, but that probably is not an issue in this population so much.

Dr. Thakur asked about the long-term implications of this if they conduct the prospective study next and have conclusive proof that mercury exposure leads to some cases of ALS.

Dr. Andrew said she thought the messaging would be very important. It is not that all fish is bad. It is about avoiding high trophic level fish, which is a good recommendation for multiple diseases. The location where fish are captured also is important, because there is a lot of variation between water bodies and mercury content. Avoiding consumption of self-caught fish from places with high mercury levels would be prevention. In terms of treatment, there have been some attempts at chelation which were disastrous, so that per se is not necessarily a good recommendation. However, perhaps there are alternative therapeutic strategies that could be used to ameliorate a person's high level of mercury.

Dr. Factor-Litvak suggested that they might want to measure levels of omega-3 or other fatty acids as well to see what is going on.

Dr. Brooks noted that University of Nebraska has found that some fish biomagnify cyanobacteria into the fish meat. The question is, could you conceptualize that this is a marker of fish consumption and not some other toxin that may be involved?

Dr. Andrew said she thought that was a good suggestion, and she would have to think about it more.

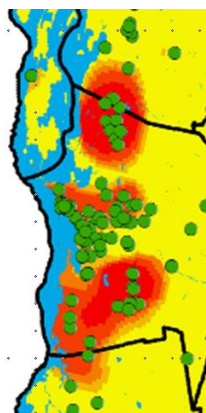
Aerosolization of Cyanobacteria as a Possible Risk for ALS and other Neurodegenerative Diseases

Elijah Stommel, MD, PhD
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Dr. Stommel indicated that the part of this study on which he was reporting was conducted primarily by students and pathologists. He explained that the link between cyanobacteria and ALS and neurodegeneration dates back to Guam in the 1940s when the American's took Guam from the Japanese. There was a very high rate of ALS, a Parkinson's-like disease, and a dementia-like disease that combined was called Lytico-bodig disease. In 1945, ALS frequency in Guam was 200-fold higher than in the rest of the world. In the search for a cause for this high rate of neurodegeneration in Guam, many epidemiologists and toxicologists went there to try to determine the cause. They found that the natives were eating cycad seeds and in the roots of these seeds were green rings, which is cyanobacteria. Cyanobacteria produce over 100 different toxins, many of which are neurotoxic. Beta-Methylamino-L-alanine (BMAA) is one that Dr. Stommel and his colleagues have been looking at very closely.

Cyanobacteria are ubiquitous. The same ones that are found in the roots of a cycad plant are found in many of the lakes they have looked at in New England, Ohio, and throughout the world. Nostoc is the particular species that was in the roots, but there are many forms of cyanobacteria that produce toxins. BMAA has been shown to cause protein misfolding and can actually incorporate the translational process in protein synthesis, substituting for L-serine. No one knows why BMAA is in cyanobacteria, and nobody has actually looked carefully to see what proteins and peptides are made by cyanobacteria using BMAA. It is very tantalizing to think that cyanobacteria are producing this non-biologic amino acid and can get into proteins. It also has been shown to decrease glutathione levels and sulfosalicylic, to increase reactive oxygen species (ROS), alter lipid metabolism, alter autophagy, to act as a glutamate receptor agonist under the right conditions, and can alter mitochondrial function. Cyanobacteria also makes an interesting toxin called Anatoxin-a(s). The "s" stands for hypersalivation. This is the only known natural organophosphate toxin. It is basically like a typical pesticide. It binds to the acetylcholinesterase and L-serine on that enzyme. It is about 1000-fold more toxic than the typical insecticides that are used on farm fields.

Over the last several years, they have been looking at the ALS distribution in Northern New England. This is the East Coast of Lake Champlain:



They have found several clusters of ALS along the shores of Lake Champlain, which has annual blooms.

A study they published a few years ago with the help of Nathan Torbick, who is a remote sensing expert, looked at water quality based on total phosphorous, chlorophyll counts, and cyanobacteria biovolume with remote sensing techniques. He was able to overlay that in Northern New England with where the ALS clusters are, and was able to show statistical geospatial correlation.

In terms of the questionnaire analysis for the “Aerosolization of Cyanobacteria as a Possible Risk for ALS and other Neurodegenerative Diseases” 294 patients with a confirmed ALS diagnosis were compared to 225 controls without neurodegenerative illness. One of the interesting associations they saw was that some water sports, such as waterskiing, were associated with ALS. In fact, based on the questionnaire data, there are people who live near these lakes who do not eat the fish out of the lake or get the water out of the lake but they have been living there for a long period of time.

Therefore, they have been looking more carefully at the idea that perhaps aerosolization is an important route of exposure. They have been setting up filter collectors that were designed by Jim Haney from the University of New Hampshire. They set these up for several hours at a time. They have a pump, filter, and cone screen. After the pump has been run for 6 hours at a time, it is possible to see with fluorescence microscopy an accumulation of cyanobacteria on the filters. They have a pigment in them called phycocyanin, which when excited with a wave length of 572 nm will emit the wave length at 640 nm and is very characteristic with cyanobacteria. They can correlate this with polymerase chain reaction (PCR) to know they are not getting a false reading.

They took this one step further and looked at 100 random postmortem cases for which they had lung and brain tissue in their databanks at the University of Vermont and Dartmouth. This was all double-blinded so that the people who were looking at the tissues did not know where the patients came from. In that group, 18 cases had evidence of neurodegeneration. Among the 18, there were 14 in which the fluorescence in the lung was positive and 4 in which it was not. The fluorescence was generally in the upper lobes of the lungs as might be seen with tuberculosis (TB). That was statistically positive, especially the univariate. Association with the odds ratio was 6.6. Out of that group of 18 patients who had neurodegeneration, there were 1 ALS case, 1 Parkinson's case, 12 Alzheimer's, and 4 cases in which the patients had not developed evidence of neurodegeneration clinically, but had evidence of neurofibrillary tangles/amyloid plaques.

They then took that another step further to look at 60+ bronchoscopy cases. These were cases that went to the bronchoscopy laboratory for diagnostic and therapeutic workups, from whom they collected bronchoalveolar lavage (BAL) samples. They have questionnaires for a lot of these patients. The idea is that there is aerosolized cyanobacteria exposure that gets into the lungs, and nasal swabs and bronchoscopy samples can be collected. The nasal swabs were done because they thought that might correlate well and might be an easier way to identify patients who had been exposed. They are still doing this to some extent. There is not a great association between the BAL and the nasal swabs, maybe because the nasal cavities are flushed out more frequently or because people are blowing their noses.

In summary, cyanobacteria produce harmful toxins that have been associated with the etiology of numerous human diseases like non-alcoholic liver disease and amyotrophic lateral sclerosis.

Using PCR, cyanobacteria were found at high frequencies in the upper respiratory tract (92.20%) and central airway (79.31%) of the study subjects. Nasal swabs were not predictive of BAL when detecting inhaled cyanobacteria. PCR findings were not significantly associated with time of year or proximity to a waterbody. In Northern New England, the lakes are frozen over and a lot of aerosol would not be expected to come from water, but it does raise the question regarding whether some of it may be coming from air conditioning systems or some other source they are not aware of. Cyanobacteria do not survive well in a dark environment. They like the sun, so they do not think they are sitting in the lungs for long periods of time and taking up part of the biome. There is a group in California looking at cyanobacteria in the gut. There is not a lot of light in the gut, so Dr. Stommel's guess is that these bacteria are being replenished from the environment over and over. They do feel that aerosol is a significant route of exposure for cyanobacteria transmission, and that perhaps people are inadvertently exposed to very high doses when they are living near a waterbody that has blooms. They have not been able to quantify exposure to cyanotoxins through aerosolization.

Discussion Points

Dr. Mehta observed that one could potentially hypothesize that with climate change and the harmful algal blooms that have been occurring in increasing numbers across the world and some parts of the US, and that there is a potential between cyanobacteria and ALS, that the rates of ALS would be increasing.

Dr. Stommel responded that there is a group in Australia who presented a lecture to a group about a year or two ago, and indicated that the death rate from ALS has doubled in the last 20 years in Australia. They have looked very carefully at potential risk factors. They have a horrible problem with cyanobacterial blooms in Australia. Knowing that there is probably a lag period between exposure and when a disease may present itself, there may be some nasty surprises down the road, though he could not say that with certainty. It is probably also important to note that there is some synergism between toxins and the idea of the theory of getting 6 hits and having genetic predisposition. It is interesting that BMAA and methylmercury have a synergistic relationship in vitro in cell culture, so they are much more toxic when they are together than when there is one or the other.

Dr. Thakur said it seemed like they were really on to something with this, and it made him wonder at what point they need to think about a public health prevention campaign. What level of evidence would trip that decision to go into a broader mode of prevention efforts? He works for the ALS Association and if there is a way to prevent more cases of ALS, that is something that they should be thinking about. He was trying to figure out at what point this line of research should lead to some kind of prevention campaign and what that prevention is. That is two separate questions, and the first one must be answered before designing preventions. The first question is do we know enough now to be trying to prevent these exposures?

Dr. Stommel pointed out that the US has a President and a large group of politicians who deny that there is any global warming. There is no doubt that global warming is a major fuel for this type of problem. Negating the blooms can be approached through diminishing runoff, having better buffers around lakes, having better septic systems, et cetera. In the City of Boston where the Charles River is now having annual blooms, the Conservation Law Foundation has sued the State of Massachusetts, the City of Boston, and the City of Cambridge because they have not taken care of runoff into the Charles River. It is a huge problem. In Vermont, there are all types of agriculture. Phosphorous banks from fertilizers and feed over hundreds of years have built up

so that even if they try to mitigate putting more phosphorous on the fields, they cannot get rid of what is already there for a long period of time. Florida is another example of that.

Dr. Bradley said that the departments of health should be responsible for answering Dr. Thakur's question, or at least raising the question about whether cyanobacterial blooms are important in terms of ALS and other conditions like that. In Florida, the department of health is in a defensive mode talking down any possibility of such an association. Florida is dependent upon tourism and these filthy algal blooms, which are now becoming increasingly prevalent, are not good for tourism. There are notices beside the algal bloom areas that contain notice that people should not go swimming in it, should not let their animals go into it, and so forth. On the other side they say, "There is some talk that this is related to neurodegeneration, but you shouldn't believe it."

Dr. Finger asked Dr. Stommel to speak about how they are using data from the Registry or will be able to share some of their data with the Registry, and if they have looked at the connection with private backyard swimming pools or ponds. They might get more geographic variation instead of having to look at all people living in one place. People dispersed around the country may have these blooms in their backyards.

Dr. Stommel responded that they are working with the Registry in that they are relying on them for support, and are planning to compare their populations to those of the Registry. They have been given nail samples, in which they are planning to measure methylmercury levels. They have a nice databank of postmortem tissue that they may request at some point. In terms of backyard ponds and swimming pools, swimming pools are not such an issue. However, he does worry about air conditioning systems, especially ones that are open to the air and ones that are not taken care of routinely. He said a technician for the air conditioning system come to their hospital, and he showed them photographs from some other places he had been. They asked him for additional data and he went to his risk management people, who forbid him to ever return to see them again. A paper was recently published in Connecticut showing the Legionnaire's disease is very common along some of the rivers in Connecticut. Legionella, the bacteria that is found in a lot of waterbodies, water fountains, and air conditioning systems also has some type of synergistic relationship with cyanobacteria and they like to be in the same waterbodies. So, they are hoping to work with the group who did that work.

Dr. Bowser observed that their aerosol experiments seemed to be done on the lake. He wondered if they had placed the apparatus on the shore at the same time to try to correlate what they are seeing in the lake versus what is seen inland and how far inland that goes.

Dr. Stommel said that they have been doing that for the last two years and are in the process of putting all of the data together. They have collected as far as a mile away, but have considered whether they should go even further than that because there are some data on Legionnaire's disease that suggest exposure can occur as much as 10 kilometers away. They are looking with PCR on the filters, enzyme-linked immunosorbent assay (ELISA) assays for microcystin, which is a liver toxin, and they are doing fluorescence microscopy on the filters.

ALS Risk in Latin Americans: A Population-Based Case Control Comparative Study with 3 European Population-Based Cohorts

**Marcienne Wright, PhD, LT USPHS
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Extramural Research Program Office
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Dr. Wright presented an update on “ALS Risk in Latin Americans: A Population-Based Case Control Comparative Study with 3 European Population-Based Cohorts” on behalf of Dr. Orla Hardiman from the University of Dublin Ireland, who was unable to attend. Dr. Hardiman was funded in 2016 for 2 years to conduct a large-scale, population-based comparative study of ALS incidence, prevalence, phenotype, and risk factors in admixed populations. Her study aims are to elucidate the true demography of ALS and test the hypothesis that there exists a differential risk of developing ALS in admixed populations and a differential ALS phenotype in populations of mixed ancestry. To investigate this hypothesis, Dr. Hardiman and her team are collaborating with partner investigators in the Latin American Epidemiology Network of ALS (LAENALS) to evaluate the incidence, prevalence, phenotype and risk factors in admixed populations and to then follow-on with a comparative analysis of these populations within an existing dataset with which Dr. Hardiman has extensive experience called the EuroMOTOR Consortium dataset. This houses ALS epidemiological data from five European population-based registries.

She is conducting ascertainment of ALS cases and matched control cases from study populations in Chile, Cuba, and Uruguay. The rationale for using these particular communities is that Chile's population is primarily of Spanish and local South American origin. Cuba's population is highly admixed compared to the populations of Chile and Uruguay with 55% of the population identifying as white, 33% self-identify as mixed, and 12% self-identify as black. Uruguay's population is primarily of European descent. Dr. Hardiman's argument is that combining these cohorts and the data that she obtains from using these 3 communities would more closely approximate what is occurring in the US. She is expecting to analyze a sample size across these three communities of 900 ALS patients and 1800 matched controls. In her Specific Aim 2, she will perform an analysis with the EuroMOTOR Consortium dataset which has 1500 ALS cases and 3000 controls to date. The EuroMOTOR Consortium primarily pulls from Ireland, Italy, and the Netherlands.

Dr. Hardiman's rationale for the study is that ALS is likely not uniform outside of the European population, and that the existing registry data in the US is imperfect with respect to the relationship that admixed or different ancestral origin would have on its relationship to the development and progression of ALS. The hypothesis is that there is differential incidence, phenotype, and risk factors that are likely reflected in US admixed populations and that characterization of these populations using the US instruments is not standardized or validated and that these studies need to be conducted. Therefore, she wishes to evaluate true population-based frequencies of ALS adjusted for population structure and elucidate better phenotypic, epidemiologic, and exposomic data to identify what the differential presentation and risk factors are.

Working with the LAENALS, Dr. Hardiman has identified 3 teams of researchers working in these communities. These teams will conduct clinical evaluation, ALSFRS, appropriate neuropsychological battery, family studies, and quantitative exposure studies. Some of the quantitative exposure studies include looking at trauma, exposure to Persistent Organic Pollutants (POPs), exposure to occupational hazards, use of drugs in the context of sports

injuries, and military history. The investigators will conduct regular follow-up for survival and will collect DNA samples.

Under Specific Aim 1, incidence and clinical phenotype of ALS in 3 genetically distinct Latin American populations, the specific objectives are to: 1) train investigators and sub-investigators in the diagnosis and evaluation of ALS, which has been achieved; 2) ascertain cases using the existing medical infrastructures in these communities supported by the trained investigators, which is ongoing; 3) establish a Latin American dataset, which has been achieved; and 4) report incidence and detailed clinical phenotype of ALS in these communities, which is ongoing. Under Specific Aim 2 regarding the exposome, the objectives are to: 1) establish the quantitative exposome in population-based cohorts from South American and the Caribbean; and 2) identify environmental risk in 3 Hispanic populations of different ancestral origin and compare them with risks in European populations using standardised methodologies.

Field work was initiated in Chile and Uruguay on March 1, 2018 and in Cuba on July 15, 2018. For Uruguay, 60 cases have been identified. Of these, 10 were deceased and 45 have been assessed. Recruitment of both ALS cases and matched controls continues there. In Chile, 40 ALS patients have been contacted, 17 assessments have been completed and 8 are in progress. Of the patients contacted, 10 were deceased and 5 declined. There were a number of administrative and political confounders to initiating enrollment in Cuba. Cuba agreed to recruitment of ALS specialists in other regions. Training of field workers in Havana has been completed, enrollment in Havana commenced and enrollment in other regions is due to commence in August/September 2018. In terms of the issues in Cuba, the kick-off meeting was delayed to May 2018 as additional approvals and permissions were required from the Ministry for Health to hold the meeting. There were administrative issues relating to funding sources, such as the change in the relationship between the US and Cuba. Additional approvals were required with the new protocol submission to the Ministry of Health.

In terms of next steps, Dr. Hardiman submitted and has been granted a no-cost extension to continue the work into Year 3. Rapid recruitment is anticipated in Chile and Uruguay. With the resolution of administrative difficulties in Cuba, rapid recruitment is anticipated in the third and fourth quarters of 2018. There is remote monitoring of the quality of data from all 3 enrollment sites, which will be uploaded to the centralized database in order to make the direct comparison to the EuroMOTOR Consortium dataset.

Dr. Hardiman's preliminary data show that there seems to be some differential reflection of ALS development, diagnosis, and progression in admixed populations as reflected in the table on the following page:

| | Cuba (n=115) | Ireland (n=1038) | Uruguay (n=220) | p value |
|--|-------------------|---------------------|--------------------|---------|
| <i>Continuous variables (mean and 95% confidence interval)</i> | | | | |
| Age of onset (years) | 53.0 (50.4, 55.6) | 61.6(60.9, 62.4) | 58.2 (56.5, 60.0) | 0.0001 |
| Age of diagnosis (years) | 54.4 (51.9, 56.9) | 63.0 (62.3, 63.7) | 59.5 (57.8, 60.3) | 0.0001 |
| <i>Continuous variables (median and interquartile range)</i> | | | | |
| Onset-diagnosis interval (months) | 12.0 (7.0, 17.0) | 11.0 (6.0, 19.0) | 10.0 (5.1-18.8) | 0.791 |
| Survival from onset (months) | 39.0 (24.0, 70.0) | 35.0 (23.0, 63.0) | 36.9 (22.9, 71.4) | 0.808 |
| Survival from diagnosis (months) | 26.0 (13.0, 48.0) | 21.0 (12.0, 41.0) | 23.5 (12.8, 42.9) | 0.718 |
| <i>Nominal variables (%)</i> | | | | |
| Gender (male) | 54.8 | 58.9 | 61.8 | 0.455 |
| Site of onset (spinal) | 60.9 | 64.1 | 66.4 | 0.603 |
| FALS present (yes) | 15.8 | 11.8 | 5.0 | 0.004 |
| Riluzole (prescribed) | 37.5 | 83.1 | 25.1 | 0.0001 |

Here, she compares Cuba (highly admixed), Ireland (highly European), and Uruguay (Spanish/local South American) and shows that there appears to be a lower age of onset in the Cuban population compared to Ireland or Uruguay, a lower age of diagnosis in the Cuban population, a higher incidence of familial ALS in the Cuban population, and a higher use of riluzole in Ireland.

In closing, Dr. Wright welcomed comments, particularly with respect to how US registries can better reflect or acquire data from minority or admixed populations.

Discussion Points

Dr. Mehta asked Dr. Wright to speak further about the internal limitations of the ALS Registry to fund and partner with institutions outside of the US.

Dr. Wright noted that this was a good forum in which to discuss this since many of the participants in the room apply for the ATSDR R01 funding opportunities that are published for the ALS Registry and Biorepository. For those funded under TS15-001, which included all of those presenting during this meeting, they were able to permit foreign institutions to apply for and be considered in peer review for awards as standalone entities. For the rollout of TS17-001 that introduced the use of the Biorepository and was funded last year, they were not able to consider foreign institutions either as standalone entities or as collaborators. They were fortunately able to push back on that somewhat for TS18-001, which was opened earlier this year. Investigators under that umbrella are allowed to have foreign collaborators with the caveat that US institutions are not acting as passthrough institutions for the foreign collaborators. She, Dr. Mehta, and the ATSDR program understand that much of the good data are in foreign

communities and with their foreign collaborators. They will do what they can in future NOFOs to ensure they are getting the best science, instruments, data sources, and resources to advance the science. As investigators look for NOFOs, she invited them to consider foreign collaborators as appropriate to their research plans, and ensure that they have healthy US leadership and institutional components.

Environmental Risk Factors and Gene-Environment Interactions in ALS Risk and Progression

Marc Weisskopf, PhD, ScD

**Associate Professor, Departments of Environmental Health and Epidemiology
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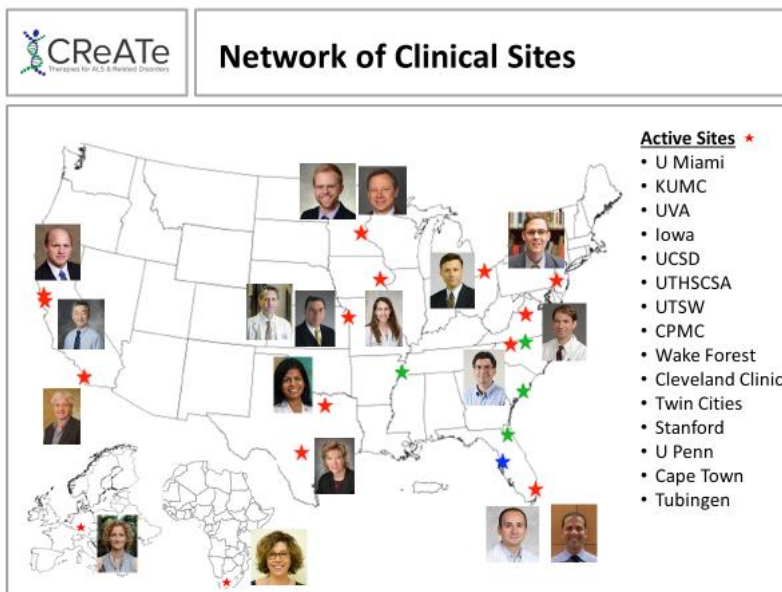
Dr. Weisskopf provided an update on their project with Dr. Benatar to examine the environmental risk factors and gene-environment interactions in ALS risk and progression, that also was funded a couple of years ago and ran into many of the same problems various other awardees have. The basic idea is that progression and incidence may be separable phenotypes and different risk factors potentially can be found. For example, the A4V superoxide dismutase-1 (SOD-1) seems equally aggressive despite age of onset of ALS.

While much of the epidemiological research has focused on the incidence of ALS, there are some factors that are thought to predict progression of ALS including the following:

- Older age of onset
- Bulbar onset
- Latency from symptom onset to diagnosis
- Lower BMI
- Frontotemporal syndrome/worse cognitive function
- Specific genetic variants
- A4V mutation in SOD-1 gene
- UNC13A (rs12608932 minor allele)

Very few studies have focused on environmental impact on the rate of disease progression and little is known about gene-environment effects, which is why they wanted to explore that space irrespective of the control issue. This is an advantage in a registry because it does not depend upon controls. In terms of progression, they are looking only at cases to examine what factors among those cases predict different rates of progression with ALS. This gets around the control issue all together. To that end, the specific aims of this study are to: 1) examine the influence of non-genetic factors on ALS progression; 2) explore the influence of gene-environment interactions on progression of ALS; and 3) use a case-only analysis to investigate the influence of gene-environment interactions on the odds of developing ALS. The third aim is a newish approach to this. It is a method that is described in the epidemiology literature that is not often used, but that is very important in the setting of a registry. The major advantage is that controls are not needed.

The overall project is based on and builds upon a large consortium that Dr. Benatar runs called the CReATe Consortium, which is a rare diseases clinical research consortium comprised of NIH's Rare Diseases Clinical Research Network (RDCRN) of physicians and scientists studying ALS and-related disorders across the US and in sites in Germany and South Africa. Active sites are shown in the following illustration:



This also illustrates the number of IRBs involved, and that they have to deal with a lot of processes to get everything they want to do added to what CReATe is already doing. The idea for the study Dr. Weisskopf et al proposed was to leverage that ongoing infrastructure and case recruitment they already were doing. What they are doing as part of CReATe is collecting very deep phenotype, genotype, and biomarker data, which is the inaugural protocol. The idea is to acquire prospectively from all of these sites a total of approximately 750 patients with ALS and other rare conditions, including frontotemporal dementia (FTD), primary lateral sclerosis (PLS), and hereditary spastic paraplegia (HSP), progressive muscular atrophy (PMA). Deep phenotypic data will be collected longitudinally, WGS will be done, and an extensive repository of biological specimens will be collected.

For phenotyping data CReATe is collecting, they are using a GUID and collecting information on demographics, family history/pedigree, medical history and medications, “onset” and “diagnosis” phenotypes, neuromuscular examination, spirometry, ALSFRS-R, SPRS, cognition and behavior, and staging. As part of this proposal, they layered on the environmental questionnaires. Ideally, it would have been the exact ones in the National ALS Registry. They produced a set of questionnaires much the same way, trying to mimic them as closely as possible, so the CReATe Consortium ALS cases can log into a website now and complete the modules in much the same way they could in the National ALS Registry. The modules included are:

| | |
|--|---|
| Socio-demographics Occupational history Military history Toxicant exposures Electrical shocks Residential history Residential pesticide exposure | Physical activity Traumatic Brain Injury (TBI) Cigarette smoking Alcohol Caffeine Reproductive history (women) |
|--|---|

For things that could change over the course of ALS (TBI, cigarette smoking, alcohol, caffeine), will be repeated to have updated exposure information to use in terms of progression with ALS.

They spent a long time trying to get all of the IRBs in place, getting the questionnaires developed, and mounting them online. Approximately 100 have completed the questionnaires. Of those, about 15 have other conditions rather than pure ALS. They are in the process of translating the questionnaires into Spanish. Most people will complete the modules online, but there is an option to complete the paper version for those who cannot do this online. The tricky part is that the investigators will have to enter them by hand themselves. Especially for Miami and other regions, the Spanish version will help them ramp up.

Dr. Weisskopf emphasized that the data are very preliminary and the numbers are small in these early days. The idea was to provide a taste of what they were trying to do, and pointed out none of this should be taken as settled by any stretch. With that caveat in mind, this table shows the data they are now trying to use:

| CReATe Population with Environmental Qx Data | | | | | |
|--|----------------|--------------------|-----------------|--------------------|---------------|
| Characteristic | Total N=76* | BMI | | | |
| | | Underweight N=6 | Healthy N=18 | Overweight N=31 | Obese N=21 |
| Onset Age, mean yrs (sd) | 56 (12) | 51 (8) | 52 (17) | 58 (11) | 58 (11) |
| Mos to Dx, median (IQR) | 23 (12-40) | 26 (18-40) | 22 (12-55) | 26 (16-46) | 19 (12-27) |
| Mos to baseline, median (IQR) | 54 (30-55) | 43 (22-50) | 67 (30-67) | 33 (15-66) | 21 (16-44) |
| Male, N (%) | 50 (66) | 3 (50) | 7 (39) | 24 (77) | 16 (76) |
| Ever smoker, N (%) | 29 (38) | 2 (33) | 6 (33) | 12 (39) | 9 (43) |
| Bulbar, N (%) | 17 (22) | 0 (0) | 6 (33) | 5 (16) | 6 (29) |
| Riluzole, N (%) | 39 (51) | 5 (83) | 8 (44) | 18 (58) | 8 (38) |
| HFE H63D C/C [^] , N (%) | 30 (77) | 2 (100) | 3 (50) | 14 (78) | 11 (85) |
| FTO G/G [#] , N (%) | 8 (21) | 0 (0) | 1 (17) | 4 (22) | 3 (23) |

* 15 others have non-ALS conditions (HSP and PLS)
[^] HFE; C/C is wildtype, variants have altered iron handling
[#] FTO, Fat Mass and Obesity Gene; G/G is associated with higher BMI

The first column are data on the participants who actually have ALS. Of these, 66% are males as might be expected. There are 38% ever smokers and riluzole use is about half at 39%. The idea is to combine with the WGS, which is ongoing but is not complete. Those who have those genotypes here is a subset of the 76 (n=39). The group is split by BMI as well just to provide a flavor of how the data are distributing. The first ALSFRS is at recruitment (baseline). Excluding a handful of the 76 who have much longer survival times, the mean ALSFRS-R points lost per month decreased -0.6 (sd=0.35).

The study design for Aim 1, to examine the influence of non-genetic factors on ALS progression is a reasonably simple analysis, is a repeated measures Generalized Linear Models (GLM) that Treats progression as linear, with the outcome of ALSFRS-R. In terms of the timeline, symptoms start at some point, diagnosis occurs at some point later, study entry is at some baseline time later than that, ALSFRS-R is set at 48 at onset, and then there are several ALSFRS-R at about 3-month intervals post-baseline. The GLM will look at how the ALSFRS-R score changes over time given different exposures based on the questionnaires. They did see that the time between onset and diagnosis, some kind of indicator of how fast someone is

progressing, is on its own related to progression. The faster someone goes from onset to diagnosis, the faster they decline after that. This is what would be expected and is heartening, because it shows they are finding what others have said before.

By throwing environmental factors into the model at this stage just to see what is going on, they typically see older age of onset and faster decline. At this point, there is no statistical difference in females and males, bulbar versus other types, but again these are small numbers. Riluzole is odd because the whole point of it is to slow progression, but this multivariable model showed increasing progression:

| Multivariable Model for ALSFRS Progression | | |
|--|------------------------------------|------------------|
| Characteristic | ALSFRS-R points per month (95% CI) | P-value |
| Age at onset | -0.009 (-0.013, -0.005) | <0.001 |
| Female | 0.04 (-0.11, 0.18) | 0.615 |
| Bulbar | 0.11 (-0.14, 0.35) | 0.385 |
| Riluzole | -0.19 (-0.29, -0.09) | <0.001 |
| Ever smoker | 0.04 (-0.14, 0.23) | 0.649 |
| BMI (Healthy is ref) | | |
| Underweight | -0.06 (-0.20, 0.07) | 0.356 |
| Overweight | -0.02 (-0.18, 0.15) | 0.830 |
| Obese | -0.29 (-0.53, -0.06) | 0.015 |

Recall: Overall average ALSFRS-R decline per month = -0.6 points (sd=0.35)

Dr. Weisskopf said he left riluzole to illustrate the difficulty in doing these kinds of things and interpret it. His guess is that one of the problems with a variable like riluzole is that there are reasons why someone might be started on it at some point, but someone might start earlier if they are progressing faster. That is called “confounding by indication.” That is, if it is given earlier to someone who seems to be progressing worse, it is going to look like riluzole is not helpful because this is not a randomized trial. These are the kinds of epidemiological factors they have to figure out. The other one that is somewhat odd is that the obese category compared to healthy individuals seems to decline faster. That is not what has generally been reported. It is very possible that this is because the number is small at this point, but it is also possible that this is confounded by something. Perhaps there is something else that is related to obesity that also is related to how someone with ALS progresses. It could be a marker of progression in some way, or it could be their diet. A fundamental problem with epidemiological studies is dealing with potential confounders or things that might bias the data.

One of the things they have been thinking about doing as part of this is taking advantage of the genetic data to get around that problem. What they really want to know is whether X causes Y. Does higher BMI (X) change the progression with ALS (Y). The problem is that something else might predict body mass like diet, lifestyle, or other exposures that also predict progression. An association may be seen between BMI and progression with ALS, but it is not because of the BMI, it is because of these other things that go along with the BMI. That is what is confounding and what investigators worry about in non-randomized trials and observational data. There is an

approach known as Mendelian Randomization which takes advantage of a genotype that is known to predict a certain phenotype and essentially uses that as a randomizer. The whole point of an RCT is that nothing else predicts the exposure than a coin flip, so there is not anything that confounds it. The genotype is treated more or less like being randomized to a genotype. If it is known that the genotype predicts the X variable of interest, it is possible to look at the genotype to determine if it relates to progression and now that genotype is not affected by all of the other things that affect BMI.

As an example of this, consideration can be given to whether BMI affects ALS progression. With BMI, there is an association between higher weight and faster progression. This is odd. Is that confounded by some other variable that predicts BMI? The fat mass and obesity gene is known to predict BMI. It is essentially an instrumental variable for BMI. It can be used in this Mendelian Randomization to look only at FTO genotype to see whether that predicts progression. Once again, it is important to remember that these are tiny numbers. They did not see anything with the HFE H63D C/C gene, but the FTO G/G genotype is associated with high body mass weight. The heavier someone is, the more likely they have this genotype. The genotype is predicting slower progression, which should be unconfounded by all of the other things that predict BMI, and BMI can be examined more specifically by taking advantage of the genetic data. That said, there are assumptions that go into this as well. The assumptions are that the FTO gene is not doing something else that is in some other way related to the outcome. That is trading one set of assumptions for another, but these are the tricks they play to figure out what actually might be going on.

Aim 2 is to explore the influence of gene-environment interactions on progression of ALS only among the cases. The example here might be something like occupational lead exposure with hemochromatosis genotype. It is known that hemochromatosis genotype variants have iron dysregulation that can affect the toxicity of lead. People with that variant may be more susceptible to lead's effects, so they can look at whether that interaction between these two affects progression with ALS. The same with the PON genotype and pesticide exposure.

Aim 3 is the case-only analysis to investigate the influence of gene-environmental interactions on the odds of developing ALS, which is this new approach to incidence of ALS. This takes advantage of another epidemiological trick, which is the case-only analysis to avoid the issue of even having to identify controls. What this analysis allows them to do is look at a gene-environment interaction. They cannot look at the direct effect of the gene or the direct effect of the environmental exposure, but under a key assumption, if there is an interaction between the two which everyone at least suspects is going on, the controls are not needed. An analysis can be done that allows them to see, when there are both a certain genotype and a certain exposure, whether the risks for ALS are higher. The one key assumption that has to be made to do that is that the genotype and the environmental exposure are independent in the population. To illustrate that further, an example of what could not be done would be to look at whether the FTO gene interacts with obesity to affect the incidence of ALS, because it is known that the FTO gene predicts obesity. Those two are related and are not independent in the population, so that is not something that can be assessed with this approach. However, occupational or residential lead exposure and genotype are much more likely to be independent. That interaction can be examined just among the cases, which is the goal of the third aim.

Again, these are very limited data. Dr. Weisskopf emphasized that he was simply showing a taste of the way they are trying to go about this. They need to consider other forms for ALSFRS-R progression, given that progression may not be purely linear. They can explore other curves to that progression. They have not yet considered the fact that these cases are coming from

many different CReATe sites across the US, but they may need to account for differences in different exposures in different places. Of course, they desperately need more numbers. However, they seem to have crossed most of the administrative hurdles, so the numbers should be increasing faster than they have been thus far. At the moment, the numbers may be sensitive to a few outliers. More data are needed to be more confident about these very preliminary findings.

Discussion Points

Dr. Sorenson noted that in the data presented in the multivariate analysis, it appeared that obesity was a predictor of faster progression. But in the gene analysis with the FTO gene, it looked like it was slower. That seemed to be a conflict within the same dataset.

Dr. Weisskopf said that there are two issues. The first very important one is that these are very small numbers, so things may change. The second is that the obesity data that appeared to show faster progression was in the 76 people with the questionnaire data. The FTO genotype is only in the 39 with the genotype, so it is a slightly different sample of people. The other important possibility is that when looking at an environmental exposure someone is reporting on such as weight, if they trust that they are providing a correct BMI, there are many reasons why BMI differs between people. It may be physical activity, diet, or all sorts of other things that could have other links to ALS in ways that are not understood. Just looking at a variable like that, there is a lot of possibility of confounding of something else explaining that so that they are not getting the true causal effect of BMI on ALS progression. The whole point of Mendelian Randomization is that an analysis is done without the BMI itself and the gene is used. If the assumption is made that the FTO gene is not doing something else that is related to progression, then its effect has to be through BMI. If their results are taken on complete face value, which he would not necessarily suggest doing, the suggestion would be that when obesity is assessed on its own, it is confounded by something else and something is related to that which is also related to faster progression that has not been properly accounted for. By using the Mendelian Randomization, they have avoided that confounding. Probably it is a sample size issue.

Dr. Wright said she presumed that if they had single nucleotide polymorphism (SNPs) or other polymorphisms or mutations in their genome, they could still use the Mendelian Randomization to make some type of association that is fairly confident. But, she wondered how dynamic epigenetics impact this model.

Dr. Weisskopf acknowledged that this is in some ways a very interesting possibility and is absolutely something that should be explored, but it does not really play into the SNP any differently. If someone actually studied the FTO gene and found that depending on its methylation state it might be more or less expressed, that would just change the average effect of the FTO gene depending on that expression pattern. If they find that FTO or any gene is related to ALS or the progression of ALS, a next extremely important question regards whether there are environmental exposures that affect the epigenetic patterning on that gene so that without the polymorphism, there might be similar effects.

Dr. Factor-Litvak asked whether everyone with the FTO G/G polymorphism was obese, which Dr. Weisskopf confirmed they were not. Therefore, she observed that the key thing about the Mendelian Randomization is that the gene has to be very strongly associated with a phenotype and have the same pattern of confounding with other variables the phenotype may have.

Dr. Weisskopf said that in fact, if it works well as an instrumental variable in Mendelian Randomization, it cannot be perfectly correlated. The issue is that it is a proxy measure for actual exposure. The worse it predicts that exposure, the less likely it is going to show up as associated. If it completely predicts BMI, then nothing could be confounding BMI than the FTO gene, so it is a tradeoff.

Dr. Brooks asked whether the analysis included the people who were greater than 5 years from onset.

Dr. Weisskopf indicated that all of the analyses included everybody, but he just did not show their slopes because they made the graphs look difficult.

Case-Control Study Nested in the National ALS Registry to Evaluate Environmental Risks

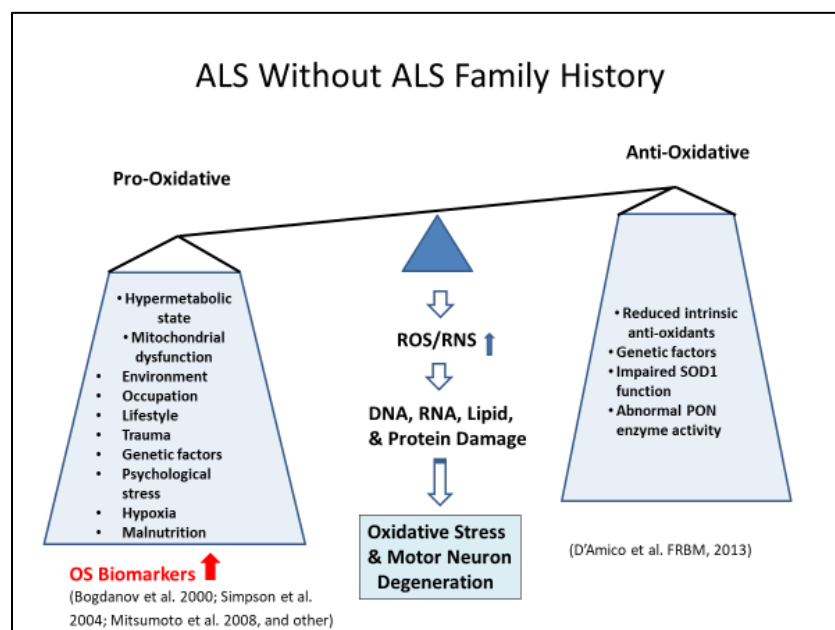
Pam Factor-Litvak, PhD

Director, Eleanor and Lou Gehrig MDA/ALS Research Center

The Neurological Institute of New York, Columbia University Medical Center

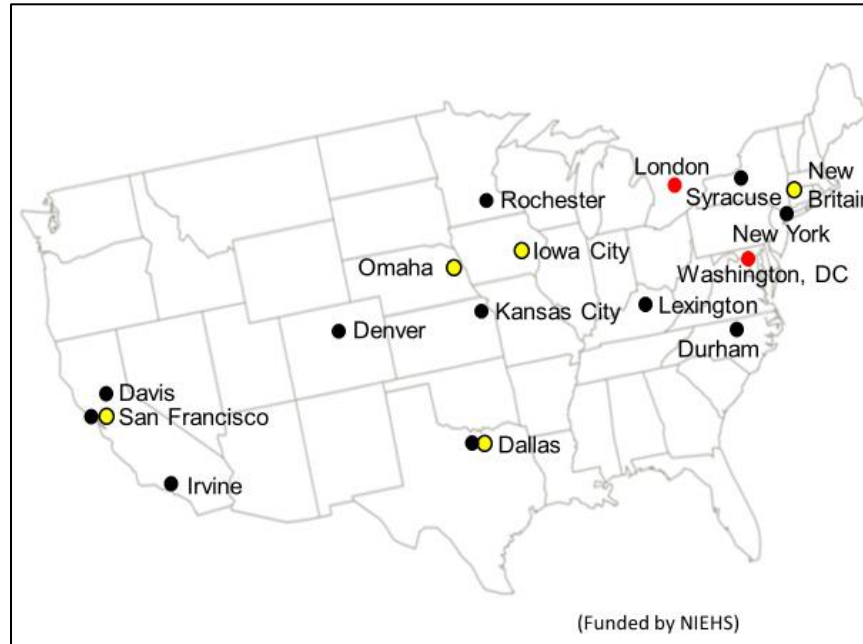
Dr. Factor-Litvak, PhD noted that she was speaking on a wide variety of researchers who have participated in both the ALS COSMOS, ARREST ALS studies, and ARREST Controls, particularly for Dr. Mitsumoto, who was unable to attend. She reminded everyone that they have had two ATSDR-funded studies. One is ARREST ALS epidemiologic studies on risk factors and the other is ARREST Controls, which is actively recruiting controls.

In terms of the basis for these two studies, prior to this funding Columbia University MDA/ALS Research Center at Columbia University Medical Center (CUMC) had a large grant called ALS COSMOS. ALS COSMOS was based on the premise that in terms of ALS progression, the primary hypothesis is that factors related to oxidative stress (OS) would be more apt to have ALS progress faster. In essence, the investigators felt that pro-oxidative factors (shown on the left side of the graphic below) would be more likely to result in faster progression of ALS:



These pro-oxidative factors are believed to tip the balance in favor of reactive oxygen species (ROS) and reactive nitrogen species (RNS) leading to DNA, RNA, lipid, and protein damage and OS and motor neuron degeneration (MND). Some anti-oxidative factors, shown on the right side of the above graphic, may counteract that.

The premise of ALS COSMOS in reality was to build indices that could combine factors related to OS and anti-oxidants to see how factors enjoined with the exposome would relate to slower or faster ALS progression. They also studied PLS in a smaller group of patients, but their 355 ALS patients came from the black dots on this map, which missed many of the mountain states:



The experience with ALS COSMOS (n=355) was the basis for the expansion and laid the background for ARREST ALS. The objectives of ARREST ALS were to:

- Expand the multicenter study on a national level by recruiting patients from the National ALS Registry
- Increase the sample size for effective analyses of the relationship between environmental risk factors and disease progression for a more robust estimation
- Study gene-environmental interactions
- Recruit 420 additional patients with ALS using inclusion and exclusion criteria identical to that of ALS COSMOS

ALS COSMOS and ARREST ALS are both cohort studies without appropriate controls, so they wanted to recruit both sibling and community-based controls in ARREST ALS. There was an advertisement on the website and ATSDR did email blasts for them. Patients diagnosed with ALS registered under the National ALS Registry were asked to initiate a call to CUMC's ALS Center at 1-855-STOP ALS. The patient had to initiate participation in ARREST ALS, which was an ATSDR guideline. All study activities were performed over the phone, including cognitive testing. Saliva DNA and urine samples are obtained by mail. Patient follow-up schedules were similar to those in the original ALS COSMOS study. Although their enrollment goal was 420 patients, they were not successful in recruiting that number.

They are still recruiting controls. Sibling controls include 1 sibling control per patient in ARREST ALS if the patient has a willing and able sibling. The hope was to get siblings closest in age and of the same gender as the patient, though this has been difficult. If no same-sex siblings are available, they took whatever they could get. Because siblings grow up in the same house, it can be assumed, though not a perfect assumption, that their early life exposures were similar and focus on the sibling comparison in terms of later life exposures. The goal for population-based controls was to select 2 controls for each patient in ARREST ALS matched by gender, age \pm 5 years, residential area, and race/ethnicity. Age has now been expanded to \pm 10 years and the gender restriction has been removed because of the difficulty in obtaining controls. They contracted with RTI International, Inc. to get the community controls, given that they have a long history of getting community-based controls in large case-control studies.

In terms of progress to date, in Year 1 they finalized all of the agreements (confidentiality and business) between Columbia University and RTI International; attained IRB approval of RTI's involvement in the research study; and attained IRB approval to re-consent patients already in ARREST ALS. In Year 2, they commenced recruitment of sibling controls in November 2016 and commenced recruitment of population-based controls in April 2017. In Year 3, they continued recruitment of sibling and population-based controls. They received a no-cost extension for Year 4 to finalize recruitment of sibling and population-based controls, analyze the data, submit a final performance report to ATSDR, and publicize the findings.

In terms of the challenges of doing all of this via telephone, they really wanted to study cognition in ALS patients and controls. They performed a cognitive pilot test using 8 ALS patients recruited at Columbia who were randomized to have testing under two conditions, once on the phone and once in person. The randomization was as to which came first, so one half got phone followed by in-person and the other have got in-person followed by phone so they would not have practice effects questioning the data.

The battery of tests included the following, which is exactly the same battery that was used in ALS COSMOS:

- ALS Cognitive Behavioral Screen (ALS-CBS)
- ALS Cognitive Behavioral Subscale (ALS-CBS-CG Caregiver Portion)
- Written Verbal Fluency Test (WVFT)
- Controlled Oral Word Association Test (COWAT)
- Frontal Behavioral Inventory (FBI-ALS)
- Center for Neurologic Study-Lability Scale (CNS-LS)
- Telephone Interview for Cognitive Status (TICS)
- Mini-Mental State Examination (MMSE)

Some of the tests were modified because they obviously could not be done on the phone, such as the finger tapping, so they had them tap on the phone. These data have been presented previously and have been published, so Dr. Factor-Litvak presented only the conclusions. In terms of intraclass correlation coefficients, the FBI-ALS and WVFT still failed to show significant levels of agreement, while other instruments corroborated previous analyses. Possible reasons include practice effects, sample size too small, test-retest reliability not established, et cetera. No sequence effects found across testing. The study suggested that telephone-based versions of the ALS-CBS, ALS-CBS Caregiver Portion, COWAT, and CNS-LS may offer clinicians valid tools to detect frontotemporal changes in the ALS population-based on strict equivalence testing. That was a very important piece of information that allowed the study to go forward.

Development of telephone-based cognitive testing for ALS could become an integral resource for large population-based research in the future [Christodoulou G et al. ALS/FTS 2016].

In terms of enrollment, not only did they do the blasts from the Registry, but also they created nice pamphlets and posters that they placed in ALS clinics that introduced the study and instructed people to enroll in the ALS Registry and to call 1-855-STOP-ALS. This table shows the number of screened and enrolled patients:

| Subject Source | Screened Current # (%) | Enrolled Current # (%) |
|--|-------------------------------|-------------------------------|
| National ALS Registry | 164 (72.2%) | 71 (67.6%) |
| Brochure | 21 (9.3%) | 12 (11.5%) |
| CUMC | 35 (15.4%) | 20 (19.0%) |
| Other (e.g. ALS forums, ATSDR conference, etc.) | 7 (3.1%) | 2 (1.9%) |

The reason the number of screened and enrolled differ dramatically is because they used the same enrollment criteria that were used in ALS COSMOS, most notably that patients had to be within 24 months of symptom onset to enroll in the study. As in ALS COSMOS, they really wanted to enroll patients as close to their symptom onset as possible. That excludes many patients, especially those with disease of longer duration. Over 40% of patients were ineligible because their symptom onset was greater than 24 months. About 13% became lost to follow-up very quickly and could not enroll in the study. Approximately 15% decided against participation. About 11% had familial ALS and they were looking only at sporadic ALS. Approximately 6% of patients are still being assessed to determine whether they meet enrollment criteria. A few (4.9%) died or had a trach before their screening was completed. Others (4.9%) had major neurological and medical co-morbidities. Some (2.5%) had an incorrect diagnosis, and some (0.8%) had cognitive impairment.

To increase enrollment after the beginning of the study, enrollment brochures were mailed to MDA and ALS Association ALS centers nationwide in November 2014, March 2015, August 2015, and December 2016. A few high enrolling ALS COSMOS sites were asked to encourage their patients to register in the National ALS Registry and participate in the study. In addition, the inclusion criterion for disease duration was expanded from 18 to 24 months. Three large-scale e-mail blasts were allowed by ATSDR to all registered patients with ALS in the National ALS Registry. The first blast was conducted in January 2018 and the last was in July 2018. E-mail blasts to newly-registered patients have been occurring on a quarterly basis since the outset of the study. The study is now being publicized on the CDC/ATSDR.

As of July 2018, there are 34 active participants from whom data are still being collected, 17 have completed the study, 15 withdrew after providing some data, 32 are deceased, 1 was lost to follow-up, and 6 were lost prior to the baseline assessment.

As was done in ALS COSMOS, patients are followed up to 24 months. They are interviewed at baseline and 6, 12, 18 months, and 24 months. Saliva is collected only at the first visit. Urine is

collected at each visit and a Food Frequency Questionnaire (FFQ) is completed at each visit and mailed in. As of July 2018, the following progress had been made:

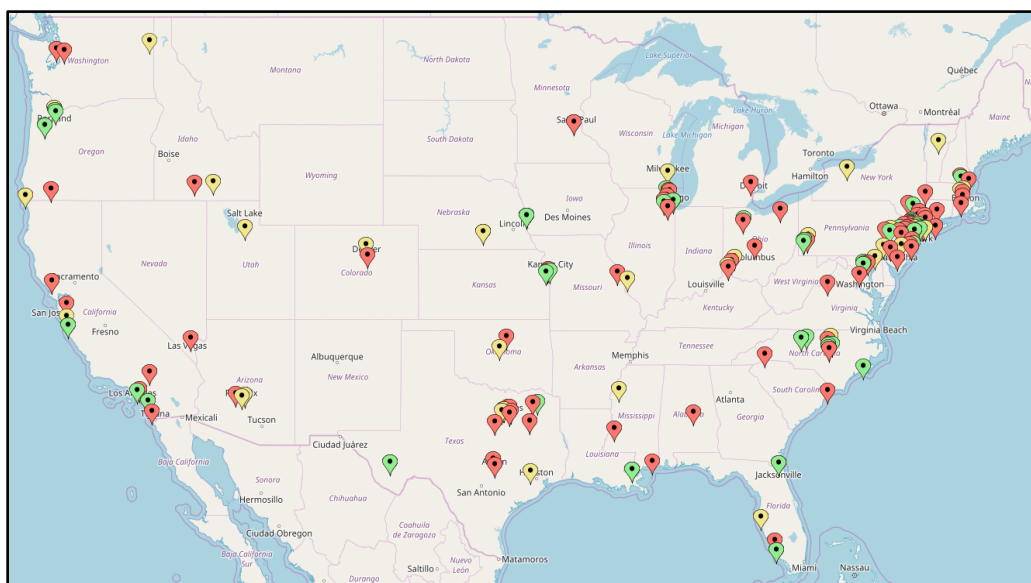
| Subject Progress (as of February 2018) | | |
|--|-----------|----|
| Baseline | Interview | 97 |
| | Saliva | 89 |
| | Urine | 96 |
| | FFQ | 85 |
| Month 6 | Interview | 66 |
| | Urine | 60 |
| | FFQ | 54 |
| Month 12 | Interview | 42 |
| | Urine | 41 |
| | FFQ | 38 |
| Month 18 | Interview | 27 |
| | Urine | 26 |
| Month 24 | Interview | 19 |
| | Urine | 18 |
| | FFQ | 15 |

In terms of controls, 47 siblings have been screened and 39 have been enrolled. Some of the 8 are still in progress and some have refused to participate. RTI has screened 110 potential population-based controls and enrolled 49. The reasons why some have not been enrolled are that 13% have not responded; 44% decided against participation (most commonly cited reasons: too little time to devote, ongoing minor health concerns, health concerns of close family, confidentiality concerns, not interested in general); 14.3% had other major neuro/medical diagnoses, 1.2% were incorrectly matched with the patient, and 3.6% did not have any willing/able study partners. There were 23.8% pending as of July 31, 2018, who they are hoping to enroll. One problem with recruiting controls for a disease such as ALS that is so rare is that most people do not have experience with it. Increasing awareness of ALS may allow them to start recruiting controls better.

A number of efforts have been made to improve population-based control enrollment. They have asked RTI to begin making weeknight and weekend follow-up calls to try to reach population-based controls who were at work during the day. Current protocol is that potential controls are called 10 times at various times during the week, evenings, and on weekends. The age eligibility criterion has been expanded to ± 10 years and the gender match criterion has been removed, both of which are pending IRB approval. Those are very small modifications that are not anticipated to be a problem. They also requested that RTI focus on patient cases who had 0 population-based control matches to ensure that every patient has at least 1 match at the end of the study.

In terms of lessons learned, there were a lot of administrative delays with setting up agreements between Columbia University and RTI and re-consenting existing ARREST ALS patients to allow for control recruitment. RTI-identified control participants are sometimes not perfect candidates. Better communication from RTI to the investigators would have helped with that. Unrecognized diseases present in candidates or candidates' families are not captured by the RTI telephone script. There is a lack of interest in ALS and/or medical research, even with compensation. Some people agreed to receive a call from CUMC, but were not really that interested. Some people are difficult to connect with consistently or at all. Some controls were really concerned about using saliva to get DNA profiles, and they were very concerned about confidentiality of their DNA.

With regard to how they did with recruitment and how nationally representative the cases are, this map shows enrollment by location, with patients in red, siblings in yellow, population-based controls in green:



There are now some cases in the mountain states and one person in Alaska has agreed to participate, and they are seeking a control for that person. Again, the majority of cases are clustered in the Northeast, California, and Texas. They are still missing some of the country, particularly Montana, the Dakotas, Wyoming, and the Northern mountain states.

Regarding data collection for ARREST ALS and ARREST Controls, once enrolled, each patient is assigned to a specific interviewer. Ideally, this interviewer follows the patient throughout the course of the 24-month study as long as they stay employed at Columbia. That helps a lot because the person develops somewhat of a telephone rapport with the interviewer. The assigned interviewer conducts structured baseline and follow-up interviews. All interviewers have been trained rigorously by multiple investigators (Drs. Factor-Litvak, Rabkin, and L. Andrews). All interviewers perform extensive shadowing prior to conducting their own interviews. The assigned interviewer coordinates remote specimen collection/shipment with FedEx. The table on the following page shows what they are doing in terms of data collection for both studies:

| Evaluation | Baseline | 6 Months | 12 Months | 18 Months | 24 Months | 30 Months |
|---|----------|----------|-----------|-----------|-----------|-----------|
| Telephone Consent | X | | | | | |
| Screening | X | | | | | |
| Formal Consent | X | | | | | |
| Medical Records Review | X | | | | | |
| Enrollment | X | | | | | |
| Case Ascertainment | X | | | | | |
| Family Pedigree | X | | | | | |
| Health Status | X | | | | | |
| Early Life | X | | | | | |
| Adverse Childhood / Stressful Life Events | X | | | | | |
| Demographics | X | X | X | X | X | |
| ALSFRS-R | X | X | X | X | X | |
| General Status and Meds | X | X | X | X | X | |
| Head Trauma | X | X | X | X | X | |
| Cognitive Testing (w/ TICS) | X | | X | | | |
| Saliva Collection | X | | | | | |
| Urine Collection | X | X | X | X | X | |
| FFQ | X | X | X | | X | |
| Residential | X | X | X | X | X | |
| Occupational and Military | X | X | X | X | X | |
| Physical Activities | X | X | X | X | X | |
| Hobbies | X | X | X | X | X | |
| Tobacco and Alcohol | X | X | X | X | X | |
| Caffeine | X | X | X | X | X | |
| Psychological | X | X | X | X | X | |
| Sleep | X | X | X | X | X | |
| Fatigue | X | X | X | X | X | |
| Office Form | X | X | X | X | X | |
| Final Outcome | | | | | | X |


Based on experience in ALS COSMOS, these additional data collection forms were used in ARREST ALS that were not included in ALS COSMOS:


- Family Pedigree
- Past Medical History / Surgery History
- Current Physical Health
- Early Life
- Adverse Childhood Experience
- Stressful Life Events
- Head Trauma
- Telephone Interview for Cognitive Status (in place of MMSE)
- Caffeine
- Hospital Anxiety and Depression Scale (anxiety portion only)
- NHANES Sleep
- Epworth Sleepiness Scale
- Fatigue Severity Scale

A preliminary comparison between ARREST ALS and ALS COSMOS investigated whether enrollment demographics, educational attainment, and insurance, and baseline clinical characteristics between ARREST ALS and ALS COSMOS subjects are comparable. Both studies seek to examine the associations between OS using questionnaire-based risk factor assessment and selected biomarkers of OS and ALS disease progression. The following graphic shows the results of that comparison:

ARREST ALS: An Extension of the ALS COSMOS Study

Jonathan Hupf, BA, Pam Factor-Litvak, PhD, Raymond Goetz, PhD, Brittany McHale, LMSW,
Camila Ibagón, BS, Madison Gilmore, BA, Marie France-Likanje, MA, Hiroshi Mitsumoto, MD, DSc
Columbia University Medical Center





BACKGROUND

Since 2008, Columbia University Medical Center has led 2 epidemiological amyotrophic lateral sclerosis (ALS) studies examining associations between oxidative stress (OS) and ALS disease progression:

- A Prospective Comprehensive Epidemiologic Study in a Large Cohort in the National ALS Registry: Identifying ALS Risk Factors (ARREST ALS)
- ALS Multicenter Cohort Study of Oxidative Stress (ALS COSMOS)

OBJECTIVES

- To investigate whether enrollment demographics, educational attainment, and insurance, as well as baseline clinical characteristics between ARREST ALS and ALS COSMOS subjects are comparable
- Both studies seek to examine the associations between OS (using questionnaire-based risk factor assessment and selected biomarkers of OS) and ALS disease progression

METHODS

ARREST ALS and ALS COSMOS

Both studies collect longitudinal data over 24 months, including:

- Environmental, lifestyle, dietary, and psychological risk factors
- Measurement of clinical disease progression
- Biospecimens to assess markers of OS

ARREST ALS

- Patients recruited from the National ALS Registry; CUMC sole lead study site
- Data obtained via structured telephone interviews
- Patients included if symptoms began within 24 months of screening
- 95 patients enrolled (to date)

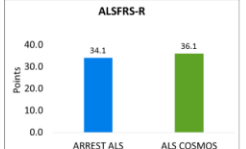
ALS COSMOS

- Multicenter study conducted at 16 study sites
- Data obtained via in-person assessments and structured telephone interviews
- Patients included if symptoms began within 18 months of baseline
- 355 patients enrolled (in total)

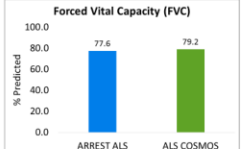
RESULTS

BASELINE CLINICAL

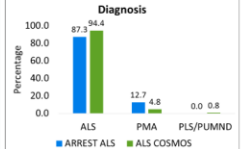
ALFRS-R



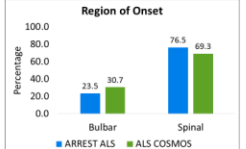
Forced Vital Capacity (FVC)



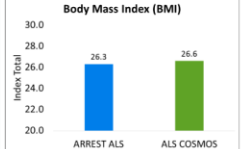
Diagnosis



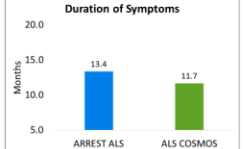
Region of Onset




Body Mass Index (BMI)



Duration of Symptoms

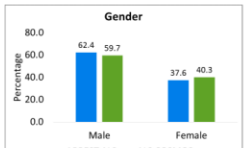


C9orf72 Positive

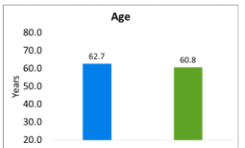


BASELINE DEMOGRAPHICS

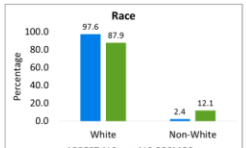
Gender



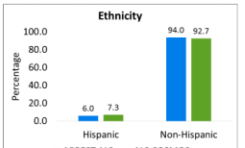
Age



Race

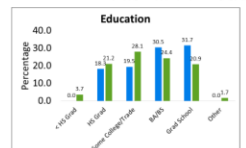


Ethnicity

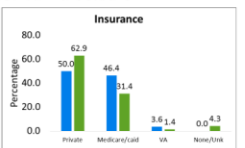


ENROLLMENT EDUCATION AND INSURANCE

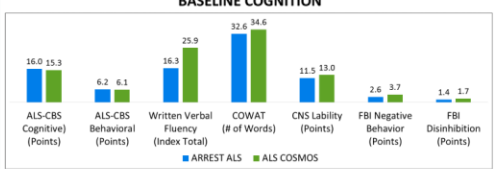
Education



Insurance



BASELINE COGNITION



CONCLUSIONS

- Gender, age, ethnicity, FVC, BMI, region of onset, and C9orf72 positive cases did not differ between ARREST ALS and ALS COSMOS
- ARREST ALS patients are more likely to be white, have higher educational attainment, use Medicare, have lower ALFRS-R scores, have longer durations of symptoms, have PMA, perform better with word generation tasks, and exhibit less emotional lability than patients from ALS COSMOS
- We believe these differences in demographic and baseline ALS functional parameters can be controlled statistically
- To our knowledge, this telephone-based study design is the first of its kind in ALS research and will be useful in future large-scale, population-based epidemiological studies

ACKNOWLEDGEMENTS

- Agency for Toxic Substances and Disease Registry (ATSDR)
- Centers for Disease Control and Prevention (CDC)
- The National ALS Registry (NAR)
- ARREST ALS study participants (and their study partners) for their time and devotion to our research

The comparison did show that there is a difference in education and insurance status. It turns out that ARREST ALS patients are more highly educated than ALS COSMOS patients. That relates to much of what was articulated the day before that they have the ability, resources, and

education to use the computer and enroll in the Registry. Conversely, they also were more likely to have Medicare or some sort of government health insurance.

The investigators have thought long and hard about the limitations of these studies. Initially, they were concerned about whether they could generate enough publicity to encourage newly-diagnosed ALS patients to register and call Columbia University. They had some success, but not as much as they hoped. They had better success in conducting telephone interviews that were sufficient in collecting all the needed information, especially with the cognitive testing. They also were concerned about whether they could obtain the needed biosamples, but they did have success in getting these. There were some limitations, a lot of which had to do with the enrollment of getting newly diagnosed patients. Patients are very overwhelmed at the start of their diagnosis, which is a problem in terms of recruiting newly diagnosed patients into non-clinical trial studies. While there were no in-person interactions or clinic visits with patients, they did try to keep the same interviewer patient assignments the same along the way. They did not have follow-up medical records for vitals and FVC. FVC was an outcome variable in ALS COSMOS, but cannot be an outcome variable in ARREST ALS.

Current research plans are to:

- Reach enrollment of at least 100 ALS participants by the end of the grant period
- Make certain that patients with a disease duration less than 24 months do not differ in demography and disease characteristics from those with a duration of less than 18 months
- Study whether the results of telephone cognitive screening tests, which were utilized for the first time in ARREST ALS, have a similar distribution in cognitive impairment compared to that of the ALS COSMOS study
- Investigate further if the patient population in the ARREST ALS project is comparable to that of the ALS COSMOS study in demographics, cognitive impairment, disease characteristics, diet, and nutritional and environmental exposures
- Analyze if self-report of environmental exposures in the National ALS Registry and those based on structured interviews are the same for patients
- Plan exome and genome sequencing for ARREST ALS patients, to be incorporated into a larger effort led by Dr. Matthew Harms at CUMC

In conclusion, they have found that ARREST ALS patients are more likely to be white, have higher educational attainment, use Medicare, have lower ALSFRS-R scores, have longer durations of symptoms, many have PMA, perform better with word generation tasks, and exhibit less emotional lability. The investigators believe these differences in demographic and baseline ALS functional parameters can be controlled statistically.

Discussion Points

Related to the difficulties of recruiting newly diagnosed patients, Dr. Finger said he thought they have to be very careful with that. For instance, he never would have been eligible for this study. There is a long diagnostic delay, so even when they are including 18 months, in actuality they are really having to get people pretty much during their first visit. Doing what they can to push that number will help. He commended these investigators for the fact that the first step in this study was a requirement to enroll in the National ALS Registry.

Dr. Factor-Litvak said that they felt for these studies in which they were interested in progression, they really wanted to diagnose patients to get them early in the disease course so they could look at progression from an early state onward rather than having to recreate the data if they were recruited into the study later.

Dr. Sorenson emphasized that this is the value of the Registry from an enrollment standpoint. Three quarters of the patients came from the Registry email blasts, with very low yield from the brochure. His center distributed 100 of those brochures, and he was disappointed to see that only 12 people from across the country enrolled from the brochures.

Dr. Factor-Litvak commended Dr. Mehta and his team for doing the email blasts for them, because she did not think they would have had the recruitment they did without them.

Dr. Brooks asked whether OS causes rapid progression.

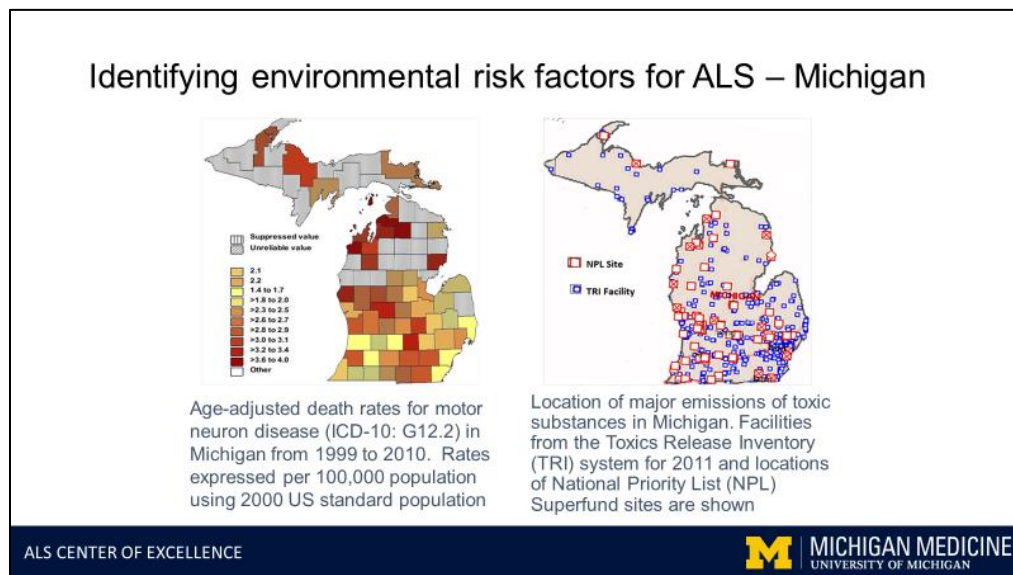
Dr. Factor-Litvak responded that they plan to show them some of those data in December, which is now being analyzed.

Identification and Validation of ALS Environmental Risk Factors

Stephen Goutman, MD
Assistant Professor of Neurology
University of Michigan

Eva Feldman, MD, PhD
Russell N. Dejong Professor of Neurology
University of Michigan

Dr. Goutman indicated that they are very interested in understanding environmental exposures in the State of Michigan. This is what they have been showing the last couple of years to illustrate the concern that the locations of individuals with ALS are associated with areas of environmental pollution in the state:



The aims of their project are to: 1) identify potential environmental risk factors associated with ALS, including environmental and occupational exposures to toxins as well as physical exertion; and 2) utilize measurements of persistent environmental pollutants to evaluate exposures based on questionnaire and environmental assessments.

During the meeting last year, they had new samples coming online. In their original publication, they used both blood and plasma samples. Now they have moved exclusively to plasma samples. Looking at the Persistent Organic Pollutants (POPs) of their cases versus controls in a

univariate model, they found that several of these POPs seemed to have some association with the odds of having ALS. Polybrominated diphenyl ether 153, cis-nonachlor, and pentachlorobenzene are of particular interest in driving this risk. This is fairly consistent with what they found before with a different dataset. Lower concentrations of POPs measured from plasma in ALS subjects are associated with a longer survival. When they used a summary measure of exposure called the Environmental Risk Score (ERS), they found that the odds of ALS when a subject goes from the 25th to the 75th percentile of exposure, increases by almost 7 times. That is a fairly significant increase in one's risk of when they adjusted for the covariates (BMI at survey consent, rate of change in BMI, age at blood draw, military service, sex, former smoker, current smoker).

They further wondered whether one's exposure to POPs could alter their survival. In their cohort of 167 individuals, the median age was 60.9. They controlled for Non-Invasive Ventilation (NIV) use, El Escorial criteria, site of onset, and their change in BMI five years into the study. Many of these POPs had a slight increase in the hazard ratios, and these were again summarized with an ERS. Individuals who had the lowest quartile exposure seemed to have a 6-month survival advantage compared to the three groups with higher levels of exposure. They looked at this in a Cox Proportional Hazard model, again controlling for covariates, and they saw that individuals in the highest quartile of exposure compared to those in the lowest quartile of exposure have a mortality rate that is much higher and a hazard ratio of 1.91 compared to those in the lowest quartile of exposure. This suggests that there is some alteration in survival based on the concentration of POPs in plasma samples.

Their hypothesis is that POP exposures will lead to conserved metabolite changes detected in both plasma and CNS tissue and could: 1) yield insights into novel biomarkers of ALS; 2) inform us of past POP exposures; and 3) increase the understanding of the disease pathophysiology.

Dr. Feldman emphasized that they really want to understand why the State of Michigan has a fairly high incidence and prevalence of ALS, along with a known very high pollutant exposure due to the fact that Michigan is both an agricultural and highly industrialized state. As Dr. Goutman mentioned, they have a new hypothesis regarding the role of metabolomics or metabolites in ALS. A metabolite is defined as any organic molecule detectable in the body with a molecular weight of < 1500 Daltons. This includes peptides, oligonucleotides, sugars, nucleosides, organic acids, ketones, aldehydes, amines, amino acids, lipids, steroids, alkaloids, foods, food additives, toxins, pollutants, and drugs and drug metabolites. This is quite a broad array of very small molecules.

In terms of the most common constituents of the human metabolomes that can be measured, there are over 3000 toxins and environmental chemicals from the Toxin and Toxin Target Database (T3DB); over 1000 drug metabolites; over 30,000 food additives and phytochemicals from FooDB; over 1400 drugs from the DrugBank; and 8500 endogenous metabolites from the Human Metabolome Database (HMDB). These are all measurable either commercially or within their own facility at the University of Michigan.

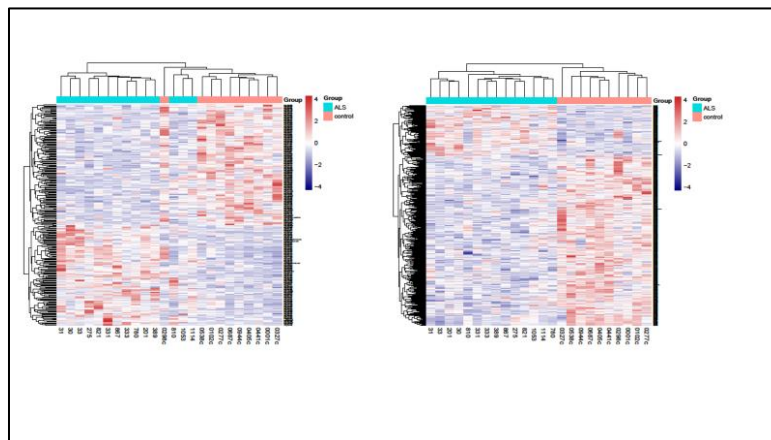
Clearly, the metabolome is connected to all of the other "omes." The constituents of the metabolome provide the building blocks for the genome, proteome, and other sources of energy. For example, small molecules AMP, CMP, GMP, and TMP are the primary constituents of the genome and transcriptome. The 20 amino acids are the primary constituents of the proteome. Lipids give cells their shape, form, integrity, and structure. Sugars, lipids, AAs, and ATP are the source of all cellular energy. Also, small molecules serve as cofactors and signaling

molecules for both the proteome and the genome. The genome and proteome largely evolved to catalyze the chemistry of small molecules, so they are very important in disease states.

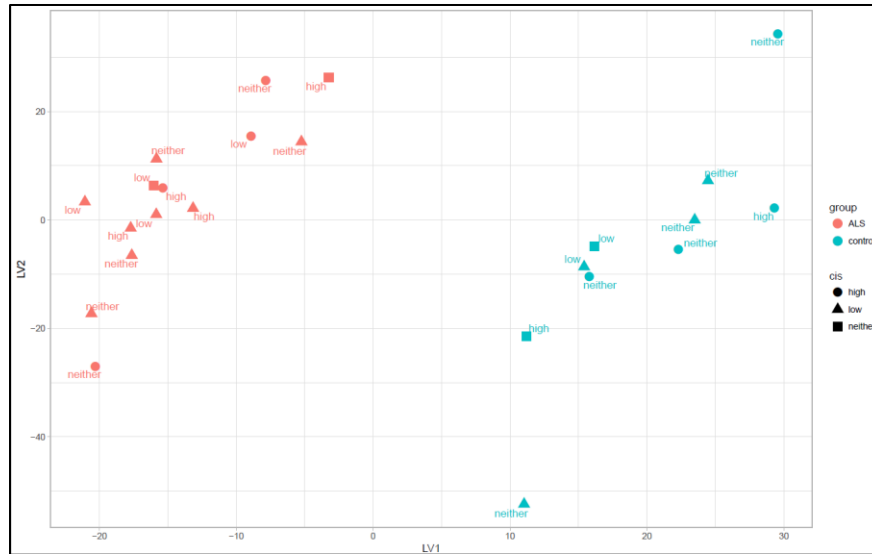
Dr. Feldman's own laboratory spent a decade looking at the metabolome in a different disease, the neurologic complications of diabetes, so they have a lot of experience doing this. This can be done in two ways, either with targeted metabolomes when one knows exactly what they want to look at, or untargeted. They have chosen to do untargeted with the ALS population. In untargeted metabolomes, in this case plasma is collected and mass spectroscopy is done for metabolite identification. They can then go from the spectra to specific lists of metabolites. From these lists, they generate pathways because many pathways of the human metabolome are well-known. From these lists, they can then generate models of how these pathways interact and identify new biomarkers.

The idea that the metabolome is important with environmental exposures is now becoming topical. Dr. Feldman said she would propose that metabolomics is an emerging tool to assess exposures, especially in circumstances where the exposure may not be known or recent. This is a new exciting tool in the armamentarium that can lead to new biomarkers and insight into pathogenesis.

As a pilot at the University of Michigan, she and Dr. Goutman selected a very small number of male subjects with cervical onset disease and control subjects. They now have about 300 individuals with ALS in their database and the same number of controls. They then compared the male subjects with cervical onset disease to the male control in terms of their pentachlorobenzene and cis-nonachlor. They were even, so the idea regarded whether the disease itself segregated out these individuals. What is really interesting is that the answer to that is "yes." Even though this is a very small number of subjects, they are very excited about this. These are heatmaps from ALS patients versus control:

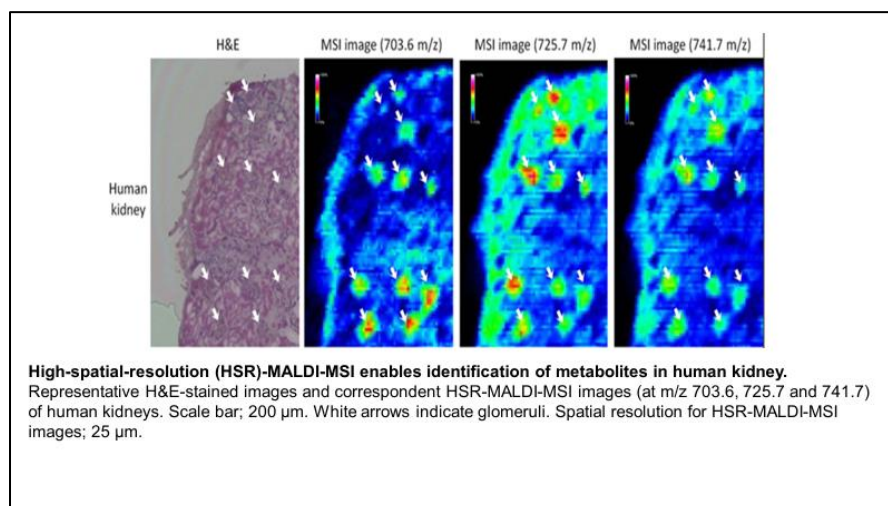


The ALS group is in blue and the controls are in red, and this shows that it is possible to see a clear difference in the metabolite and metabolome of ALS patients versus the controls. These are looking at it in two different ways. One is simply doing a T-Test on the left and partial least squares regression-discrimination analysis (PLS-DA) on the right. Again, there is a really robust separation between the two groups. This is very exciting new, unpublished data. The new data that Dr. Goutman presented of 110 new plasma samples are also new, unpublished data. Here are the PLS-DA Score-Plots, showing the major difference between ALS and control subjects:



They are very interested in examining the correlation between pollutant levels and metabolite levels. So far for cisonachlor they have found 120 metabolite species, including 2 known ones: D-GLUCOSE ($r=0.50$) and METHYL JASMONATE ($r=0.41$). For pentachlorobenzene, they have found 139 metabolite species, including 4 known ones: L-CARNITINE ($r=0.49$), D-GLUCOSE ($r=0.49$), 3-METHYL-2-OXOVALERIC ACID ($r=0.44$), and (2E)-OCTENOYL CARNITINE ($r=0.42$). It is very interesting that these metabolites are very involved in energy production.

In terms of future direction, the goals are to: 1) identify the metabolomic signatures of POP exposures in their ALS cohort; 2) correlate metabolomic signatures with residential and occupational exposure histories to yield insights into causal ALS mechanisms; and 3) determine whether metabolomic signatures in ALS subject plasma are present in postmortem brain and spinal cord tissue and correlate that with exposures. All of the 300 patients and controls they have in their sample filled out a 30-page, detailed epidemiological survey. In addition, they have 70 autopsies as of last week and these individuals all have POP measurements and have the ability to have metabolomic measurements. Dr. Feldman ended by showing what can be done in diabetes as a proof of concept, because this also can be done in ALS patients:



Discussion Points

Dr. Kaye asked what the values were adjusted for, and adjusting for gluten concentration for lipids in the blood.

Dr. Goutman indicated that the values were adjusted for the covariates. In terms of gluten concentrations for lipids in the blood, they adjusted based on the change in decline of BMI. Measurement for lipids in the blood is done in the laboratory.

Dr. Feldman added that what they have been told by their collaborator, Dr. Stuart Batterman, who does their measurements is that they make an adjustment in the laboratory when they do the readings to the lipids. They met with the NHANES group and have adjusted their protocol to match the NHANES protocol. They believe at this point they are doing the measurements exactly as CDC.

Dr. Feldman clarified that they are reporting lipid-adjusted values, not crude values.

Given the findings in the blood, Dr. Brooks asked whether the Cox Proportional Hazard analysis includes occupation to see if they have corrected for that. There is a host of epidemiological literature relating occupation to some aspects of ALS. The question regards whether that is a covariate that should be adjusted for.

Dr. Goutman replied that they have not yet looked at occupational data as it relates to the survival. This is essentially saying adjusted for these known prognostic factors in ALS, how does the concentration of pollutants in one's plasma impact survival? In terms of the question regarding whether that is a covariate that should be adjusted for, they have not looked at it yet but they have the data.

Dr. Bowser asked how the list of metabolites they identified in their patient population and linked to the environmental factors relate to the already published metabolomics data in ALS.

Dr. Feldman indicated that there is overlap. What they did not find was as many identified metabolites. The initial report to which Dr. Bowser was referring used a commercial company, Metabolon, to do the measurements. For their study, these were done in-house by the University of Michigan Metabolomic Core. They have a proposal to use Metabolon to see if they would have more of an intersect between what has been published. There is an overlap with what they found, but they also found many more unknown yet to be identified metabolites than were found previously.

Dr. Bowser noted that in going from the metabolomics that can be done randomly in blood to MSI, the resolution is not too great, but the number of peaks on the mass spec are greatly reduced. One important question would be, out of all of your interesting metabolites, which ones can you actually ionize out of the tissue?

Dr. Feldman agreed and emphasized that they have a lot of experience based on their diabetes work. Once they have a more complete list of the metabolites and the known metabolites, they will try to use Metabolon and she thinks they will be able to see them with the MALDI-MSI.

Dr. Bowser indicated that in their initial work, they found a great unidentified peak by mas spec 100% specific for ALS. With Metabolon, they spent months sequencing and identifying that

peak. It turned out to be a metabolite of riluzole. Their data greatly showed that if someone is taking riluzole, they are an ALS patient.

Mitochondrial DNA and Micro RNAs in ALS

Pam Factor-Litvak, PhD

Director, Eleanor and Lou Gehrig MDA/ALS Research Center

The Neurological Institute of New York, Columbia University Medical Center

Dr. Factor-Litvak presented an update on two preliminary analyses investigating trends in mitochondrial DNA copy numbers and DNA damage and microRNA (miRNA) among a sample of National ALS Registry and Biorepository patients. The investigators are interested in explaining any potential mechanism that OS may have on the progression of ALS. Why are OS associated with ALS and various risk factors like smoking, inflammation, air pollution, POPs, et cetera associated with an increased risk of ALS? Part of it may be just general nuclear DNA damage in the neurons. The other part of it is that many of these potential OS stressors also may be associated with damage to mitochondrial DNA (mtDNA). mtDNA are the energy producers of the cell and have their own DNA passed down from the maternal line.

They are interested in looking at whether damage to mtDNA may reflect an early process in ALS, so it could be used for early diagnosis. miRNAs also may be used for diagnostic purposes. mtDNA is one strand in a circle and there are 22 coding RNA genes and 13 protein coding regions. Most of them are related to OS. The hypothesis is that either antioxidants may curtail ROS, but ROS may actually incur damage to mtDNA. That can be measured looking at copy numbers or looking at breaks in the mtDNA in the DNA, and that there also is a mechanism of repair that fixes it, but the sites that are fixed may be subject to mutations.

| Study | Measures | Results |
|--------------------------------------|--|--|
| Menzies et al 2002 | Electron Microscopy | Structural defects in mtDNA in muscle, liver, spinal motor neurons, motor cortex |
| Comi et al 1998 | Single patient: MND phenotype | Mutation in cytochrome c oxidase subunit 1(COX) |
| Borthwick et al 2006 | Single patient: MND disease | Mutation in mtDNA gene: tRNA Ile |
| Mawrin et al 2004 | Single cell analyses of motor neurons from ALS patients | No accumulation of common mtDNA4977 mutation, which is common and non-uniform in the brain |
| Dhaliwal et al 2000 Ro et al 2003 | ALS patients | mtDNA deletions in brain and skeletal muscle |
| Appel 2006 Crugnola et al 2010 | ALS patients, isolated cases | COX negative fibres in muscles point to defects in cytochrome c oxidase |
| Liu et al 2004 | | Mutant SOD1 genes lead to disrupted mitochondrial membrane permeability |
| Ladd et al 2017 | RNA-seq analyses of cervical spinal cords and anterior motor neurons from ALS patients | Reduced expression of mitochondrial DNA-encoded respiratory genes |

There has been some previous work looking at mtDNA and ALS. Some of these studies were either case series or in single patients. In general, they found some structural defects in mtDNA, sometimes in the blood, sometimes in the brain and skeletal muscles, and sometimes reduced expression of mtDNA-encoded respiratory genes in some of these. So, there is some previous

evidence that may suggest that the mitochondria might be an early site of oxidative damage that may be a lead in to ALS symptoms.

Their first study using biospecimens from the Registry/Biorepository was to evaluate the correlations between mtDNA copy numbers in blood, motor cortex, and spinal cord. For this study, there were 308 subjects with whole blood samples. There also were 17 subjects with blood, brain, and spinal cord samples. All of these samples were tested for mtDNA in the laboratory of Dr. Andrea Baccarelli at Columbia. These patients had enrolled in the National ALS Registry voluntarily. The mtDNA copy numbers were measured using duplex quantitative PCR (qPCR). The results have to be standardized. In this case, they were standardized to a pooled sample that represented the population average. Spearman correlations were calculated between 3 different tissues' mtDNA copy number. T-tests, ANOVA, and linear regression were used to analyze mtDNA copy number with other demographic variables.

Of the 17 deceased patients with samples of whole blood, motor cortex, and cervical spinal cord tissue, the mean age at diagnosis 60.9 (SD 9.13) years. All were white, non-Hispanic. In this select group, 61% were female, so it is not a typical ALS population. They did not have sex on 5 patients because they did not complete the questionnaire. This is a problem and relates to the issue of missing data in the Registry and how hard it would be because 5 of the 13 did not answer the questionnaires and are deceased, so there is going to be quite a bit of missing data in the Registry. In terms of the demographics with blood and motor cortex mtDNA copy number, they did not find much of anything going on. They found that males had fewer copy numbers than females in the blood samples, but there was nothing of any importance except age at diagnosis such that the older a person was, the more copy numbers they had. That also has been shown in non-ALS populations. The Spearman correlation was not very high at 0.21, but Dr. Factor-Litvak emphasized that the sample was very small. There was one outlier for which they are trying to evaluate why the person had so many mtDNA copies in the blood.

The strengths of this component of the study were the availability of rare motor cortex and cervical spinal cord tissue from individuals with ALS to conduct this proof-of-concept study, and that consistent laboratory methods were used across tissue types. In terms of limitations, the sample size is extremely small. Missing questionnaire data further reduced the sample size among those with all 3 biospecimens. The conclusion is that a modest correlation may exist between blood and motor cortex mitochondria copy number, meaning that an easily attainable blood biomarker may reflect the impact of ALS on the brain. Dr. Factor-Litvak emphasized that she was taking these findings with a great deal of caution, but hopes to have additional samples at some point so that they can increase the sample size.

The second part of the study was to analyze mitochondriomics, or mtDNA copy numbers, in a subset of ALS patients from the National ALS Registry. For this component, 308 blood samples were analyzed for mtDNA copy number. Of these individuals, 279 completed some data in the questionnaires. The mean age at diagnosis was 58.6 (SD 11.0) years, 60% were male, and 97% were white, non-Hispanic. The overall mean blood mtDNA copy number was 1.014 (SD 0.39), which is about what might be expected. It is important to note that there are no controls for these analyses, which is another problem with these analyses because a control population is really needed to perform these analyses. They have an application pending that might allow them to do this using both cases and controls.

In terms of demographics with blood mtDNA copy number, there was not much going on with this ALS population. Something might have been expected with "Ever Smoking," but nothing was found there. Additional exposures of potential interest were assessed that were available

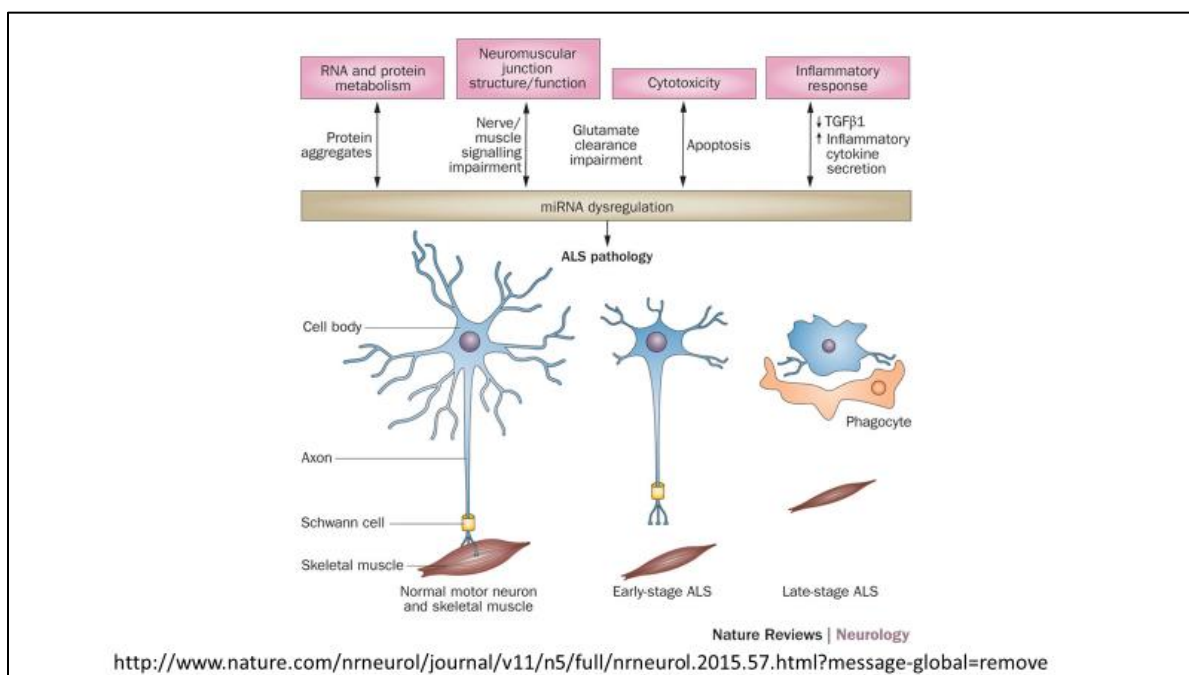
on a limited number of cases from the Registry. There was some trend for fewer mtDNA copy numbers among those who served in the Armed Forces, but no associations with vigorous exercise, pesticides, hobby exposures, or head and neck injury.

In terms of limitations, again the mtDNA copy number was normalized to a sample population average all ALS cases because they did not have a set of controls, which limits the ability to compare values to non-ALS cohort values. Regarding conclusions, similar trends were seen between age and decreasing mtDNA copy number as previously reported in non-ALS individuals. Future studies plan to look at mtDNA damage in addition to mtDNA copy number. Copy number may not be the right biomarker here. It may be the mtDNA damage.

They also were able to look at plasma extracellular vesicle (EV) miRNA expression in ALS patients from the National ALS Registry. miRNA are epigenetic modifications in the cell. The DNA have some genes that code for these miRNAs. Whereas a typical gene will code for a messenger RNA, the miRNAs bind to the messenger RNAs so that the protein is blocked. Some miRNA may block essential proteins, while if there is not a miRNA form, potentially harmful proteins may be formed. It works in both ways, very much like an epigenetic modification.

There are short, non-coding RNA molecules of between 19-22 nucleotides. They regulate post-transcriptional regulators of messenger RNA. About 2000 miRNAs have been annotated. They regulate about 33% of all human genes, and are phylogenetically well-preserved. Altered miRNAs are associated with many diseases, including cancer, diabetes, and a variety of neurological diseases. Many miRNAs are expressed only in single tissues just like epigenetic changes may be restricted to specific tissues. For example, miRNA-138 is differentially expressed in the CNS, miRNA-124 is expressed as neuronal differentiation of mesenchymal stem cells, and miRNA-9 is expressed in neurons.

This graphic is from one of Dr. Feldman's papers that shows that miRNA dysregulation may actually lead to ALS pathology by interfering with normal motor neuron and skeletal muscle, and may be markers of early- and late-stage ALS:



So here, controlling for duration between symptom onset and when the blood sample was collected is going to be very important to be able to differentiate between early- and late-stage ALS.

There has been previous work on miRNA and ALS that suggests that there may be interactions between ALS-associated genes like TDP-43¹ and miRNA processing. A series of miRNAs are dysregulated in ALS biospecimens (blood, muscle, spinal cord, cells derived from patients, and animal models), including miR-27a, miR-155, miR-146a, and miR-532-3². These alterations of the miRNA profile importantly could precede symptom onset and thus be involved in early ALS pathogenesis such that when a patient presents with mild muscle weakness, it could be used as a screener if these results pan out. Dr. Factor-Litvak stressed that this is very early data based on only a few studies, so she did not want to promise anything because not enough is known yet [¹Honda et al 2013; ²Butovsky et al 2012].

In the brief literature review, there were patients with sporadic ALS compared to controls. DeFelice et al 2014 found that miRNA-338-3p was upregulated in blood leukocytes, CSF, serum and spinal cord and also modulates mitochondrial function relating the mtDNA and miRNAs, which is something Dr. Factor-Litvak and colleagues will be able to explore once they have all of the assays completed. Other studies looked mainly at patients with ALS and in mice showing that there have been differential miRNA changes either upregulated or downregulated, depending on the actual study. With the exception of DeFelice et al 2014, these studies did not have controls:

| Study | Design | miRNA |
|------------------------|---|--|
| Freischmidt et al 2013 | Patients with sporadic ALS | Expression of miRNAs which bind to TDP-43 altered in CSF and serum miRNA-9-5p, miRNA-132-5p, miRNA-558-3p : normally found in serum were more abundant in CSF among sporadic ALS cases In familial ALS, mi-RNA-143 downregulated Other miRNAs downregulated depending on genetic mutation (e.g. FUS, C9orf72, TARDBP, FUS) |
| DeFelice et al 2014 | Patients with sporadic ALS compared to controls | miRNA-338-3p upregulated in blood leukocytes, CSF, serum and spinal cord miRNA-338-3p also modulates mitochondrial function |

| Study | Design | miRNA |
|---|--|---|
| Morel et al 2013 | SOD1 mice | miR-124a decreased in spinal cord, may be related to glutamate transport dysregulation |
| Russell et al 2013; Williams et al 2009 | Patients with ALS | Increased expression of miRNA-23a, miRNA-29b, miRNA-206, miRNA-455 in skeletal muscle miRNA-206 increased in symptomatic SOD1 mice Loss of miRNA-206 accelerates disease progression in mice (involved in skeletal muscle development, nerve to muscle communication) |
| Campos-Melo et al 2013 | Patients with ALS | Numerous miRNAs downregulated in spinal cord |
| Butovsky et al 2012 | Patients with ALS (blood) SOD1 mice | Pro-inflammatory miRNA profiles |

Dr. Factor-Litvak and colleagues have looked at miRNAs in EVs that are specific to the nervous system. EVs are formed by the cells. There are endosomes that turn into exosomes, and they are released from the cell. In these are a variety of things like miRNAs, lead, and other kinds of exposures. The ones from the nervous system can be differentiated in assays. That is the assay they chose to do so that they know they are looking at miRNA from the actual nervous system.

In terms of the laboratory methods, ExoRNAeasy serum/plasma maxi kits (Qiagen) are used to isolate EV-encapsulated miRNA from plasma of 100 patients. Agilent Bioanalyzer 2100 small RNA kits are used to measure miRNA yield/purity. miRNAs are profiled using TaqMan OpenArray Human MicroRNA Panel (ThermoFisher). With regard to data cleaning, all miRNAs with an Amp Score < 1.1 were excluded, because those are probably artifacts. All miRNAs with cycle number (Cq) < 0.8 and/or Cq less than the control probe Cq (here Cq < 7.2) were excluded, because they probably also are artifacts. The global mean method was used to normalize miRNA expression.

Regarding the results, they found 514 distinct miRNAs overall in at least 1 sample. Of these, 42 miRNAs were detected in 100% of the ALS Registry samples. An additional 60 miRNAs were detected in 90% to 99% of the samples, and 90 were expressed in more than half of the samples. The current analysis is restricted to only the 42 miRNAs detected in 100% of samples, although there are a lot more analyses to perform on these data. Of these 42 miRNAs, 24 (57%) have been previously described to be dysregulated in ALS. Therefore, they have at least confirmed what others have reported previously.

Butovsky et al conducted a very interesting study comparing miRNA in healthy controls, MS patients, and sporadic ALS patients and found distinct patterns for each. All miRNAs in MS and ALS patients were significant and were related to inflammation and OS. miR-155, miR146a, miR-532-3p, miR-27a, and miR-223 are especially interesting because they have been previously seen in mouse SOD1 models. Although there is some overlap between MS and ALS miRNA expression in inflammation, both MS and ALS were very distinct from the healthy controls [Butovsky et al. 2012].

Dr. Factor-Litvak and colleagues found that 5 of these were found in at least 93% of their samples that expressed miRNA. miR-155 was found in 93% of the National ALS Registry samples and miR-27a, miR-146a, miR-223, and miR-532-3p were found in 100% of the samples. This is a fairly important result, which confirms what Dr. Butovsky et al found. This is a fairly important result that is now in another sample of ALS cases, findings were confirmed for the signature of miRNAs.

While there are a lot more analyses to be done, they were able to confirm the previously reported miRNA signature using the Registry. This is the largest analysis of EV-miRNA in ALS patients to date. The strengths of this study are that neuronal EV-miRNAs were used for the analysis, and a previously reported proinflammatory miRNA signature was confirmed using the US ALS Registry participants. Future planned analyses include qRT-PCR to validate expression of the miRNAs found using the array platform, use of controls to explore relative expression of miRNAs, and identification of novel miRNAs not yet reported to be associated with ALS.

Discussion Points

Dr. Benatar asked whether when they are looking at copy number they control for white cell and platelet count.

Dr. Factor-Litvak replied that it is controlled for white cell count, but that she would have to check with the laboratory on the platelet count.

Dr. Feldman indicated that she and her colleagues did a fairly extensive miRNA analysis on spinal cord tissue in ALS patients versus controls. They received the controls from the Miami Brain Bank. They found a very interesting array of miRNAs that made teleological and scientific sense to them. Because they have a large biorepository, they went back to assess whether there was any correlation between what they would be measuring in plasma versus what they actually see in CNS tissue. That was where the disappointment was. They have a paper they are ready to submit on this, but in a way, it is negative data. That is, what has previously being reported in plasma they are not seeing in human CNS tissue. They have now expanded the initial number on which they published, but they need to get controls. The big problem with their autopsy studies is that they do not have robust controls.

Dr. Factor-Litvak asked whether in the plasma miRNAs they used neuronal EV-miRNAs or just used plasma miRNAs.

Dr. Feldman indicated that they used just plasma miRNAs. They did untargeted miRNAs to look at all of the miRNAs.

Dr. Factor-Litvak indicated that theirs were from nervous tissues because they are the EVs that are expressed from neurons. This is an untargeted miRNA analysis, but within the EVs from neural tissue that are in the plasma. Neural tissue releases EVs into the plasma, so these are exosome tissues.

Dr. Feldman indicated that they have done exosomes on brain, spinal cord, and plasma in collaboration with their bioengineers and are not seeing a big overlap. These are unpublished data, though they did present them at the Neuroscience Meetings last year. She said she would share them with Dr. Factor-Litvak.

Dr. Bowser observed that what Dr. Factor-Litvak showed for their methodology for EVs was not neuronal. EVs are created everywhere, so what is in the plasma is from a deluge of organs. That does not isolate CNS-derived EVs.

Dr. Factor-Litvak clarified that she was told that they were sorted to the neuronal EVs, which she will double-check.

Next Steps Panel Discussion

| | | |
|-------------------|-----------------------------|-------------------------------------|
| Moderator: | Wendy Kaye, PhD | Biorepository Representative |
| Panelists: | Stephen Finger | Person Living with ALS |
| | Eva Feldman | Researcher |
| | Stephen Apple | Pharma Representative |
| | Andrea Pauls Backman | ALS Advocate |
| | Jaimie Raymond | Registry Representative |

Session Overview

During this session, each panelist shared their observations/insights about what the top priorities should be for the Registry and Biorepository in the coming year from the perspectives they were representing. Dr. Kaye then presented specific recommendations made by participants throughout the meeting that were captured and categorized, which was followed by an open discussion period.

Panelist Observations

Stephen Finger, Person Living with ALS

Dr. Finger said that thinking from the point of view of a general patient, patients want to see value in a number of ways. The value of the Registry and Repository should be presented to patients prior to enrollment. After they are enrolled in the Registry and are actively completing surveys, the value of that also should be made clear. If patients are expected to become advocates, it is important to continue to show value. As Mr. Alderman mentioned, efforts should be made to disseminate information about the progress that is being made. For example, summaries should be distributed of research/papers like the exciting work that was presented by the ATSDR-funded researchers. It would be valuable to present gold stars to states that are doing great with enrollment, and doing more to keep patients apprised of the number of enrollments and how that is making it possible to support more research to find a cause and cure. It is important to continually keep people excited about the Registry and Biorepository. Continued efforts must be made to ensure that they are doing the best job they can in providing estimates of the number of patients and demographics. Getting the demographics right is so important. The surveys must be done in a way that makes it easier and not harder for patients to be a part of this, and setting them up in a way to maximize the effort patients are putting into it. It is imperative that the Registry and Biorepository be put into action. It would send a strong signal if after this meeting, an action plan was disseminated regarding how these efforts will be made, followed by a progress report in six months. There is nothing more frustrating in having the same conversations every year.

Eva Feldman, Researcher

Dr. Feldman said that she was very excited to learn in the last 12 months that the Registry data and biosamples are available to the greater scientific community. For investigators who are interested in the association of the ALS exposome and understanding genetics, the environment, potential biomarkers, metabolomics, proteomics, genomics, et cetera, to understand that this is a treasure trove. She thought one way improvements could occur at this point would be to have a clear understanding among the scientific community, not just the individuals around the table, but the greater scientific community, about how to access the available data and samples to conduct very basic research. It also is important to understand the Registry's standard operating procedures (SOPs) in terms of biological sample collection so that, for example, if she or others would want to test their particular hypothesis or findings in a collection from the Registry, they would want to know that they are performing the analyses in a very similar way. The fact that it is now available to the greater scientific community is an amazing, amazing new resource that she is sure many people, including herself, will now tap into once they understand the best practices of how to access the Biorepository and the National ALS Registry data. In terms of improving people joining the Registry, what they have found in their own clinic is that it is not for a lack of wanting to join. It is usually for a lack of being too tired, feeling like there is not enough time, and not having a caregiver or supporter to help them join. As others have described, they have the iPads in their clinic and they have someone helping each person join the registry. Just the simple tools that were discussed earlier in terms of increasing Registry entry were very basic and certainly could improve how many people register. It really does not take a lot.

Stephen Apple, Pharma Representative

Dr. Apple pointed out that the first thing that usually comes to mind about a pharmaceutical company is sales and marketing, but a pharmaceutical company really is a lot more than that. They are comprised of PhDs, PharmDs, and physicians who work in the Clinical Development and Medical Affairs Departments. He applauded everyone for the work that they have done. From a pharmaceutical perspective looking at it from a medical affairs/clinical development standpoint, there are a lot of ways they could partner. ATSDR has a lot of robust data. Considering the types of things pharmaceutical companies want to do, it would help them if there was some type of data sharing at the patient level. They know that there are limitations for lead times in historic controls in their trials, and it would be nice if patients who are part of the Registry who are also enrolled in any pharmaceutical trials, could opt in if they wanted to. Then the pharmaceutical company would have the ability to get the information collected in the Registry, which would give them robust insight into what is occurring with these patients in terms of time to event, progression, and other information those surveys collect. Dr. Horton mentioned that beginning with the 2017 data, Radicava™ (edaravone) is now a criterion. It would be nice if they could collaborate on what those surveys might look like in terms of the questions being asked. They may be just as beneficial to pharmaceutical companies as they are to ATSDR in terms of the information that is captured. From their standpoint, it is about having continual dialogue and being open with data in a compliant manner. They realize that as an industry, Pharma is heavily regulated. They have a lot of compliance rules, as does the government. But, there are opportunities for them to be able to do that.

Andrea Pauls Backman, ALS Advocate

Ms. Backman indicated that this was the third annual Registry meeting that she has attended. Each year, she walks away being more impressed with the depth of the research that is being done from the Registry. One of the things they can do better is to make sure that they are all describing the results that are coming out of this Registry. While they do this to some extent, they must talk about the research findings and most lay people and certainly a lot of people with ALS think the Registry is just about counting noses. Those who know about it know that it is more than that and know that it is still relatively immature in the lifespan of Registries. For that reason, the noses that they count are not reliable at this point. They know that, but she thinks they are at a point where they can extrapolate the data based on the number of cases that have been identified to calculate some better numbers that can be used until the Registry itself is more mature. There also are several things they can do with respect to improving enrollment. As they have discussed, there is under-enrollment in certain areas. If national partners (Les Turner Foundation, ALS Association, and MDA) can focus on those large states in which they know there is under-enrollment, that would do a lot to move the needle on the numbers. Very specific areas in which they should focus include Texas, New York, and California. Regarding the issue of why the Registry matters, the Registry matters because ALS is about people and the Registry is about people who are living with ALS. If they could develop more of a peer-to-peer validation of the Registry based on the many comments they had heard over the last two days and put some of those into a patient blog, something other patients could read and relate to, perhaps more patients would be motivated to enroll.

Jaimie Raymond, Registry Representative

As someone who is part of the National ALS Registry for the past two years, Ms. Raymond said she has seen the focus on getting people enrolled and not as much focus on the surveys. She would like to see a focus on improving the completion rate of the surveys. There has been a major push about people enrolling in the Registry to be part of a study or receive notifications, but almost 40% of those enrolled have not taken any surveys. She wondered how many of that 40% enrolled do not know that there are surveys they could take. Placing more of an emphasis on letting people know about the surveys and that it is a way to tell their stories might help to get more and better quality survey data.

Recommendations Presentation/Discussion

Wendy Kaye, PhD, Biorepository Representative

Following the panelists' observations/insights, Dr. Kaye reviewed the recommendations captured throughout the meeting to determine whether anything was missed, needed to be added, and/or there were gaps. The recommendations captured were categorized as follows, with the general discussion following:

Communications/Outreach

- Send out newsletter Registry updates to go out to people who are participating (e.g., surveys, new research)
- Translate research articles into 1-line summaries for distribution via social media
- Use findings from studies to show the benefits of the Registry and promote joining to patients and caregivers

- Provide more information on how the Registry is contributing to the fight against ALS
- Continue efforts to update the website, make information for patients and caregivers more engaging and easier to find, make sure links work, et cetera
- Work with clinics to get the message out about the Registry and the surveys
- Make the Registry more prominent on partner websites
- Analyze data on what activity led to enrollment in the Registry (e.g., social media, promotional material, clinical staff suggestion); that question was added to the registration in January 2017, so they now have some information on this
- Evaluate what activities within clinic encounters increase the awareness of the Registry; there is limited time and it is better to spend the time on efforts that are thought to have a good penetration rate rather than things that do not

ALS Prevalence Estimate

- Provide an estimate of ALS prevalence that adjusts for under-ascertainment
- Consider changing the label of “definite ALS” to something else because it is being equated with “definite” using El Escorial criteria

Additional Analyses with Existing Data

- Update the proximity to referral center GIS analysis to include prevalence data from 2014 and 2015
- Analyze survey completeness by year to look for improvements (e.g., how many enrolled, how many surveys were completed)
- Evaluate if marital status impacts survey completion
- Evaluate riluzole use, marital status, and number of surveys completed to determine if they are related
- Compare the statistics for the under-enrolled states with the number identified through the administrative data to determine whether they are being missed there as well or they are just not registering, which are two different problems

Other

- Keep track of recommendations from the annual meeting and present progress at the next annual meeting (recommendations made year after year, but no one sees what progress is made), or at 6 months as Dr. Finger suggested earlier
- Decide on needed sample size for an analysis of a particular survey and decide if that survey could be “retired” and/or replaced with another survey because there is a limited amount of time and energy
- Measure the impact of individual activities on Registry enrollment and survey completion to ensure that time and money are being spent on things that will result in improvements
- Inform researchers about data/specimens for research

Discussion Points

In terms of completing surveys, Dr. Kaye said that they are trying very hard to increase the number of people completing surveys who are part of the Biorepository. They received permission from the IRB to change the “Thank You” letter to include an invitation to encourage people who have not completed the surveys to do so because it will make their specimens more valuable. She did not know whether that had helped. They would like everybody to complete the surveys, but especially those who have provided samples.

Dr. Finger suggested framing the request for people to complete the surveys on the studies that have been done based on surveys to show them what they would be contributing to.

Dr. Bowser was not sure that they should retire surveys. The sample size needed for a study is dependent upon a study, which may vary considerably. Some studies may need an N of 10,000 and they are not there yet. Instead of retiring surveys, perhaps they could institute some sort of prioritization of survey in terms of the ones that need to be completed first, second, third, et cetera.

Dr. Kaye agreed. Her concern was she once conducted a study with 500 cases of childhood brain cancer and initially thought that was so many. But, once they got the specific exposures, they had 3 people. There may be a way to prioritize the surveys or present them in a different order.

Dr. Finger thought it would be helpful from the patient's perspective if an estimated time could be placed next to the description of the survey. People want to feel like they are contributing, but some of the surveys are super frustrating. He thought they would get much better responses if someone could look at the list with the times for each survey and determine which ones they could complete quickly first.

Dr. Kaye agreed, but reminded everyone that they have to estimate a burden with OMB and they have done that. The tiny fine print on the page states that to complete them all will take X amount of time, and that on average they take Y amount of time. They have to be careful about pointing one out that is longer, like Residential History.

Dr. Finger emphasized that while they have to be careful about that, they also have to be realistic about the cost of not doing that. Again, the cost is that people do not get around to taking the 3- to 5-minute ones.

Dr. Bowser suggested that perhaps there could be a list placed on the site about how many respondents there are for each of the surveys and an ongoing tally, and a couple of sentences at the top that say something to the effect of, "We know this is time-consuming. This is really important information. In order to link genetic and environmental risk factors that contribute to this disease, we need tens of thousands of surveys from patients." Perhaps that would be an additional way to stimulate people to continue on.

Dr. Finger said if the page said tens of thousands are needed and the count is at 4, probably not. If it said tens of thousands are needed and there are 9999, he would do it.

Dr. Mehta suggested giving each survey a difficulty rating next to the survey (easy, moderate, difficult). They could use green for easy, yellow for moderate, and red for difficult.

Dr. Kaye said perhaps when the residential survey is opened, it could say something to the effect of, "Before you start this, you might want to do A, B, and C." Some people have stayed in one place for a long time, but people in the military might have moved every two years, so this survey can be difficult.

Dr. Thakur said he was thinking about what will happen when he gets back to work and a lot of people continue to tell him the Registry is inaccurate and a waste of money. He does not agree with them, but he wants to be able to make the case for them. The opportunity to complete these 17 surveys to provide rich detail on why people get ALS or why some people do and

some people do not, is really important. However, he does not know why there are these 17 over 21 or 15 or 13 or some other number. He was sure that work had been done, but he does not know where it is, how to find it, or how to summarize that information. There is a bigger point as well. What they are calling the Registry is really three very different programs. There is a registry, a repository, and a grant program. They are all very important, but they also are all coming from the same pot of money. They have the opportunity to consider taking fewer specimens and spending more money on the surveys. Or maybe spend less money on the surveys and spend more money on extramural awards. He had not heard a discussion about all of the tradeoffs that are happening that ATSDR has to do on a daily basis to run this program. He thought everyone there would probably have some thoughts on that and could help ATSDR prioritize. In turn, he could use this to help justify the program. It is not just a registry, it is a repository. It is not just a repository, it is an extramural program that does all kinds of exciting science building on the repository and the registry. They have to have a crisper framework for saying what it is they are working on and why they are making the decisions they do. It is a hard thing to communicate to people.

Dr. Mehta indicated that they hear those same questions every year internally when they set priorities for exactly what they want to do, whether it is increasing samples for the Biorepository, or adding another research award, et cetera. The Biorepository is very expensive to run, so they have to make decisions about whether to increase postmortem collections, or saliva collections, or just blood collections. They also have to consider what proportion of the funds they want to allocate for outreach efforts, advertisements, et cetera. If they have an extra \$500,000 they have to consider whether they are able to fund another extramural project. He has to call Dr. Wright at ERPO to ask whether they could potentially fund a grant that was not funded the previous year. When they go out to give talks, they hear how important research is. Research is tied into the Biorepository. He agreed that they must do a better job internally to let people know what they have done and what has been accomplished around the room. In the past, they have posted the articles that have been published on the website. However, he acknowledged that they must do a better job communicating to the public what they have funded, what the studies have found, and how it is value-added for the Registry.

Dr. Wright added that they have internally discussed potentially supporting a special issue of publications that arise from the extramural research program that would highlight the work that scientists are doing in this area. She also asked how patients who do not have access to the internet can provide answers to the Registry.

Dr. Kaye replied that ATSDR has contracts with the ALS Association, MDA, Les Turner, and the chapters to provide support for people who may not have the capability from home. Some thought was given to whether it could be done in hard copy versus over the Internet, but that is somewhat complicated. For example, how do data collected via interviews compare with data that are self-entered? It becomes a methodological problem, so it is better to get support.

Dr. Brooks observed that one of the points Dr. Finger raised pertained to the value-added of the Registry. One value-added might be hope. The first natural history study published in the US about ALS separated prevalent cases from new cases. They heard from Dr. Factor-Litvak's data that over 60% of the patients she tried to get into her study she could not because they were prevalent cases. He asked whether there is an analysis of the National ALS Registry with respect to prevalent people who were before and after a certain point in time and if they synch with what is known in the epidemiological literature about what it is correlated with (e.g., young onset, et cetera).

Dr. Kaye replied that they could do this analysis. When people register, they provide date of diagnosis, so they have registration date and date of diagnosis. So, they know the time from diagnosis to registration. If they had a cutoff for what constituted “new” they could look to see if there was any difference between Group A and Group B.

Dr. Brooks asked Dr. Factor-Litvak if she asked ATSDR for the date of symptom onset for the Registry patients sent to her.

Dr. Factor-Litvak clarified that that was for ARREST ALS. They asked patients when their symptom onset was when they interviewed them. But, they asked them in relationship to when they interviewed them, not when they joined the Registry. For ARREST ALS, they do not have access to the Registry data about symptom onset date in relationship to when they joined the Registry. They had a cutoff of 18 months and then changed it to 24 months. She did not think they were getting any incident cases, because they could not get someone at the moment of disease onset. But, they can get them at diagnosis and then ask them when their symptoms began. Looking from the point at which their symptoms began when they first experienced weakness or another symptom is the way to ascertain whether they are newly prevalent or really prevalent cases. They had a substantial number who were not eligible because they did not call the Columbia number until well after they were newly prevalent.

Dr. Brooks asked which form includes symptom onset.

Dr. Kaye indicated that this is included in Survey 17, which went up after 7 but was the 8th survey up so a lot of people have completed it.

Dr. Factor-Litvak said one problem is that the surveys went up at different times. Some of the later numbered surveys collect information that would be very important to researchers, so they will miss data on patients who were enrolled in the Registry early on. It is very difficult to play catch-up with these patients because of their disease course. Thinking about which data is going to become essential for research studies, the easy answer is everything. In terms of prioritizing, basic information about demographics, disease course, and exposure is important. But, they do not know about exposures that may become important in the future. Trying to get a lot of information is great, but perhaps the order should be shifted to collect important information early on. Certainly, putting in estimates of time to completion is very important. For residential history, it might help to have maps and have the patients at least put a dot on a map about where they lived at a certain point in their life. That is an easier thing to do than remember old Zip Codes.

Dr. Brooks suggested that perhaps the demographic questionnaire should ask about when symptoms began. They heard throughout the day how important and strong that predictor is.

Dr. Mehta pointed out that the only time they can make these changes is coming up in November 2019; therefore, it is important to collect information about proposed changes. Any changes made in any of the surveys must be approved by OMB. This is important, but they need to put it in their next OMB packet.

Dr. Thakur said he hoped ATSDR would feel free to draw upon all of them for help in going through the surveys, setting priorities, and making those kinds of decisions. He got the sense that everyone there would be happy to help in any way they can.

Dr. Feldman noted that their 30-page survey includes what they call “core questions,” which she said she would be happy to share so that they could correlate those to what they are currently asking in the Registry. She asked how ATSDR is notified when a patient dies.

Dr. Kaye indicated that they are not notified. It would be because once a year the data go through NDI. They use NDI in two ways. One is within the algorithm. Criterion 1 is 2 of the following 3: a visit with a neurologist, a prescription for riluzole, or a death certificate with G12.2. They also use that to calculate prevalence, because they calculate cumulative prevalence. Someone does not have to qualify every year to be a case. They remain a case until ATSDR gets notification from NDI that the person has died. However, there is always between an 18- and 24-month lag. Currently, 2015 NDI data are available but 2016 may not be available yet. CMS data have a similar lag time. Only VA has real-time information.

Given that the data that occurred the 20 to 40 years before the diagnosis are important, Dr. Brooks asked whether they could have a campaign to ask patients to fill out the residential module to help make the Registry stronger.

Dr. Kaye emphasized that while the residential history survey is somewhat long and onerous, it is asking for city and state, not Zip Code. There are a few other questions about the type of water they had, whether they lived near a farm, and a few others that might increase one’s risk for exposures to certain types of chemicals.

Dr. Horton asked whether ATSDR has reached out to the partners about putting a banner on their sites, and if they are either not reaching the right person or some chapters are indifferent. He recalled that Alan Alderman mentioned querying 20 websites, and only about 6 or 7 had the Registry web sticker. Even though it is anecdotal, it is telling. He thought the suggestions were great, but emphasized that these are multi-directional efforts. If the ALS Association, MDA, Les Turner Foundation, and others can help ATSDR push a consistent message down to their constituents (clinic directors, chapter leads, executive directors, et cetera) so that patients are all hearing the same constant message and organizing, using, and sharing best practices for enrollment among the chapters.

Dr. Kaye indicated that she does not have anyone in the Biorepository from Rhode Island. There cannot be that many cases in Rhode Island, so it is unclear how she could not have a single person who is interested in participating. It has to be that the people in Rhode Island are not getting information about it. They had one person in the pilot. The same is true with Hawaii. These are the only two states for which they do not have at least one person, versus other states where the partners are doing a great job. She just got her 4th person from South Dakota, which she was certain is because somebody is recruiting heavily in the Dakotas to tell them about the Registry and Biorepository, and that ATSDR will come to their house to draw their blood and they do not have to go anywhere.

Dr. Thakur indicated that he has not been tracking state-by-state enrollment into the Repository.

Dr. Kaye indicated that Tom Hicks is tracking this and it is in the emails he sends out to everyone.

Dr. Mehta suggested that perhaps they needed to have a grading system for the clinics and chapters for ALS Association and MDA for top-tier chapters who are doing their job.

Dr. Finger pointed out that if they looked at the current enrollment numbers and where they could be, it is going to come from the clinics. There are tens of thousands of patients going to clinics. Not everyone, but a lot. He thought in addition to states, it would be informative to look at clusters around these clinics to determine not only what chapters are doing great, but also what clinics are doing great. Give those a gold star and talk to them about how the information is presented, what their best practices are, how this can be done best given their limited time and resources, et cetera.

Dr. Sorenson recalled that Dr. Kaye had data showing that only about half of ALS patients are seen in ALS clinics.

Dr. Kaye replied that based on the State/Metro project, approximately 25% to 30% of ALS patients were not seen in an ALS clinic and were seen by a general provider.

Dr. Finger stressed that even if 30% of people are not seen in a clinic, there are still 15,000 people who are and they do not have near that in terms of the number of self-enrolled in the Registry. Every one of the bullets in the recommendations is about how to get people to sign up. Just improving the rate at the clinics where there are 50 people on a Friday morning sitting in a room is going to be the cost-effective way of doing this. It is not going to be driving around North Dakota. Boosting the number of people self-enrolling by 10% would mean very different numbers.

Dr. Kaye emphasized that under-enrollment in the Biorepository is in California, Texas, and New York. She cannot figure out why, because she is looking for only 30 people in California to participate. There are a lot of people in California and she should be able to get 30 of them.

Dr. Mehta pointed out that in California, Texas, and New York enrollment is most likely low because the chapter penetration of Registry outreach and promotion is very low. There are chapters and clinics there that do not push the Registry. Having someone approach the people sitting in the waiting room to ask them if they would like to sign up for the National ALS Registry and offering to help them by itself is much more cost-effective to get people enrolled and interested in the Registry than it would be for anything else.

Dr. Oskarsson suggested that perhaps sending notification to the clinics and chapters from the Registry about how they are doing on the local level would be helpful.

Dr. Kaye thought perhaps that could be done for larger states, but they have to be careful about smaller places because of OMB. Perhaps they could put information out by health districts so they would at least be able to see the general area around their locations. They could perhaps divide Florida into three sections: North, Central, South. People probably migrate to a particular center depending upon whether they live in Miami or Tampa, for example. Perhaps that would be helpful.

Mr. Hicks agreed that providing the data to the clinics is important, but he pointed out that equally important is going to be providing information about best practices. They and their partners need to be able to provide clear guidance on what is working in clinics, and then that can be measured.

Dr. Factor-Litvak said that based on her studies of other types, they have had immense success working with nurses. When she recruits pregnant women, for example, they are much more responsive to a nurse asking them to do something than the physician. It would be a way to get the nurses in the clinics involved, and rewarding those nurses for getting patients involved in the Registry. They probably do have more contact time in terms of minutes with the patients than the physicians do. Probably the partner outreach has not hit the patients yet, but the nurses can really develop a rapport with the patients. Perhaps that would be a way to increase enrollment, especially in clinics that are not really recruiting.

Dr. Finger observed that one thing that seems to be increasing in terms of the budget with the Registry and hopefully will continue going forward is the support of external research. It is really important for those grants to reinforce the value of the Registry in two ways, by producing research that is valuable to patients and to other researchers to get them motivated and to make crystal clear how they are leveraging the Registry itself. It is somewhat of a disconnect when the Registry is funding research that does not require researchers to share data with the Registry. When he as a patient is trying to tell other people why they should be in this Registry as opposed to signing up for one of the other 50 other registries, it does not make his job easier if the Registry is kicking in \$100,000 a year just so someone else can duplicate the effort. It is very important that this money is used to leverage the activity around this, because that pushes researchers to use it more and it pushes patients to want to be more involved.

Dr. Horton said he thought they need to do a better job of making it known to researchers that they have these data and biospecimens available, whether they do that through some type of media campaign or peer-to-peer effort. They are not collecting specimens just for the sake of collecting them. They want to make sure that they are being used, but in order for them to be used people need to know about them.

Dr. Mehta indicated that all of their grant funding opportunities include language encouraging applicants to use the Registry data, but they cannot make them use it. The minute they make them use it, it becomes a contract. These grants are structured to be investigator-initiated. If they did research contracts, it would take 12 to 18 months getting OMB approval for data collection activities. There is standard language in the NOFO stating that data must be shared.

Dr. Wright added that there is a requirement for any grant, which is called an "Assistance Mechanism" as opposed to a contract.

Dr. Finger asked who evaluates the applications.

Dr. Mehta indicated that the grant cycle is a firewall. He has no information about who the applicants are. Dr. Wright will not tell him and Dr. Horton anything at all about the applications. This is done using the NIH peer-review model. He suggested that Dr. Finger request to serve as a reviewer on future grants. ERPO does everything. They contact the subject matter expert (SMEs) who sit on the panel, oversee the primary review by the peer-review committee and secondary review that is conducted by ATSDR's Associate Director of Science (ADS), and even then he has no knowledge of who has applied. Then there is a tertiary review by the ATSDR Director, who makes the final decision about what to fund and in what order to fund based on the priorities. Only around September does he receive a list from Dr. Wright indicating who the recipients are.

Dr. Wright explained that for each NOFO, it is a requirement within HHS at large that it is expected for public health research that resources be shared, that data management and sharing plans be in place, and that attribution to the funding sources and resources be made. This year, they are ramping up data management and data sharing requirements and providing more guidance.

Dr. Mehta indicated that 4 grants are coming offline this year that end in September, so they want to fund 4 new ones as well with those funds. The purpose of the grant cycle is to take care of that.

Dr. Kaye received a call from someone about the Biorepository who she asked about how he found out about them. He said that a Department of Defense (DoD) NOFO listed the National ALS Biorepository as a place to get specimens.

Dr. Mehta added that this resulted from ATSDR's conversation with DoD requesting that they include language in their NOFOs to encourage using the specimens from the Biorepository, so they do cross-collaborate with the DoD on this effort.

Dr. Brooks asked where the Biorepository stands in terms of increasing the number of patients it can accept.

Dr. Kaye indicated that the number they can do each year is dependent upon the budget. The maximum that they can do because of IRB and OMB is 325 bloods and 350 salivas. Last year the budget was for 250 bloods and 50 salivas. There are plans to bump that for next year. The post-mortem is closed unfortunately unless there are additional funds. They are still following 22 people.

Dr. Brooks asked whether voluntary agencies, industry, and patients could help them in terms of identifying a need for this effort.

Dr. Kaye indicated it would be a matter of whether they want to increase the numbers and the cost. Postmortem collections are very expensive.

End of the Day Wrap Up

Robert Kingon, MPA, Facilitator
Carter Consulting, Inc.

Wendy Kaye, PhD, Senior Epidemiologist
McKing Consulting Corporation

Dr. Kaye thanked everyone for participating in this session, which she always found to be very interesting. She offered special thanks to Mr. Kingon, as he indicated to her that this would be his last meeting. He has served as the facilitator for about 10 years.

Mr. Kingon said that he and Dr. Kaye had often crossed paths at CDC, but 10 years ago they began working together on this project. He said it had been his pleasure to know everyone and participate in these sessions.

Closing Remarks

Paul Mehta, MD
National ALS Registry Principal Investigator
Environmental Health Surveillance Branch
Division of Toxicology and Human Health Sciences
Agency for Toxic Substances and Disease Registry

Dr. Mehta thanked everyone for attending, acknowledging that it is not easy to travel to Atlanta. He especially thanked the persons living with ALS. He emphasized that this is their Registry and ATSDR wants to make sure it works for persons living with ALS. They certainly value their input and feedback whether it is good, bad, or ugly. The ATSDR team is committed to making it better. He also thanked all of the neurologists who were in attendance and had dedicated their lives to seeking a cure for ALS and helping their patients. In addition, he thanked pharma for sharing their information. He also thanked their partners. The National ALS Registry staff are a small group, but they are completely transparent and want to hear comments, questions, compliments, and criticism and will respond. He answers his emails 7 days a week and will personally answer questions. He thanked everyone again and said he looked forward to seeing them next year.

Participant Roster

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