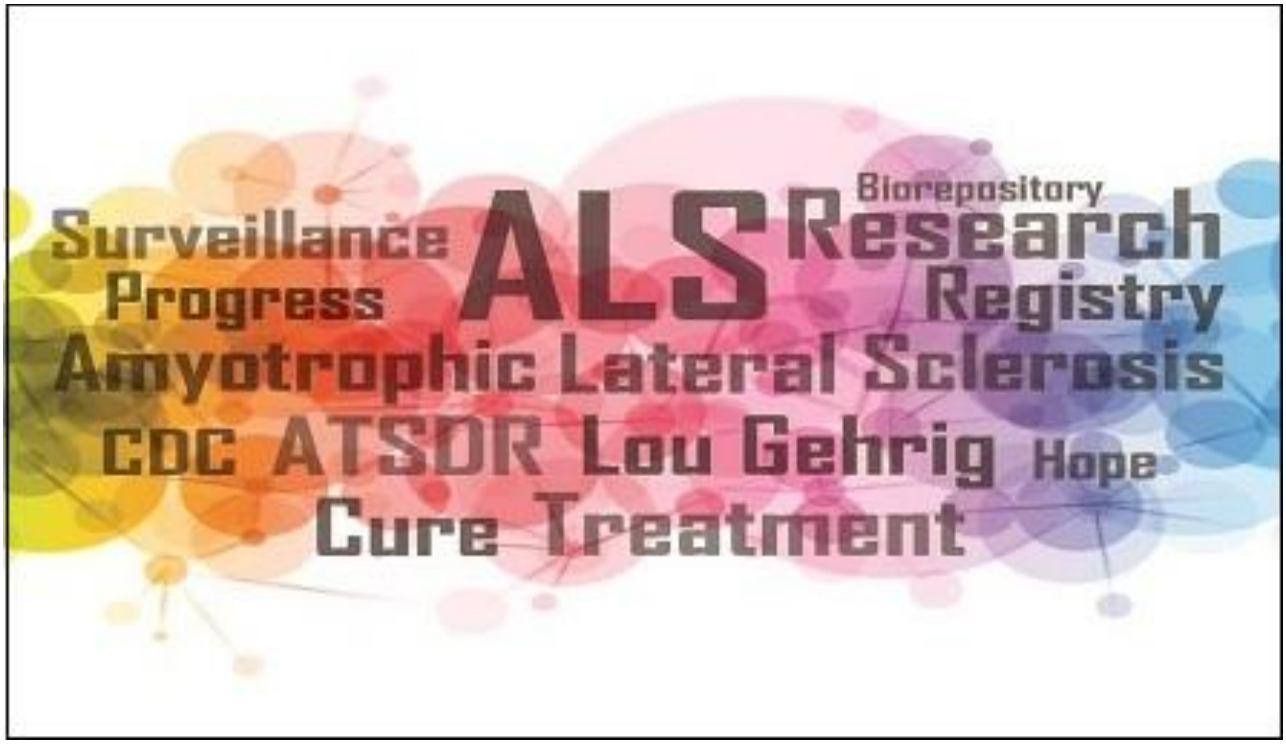
Department of Health and Human Services
Centers for Disease Control and Prevention
Agency for Toxic Substances and Disease Registry

2019 National Amyotrophic Lateral Sclerosis (ALS) Registry Annual Meeting



July 23-24, 2019
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.

2019 National ALS Registry Annual Meeting Executive Summary

The National ALS Registry meeting was held in Atlanta on July 23-24, 2019.

National ALS Registry Update: Goals, Methodology, and Achievements

The goals of the National Amyotrophic Lateral Sclerosis (ALS) Registry are to determine the incidence, prevalence, demographics, and risk factors for ALS in the United States (US). Because ALS is a non-notifiable condition in the US, Agency for Toxic Substances Disease Registry (ATSDR) uses a two-pronged approach to ascertaining ALS cases including (1) online registration by ALS patients via the web portal and (2) identifying ALS cases from large national databases (i.e. Medicare and the Veterans Administration). Persons with ALS can also provide information about risk factors for ALS by completing one or more of the Registry's 17 online surveys.

The Registry does more than just count cases, it is also:

- Funding investigator-initiated research for ALS epidemiological studies and clinical trials,
- Collecting biospecimens including tissue, hair, nails, and blood and post-mortem samples (brains, spinal cords, and other specimens),through the National ALS Biorepository,
- Connecting patients with researchers recruiting for ALS clinical trials or epidemiological studies,
- Gathering etiologic data from Registry enrollees via online risk factor modules such as, occupational history, military history, residential history and history of traumatic brain injury (TBI),
- Providing data and biospecimens to scientists to further ALS research.

Registry accomplishments since the last meeting include:

- ATSDR funded 16 research studies to date, with three new studies funded in Fall 2018 and another to be funded in Fall 2019.
- Assisted over 45 institutions (e.g., pharmaceutical companies and academia) with their clinical trials and epidemiological studies resulting in over 1000 patients recruited to date.
- The National ALS Biorepository has received blood and saliva samples from over 800 participants and over 40 post-mortem collections.
- The fourth *Morbidity and Mortality Weekly Report* (*MMWR*) report on the Prevalence of ALS in the US was published on November 23, 2018, covering calendar year 2015.
- ATSDR held its first-ever Registry webinar for partners that was attended by 123 people.
- ATSDR is in the process of launching a new user-friendly Registry website.
- A new Spanish Registry website was launched on July 22, 2019.
- New social media, graphics, and other digital assets have been created to enhance the Registry communications and outreach efforts.
- Over 60 peer-reviewed publications/abstracts from Registry staff and research partners (over ½ dozen more since last year) have been published.

- A State Outreach Project was conducted jointly with the ALS Association, MDA, and the Les Turner ALS Foundation to increase Registry enrollment in health districts that were currently under-enrolled.
- Targeted 56 percent of Registry funding to supporting ALS research.

Research Update

The most recent findings from the Registry indicate that in 2015, there were 16,583 persons identified in the US as definite ALS cases through the national databases and the Registry portal. This equates to a prevalence estimate of 5.2 cases of ALS per 100,000 persons, representing a slight increase since 2014. ALS continues to be more common in whites, males, and persons aged from 60-69 years of age.

Persons with ALS can complete 17 risk factor surveys on the Registry portal, which has created a rich source of risk factor information for ALS. Data requests are being submitted from researchers for the risk factor surveys and releases have begun. Some of the institutions conducting analyses of the data include the Mayo Clinic, Rutgers University, and Columbia University.

The Research Notification System is connecting ALS patients to researchers who are recruiting for participants in their new studies and clinical trials. Approximately 95% of Registry enrollees opt in to receive notifications about opportunities to participate in these research efforts. As of the meeting date, 45 institutions have used the notification system.

ATSDR is also supporting ALS research with 56% of the Registry's funding being allocated to external research.

National ALS Biorepository

Persons with ALS who are enrolled in the National ALS Registry may also take part in the National ALS Biorepository. The Biorepository sends a phlebotomist to the patient's home to collect the biospecimens, including blood, urine, and saliva, at no charge to the patient. Postmortem specimens are also collected including brain, spinal cord, cerebral spinal fluid (CSF), bone, muscle, and skin. Biorepository participation from January 2017 – June 2019 resulted in the collection of 678 in-home blood and urine samples, 154 saliva only samples, and 20 postmortem samples. Researchers can request samples for their ALS research projects. Samples can also be paired with demographic and risk factor data from the Registry. The types of specimens most likely to be requested are blood and postmortem tissue. To date, over 5,000 samples have been provided to researchers.

Research Notification System

This past year the Registry used its Research Notification System to assist academia and pharmaceutical manufacturers to help them recruit for their clinical studies. The system was used by Brainstorm Cell Therapeutics, Orphazyme, Orion Pharma, Amylyx Pharmaceuticals, The ALS Association, Columbia University, and the University of Sydney.

Enrollment in the Registry

In 2018, the Registry began collecting data on how participants are being referred to the Registry. The findings indicate most referrals were made by the ALS Association and

doctors/neurologists. Regarding the risk factor surveys, there are now 17 surveys available on the Registry for enrollees to complete. The survey that has the highest rate of completion is the demographics survey, with nearly 60% of enrollees completing the survey in 2017. Currently, on average, enrollees are completing about six of the 17 surveys. Comparing registration date to date of diagnosis, those registering in 2017 were diagnosed just under a year earlier. The findings also show that states that are registering the highest percentage of persons with ALS have a slightly higher percentage of survey completion than states with the lowest percentage of registered patients.

Under-Enrolled States Outreach Project

The Under-Enrolled States Outreach Project was a six-month study conducted jointly by ATSDR, the ALS Association, MDA, and the Les Turner ALS Foundation during July - December 2018. The goal was to determine if increased specific outreach efforts in under-enrolled states would improve the percentage of persons with ALS who enrolled in the Registry. The states participating in this project were Hawaii, Mississippi, New York, Utah, West Virginia, and Wyoming. The outreach efforts included the posting of targeted social media and graphics, outreach via partner-specific events, such as support groups and walks, and standardized phone calls by the local ALS chapter and clinic staff to persons with ALS served by their chapters/clinics. The results showed that all six states did have an increase in enrollment in 2018 as compared to the same time period in 2017. Regarding next steps, the Under-Enrolled States Outreach project was successful in bringing partners together to develop outreach methods that are now available to all states and in establishing methods to increase enrollment through outreach. The next steps in Phase II of the project are to focus on the higher populated and under-enrolled states of California, Florida, and Texas.

Recommendations from the 2018 Meeting

The purpose of the Registry's annual meeting is to update the ALS stakeholders on the progress of the Registry, to provide a forum to discuss challenges faced by the Registry, and to receive expert advice and discuss strategies to further enhance the Registry. In many ways, the annual meeting functions like an advisory committee to the Registry. The suggestions and recommendations that patients, caregivers, partners, and researchers provide are valuable and critical to the success of the Registry. There were 18 recommendations from 2018 that were presented in the following categories: Communications and Outreach, ALS Prevalence, Analysis and Existing Data, and Other. The activities that are being implemented to address each recommendation, the organization that is taking the lead on the recommendation, and the status of each recommendation were presented in several tables.

Communication & Outreach

ATSDR

This year, ATSDR created for the first time the National ALS Registry newsletter that features a patient spotlight and updates for partners and researchers. The goal of the newsletter is to increase awareness of the Registry and highlight the variety of resources and tools that are readily available on the ALS website. In addition to the newsletter, the redesign of the ALS website is another key marketing strategy ATSDR is focusing on in 2019. The new website will group subject matter topics by target audience so that users can navigate the new website efficiently. The Spanish website is also forthcoming.

Further communication outreach efforts from 2019 include:

- The first ever national training webinar for partners, with over 120 participants.
- Feature article on CDC's website for ALS Awareness Month.
- A "matte" article in community newspapers, which resulted in over 2500 placements.

Brunet Garcia

Since 2015, Brunet- Garcia has been working with the National ALS Registry to raise awareness of the Registry and also support partners, stakeholders and persons with ALS. Burnet- Garcia is supporting the Registry by creating new and innovative marketing materials such as graphics, posters, factsheets and more. In 2019, Brunet-Garcia created squeeze balls for patients and partners, appointment card reminders, and print materials to explain the importance of risk factor surveys and several posters in different content and design elements for partners.

Brunet-Garcia is continuing their work in the development of materials that explain the difference between the Registry and partner organizations.

ALS Association

The ALS Association is the only nationally affiliated not-for-profit health organization dedicated solely to ALS. The Association's nationwide network of 39 chapters provides comprehensive patient services and support to the ALS community. The ALS Association plays a vital role in promoting the work of the Registry through their chapters. For example, in 2019 the ALS Association conducted a series of focus groups of clinical staff in chapters to work cohesively on promoting the Registry. The focus groups also provided feedback and challenges about print materials and registration. Furthermore, the ALS Association requested help and support to their clinic staff and caregivers in understanding the process of practicing how to register online.

Overall, the ALS Association and their clinics promote the work of the Registry by holding ALS walks and engaging with persons with ALS about the importance of not only the Registry but also the Biorepository and have also collected specimens. The ALS Association continues to use their social media platform as a way to promote the Registry.

Muscular Dystrophy Association

The Muscular Dystrophy Association (MDA) is an umbrella organization that covers 43 neuromuscular diseases (NMDs), one of which is ALS. They offer a number of support services to the community, in addition to the research that they fund. MDA works as a partner with ATSDR to promote the Registry and in 2019 MDA has increased its social media promotion of the Registry considerably. In addition, MDA create regular online postings on their national site, including postings during ALS Awareness Month in May and the more traditional print media, such as MDA's Quest Magazine to reach a different target audience.

Furthermore, MDA has recently started a new effort to ensure that all of its staff are officially and adequately trained on the National ALS Registry. The new MDA Engage program is a community gathering event they recently hosted in Boston that focused on ALS and served as a great opportunity to share information about the Registry to the 80 patients and family members that attended.

Les Turner ALS Foundation

Founded in 1977, the Les Turner ALS Foundation is one of the oldest ALS groups in the world aiming to serve persons living with ALS and their families in the Chicago area. They provide wide-ranging ALS care through patient service programs including local support groups, community educational programs and in-home consulting. In addition, the Les Turner ALS Foundation has a National ALS Registry Associate and their main objective is to meet with patients in clinics and at the comfort of their homes to provide information about the importance of the Registry and help persons living with ALS successfully enroll in the Registry. They estimate that about 85% of the individuals they serve are currently enrolled in the Registry.

In 2018, the Les Turner ALS Foundation has promoted the National ALS Registry through monthly features on their website, marketing the Registry from their social media channels, print newsletters, annual education meetings for medical professionals and more. They also promote the Registry in 5 support groups in the Chicagoland area.

Update from Pharma

Biogen

Dr. Cho, associate Medical Director presented on several Biogen clinical trials, including the EMPOWER Phase III study with dexpramipexole, which did not demonstrate any difference in efficacy with placebo. Although the Phase III study failed to demonstrate the prespecified efficacy, the study provided an opportunity to examine the rich datasets generated from the study with over 800 patients to reshape the approach. Key findings from this assessment suggested the need to evaluate genetically validated targets in defined patient populations, pursue the most appropriate modality for each target, implement biomarkers of target engagement and disease activity in early-stage studies, and employ sensitive clinical endpoints. Biogen is also focusing on applying what has been learned from genetic targets, such as SOD1 and C9orf72, to target sporadic ALS.

Dr. Cho presented on a number of other studies that are in Phase I and Phase III development, including Toferson, an antisense oligonucleotide (ASO) targeting SOD1 mRNA. The hypothesis is that if the SOD1 protein levels are reduced, this may slow disease progression. The first report of tofersen in participants with SOD1-ALS supports its continued development. A Phase III study with tofersen has been initiated called VALOR, which is currently enrolling patients with SOD1 mutations who demonstrated weakness attributable to ALS. The treatment duration for VALOR will be 6 months.

Other studies were described which focus on sporadic ALS and the assessment of a potential complementary therapy for muscle strengthening.

Persons Living with ALS Perspective

An open panel including three persons with ALS provided their journey living with ALS and perspective of the Registry. Each participant expressed their appreciation for the Registry and for the meeting. Participants also provided helpful insights on ways to better promote the Registry and Biorepository.

ATSDR-Funded Research Update

ATSDR provides funding to support ALS research studies to help the ALS community learn more about the disease and to also help prioritize new risk factor modules for the Registry. Principle investigators presented updates of the following ATSDR-funded studies:

- Environmental Risk Factors for ALS: Critical Time Periods and Genetic Interactions
- Identification and Characterization of Potential Environmental Risk Factors for ALS Using the ALS Registry Cases and a Control Population
- Novel Extracellular Vesicle and Molecular Biomarkers of Environmental Exposure and Disease Progression in ALS
- Metabolomic Signatures Linking ALS to Persistent Organic Pollutant Exposures
- A Population-Based Ohio ALS Repository and a Case-Control Study of ALS Risk Factors
- Case-Control Studies Nested in National ALS Registry to Evaluate Environmental Risks
- Antecedent Medical Conditions and Medications: Associations with the Risk and Prognosis of ALS
- Identification and Validation of ALS Environmental Risk Factors

National ALS Registry Action Items for 2019/20:

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 implement the following new recommendations:

- Create new materials about how to sign up for the Biorepository.
- Create new materials explaining the importance of risk factor surveys and their completion.
- Explore universal branding for ALS.
- Identify new and better ways to engage minority populations to join the Registry.
- Provide increased guidance to neurologists on the most effective way to engage PALS about the Registry.
- Provide registration information to PALS at multiple time points.
- Have someone designated or information about the Registry available at the doctor's office.
- Randomly order surveys for each participant to help increase completion rates.
- Place information about the Registry on the same side of the appointment card as the appointment information.
- Have a checklist or card for Registry participants to note user ID and password.
- Have a Registry practice site/test account for partners and clinic staff. Alternatively, have a webinar that steps partners/clinic staff through registration and a sample of surveys.
- Have a central location for information on all ALS Biorepositories.

Table of Contents

Acronyms Used in this Document

Acronym	Expansion
AAN	American Academy of Neurology
ACS	American Cancer Society
ADA	Americans with Disabilities Act
AE	Adverse Event
ALS	Amyotrophic Lateral Sclerosis
ALS-CBS	ALS Cognitive Behavioral Screen
ALS-CBS-CG	ALS Cognitive Behavioral Subscale Caregiver Portion
ALSA	Amyotrophic Lateral Sclerosis Association
ALS COSMOS	ALS Multicenter Cohort Study of Oxidative Stress
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
ASO	Antisense Oligonucleotide
ATSDR	Agency for Toxic Substances and Disease Registry
BMI	Body Mass Index
CCW	Chronic Conditions Data Warehouse
CDC	Centers for Disease Control and Prevention
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CMS	Centers for Medicare and Medicaid Services
CNS	Center for Neuroscience
CNS	Central Nervous System
CNS-LS	Center for Neurologic Study-Lability Scale
COWAT	Controlled Oral Word Association Test
CPS	Chlorpyrifos
CReATe	Clinical Research in ALS and Related Disorders for Therapeutic Development
CSF	Cerebrospinal Fluid
CVD	Cardiovascular Disease
HHS	(Department of) Health and Human Services
Da	Daltons
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
DNA	Deoxyribonucleic Acid
DPH	Department of Public Health
DSMB	Data Safety Monitoring Board
DTHHS	Division of Toxicology and Human Health Sciences
DUA	Data Use Agreement
EHSB	Environmental Health Surveillance Branch
EPA	Environmental Protection Agency
ERPO	Extramural Research Program Office
ERS	Environmental Risk Score
EVs	Extracellular Vesicles
XPO	Exportin
FALS	Familial ALS
FBI-ALS	Frontal Behavioral Inventory
FDA	Food and Drug Administration
FDR	False Discovery Rate
FIPS	Federal Information Processing Standard
FOA	Funding Opportunity Announcement
FUS	Fused in Sarcoma

FVC	Forced Vital Capacity
FY	Fiscal Year
GC/MS	Gas Chromatography-Mass Spectrometry
GUID	Globally Unique Identifier
GWAS	Genome-Wide Association Study
HHD	Hand-Held Dynamometry
HHS	(United States Department of) Health and Human Services
HMDB	Human Metabolome Database
ICD	International Classification of Diseases
iPSCs	Induced Pluripotent Stem Cells
IRB	Institutional Review Board
IT	Information Technology
JAMA	*Journal of the American Medical Association*
JHU	Johns Hopkins University
LC-MS	Liquid Chromatography–Mass Spectrometry
MAD	Multiple Ascending Dose
MDA	Muscular Dystrophy Association
miRNA	microRNA
MG	Myasthenia Gravis
MGH	Massachusetts General Hospital
MMWR	*Morbidity and Mortality Weekly Report*
MMSE	Mini-Mental State Examination
MND	Motor Neuron Disease
MOVR Data Hub™	neuroMuscular ObserVational Research
MS	Multiple Sclerosis
MS	Mass Spectrometer
MTA	Material Transfer Agreement
MTDA	Mitsubishi Tanabe Pharma Development America
MTPA	Mitsubishi Tanabe Pharma America
MTPC	Mitsubishi Tanabe Pharma Corporation
MVP	Million Veteran Program
NCEH	National Center for Environmental Health
NDI	National Death Index
NEALS	Northeast Amyotrophic Lateral Sclerosis Consortium
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIV	Non-Invasive Ventilation
NMD	Neuromuscular Diseases
NOFO	Notice of Funding Opportunity
NPL	National Priority List
NRA	National Rifle Association
NYGC	New York Genome Center
OMB	Office of Management and Budget
OPLS-DA	Orthogonal Partial Least-Squares Discriminant Analysis
ORISE	Oak Ridge Institute for Science and Education
OS	Oxidative Stress
PALS	Persons with Amyotrophic Lateral Sclerosis
PARALS	The Piemonte and Valle d'Aosta Register for ALS
PBDEs	Polybrominated Diphenyl Ethers
PBMCs	Peripheral Blood Mononuclear Cells
PCBs	Polychlorinated Biphenyls

PD	Pharmacodynamics
PI	Principal Investigator
PII	Personally Identifiable Information
PK	Pharmacokinetic
PLPS	Post-Lumbar Puncture Syndrome
PM	Particulate Matter
pM	picaMolar
PMA	Progressive Muscular Atrophy
pNfH	Phosphorylated Neurofilament Heavy Subunit
POPs	Persistent Organic Pollutants
PPM	Parts Per Million
REFINE-ALS	Radicava (Edaravone) Findings in Biomarkers From ALS
RNA	Ribonucleic Acid
SES	Socioeconomic Status
SfN	Society for Neuroscience
SMA	Spinal Muscular Atrophy
SME	Subject Matter Expert
SOD-1	Superoxide Dismutase 1
SOP	Standard Operating Procedure
SVC	Slow Vital Capacity
TICS	Telephone Interview for Cognitive Status
UCLA	University of California Los Angeles
VA	(United States Department of) Veterans Affairs
VOCs	Volatile Organic Compounds
WGS	Whole Genome Sequence
WHI	Women's Health Initiative
WQS	Weighted Quantile Sum
WVFT	Written Verbal Fluency Test
ZCTA	ZIP Code Tabulation Areas

Centers for Disease Control and Prevention (CDC)
Agency for Toxic Substances and Disease Registry (ATSDR)
2019 National Amyotrophic Lateral Sclerosis (ALS) Registry Annual Meeting

Minutes of the Meeting
August 23-24, 2019

Welcome and Introductions

Cherie Imam, Facilitator
Carter Consulting, Inc.

Ms. Imam called the meeting to order at 8:30 AM and welcomed everyone. She described the 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
Agency for Toxic Substances and Disease Registry

Dr. Breysse welcomed everyone to Atlanta and emphasized what an honor it was to be there and to kick off the meeting for the last 4 years. The Agency for Toxic Substances and Disease Registry (ATSDR), and indirectly the National Center for Environmental Health (NCEH), are particularly proud of the National ALS Registry. This is a very unique and important resource to the country. He expressed appreciation for everyone's attendance. Having clinicians, researchers, and especially persons living with ALS assembled at the annual ALS meetings allows ATSDR to gather feedback that helps to shape the National ALS Registry. He also extended gratitude to those who were taking time to view the meeting online through the streaming link. He stressed how valuable everyone's feedback is and that it could not be emphasized enough that the success of the National ALS Registry depends upon effective collaboration from many ALS stakeholders. The National ALS Registry is a groundbreaking effort to help scientists identify possible etiologies and risk factors as they work toward a cure for ALS. The National ALS Registry is making considerable progress, which they would hear about over the next two days. ATSDR is currently working on the fifth national prevalence estimates, with a late Fall to early Winter publication date anticipated.

ATSDR also is excited about the National ALS Biorepository, which is a unique resource. In-home and post-mortem patient specimen collections are ongoing. These samples are being paired with risk factor survey data, which makes the National ALS Biorepository a very special and important resource. In addition, specimens are undergoing a variety of analyses that internal and external partners would describe during the meeting. To date, eight studies are underway to evaluate genetics and exposures to heavy metals and organophosphates. Data from the National ALS Registry also are being used to disseminate research for further analyses. ATSDR has funded 16 external research studies and looks forward to funding one additional study in the Fall. This meeting would include updates on research being conducted

with National ALS Registry and National ALS Biorepository data, as well as opportunities for participants to provide feedback on these and other topics. ATSDR's partners also would provide updates on their initiatives related to the National ALS Registry. The ALS National Registry's Communication Team also would discuss ways in which ATSDR is increasing awareness of the new digital and print assets that are available.

Dr. Breysse said that he was happy to report that the National ALS Registry's Research Notification System has been extremely well-received by enrollees and researchers. To date, 45 institutions have used this system for clinical trials and epidemiological studies. Over 95% of the National ALS Registry enrollees have opted in to receive notification about ALS research for which they are eligible. ATSDR also was excited to have their pharmaceutical partners in attendance who would present on their drug development efforts, and to hear from Persons with Amyotrophic Lateral Sclerosis (PALS) who would speak about their prospective about living with ALS and the importance of the National ALS Registry. In addition, they would hear much more about new initiatives and ATSDR's progress on the National ALS Registry over the next two days. He emphasized that as ATSDR turned to the attendees as the leading experts in ALS to continue to shape the National ALS Registry to be the best it can be, they should feel free to share their thoughts and comments throughout the meeting.

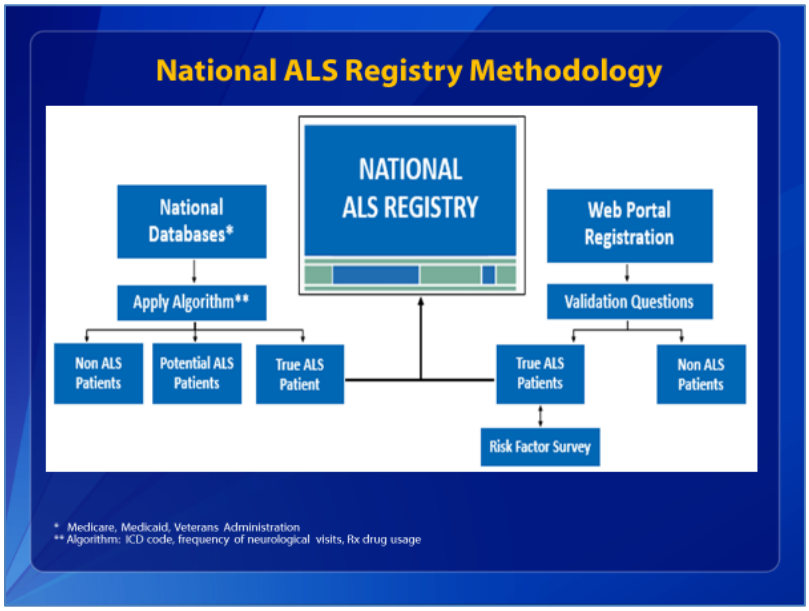
National ALS Registry Update

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, especially PALS given the difficulty involved in attending. He emphasized that ATSDR greatly values PALS' input, who are the true experts in this disease. He also welcomed those attending via Livestream. He recognized that some participants may have heard his presentation previously, but that not everyone in attendance was familiar with the National ALS Registry in that new individuals are invited to attend each year. He explained that ATSDR, as part of the Department of Health and Human Services (HHS), is the US health agency that is charged with protecting Americans from toxic and environmental exposures. ATSDR is co-located with its sister agency, CDC, in Atlanta, 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 PALS are directly responsible for the passing of this Act. ATSDR certainly would not be working on this Registry if not for the hard-fought efforts of the people in the room. The Amyotrophic Lateral Sclerosis Association (ALSA), the Muscular Dystrophy Association (MDA), and the Les Turner ALS Foundation were instrumental in going before Congress to tell the story about how ALS is such a devastating disease and why the federal government should allocate more resources to ALS. The law directs CDC/ATSDR to create and maintain a population-based ALS registry for the US. The National ALS Registry launched in October 2010, after pilot-testing and development. As specified by the Act, the purpose of the Registry is to describe the incidence and prevalence of ALS, describe the demographics of ALS patients, and examine risk factors for the disease. Although Lou Gehrig was diagnosed over 75 years ago and a lot of progress has been made on the science front, many questions remain about the disease, especially for sporadic cases.

One of the primary goals of the Registry is to determine what leads to sporadic ALS. Because ALS is a non-notifiable disease, the Registry needed novel approaches to track ALS cases. That is, when a doctor diagnoses someone, he or she does not have the responsibility to report the case to the state health department which in turn notifies CDC. Therefore, nothing was known about these cases and ATSDR had to develop a novel approach to identify ALS cases in a country the size of America (≈ 325 million people). Therefore, ATSDR had to establish a case-finding strategy that would allow them to identify new and existing cases of ALS. To that end, the Registry takes a two-pronged approach for identifying 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. The algorithm separates people into three categories: Non-ALS Patients, Potential ALS Patients, and True ALS Patients who are automatically added to the Registry. The algorithm includes elements such as the International Classification of Diseases (ICD)-9 code for ALS, prescriptions for RILUTEK® (riluzole) or RADICAVA® (edaravone), and frequency of visits to neurologists or ALS clinics. Based on pilot testing and other previous studies in the literature, ICD codes alone cannot be relied upon because there is a lot of miscoding (e.g., an ALS case being miscoded as supranuclear palsy). While the bulk of cases can be captured using ICD codes, it is not possible to capture all of them in that way. All of the components of the left side of the above algorithm are done behind the scenes, so that PALS do not need to do anything on that side. The majority (~80%) of cases are captured through the left-hand side of the algorithm.

The other approach of the Registry methodology is registration through the web portal, which is the right side of the algorithm and is the component people know best. The goal is for PALS to come to the web-based portal to enroll. Potential enrollees answer a series of validation questions and are either considered an ALS case or not an ALS case. True cases are added to the Registry and are asked to complete the enrollment process and the next step, which is to answer a series of brief risk factor survey modules. Not only does ATSDR want to know whether someone has the disease, but also they want to know information about military history, occupational history, et cetera to help better understand the risk factors for ALS. People often ask how ATSDR avoids patient duplication, given the two methods for enrollment. ATSDR uses

a partial Social Security Number (SSN) as the identifier and is able to merge cases from both approaches in order to avoid duplication of records and double-counting of cases. Another important aspect of the web portal approach is the ability to collect information about risk factors. There are now 17 online surveys patients can take.

It is also important to note that the Registry does much more than just count cases. ATSDR also provides funding for researchers to recruit patients into clinical trials and epidemiological studies. A critical component of the Registry is the Biorepository, which enhances the Registry. Now not only is detailed epidemiological information being collected, but also biospecimens are being collected (hair, nails, blood, tissues). There is a post-mortem aspect of the Biorepository in which brains, spinal cords, and other specimens are being collected. When these types of specimens are paired with the epidemiological data, it makes for a very rich source of data. Researchers are already submitting requests for biospecimens along with the epidemiological data. A number of results have been published or are soon to be published, and ATSDR posts these on its website as soon as they are published.

In terms of accomplishments and activities since the last annual meeting, a major goal is to publish a new report annually. The first report was published in 2014 and covered largely 2011 data. The second *Morbidity and Mortality Weekly Report* (*MMWR*) published in August 2016 covered January 1, 2012 through December 31, 2013. The data published in the third report included calendar year 2014. The fourth report included data through November 23, 2018 and covered calendar year 2015. ATSDR currently is working on the fifth report covering the calendar year 2016, which is anticipated for release in late Fall/Early winter as Dr. Breysse mentioned earlier. The last data cleaning and calculations are underway.

With respect to the National ALS Biorepository, blood and saliva samples have been acquired from over 800 participants and over 40 post-mortem collections have been made to date. Biospecimens samples include hair, nails, blood, tissue, cerebrospinal fluid (CSF), bone, etcetera. This speaks to how great ALS patients are. They are very altruistic and want to help as much as they can. This is demonstrated by the number of patients who have donated specimen samples and post-mortem collections to the Biorepository. ATSDR cannot express enough gratitude to patients and their family members for contributing these specimens.

Regarding communications and outreach, ATSDR held its first-ever Registry webinar for partners that was attended by 123 people. We are also launching a new user-friendly website and a Spanish mirror site. The Spanish site went live on July 22, 2019. This presents another good opportunity for individuals with ALS who are non-English speakers to take part in the Registry. ATSDR is also assessing whether there are other languages that should be included. There also are new digital assets, such as videos and infographics. Not only is it important to collect the data, but also ATSDR must promote the Registry so that people with ALS know about it—especially those who are newly diagnosed. This is an area in which ATSDR's partners have stepped up to help promote the Registry to their constituents.

ATSDR has funded 16 research studies to date, with 3 new studies funded in Fall 2018 and another to be funded in Fall 2019 subject to availability of funds. They also are working on a new Funding Opportunity Announcement (FOA) for Fiscal Year 2020 (FY20). To date, 45 institutions (10 more since last year) have used the notification mechanism, including pharmaceutical companies testing new drugs. ATSDR has to get out and about to connect with researchers and physicians, so they attend a lot of scientific conferences and present the findings there. They have attended 19 conferences and ALS patient symposiums with platform, panel, or poster presentations. They try to publish as much as possible from ATSDR studies

and studies that they are funding. Over 60 peer-reviewed publications/abstracts from Registry staff and research partners (over ½ dozen more since last year) have been published. ATSDR tries to publish the open access rights to articles as soon as they are published. Many articles are behind a firewall, and there is nothing more frustrating than being given a link to go to an interesting article and then being asked to pay for it. They have produced new print and digital assets for dissemination to partners, launched a new Spanish website, will begin an awareness campaign in August 2019, and are working on a new user-friendly website. They are conducting state outreach to try to determine where there are gaps in enrollment. There is heavy PALS participation in some areas, but the penetration rate is not so good in other parts of the country. They are trying to conduct national outreach activities based on states and major cities to determine where efforts can be made to increase awareness and enrollment.

The National ALS Registry funding has largely gone unchanged since last year. While some people may perceive that as being stagnant and not good, ATSDR is very appreciative of the funding it has received from Congress in this economic climate. ATSDR received about $7.9 million for FY18 which is allocated to research activities (56%), communications (3%), information technology (IT) and support (17%), outreach and education (13%), personnel (10%), and miscellaneous (1%). The hope is that the budget will at least remain the same for the next cycle.

In summary, the National ALS Registry is the first and only population-based ALS registry for the US. ATSDR is doing its best to fulfill the Congressional mandate to determine the incidence, prevalence, demographics, and risk-factors for ALS. The Registry has added the National ALS Biorepository that contains sample collections from PALS that are disseminated to researchers. ATSDR is in the process of updating the Registry website to increase visibility and usability, continues to fund research on ALS risk factors and etiology, and seeks to increase awareness by targeting underperforming areas. ATSDR has been contacted by other disease organization groups because they are interested in the methodology being utilized. For example, they have interacted with groups such as Spina Bifida, the National Firefighters Association, and the new National Neurological Conditions Surveillance System. The National ALS Registry could be used in part or whole for some of these other conditions, especially those that are non-notifiable. The more time that passes, the better the case finding methods are as with any surveillance system. The Registry continues to mature and ATSDR is better able to tell the story to its partners and Congress. Dr. Horton closed by emphasizing that ATSDR cannot do this alone and that it is critical to receive input from its partners, including other federal agencies, support groups, researchers, pharmaceutical companies, and especially PALS and their caregivers.

Discussion Points

In terms of patient enrollment flow, Dr. Kasarskis recognized that ATSDR has focused on getting people from national databases into the Registry and there is a holding pattern of waiting for more data to determine whether someone is a true case. He wondered whether they also monitor people who are enrolled in the Registry and have found cases entered erroneously as a case and removed them later if found not to be a case.

Dr. Mehta indicated that they engage in quality control/quality assurance (QC/QA) of cases, especially from the portal, to ensure that there are no duplications. On occasion, they will get an individual who registered but turned out to be a dummy case. They do remove those from the system if they are identified as not being a case. There are checks to ensure that people who claim to be cases are cases. When a patient passes away, they are removed automatically. This is verified through the National Death Index (NDI), which is housed within CDC. Prevalence

is cumulative, so if someone is a case in 2014, they are a case in 2015 or 2016 unless there is a record of someone passing away.

Dr. Horton added that for the web portal approach, the validation questions he mentioned were taken largely from the Veterans Administration's (VA's) ALS Registry that was in existence 10 years ago. The VA had high sensitivity and specificity rates in terms of identifying actual patients and enrolling them in their registry, so ATSDR decided not to try to duplicate the validation questions. Dr. Kasarskis was one of the architects of that system, which demonstrated the importance of collaboration and use of available resources.

Dr. Kaye added that because of the idiosyncrasy of the coding on records, they have not attempted to dis-enroll anybody based on codes. They have had people call them to say that they registered, but their diagnosis later changed. Those can be removed.

Ms. Backman asked whether the data for an individual who has passed away remains in the Registry.

Dr. Mehta replied that their data remains in the Registry, including the surveys they have completed, and their biospecimens remain in the Biorepository.

Dr. Horton emphasized the importance of everyone speaking up. They know they are not perfect and are trying to make this Registry as good as it can be.

Research Update and Overview of National ALS Registry and 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

Dr. Mehta welcomed everyone to Atlanta, extending particular appreciation to those with ALS and recognizing that it is not easy for them to attend. He emphasized that ATSDR is the caretaker of the Registry, but it belongs to those with ALS. He thanked each of the patients for their input and support. While ATSDR wants to make sure they fulfill their Congressional mandate, more importantly, they want to ensure that they listen to patients and acquire their feedback as well. He called out patient and advocate Alan Alderman who sailed across the Atlantic ocean last year to raise awareness for ALS, which is extremely inspiring.

During this session, Dr. Mehta presented a high-level overview of the National ALS research initiatives. The fourth annual national ALS prevalence report, *Prevalence of Amyotrophic Lateral Sclerosis — United States, 2015*, was published on November 23, 2018 in the *MMWR*. The report covers the calendar year 2015. As a reminder, there is approximately a two-year lag to get these data from Medicare. In 2015, there were 16,583 persons identified as definite ALS in the national databases and the portal. This equates to a prevalence estimate of 5.2 cases of ALS per 100,000 persons. ALS continues to be more common in Whites, males, and persons aged from 60-69 years of age. The lowest number of ALS occur among those between 18-39 years of age and those 80 years of age and older. Males had a higher prevalence than females across all data sources. In terms of initial observations based on the fourth report, there was a slight increase in cases and prevalence rate compared to 2014 which had a prevalence rate of

5.0/100,000 and 15,927 cases. Prevalence is slightly increasing, which is most likely due to better case ascertainment rather than an actual increase in ALS. The demographics of disease are not changing. It is likely that a few more years of data are needed to estimate national ALS prevalence trends.

As noted earlier, the fifth report is under development and is scheduled to be published in late Fall/early Winter and will cover calendar year 2016. In this report, two national prevalence estimates will be published. The first estimate will utilize established validated algorithm/methodology, while the second estimate will use capture/recapture methodology. Dr. Lorene Nelson, the capture/recapture subject matter expert (SME), will employ this methodology to provide an estimate of the percentage of missing cases in the US. For example, if there are about 17,000 cases in 2016 and the capture/recapture strategy estimates that between 15% to 20% are missing, extrapolating that will result in approximately 20,000 to 22,000 cases in the US. This is still an estimate, but it will help to identify the missing percentage of cases. Because two prevalence estimates will be released, one based upon the traditional algorithm and one based on capture/recapture, this will provide a baseline and high end point. Dr. Mehta personally feels that there are 20,000 to 22,000 cases in the US currently. With the new capture/recapture methodology, they will have a better estimate in terms of the high number of cases.

There currently are 17 risk factor surveys and another is soon to be added. To date, 84,856 surveys have been completed and are being analyzed:

Risk Factor Surveys-Taken After Registration

Survey (n=17)	Release Date	No. Completed
1. Demographics	October, 2010	9171
2. Occupational history	October, 2010	8341
3. Military history	October, 2010	8169
4. Smoking and alcohol history	October, 2010	8028
5. Physical activity	October, 2010	7704
6. Family history of neuro. Diseases	October, 2010	7509
7. Disease progression (ALSFRS)	October, 2010	7536
8. Lifetime residential history	May, 2014	3476
9. Lifetime occupational history	May, 2014	3453
10. Residential pesticide use	May, 2014	3228
11. Hobbies with toxicant exposures	August, 2014	2968
12. Reproductive history (women)	August, 2014	1513
13. Caffeine consumption	August, 2014	2781
14. Head and neck injuries	December, 2014	2446
15. Health insurance status	December, 2014	2483
16. Open-ended etiological questions	November, 2013	2890
17. Clinical data (e.g., devices used, body onset)	November, 2013	3160
Total (as of 7/15/2019)	---	**84,856**

This is one of the largest and richest sources of ALS risk factor information in the US. The 17 surveys are taken by persons with ALS when they enroll in the Registry and log in to the online portal. The surveys are wide-ranging, including the ALS Functional Rating Scale (ALSFRS) disease progression survey that allows patients to report how they are doing over time. Data requests are being submitted for the risk factor surveys and releases have begun.

To update the risk factor analyses, ATSDR plans to publish on reproductive history and ALS. They also are analyzing Survey 7, which is the Disease Progression/ALSFRS survey. They

have published on surveys 15 and 17. Bjorn Oskarsson, MD at the Mayo Clinic in Jacksonville, Florida received data from Surveys 15 (Health Insurance Status) and 17 (Clinical Module) and these data have been published. Heather Jordan, PhD at Rutgers University received data from the open-ended survey so that she can analyze patients' theories about what may have caused their disease. This publication is currently in development. ATSDR and Dr. Pam Factor-Litvak at Columbia University will be analyzing Survey 5, which is the Physical Activity module. Dr. Factor-Litvak is an SME in physical activity and oxidative stress. ATSDR hopes to receive Office of Management and Budget (OMB) approval in Fall 2019 to add a new survey. Currently, there are surveys on traumatic brain injury (TBI) and physical activity, but nothing on sports people have played. If approved, the new survey will allow ATSDR to ask specific questions regarding the sports responders played in high school, college, and professionally.

Preliminary results have been published on surveys 1 through 6 and 15 and 17. The analysis published on Survey 17, *Clinical characteristics of a large cohort of US participants enrolled in the National Amyotrophic Lateral Sclerosis (ALS) Registry, 2010–2015*, covered the years 2010-2015. Regarding the results, 6352 adults registered via the online portal. Of these, 1758 (27.7%) completed Survey 17, which was released in November 2013. The demographic characteristics from this survey were well-matched to what ATSDR is seeing internally. About 60% of the males and 40% of the females took the survey. Whites comprised the highest majority taking the survey at 95.5%, while Non-White was 4.5%. In terms of Census regions, the South (33.1%) and Midwest (30.4%) represented the highest numbers taking the survey. Limb onset was 71.8%, bulbar onset was 22.1%, and trunk/global onset was 6.1%. These are self-reported, but still align with what already has been published. In terms of other symptoms, the majority of respondents experienced cramps (56.7%), twitching (56.3%), and falls (25.4%). Regarding use of interventions among this particular cohort, 32% reported using a wheelchair or scooter, 30% reported using non-invasive breathing equipment, and 16% reported using communication devices. Current RILUTEK® (riluzole) use was reported by 48.3% of respondents, while RADICAVA® (edaravone) was not yet in use during this period of analysis. RADICAVA® (edaravone) has now been added to the survey. These results show how ALS clinical characteristics differ widely from patient-to-patient. Better characterization of symptom onset may assist clinicians in diagnosing ALS sooner, which could lead to earlier therapeutic interventions. Future analyses planned include the following:

- ❑ Exposure Matrix Development and Analysis:
  - ➢ Occupational history-brief
  - ➢ Residential History
  - ➢ Lifetime Occupational History
  - ➢ Home Pesticide Use
  - ➢ Hobbies

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

- ❑ Survival Analyses (Limb vs Bulbar Onset)
- ❑ Survey 5 (Physical Activity) in conjunction with Columbia University (Pam Factor-Litvak)
- ❑ Military History and Survival Analyses (Ted Larson/Tracy Peters and John Beard/BYU)
- ❑ Non-Surveys: Surveillance paper looking at Atlanta and Chicago metropolitan areas

ATSDR also is collaborating with the Massachusetts Department of Public Health (DPH) on an application that has been submitted to IRB.net. Massachusetts is the only state where ALS is a

reportable disease at the state level. This harkens back to the Governor being diagnosed with ALS many years ago and making it a reportable disease. This study will allow the investigators to evaluate the overlap of cases captured (completeness) by the Registry and the state data in terms of demographic comparison and geographic variations (urban vs. rural).

The Research Notification System is a highly important facet of the Registry through which ATSDR can work with academia and pharmaceutical manufacturers to help them recruit for their clinical studies. At this point, 45 institutions have used this system. This system is user-friendly and the approval process typically takes 2 to 4 weeks, depending upon whether the request is for a survey or clinical trial. CDC Institutional Review Board (IRB) approval is not needed. IRB approval comes from the applicant's institution. For multi-site clinical trials, single IRB approval is satisfactory and protocols are not necessary. The take-home message with regard to this system is really for Big Pharma. Many drugs are under development, so ATSDR is working with pharmaceutical companies to recruit for their clinical trials. Patient recruitment for research can be difficult, but approximately 95% of Registry PALS want to participate in research. The Registry links PALS with scientists who are recruiting for research (e.g., clinical trials, studies), and domestic and international researchers are using the tool for recruitment purposes.

Dr. Mehta highlighted the following clinical trials and epidemiological studies for which ATSDR helped to recruit:

Multi-Site Clinical Trials	
Institution (Principal Investigator)	**Study Description**
Brainstorm Cell Therapeutics (Berry)	❑ Repeated dosing of NurOwn® (mesenchymal stem cells/MSC) derived from patient's bone marrow ❑ Contacted by over 100 patients on first notification, second notification June 2019
Orphazyme (Benatar)	❑ Arimoclomol, extends independent breathing, improves survival, functional health and safety
Orion Pharma (Cudkowicz)	❑ Levosimedam, ODM-109, improves respiratory function
Amylyx Pharmaceuticals (Paganoni)	❑ AMX0035, slows disease progression and improves muscle strength
Epidemiological/Risk Factor Studies	
The ALS Association (Thakur)	❑ Patient- and caregiver-focused care services and preferences ❑ Assisting in a future survey for the Association, ALS Focus later in 2019
Columbia University (Mitsumoto)	❑ Examine the relationship between oxidative stress (OS) and ALS ❑ Helped to recruit about 100 patients
University of Sydney (Pamphlett)	❑ ALS Quest survey system ❑ Four publications to date using his own data and ATSDR data: ➢ A Comparison of Mercury Exposure from Seafood Consumption and Dental Amalgam Fillings in People with and without Amyotrophic Lateral Sclerosis (ALS): An International Online Case-Control Study. International Journal of Environmental Research and Public Health, 2018. ➢ Are people with amyotrophic lateral sclerosis (ALS) particularly nice? An international online case-control study of the Big Five personality factors. Brain and Behavior, 2018. ➢ Is psychological stress a predisposing factor for amyotrophic lateral sclerosis (ALS)? An online international case-control study of premorbid life events, occupational stress, resilience and anxiety. PLOS One, 2018. ➢ 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, 2017.

Upcoming notifications using the Registry include a Mitsubishi Tanabe Pharma (Apple/Agnese) national biomarker study in multiple sites, and a Dartmouth Hitchcock Medical Center (Stommel/Bradley/Cox) L-Serine clinical trial, the application for which is pending.

It is very important for ATSDR to disseminate the work that it is doing, as well as the work from those with whom they are collaborating. Over 60 peer-reviewed publications/abstracts have been published. As a reminder, the Registry pays for open-access when possible. Abstracts have been presented at the American Academy of Neurology (AAN), the Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS), and the International ALS/MND Symposium. Notable publications in 2018 and 2019 include the following, some of which were mentioned earlier:

- Raymond et al: *Clinical characteristics of a large cohort of US participants enrolled in the National Amyotrophic Lateral Sclerosis (ALS) Registry, 2010–2015*.
- Goutman et al: *High plasma concentrations of organic pollutants negatively impact survival in amyotrophic lateral sclerosis*.
- Rechtman et al: *Increasing Patient Self-Enrollment in the National Amyotrophic Lateral Sclerosis Registry: Lessons Learned From a Direct to Provider Campaign*.
- Nelson et al: *Estimation of the Prevalence of Amyotrophic Lateral Sclerosis in the United States Using National Administrative Healthcare Data from 2002 to 2004 and Capture-Recapture Methodology*.

It is very important for ATSDR to promote and support ALS research, particularly given that there are a lot more unknowns than knowns about ALS. To that end, almost 60% of ATSDR's funding is allocated to extramural research being conducted by leading academic partners to learn more about ALS etiology and risk factors. To date, 16 research studies have been funded. The information gleaned from these studies also will help ATSDR prioritize topics for future risk factor surveys. There were 3 newly funded R01 grants in 2018, which included the following:

- Dartmouth Hitchcock Medical Center (Stommel): Environmental Risk Factors for ALS: Critical Time Periods and Genetic Interactions
- University of Michigan (Feldman): Metabolomic Signatures Linking ALS to Persistent Organic Pollutant Exposures
- Columbia University (Schneider): Novel Extracellular Vesicle and Molecular Biomarkers of Environmental Exposure and Disease Progression in ALS

In closing out FY19, ATSDR hopes to publish one additional study, TS20-001: Identify, Analyze, and Evaluate Potential Risk Factors for Amyotrophic Lateral Sclerosis (ALS). The objective of this RFA 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 hope is to receive applications in particular areas, including: environmental and occupational, military service, infectious agents and viruses, nutritional intake, physical and sports activities, pharmaceutical use, and TBI. It is anticipated that 1 to 4 awards would be made for FY20 at $400,000 per year for 3 years, subject to availability of funds.

In terms of Registry review committee members, researchers are needed to review applications for the notification system and the Biorepository. A Science, Technology, Engineering and Mathematics (STEM) background is preferred and membership is open to PALS, researchers, and neurologists. The requirement would be to review 1 to 3 applications per year, which is anticipated to take 1 to 2 hours at the most per application. Those interested may contact als@cdc.gov or Dr. Mehta at pum4@cdc.gov.

In conclusion, impact of the National ALS Registry has continued to grow. As a result of the Registry, there is a better understanding of prevalence, incidence, and mortality. Prior to the first report being published, the numbers varied widely and were not based on the science. With the fifth report in development, the numbers are getting more mature and case ascertainment is improving. There also is a better understand of disease demographics in terms of who gets ALS, which is particularly important in terms of therapeutics and the development of drugs. Instead of pharmaceutical manufacturers having to establish their own patient registries, they can come to ATSDR to access patients in the National ALS Registry for their clinical trials. ATSDR is seeking to expand the work on potential risk factors for heavy metals and persistent organic pollutants, as well as to advance work on biomarkers and genomics in the National ALS Biorepository. They believe that in 3 to 5 years, the National ALS Biorepository will house the largest collection of pristine ALS samples in the world. They have funded 16 studies and hope to fund 1 additional study, which certainly will add to ATSDR's portfolio of funded research. Lastly, ATSDR works with its partners to inform patients about the importance of the Registry and to encourage them to take part in research through clinical trials or the National ALS Biorepository.

Discussion Points

Dr. Tessaro asked whether there is a line item on the state budget for Massachusetts indicating how much is spent to get reportability. While all of the extrapolations that are done are predictive or are hoped to be, but they may have a case to make in other state legislatures based on what Massachusetts knows beyond what is learned from extrapolations nationally. Massachusetts data should be very instructive.

Dr. Mehta said that while he did not know what the line item of funding is for Massachusetts, the team is pretty small with only one or two individuals. However, they are able to work with their clinicians and have made this reportable at the state level to the state health department on a mandatory basis. ATSDR has been approached by other states regarding making ALS reportable, which states can do. It often depends upon their budgets, particularly given the number of other diseases health departments may be mandated to report. In terms of the findings for Massachusetts, the application was submitted in June so ATSDR has not yet received their data. This is personally identifiable information (PII), so ATSDR will be able to determine what percentage they are matching. There also is a slight bias in Massachusetts because a lot of patients go to Massachusetts General Hospital (MGH) for second opinions, so it is important to ensure that if patients are presenting there from surrounding states as well, they are counted as a case only in Massachusetts.

Dr. Thakur asked how much ATSDR thought the numbers would improve with the new capture-recapture method.

Dr. Mehta said that he did not know what the actual numbers were for 2016. At this point, they are at 16,583 and they are not sure whether that may increase or decrease. If it increases to 17,000 and capture-recaptures estimates show that 15% to 20% of cases are being missed, that percentage will be extrapolated on to the 17,000 so that it could potentially be between 20,000 to 22,000 cases as the ceiling. ATSDR feels that this will be a better estimate of the number of cases. It is important to keep in mind that they are unable to capture the private payer cases through the Registry at this point, unless privately insured individuals register via the online portal or are in Medicare Part C. However, they will receive Medicare Part C data this year.

Dr. Bowser asked what methods would be employed to try to increase registration rates within low registration areas to better understand ATSDR's estimates versus the estimates from Massachusetts and other states.

Dr. Mehta indicated that last year, they implemented a state outreach project in under-performing states. They are hoping to employ that same outreach project in other states as well. Some of the under-performing states include California, Texas, and Florida. In addition to increasing outreach within these states, they hope that the new Spanish website will be able to capture Spanish-speakers in these states. One goal is to move the Tier 3 states into Tier 2 category.

Dr. Tessaro asked how the VA's Million Veteran Program (MVP) data are being mined and ATSDR's connection with them science-wise now that the MVP is in its third year and given the knowledge that Veterans have a 50% greater incidence of ALS.

Dr. Mehta responded that case-wise, ATSDR receives the VA case ascertainment data directly. ATSDR has a Data User Agreement (DUA) with the VA. ATSDR receives all of the case data and does the case ascertainment, cleans it, and so forth. Scientific-wise, he thinks that ATSDR must do a better job of working with their intergovernmental partners such as the VA to determine how they potentially can collaborate. He noted that Dr. Marcienne Wright, who was responsible for all of the Notices of Funding Opportunity (NOFOs), was present from the Extramural Research Program Office (ERPO). In the past, they have worked with the National Institutes of Health (NIH). He completely agreed that they must do a better job of working similarly with the VA. They have been having discussions with Dr. Richard Bedlack at the Duke ALS Clinic about mapping all of the VAs in the country to determine where the patients are coming from. One of the issues with that is that it creates inherent bias, because they would be looking only at people who are VA recipients.

Dr. Thakur expressed excitement about the new RFAs that would be published and wondered whether they would be tracking the risk factors that have been previously identified, or if they would be trying to coordinate the follow-on funding to verify the risk factors using non-epidemiologic methods.

Dr. Mehta indicated that with their successive NOFOs, they want to ensure that they are not funding identical research. The new applications are assessed for uniqueness and scientific merit. The one that will be funded this fiscal year represents novel research.

Dr. Kasarskis said it sounded judgmental to say that a state is under-performing meaning that the cases are there but they are just not finding them with this mechanism. He wondered whether Dr. Nelson's approach with capture-recapture methodology would shed light on that. It is conceivable theoretically that the cases just are not there. He wondered how ATSDR was approaching that problem.

Dr. Mehta said he did not think that capture-recapture is looking at the actual state, but instead examines what is estimated to be missing overall. ATSDR looks at the number of cases expected in states, but it appears that there should be more cases coming in from the Tier 3 states. He agreed that there could be states in which there simply are not a high number of cases.

Dr. Pioro agreed that while the graph shown with the increasing number of cases was probably the result of better ascertainment, he wondered whether there is some way within the data to actually confirm that this is better ascertainment versus true incidence.

Dr. Mehta indicated that they will need more years of data to make that evaluation, especially in terms of trends. Typically, 7 to 10 years of data are needed to perform trend analyses. Another variable may be that ALS patients are living longer, which could factor into cumulative prevalence as well.

Dr. Kaye added that one of the increases was due to a slight change in the algorithm one year. Criterion 1 originally was having an ALS diagnosis from a neurologist in the records and either a death certificate or a prescription. That was changed to be 2 of the 3, so it could be a death certificate and a prescription. Part of the reason for that is that people who have Medicare Advantage still get their prescriptions in a way that ATSDR sees them. However, often there are people who seem to be on riluzole without a corresponding record and a positive death certificate. That was a way to tweak the algorithm to get more people in who are in the "Maybe" category, but for whom they are pretty sure have ALS.

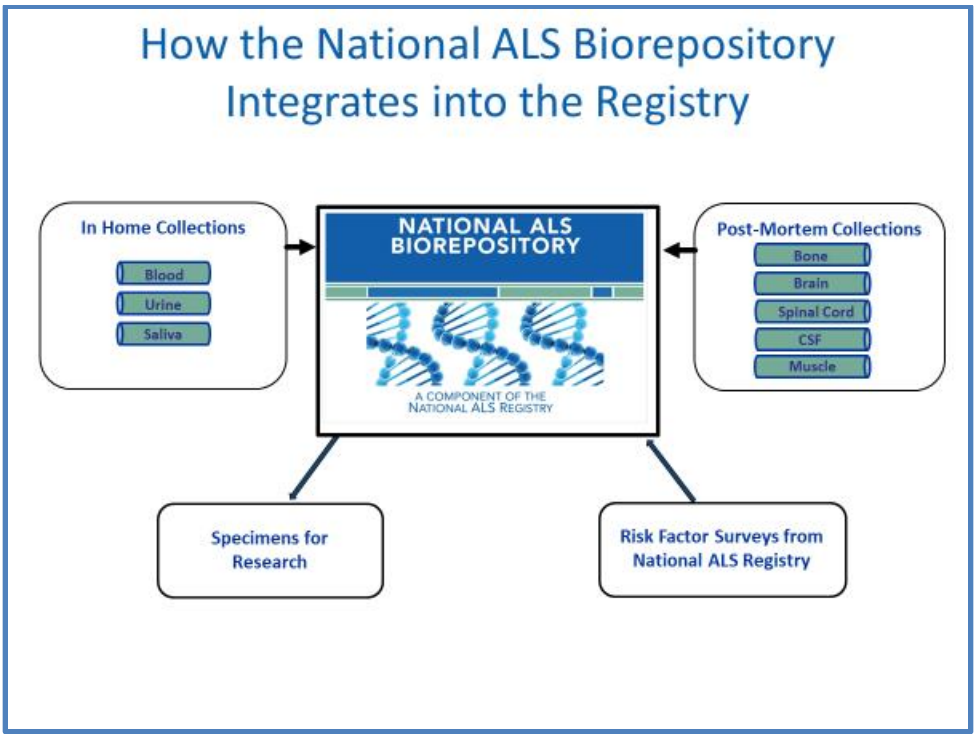
Update on the National ALS Biorepository

Biorepository Overview

Laurie Wagner, MPH
National ALS Biorepository Coordinator
McKing Consulting Corporation

Ms. Wagner presented a brief history and update on the National ALS Biorepository. A pilot study was conducted that lasted for about 4 years from September 2012 through September 2015. The first year was largely paperwork and IRB approvals, with collections beginning in 2013. At the conclusion of the pilot study, 330 Registry participants had been enrolled to provide blood, urine, hair, and nails. Specimens were collected on two occasions approximately six months apart. This protocol was recommended by the Expert Panel. Participants were recruited to be geographically representative of the US in rural and urban areas, 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 post-mortem.

ATSDR was funded to continue the National ALS Biorepository, which is currently being conducted. Changes from the pilot project are that persons with ALS can sign up to learn more about the Biorepository when they join the National ALS Registry. From the pilot study, they had email addresses only for people who were in the Registry. They sent a "warm" email to people who could participate and waited for them to call ATSDR for more information. Specimens are collected only one time now, and hair and nails are not being collected currently. Saliva is collected from those who cannot donate blood and a sample of persons interested in the Biorepository. This diagram illustrates how the National ALS Biorepository integrates into the Registry:



When individuals sign up for the Registry, a National ALS Biorepository sign-up form appears. This form allows individuals to click a box to receive more information, indicate what part of the Biorepository they are interested in receiving more information about, and provide their address and telephone number. ATSDR would then send the packet to their homes. The ability to sign up for the Biorepository offers individuals a great opportunity. Previously enrolled patients can update their accounts and choose to take part in the Biorepository as well. On a monthly basis, McKing receives a list of enrollees who are interested in the Biorepository. McKing coordinators call potential participants approximately one week after the package is mailed at which time their questions are answered, the consent form is reviewed with them if interested, and they can schedule an appointment to give blood or mail saliva kit.

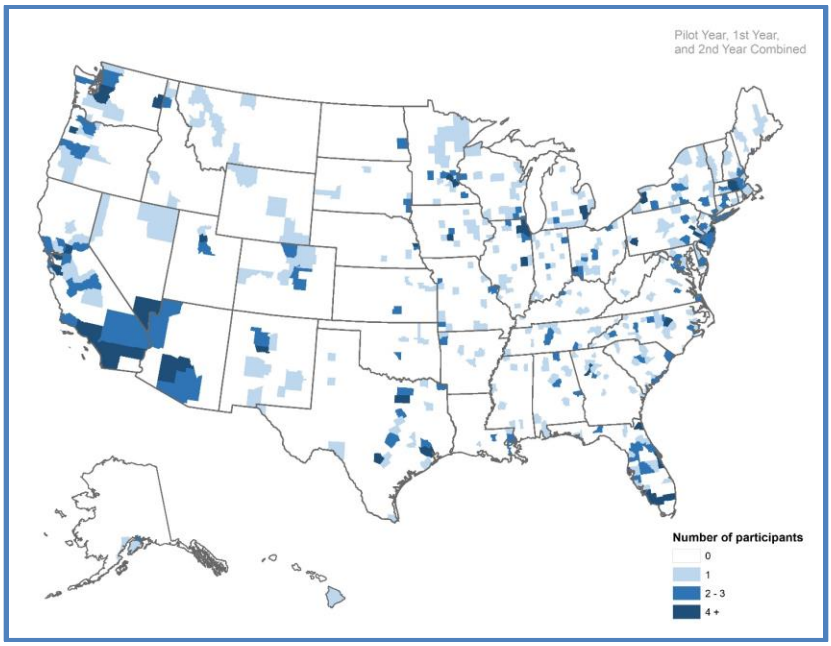
For in-home collection for the Biorepository, an appointment is made for a phlebotomist to visit the participant. Specimen collection is coordinated between the phlebotomist and the participant. The phlebotomist will go to the participant's house, collect specimens using the kit mailed to the house, and ships specimens to the laboratory for next day delivery. The participants are instructed to open the kit and remove the bag for urine collection, which they do themselves the morning they are scheduled for their draw. Once they pull that out, the rest of the items remain inside of the kit. The kit includes the FedEx shipping label required for the phlebotomist to ship the kit back to the laboratory once the specimen collection is completed. The phlebotomist draws 5 tubes of blood that will be aliquoted once received by the laboratory. The kit that is mailed to the home contains everything the phlebotomist needs as depicted in this photograph:

Once received in the laboratory, 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

Biorepository participation from January 4, 2017 through June 30, 2019 resulted in consent of 734 participants for in-home blood and urine samples, 167 for saliva samples only, and 33 postmortem samples. The number actually collected during that timeframe included 678 in-home blood and urine samples, 154 saliva only samples, and 20 postmortem samples. In terms of the demographics of Biorepository samples during that timeframe, there were participants from 50 states and Puerto Rico, 63% were male, and the ages ranged from less than 40 to over 80. Note that these figures (consent, sample, and demographics) do not include the samples collected during the pilot study. The geographic distribution of all participants is shown in the following map:



More saliva collections were added during the January 4, 2017 through June 30, 2019 timeframe from participants who were unable to give blood for various reasons. Some participants are selected purposely to give saliva only in order to extract DNA. These participants complete the saliva collection in their home and ship the samples via FedEx for next day delivery. Here is a photograph of the saliva collection kit:

The saliva kit includes directions, but participants can contact McKing Coordinators if they have any questions and the Coordinators will walk them through the steps.

In terms of postmortem, 42 participants have donated postmortem specimens including brain, spinal cord, CSF, bone, muscle, and skin. Of the total participants who have been consented for postmortem collection, 6 participants withdrew and did not donate and 15 participants continue to be followed. Note that these totals do include pilot participants. Regarding processing of postmortem specimens, Boston University is the subcontractor for storing samples and they follow the same guidelines as the VA so that the Biorepository samples can be compared with the VA postmortem collections. Brain and spinal cord are stored fixed and frozen, CSF is collected, bone is stored in formalin, muscle is stored in paraffin blocks, and skin is collected for fibroblasts. The demographic distribution for those from whom samples have been collected are as expected in terms of the age range, and there is nearly equal distribution between male and female participants.

Evaluation of Specimen Demand / Researcher Requests & Sample Distribution

Wendy E. Kaye, PhD
Senior Scientist
McKing Consulting Corporation

Dr. Kaye indicated that as part of the Biorepository, McKing tries to project the types of samples people will need for research. Multiple approaches are used to evaluate potential demand for specimen types, including the following:

- ❑ Evaluation of historical use of specimens from PALS in the literature
- ❑ Review of the literature to identify pressing questions in ALS research
- ❑ Review of specimen types used in currently funded research

In terms of findings and recommendations for next year, blood and postmortem tissue continue to be reported frequently as the specimen types used or going to be used in both the more recent literature and grant awards. Induced pluripotent stem cells (iPSCs) were the most frequently reported biospecimens used in newly funded grants. The ability for researchers to create iPSCs has been added for a subset of participants each year. For the last two years, peripheral blood mononuclear cells (PBMCs) have been isolated and immortalized so that investigators can create iPSCs. No studies identified urine as a specimen type and there have been no requests for urine other than for metals analysis that ATSDR is conducting with NCEH laboratory. Therefore, McKing recommended that urine not be collected next year. Urine samples already have been collected from over 1100 individuals. Based on these analyses and requests for samples, although researchers are interested in identifying ALS patients with specific genetic mutations, the use of DNA alone in research has decreased.

With regard to research requests and sample distribution, a significant amount of research outreach is done to inform investigators about the Registry and Biorepository. This is done through the Registry website, by attending meetings, through journal advertisements, and via referrals from other federal agencies in RFPs. The largest meeting and the one through which they get the most coverage is the Society for Neuroscience (SfN). The journal advertisements are targeted during the peak season for people to submit grant applications. An example of referrals from other federal agencies is that the Department of Defense published an RFP that listed the National ALS Biorepository as a place from which to obtain samples, and several calls were received as a result of this.
Researchers can request samples for their ALS research projects. There is a large application process that is outlined on the website that includes a research application form, cover letter, full

protocol, and sample request forms. Researcher submit applications and all supporting documentation online. Complete applications go through multiple reviews, including a laboratory review to determine whether the samples requested are available, that there is a sufficient number of samples, and that the tests being done are proposed to be used with the right type of specimen. If approved, the application is then submitted to an ATSDR committee for review of scientific merit. After approval from ATSDR, the researcher signs a Material Transfer Agreement (MTA) and pays the invoice if not funded by ATSDR, McKing selects the appropriate samples, and the laboratory pulls and ships the samples to the investigator. This table identifies the researcher requests received, the group conducting the analyses, and the sample types requested:

Description of Project	Group Conducting Analysis	Sample Types Requested
Metals analysis of samples from the Biorepository	CDC/ATSDR	Whole blood, serum, urine
Genotyping of Samples from the Biorepository	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
Novel extracellular vesicle and molecular biomarkers of environmental exposure and disease progression in ALS	Columbia University	Hair, whole blood, brain
Identification and Characterization of potential environmental risk factors for ALS using the ATSDR ALS Registry cases and a control population	University of Pittsburgh	DNA
Persistent organic pollutants (POPS) analysis of samples from the Biorepository	ATSDR	Serum
RNA seq driven drug discovery: gene expression profiling of vulnerable neurons in ALS	Cerevance, Inc.	Serum, brain, spinal cord
Biomarkers in neuronal exosomes for assessment of ALS progression	UCLA School of Medicine	Serum

To date, over 5000 samples have been provided to researchers. That includes postmortem materials. The two most recently approved projects are Cerevance, Inc. for their RNA-driven drug discovery project; University of California Los Angeles (UCLA) School of Medicine for their biomarkers in neuronal exosomes study; and the Center for Neuroscience (CNS) in California for their plasma study.

In summary, the Biorepository is now an integral part of the National ALS Registry. This makes identifying and recruiting participants much easier. Only people taking part in the Registry are eligible to join the Biorepository, which is double-checked before samples are collected. From among those interested, participants are selected to be geographically representative. A phlebotomist goes to the participant's home to collect samples, and researchers can request samples for their studies. To date, 12 researchers have been approved and over 5000 samples have been distributed. PALS can take part in the Registry and Biorepository even if they have donated specimens to other biorepositories and studies.

Discussion Points

Ms. Backman thanked everyone involved in the Biorepository and recognized how much progress has been made in the last couple of years. That said, she wondered whether with additional funding the postmortem sample collection might begin again. Regarding communication assets, it is possible and preferable for those who already are enrolled in the Registry to go back and sign up to donate other samples. She wondered whether it would be possible to get some communication materials so that those who are promoting the Registry can use that information.

Dr. Kaye indicated that the funding for the next fiscal year has been received and it is the same as the previous year. Thus, they are not currently recruiting for postmortem samples. However, that could change in future fiscal years. They also are assessing different ways to recruit people for postmortem samples. In terms of communication materials for those promoting the Registry and Biorepository, she was not certain they had anything specific. Every month when she receives the list from ATSDR of the people who have signed up, she looks to see when they registered. Most people are now signing up for the Biorepository when they register or within a very short time of registering. For example, no individuals on the June list had signed up a year ago. She agreed that this is an important message to get out.

Dr. Mehta added that ATSDR is reaching back out to patients who already have registered via email to inform them about joining/participating in the National ALS Biorepository as well, and to give them instructions about consenting. He also agreed that having some materials/information to disseminate would be beneficial. Some patients still may not be aware that they can participate in the Biorepository.

Dr. Kaye added that they have permission from the IRB to send the email to which Dr. Mehta referred twice a year. The first reminder was sent on June 5, 2019. The number of people who signed up in June was somewhat higher than it had been, but nobody was from the past. Thus, it was unlikely the email that drove them to sign up for the Biorepository.

Dr. Gubitz reported that NIH maintains a postmortem tissue bank. While it is not ALS-specific, it is CNS disease-specific and is co-funded by multiple institutes. They may have slots for ALS brains and spinal cords, so they can coordinate. The idea is to help one another and complement each other's efforts.

Dr. Mehta indicated that the VA has their own brain bank as well, which Veterans can join.

Dr. Bowser added that there might be an opportunity with Target ALS that he helps run, which has grown quickly into a very large postmortem bank. A unique aspect of this biorepository is that whole genome sequencing (WGS) and multiple region whole tissue RNA sequencing (RNA-Seq) analysis is done of six spinal cord regions on each postmortem case. These data are then made publicly available. A major amount of traffic that goes through that website and portal to look for a favorite gene of interest, what patients have it, and what region of the brain and spinal cord express it at different levels. There is an ability to click on and select cases from which to request tissue and slides, and they receive multiple requests for tissue every week. Perhaps there is a way they could cross-fertilize with the National ALS Biorepository. With some funding, Target ALS could perform all of the sequencing on the cases that are currently in the ATSDR Biorepository and make those data available to allow investigators even greater access to utilization of the samples already collected by the Registry and Biorepository.

Dr. Kaye indicated that there are genetic data on the population from the NeuroChip. Dr. Traynor at NIH has been busily verifying the ones that are not C9ORF72, which he already has done. Not surprisingly, some of the others come back as not really there because the NeuroChip has only about 80% specificity and there are some false positives. Most of the mutations identified thus far are C9s.

Dr. Mehta indicated that all of their data have Global Unique Identifiers (GUIDs) through NeuroBANK™ at MGH if the participant has consented and provided the required variables. This is a potential way to determine whether there are any matches between Target ALS and ATSDR genotyped patients. In terms of whether there is any funding to perform WGS and RNA-Seq on all past and future samples, availability of resources is always a question. They try to genotype all samples coming into the ATSDR Biorepository.

Dr. Bowser indicated that Target ALS is up to about 200 cases, most of which have gone through NEALS and have GUIDs just like what ATSDR is generating. This would be a great way to facilitate even greater access to the samples currently in the bank, and then to provide additional genetic information in an open-source manner to the research population. Target ALS needs small pieces of frozen tissue for sequencing purposes.

Mrs. Kennedy pointed out that while she is pretty active, she has been deactivated from the Registry at least three times. It was unclear to her why they were doing this if they were not eliminating people.

Dr. Kaye acknowledged that this is a continuing battle. It is a government rule that passwords have to be changed. If the password has not been reset within a specific period of time, it becomes locked.

Dr. Mehta added that they are still a case in the system, but their password has expired. The history behind this is that there used to be a three-month window for password expiration. This was increased to a six-month window. Those who do not reset their password before that expiration window closes are locked out but can email or call ATSDR to have it reset to regain access to their accounts. A patient would be removed only if ATSDR is notified that they have passed away. This way, the family will not receive emails and so forth. They eventually will be removed as a prevalent case. For example, if they were alive in 2015 and pass away in 2019, they will not be removed as a prevalent case until ATSDR gets to 2019 data and verifies them through the NDI.

Dr. Horton emphasized that the timeframe for changing passwords was not an ALS Registry decision. This is a CDC IT requirement and ATSDR and the National ALS Registry are bound by their rules. The timeframe was extended because ATSDR went to the IT group and stressed what an undue burden this was placing on PALS. The result was the increase to 180 days, and ATSDR will continue to try to get this increased.

Dr. Kaye added that thanks were due in part for the extended timeframe to Dr. Kasarskis for having written a compelling letter as a neurologist with regard to why this is burdensome.

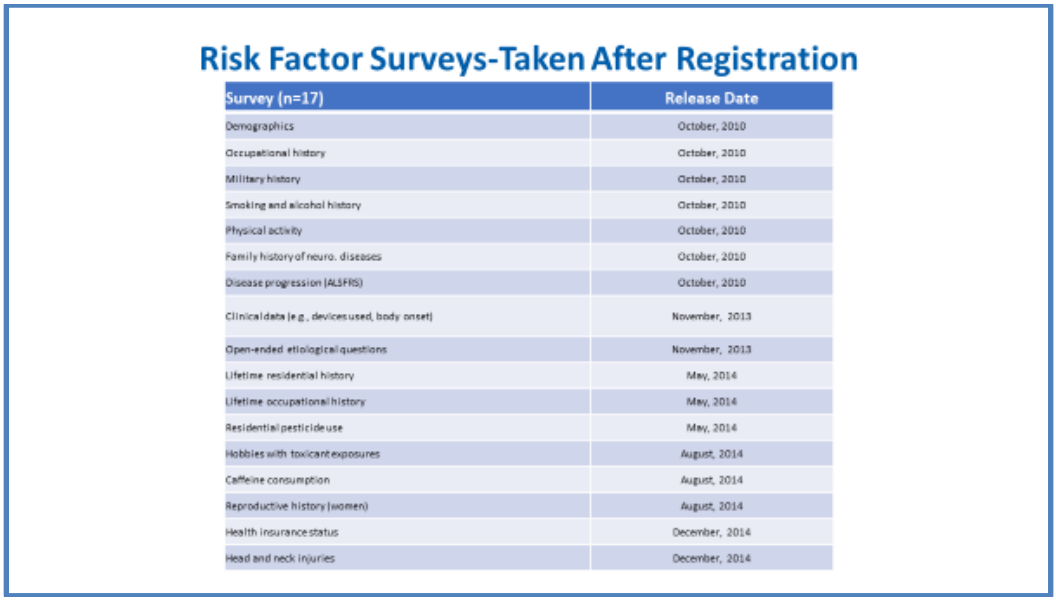
Mr. Kennedy commented that ALSFRS should include "I am able to maintain my activity on the ALS Registry" and should be worth a point.

Increasing Registry Enrollment

Agency for Toxic Substances and Disease Registry

Jaime Raymond, MPH
Epidemiologist/Data Manager, National ALS Registry
National Center for Environmental Health
Agency for Toxic Substances and Disease Registry

Ms. Raymond presented on the enrollment component of the web portal component of the National ALS Registry; Registry referral items that have been added; data from October 19, 2010 through December 31, 2018; diagnosis vs. registration, and survey completion by Tier 1 and Tier 3 states. A question has been added to the registration process asking patient to indicate how they were referred to the ALS Registry that permits them to check all sources that apply. The Registry began collecting these data in October 2018. The ALS Association and doctors/neurologists tend to have the most referrals. As a reminder, the following table identifies each risk factor survey and its release date:



Risk Factor Surveys-Taken After Registration

Survey (n=17)	Release Date
Demographics	October, 2010
Occupational history	October, 2010
Military history	October, 2010
Smoking and alcohol history	October, 2010
Physical activity	October, 2010
Family history of neuro. diseases	October, 2010
Disease progression (ALSFRS)	October, 2010
Clinical data (e.g., devices used, body onset)	November, 2013
Open-ended etiological questions	November, 2013
Lifetime residential history	May, 2014
Lifetime occupational history	May, 2014
Residential pesticide use	May, 2014
Hobbies with toxicant exposures	August, 2014
Caffeine consumption	August, 2014
Reproductive history (women)	August, 2014
Health insurance status	December, 2014
Head and neck injuries	December, 2014

Survey 1 (Demographics) was launched at the same time as the Registry, so all of the years are available for this survey. Each participant was given up to a year to complete Survey 1. In 2010, about 50% of registrants completed Survey 1. This was almost 70% in 2014 and just below 60% of 2017 participants had completed a survey by 2018. In terms of the average number of surveys completed by year for registrants entering the survey, until 2016 only 6 surveys had been launched. About 4 out of 6 surveys were being completed through 2013 looking at the 2014 data. By 2015, all 17 surveys had been launched and completion hovered just under 7. Currently, about 6 out of 17 surveys are being completed on average.

One of the recommendations from last year's meeting asked ATSDR to look at marital status and the number of surveys completed. Marital status is included in Survey 1. In order to complete this, all participants had to take at least one survey. Those who were married had completed the most surveys with about 8.7 surveys completed, while those who were never married had the lowest at 8 surveys completed. However, there was not a major difference in whether marital status had any impact on the number of surveys completed.

Switching from survey data to registration dates versus diagnosis dates, there were about 1100 days on average from diagnosis date to registration date on October 19, 2010 when the Registry launched. This is not surprising since some people had been diagnosed years prior who did not have the opportunity to register. Those who registered in 2017 had a diagnosis date that was just under a year.

In terms of the percentage of survey completion compared to the number of patients registered in some of the top Tier 1 states, about 70% of individuals registered in South Dakota are taking at least one survey down to about 50% in Wisconsin. There is a slightly lower completion rate in some of the Tier 3 states ranging from 38% in Nevada to 58% in Hawaii of individuals having completed at least one survey.

In conclusion, almost 50% of patients heard about the Registry from the ALS Association. Even after ignoring the initial push for registration, the number of registrants by year has dropped 30% since 2013. The percentage of patients completing Survey 1 has increased almost 20% across time. The average number of surveys completed by year has more than doubled, but the number of surveys released has almost tripled. Marital status did not have a significant impact on the number of surveys completed. The time between diagnosis and registration has dropped by almost 75%, but is still almost 1 year. Top Tier 1 states with registered patients (MN, SD, IA, ND, WI) show slightly higher percentage of survey completion compared to Tier 3 states (TX, OK, HI, UT, NV). Tier 1 percentages ranged from 47% to 72% and Tier 3 percentages ranged from 38% to 58%.

Discussion Points

Dr. Horton emphasized that while it is critical to get people enrolled in the Registry, they also want them to take the extra step of completing as many surveys as they can. He requested that ATSDR's partners continue to promote the Registry, given that it is highly critical for learning about risk factors for ALS. The more people who answer the surveys, thebetter the data will be.

Ms. Chalfant indicated that she is a respiratory therapist, but is not hearing doctors promoting the Registry and surveys in their offices. In addition, she requested clarification about whether patients are to register and complete surveys on their own when they get home and if the information is available in the doctors' offices to inform them that this is available to them. She also emphasized that just because materials are laying around does not mean that patients will follow through. If they receive them but put them in a drawer when they get home and never take them out again, they serve little purpose. They should find ways to make the materials stand out.

Dr. Mehta stressed that registration is driven by neurologists. The ALS Association, MDA, and Les Turner chapters and clinics also are driving forces. Minnesota and South Dakota do a great job of enrolling patients into the Registry. In terms of when patients complete registration and surveys, assistance is available to patients. For example, the Les Turner ALS Foundation in Chicago uses a concierge approach to help people register and help them take the surveys either in the facility or in their homes. This is a different model than a national approach, but they do a great job. In terms of information, all patients are given an informational packet. Some revisions will be made to that packet in the coming fiscal year to make it much more specific. For example, the Registry's branding will be on the folder itself as a reminder for them to join the Registry. ATSDR is at the "30,000 foot level" while the partner organizations are "boots on the ground." ATSDR's resources are somewhat limited. They give a lot of patient talks and will see a spike in enrollment afterwards, but those certainly are not enough. They work with the partner organizations since they know their patients best. This is a lifechanging diagnosis, so chapter or office staff let them know about the Registry during the second or third time they are at the clinic. The new materials will include appointment cards with information about the Registry that will be made available for clinics to give out to patients.

Dr. Horton added that ATSDR knows that there are certain clinics, especially large referral clinics, in which clinic directors are much better than others at promoting the Registry. This is why it is critical for ATSDR to work with the national offices of ALSA, MDA, and Les Turner to ensure that there is a uniform effort to disseminate the message. It would be great if everyone across the country was getting the same message in the same way in a consistent format. ATSDR is addressing this. The neurologist is someone the patient trusts, so if they tell a patient this is something they should look into, that tends to be a very strong motivator for some patients to enroll. However, they must do a better job collectively of getting the message out through doctors and support groups that the Registry is in existence and there are surveys. This is an ongoing challenge.

Mrs. Kennedy pointed out that they also need to get the message out that the Registry is an ongoing living system in which patients need to continue to participate.

Ms. Embro requested whether Tier 1, Tier 2, and Tier 3 referred to ongoing activity that ATSDR is tracking from the enrollees of completion of surveys or tracking number of enrollees. A source point for local chapters when promoting this would be to understand whether their tier rating is based on just initial enrollees or ongoing activity.

Dr. Mehta clarified that for this particular presentation, that was based on survey completion. Normally, the tiers are based upon actually registrants enrolled in the Registry.

Mr. Tessaro stressed that Ms. Chalfant's point was very good that having the materials laying around to be filled out did not make them beneficial. There must be a strategy to get inside the heads of big organizations, neurologists, and clinics to increase the percentage that gives

ATSDR what it needs. If Ms. Chalfant works with doctors all of the time and her experience is that promoting the Registry is not happening or not happening consistently, consideration must be given to how to get them to do better. That seemed like an insufficient place to leave her question. He hated to think that within the professional ranks, they were just indifferent to the fact that highly skilled and dedicated professionals are not telling patients to register and how that is one of the most important things they can do.

Ms. Cory acknowledged these as very legitimate concerns. It is known that for all health behaviors, the single biggest predictor is clinicians. They have engaged in some direct clinician outreach using Medscape and other mechanisms that go directly to doctors. So that packets are not just laying around, they also are giving consideration to how to standardize the discussion whether in a small town where a doctor may see only one patient to a large town where a doctor may see many patients. She indicated that she would be talking about some of this later in the day.

Dr. Oskarsson emphasized that the time doctors have with patients is limited and they have to prioritize the things they talk about. In many states, the Registry has a very strong focus in the initial discussions with patients. However, community neurologists may not keep the Registry as high in their mind as they do not have the same routine with ALS discussions. The Registry has been visible in attending and reaching out at national neurology meetings, not just ALS-specific meetings but to the general neurology community at large. For anybody in the ALS field, it would be difficult not to be familiar with the Registry at this point.

Dr. Mehta added that it has been a challenge to reach out to community and "mom and pop" neurologists and patients who are seen outside the large metropolitan areas. Some patients may receive a diagnosis of ALS in a large facility, but may seek care in their own hometown. ATSDR is trying to reach out to neurologists in rural areas so that they are aware of the resources that are available for patients. He acknowledged that they must do a better job, and this is why they work with their partners to reach out to these areas. However, even the partners' reach can be limited in some of the rural areas.

Mr. Tessaro emphasized that this did not answer why New York, Florida, and Texas have such low enrollment numbers and that perhaps they should start there.

Dr. Kasarskis made a few observations from the neurologist's point of view. They have a multidisciplinary clinic, and in attempts to improving the clinic workflow, he has been sitting in on everybody's interactions with patients to observe what they are all doing. These are very intense clinics. Not to overly dramatize, but in the space of three hours of face time with the patient, families, and various clinicians, there is a huge amount of "nuts and bolts" survival information that is discussed. As important as research is, it is so easy to get wound up with the business of typical issues such as getting a wheelchair, handicapped parking tag, et cetera. He emphasized that while everyone in the meeting room is passionately involved with the success of the Registry, this is a sociology problem. Even though he loves the Registry and it is extremely great, he does not have time, concentration, or memory enough in order to pitch this to patients. From the doctoring side of things, if he gets through that afternoon, that is pretty good. Therefore, they do rely on the ALS Association, MDA, and everyone else to make the Registry a focus of contact with the patients and constant reminding of the importance of enrolling. From the patient's standpoint, when they leave the office they have encountered each discipline with specific recommendations and action items that take their time and focus. If an individual family is resource-rich, they can handle this. However, a lot of patients in Kentucky are not in the resource-rich category. Therefore, this is partially about sociology. He wrote down during the

last presentation that they see the Lake Wobegon effect here. The highest enrolling states that respond to registries are ones that, not curiously, have the highest percentage of high school graduates and just like Lake Wobegon, everybody is above average. This shows through in the data. There is a population bias in terms of approaching responses to things like this. It would be interesting to map out the National Rifle Association (NRA), versus graduates, versus opioid epidemics, versus other issues that they are navigating.

Dr. Mehta indicated that they are going to Texas in August to San Antonio and Austin to do saliva collections at a support group meeting. Saliva collections are somewhat limited in terms of what can be extracted. But, the plan is to have some staff members there and a system for enrollment. He agreed that perhaps they need to look beyond the clinic level to work through some other types of events. They are working with Ms. Embro and her team at the Georgia ALS Association to do something like that. For example, they could possibly do saliva collections at a community event or support groups in Macon so that it is outside the clinic and they have much more hands on contact. A great example is that over 25 saliva collections were done during an ALS Association advocacy event in DC, and they had team members available to help people enroll as well. That was a very successful event in a neutral conference environment outside of the clinic setting. They are limiting the FY20 saliva collections to only 50, given the limitations of what can be done with it. Blood is much more valuable, so perhaps they could have a phlebotomist go to community events, support groups, and so forth to collect blood samples.

Dr. Horton stressed that they hear loud and clear that clinicians have limited time with patients. If ATSDR could just have their literature inserted into whatever standard packets neurologists provide, that would make a difference as well. That way, patients could go home, read the information at their own leisure, and hopefully decide to take part in the Registry.

Mrs. Kennedy emphasized that Dr. Kasarskis's points were very good. At the time of the first diagnostic clinic visits, patients are in "deer in the headlights" survival mode. One thing they had not discussed was that there is under-representation of minorities. While there is Hispanic language outreach, that does not address African Americans. It is not clear why they are missing minorities.

Dr. Kaye indicated that unfortunately, minorities are under-represented in support groups and registries for most diseases. Her personal opinion is that it may be an opportunity cost. Some people have limited time, limited resources, have just been given a devastating diagnosis, and are trying to figure out how they are going to feed their children. Going to support groups and activities and signing up for things is very low on their priority lists.

Mrs. Kennedy stressed that this is not relegated just to minorities. Everyone diagnosed with ALS is facing that. Lower socioeconomic status (SES) is not necessarily just race-related.

Dr. Kaye agreed, but pointed out that there is a higher percentage of minorities in that population. She spoke with representatives at the American Cancer Society (ACS), which reported to her that minorities are under-represented in their annual online surveys. The National Multiple Sclerosis Society reports the same. Everyone is trying to determine ways to engage minority populations other than by just having surveys and registration in Spanish.

Dr. Mehta added that they will most likely capture minority populations as a case if they come in through Medicare or the VA system. However, they must do a better job in minority communities to raise awareness in order to get them enrolled in the Registry, take the risk factor surveys, provide samples for the Biorepository, and get information about clinical trials.

Mrs. Kennedy inquired as to whether ATSDR receives Medicare Advantage data.

Dr. Mehta replied that the Medicare Advantage file, which is Part C, was recently made available on the menu of options from Centers for Medicare and Medicaid Services (CMS) and they requested it for 2015. Anyone who is a unique case from 2015 will be included in 2016 as well.

Under-Enrolled States Outreach Project

Reshma Punjani, MPH
Oak Ridge Institute for Science and Education (ORISE) Fellow
Agency for Toxic Substances and Disease Registry

Ms. Punjani provided an update on the Under-Enrolled States Outreach Project in terms of the results from the six-month project period from July 1, 2018 through December 31, 2018; the lessons learned; a comparison of state performance for Registry enrollment; and next steps.

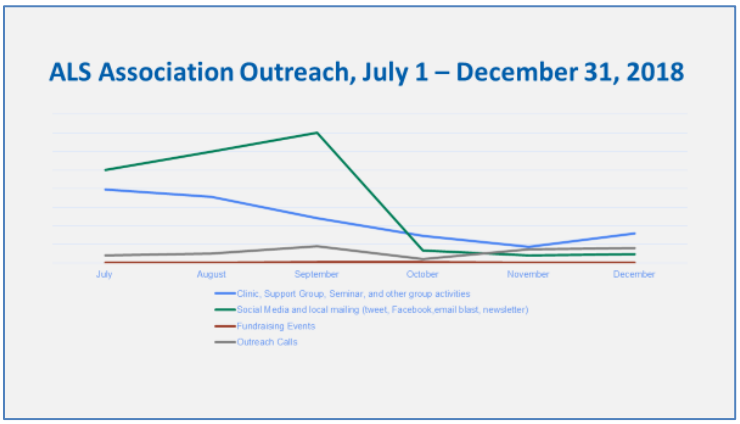
In terms of background, the Georgia Pilot Project was conducted in 2015 by the ALS Association Georgia chapter with the objective to increase enrollment in health districts that were currently under-enrolled. Some of the successful strategies implemented included having Registry information being provided in new patient packets to ALS patients, providing tablets in clinics to assist with enrolling patients, and increasing outreach to support groups by having peer speakers discuss the purpose and ease of the Registry. These strategies helped Georgia move from being an under-enrolled state to being comparative in enrollment.

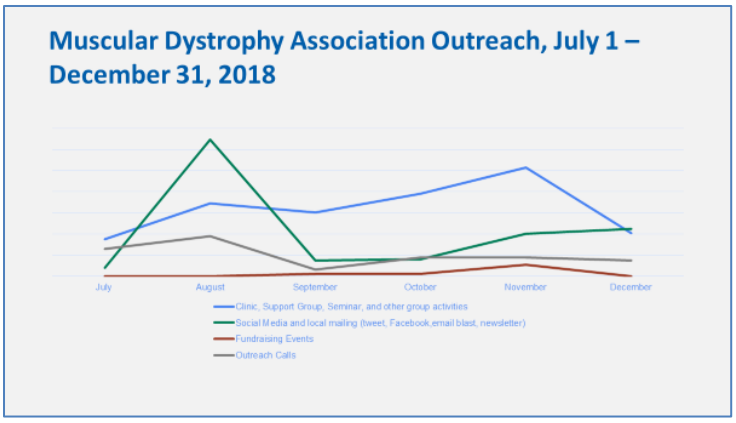
The Under-Enrolled States Outreach Project was based on the success of the Georgia Pilot project conducted in 2015. The goals and objectives are to focus on under-enrolled states and identify health districts within those states which could benefit from increased Registry outreach. Prior to the start of the project, the available data included self-enrollment in the National ALS Registry by city; geocoding of city data to the appropriate county using the Registry data in order to cluster the counties into health districts; Census data for 2010; and registration data from the ALS Association, MDA, and Les Turner ALS Foundation by county.

In terms of the methods, the first step was to identify the under-enrolled states in the US. At the time of this analysis, the states included in this project were Hawaii, Mississippi, New York, Utah, West Virginia, and Wyoming. The counties from these states were categorized into health districts and the number of people in the Registry per health district were compared to the number of cases expected. The number of expected ALS cases for each state was determined by multiplying the number of persons in the state using the most current Census data by the ALS prevalence rate for the US. The Registry enrollment data also were compared to data received from the ALS Association and the MDA.

Prior to the start of the project, the first step was to train the local staff on the purpose of the outreach project and resources available. The ALS Association and MDA conducted webinars to train local staff on what resources would be available to them during the six-month study period and how to use them going forward. Outreach was conducted to the under-enrolled states for the six months from July 2018 through December 2018. Every month, both organizations reported their outreach numbers to ATSDR, including the number of calls made per state, social media outreach, et cetera. ATSDR reviewed and assessed these data at the end of the six-month period to determine the effectiveness of increased outreach to under-enrolled districts. That data on the number of enrollees for the six-month outreach period was compared to the same time period in 2017 for the under-enrolled states.

Several plans and resources were available to the partners. The first was the phone script, which was a template created by the Registry to be used by the partners during periodic outreach calls to ALS patients served by their local chapters and clinics. This script was a crucial resource because it standardized the information the local staff provided to ALS patients and their families. During the webinar, staff were trained on how to conduct these outreach calls. The second component was social media outreach. The Registry and ATSDR has a Registry Master Table that includes all pre-approved messages for Facebook and Twitter, as well as approved graphics for promoting the Registry. These resources are available for all ATSDR's partners to use to promote the Registry. This was part of the outreach for under-enrolled states as well. The last component was partner-specific events. ATSDR encouraged the local chapters to engage in targeted outreach during their local events, such as support groups or walks. These graphs show peaks in ALS Association and MDA outreach based on what activities were being promoted during the project timeframe:





After the six-month period ended, ATSDR collected the data to determine whether there was a difference in enrollment from 2017 to 2018. All six states did have an increase in enrollment. West Virginia, Utah, New York, and Mississippi had a higher percentage. Hawaii and Wyoming had zero cases enrolled in 2017, but their enrollment increased in 2018. This illustrates that the increased outreach worked in these six states. Cumulative enrollment during the same timeframe showed similar trends.

In terms of conclusions, the outreach project overall was successful in multiple states. The under-enrolled states improved within each tier; however, the under-enrolled states did not move into the next tier. Through the project, a nationally approved phone script was created and approved for use in all states. That resource is now available for all 50 states so that everyone can make sure they are delivering the same information to patients and their families. There were some challenges in the project. Due to staffing issues in some local chapters and clinics, the full outreach was limited to those who were trained to make the outreach calls and focus on the under-enrolled states. One limitation was that because all this outreach was going on simultaneously, it is not possible to pinpoint which aspect of the outreach had the most effect (i.e., phone script, increased social media marketing, or regional events).

This table, which is generated every month, compares state performance for registering PALS in the National ALS Registry through June 19, 2019 by tier:

Tier 1	Tier 2	Tier 3
1. Minnesota	1. Delaware	1. Arizona
2. South Dakota	1. Nebraska	1. Connecticut
3. Iowa	2. Alaska	1. Kentucky
3. North Dakota	2. New Mexico	1. Maryland
4. Wisconsin	2. Tennessee	1. Pennsylvania
5. Missouri	3. Wyoming	2. Indiana
5. North Carolina	4. Florida	2. Massachusetts
6. Montana	4. Louisiana	2. New Jersey
6. Oregon	4. South Carolina	2. Rhode Island
7. Alabama		3. Arkansas
7. Maine		3. Kansas
7. Vermont		3. Mississippi
7. Virginia		3. New York
7. Washington		3. West Virginia
8. Ohio		4. California
9. Colorado		4. District of Columbia
9. Idaho		4. Nevada
9. Michigan		4. Utah
10. Georgia		5. Hawaii
10. Illinois		5. Oklahoma
10. New Hampshire		5. Texas

These data are provided as one measure of registration and performance to help partners gauge whether what they are doing is effective in these states. For example, those in the Tier 1 group should probably maintain what they are doing and to make changes if their performance decreases. Those in the Tier 3 group may need to reconsider implementing routine practices to ensure that their ALS patients are aware of the Registry and its importance. Because OMB does not allow ATSDR to provide percentages, the tier systems permits states to see qualitatively where they lie in comparison to other states in the US.

As mentioned earlier, performance is determined for each state based on the number of ALS patients enrolled in the Registry compared to the number of expected ALS cases for each state (i.e., percent registered = number registered ÷ expected number of cases). The number of expected cases of ALS for each state is determined by multiplying the number of persons in the state, as per the most current Census data, by the ALS prevalence rate (5.2 per 100,000 population). The percent registered for each state is compared to the percent registered for the US to determine which states are above and which are below the US average. States are ranked ordered from the highest performing state to the lowest performing state (i.e., the highest performing state, Minnesota, to the lowest performing state, Hawaii, Oklahoma, and Texas).

Regarding next steps, the Under-Enrolled States Outreach project was successful in bringing partners together to develop outreach methods that now are available to all states and in establishing methods to increase enrollment through outreach. The next steps in Phase II of the project are to focus on the higher populated and under-enrolled states of California, Florida, and Texas.

Discussion Points

Dr. Thakur wondered with all of the various efforts underway they could estimate whether they would achieve the overall goals stated earlier of determining a more accurate prevalence of PALS, enrolling more PALS in the Registry and take the surveys, and getting more people to submit specimens to the Biorepository. For example, if they identify under-enrolling states based on a 5.2 prevalence rate and then got those under-enrolling states to a 5.2 prevalence, they would still be lower than what the real prevalence is thought to be. He thought the bigger question pertained to the overall strategy and modeling out what it would take to get to whatever they think the prevalence is, whatever they want the survey participation to be, and whatever they want specimen collection to be, and then work from there. While it is important to optimize the approaches they have, but if they are trying to optimize based on a 5.2 prevalence, perhaps the best they can ever do is get to a 5.2 prevalence.

Ms. Punjani emphasized that this project is focused only on under-enrollment.

Dr. Mehta indicated that prevalence with capture-recapture is around 6/100,000. What is expected should be at the 6/100,000 estimate, but for now they have only 5.2/100,000. Once they release 2016 data, they should readjust for the new prevalence rate.

Dr. Thakur stressed that they were adjusting for the new prevalence rate through an error approach. It was not like they were collecting enough people to get to 5.2/100,000 in the under-enrolled states. That is just one of the three numbers they are chasing, so he was wondering if these were the right approaches.

Dr. Bradley said he wanted to understand how they viewed the situation that a state with mandatory reporting was positioned as a Tier 3 state.

Dr. Mehta said he thought they were in Tier 3 because high enrollment in the Registry has not been achieved yet. What providers are reporting to health departments is different from what is being reported to ATSDR, which certainly could be a factor in terms of the comparison. They told ATSDR that their ascertainment is above 90%, which certainly could be the case. Lifting them into Tier 2 as far as enrolling in the Registry requires resources in terms of working with the chapters and clinics. MGH is huge and is a NEALS member, but there needs to be a more concerted effort to get PALS enrolled in the National ALS Registry. ATSDR provides a lot of clinical trials assistance for all of the PIs in Massachusetts and they are very pleased by the response rate.

Dr. Bradley asked whether they could provide a transfer of data.

Dr. Mehta indicated that ATSDR will get PII data from Massachusetts. They could compare ATSDR data and Massachusetts data, but they cannot add their data to the Registry.

Dr. Kaye clarified that under Massachusetts law, they are permitted to use the data only for the comparison. Putting the data into the Registry may have consent issues. This is the same issue they had with the surveillance project of the 3 states and 8 metropolitan areas. The cases identified could not be added to the Registry population. Another reason that Massachusetts might be a Tier 3 is that they hear anecdotally that people are very confused by all of the other efforts people refer to as "registries." Some materials are being developed to help clarify that people can be in more than one registry, which may help solve this issue.

Dr. Nelson noted that the method for identifying under-ascertained states was based on the assumption that the geographic distribution of ALS is uniform across the US, but there have been some past studies with death certificate data that suggest that there is South to North increase in mortality from ALS, of course with all of the caveats related to death certificate studies. She wondered if they had thought about that and if they were seeing more under-ascertained states in the Southern states. She also wondered whether ATSDR could repeat the earlier mortality studies looking at geographic distribution to see whether this holds up.

Ms. Punjani said she thought the states were uniformly spread out, but this was done for a national number rather than looking at Northern or Southern states. If there is a difference, she wondered how that plays into the expected number as well.

Dr. Mehta added that Ted Larson published a study last year in which mortality was shown to be higher in the Midwestern states.

Dr. Oskarsson wondered whether the age of the population and gender would change the tiering of states.

Dr. Thakur asked what the prevalence would be if every under-performing or low ascertainment state was brought up to the current baseline, and how that would impact the capture-recapture estimates ATSDR is working on now in terms of whether that would move the estimate of error up somewhat. That is, if they moved everything up, would they go from a 5.2 to a 5.5 prevalence and then when capture-recapture analysis is done, instead of the estimated prevalence being 6 would it be 6.1 or 6.2. He was trying to find out the ultimate effect size of this approach and at what point it will actually get them to the numbers they want, or if they are just

doing some very hard work and doing it well, but it is not big enough in its potential magnitude to get at true prevalence and other numbers they are trying to reach in terms of survey completion, specimens, et cetera.

Dr. Mehta said that even if they had a prevalence of 6/100,000, that is still an estimate because the disease is not reportable at the state and federal levels. These are still estimated case rates. With the new report coming out for 2016, there will be a higher threshold or something above baseline (their own algorithm) and a capture-recapture prevalence rate (the high end). Once they get that, they need to readjust it to have a median prevalence estimate with which to do these calculations.

Dr. Horton added that since about 80% of the cases in the Registry are found through the national database approach, it is not clear that bringing the Tier 3 states up to Tier 2 states would necessarily impact the prevalence rate in a radical way.

Recommendations from the 2018 Meeting

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 presented an overview and current status on the recommendations from the 2018 meeting. He emphasized that patient, caregiver, partner, and researcher feedback is very valuable and is critical for success and establishing the Registry's priorities. The recommendations are broken down into the following categories: Communications/Outreach, ALS Prevalence, Additional Analyses with Existing Data, and Other. The recommendations within each are shown in the following six tables along with the lead organization and status:

Communication/Outreach Recommendations

Recommendation	Suggestions	Lead Organization	Status
1. Send out Registry updates in newsletters	-Topics: Risk factor surveys, new research, research results, biorepository, funded studies -Frequency: semiannual	ATSDR	Completed/Ongoing
2. Use findings from studies to show impact of the Registry and promote joining to patients and caregivers	-Communicate through the newsletter	ATSDR	Completed/Ongoing
3. Provide more information on how the Registry is contributing to fight against ALS	-Communicate through the newsletter	ATSDR	Completed/Ongoing
4. Continue efforts to update website, make information for patients and caregivers more engaging and easier to find, make sure links work, etc	-Develop Spanish website -Updating website homepage	ATSDR	Completed/Launched July 2019
5. Develop and ensure that clinic staff are aware of guidelines to provide consistent info about Registry to persons with ALS	-Develop guidelines -Train staff to follow guidelines	ATSDR Partners	Completed/Ongoing via Webinar

Communication/Outreach Recommendations

Recommendation	Suggestions	Lead Organization	Status
6. Make the information about the Registry more prominent on partners' website homepages		Partners	In progress for MDA Completed for ALSA and Les Turner ALS Foundation
7. Analyze data on what activity led to enrollment in the Registry, e.g. social media, promotional material, clinical staff suggestion	-Add question to registration inquiring: "How did you hear about the Registry?"	ATSDR	Completed, to be presented by JR
8. Increase researcher awareness of data and specimen availability	-Email researchers -Conferences, symposiums -Social media targeting researchers -Paid aids	ATSDR	Ongoing, will be presented by Brunet-Garcia
9. Provide enrollment statistics at smaller level than state e.g., health district	-Under-Enrolled States Project -If successful, consider expanding to include highly populated states (CA, FL, TX)	ATSDR	Project ended 12/18 Data analyses are in progress Preliminary results to be presented by RP

Prevalence Recommendations

Recommendation	Suggestions	Lead Organization	Status
1. Provide an estimate of ALS prevalence that adjusts for under-ascertainment		ATSDR	Ongoing
2. Consider changing the label of 'definite ALS' to something else because it is being equated with definite using El Escorial criteria		ATSDR	Completed, distinction made in *MMWR* article

Other Recommendations

Recommendation	Suggestions	Lead Organization	Status
1. Track status of recommendations from the annual meeting. Provide an update at 6 months and present progress at the next annual meeting	-Report progress via email to 2018 Annual Meeting Participants in January	ATSDR	Completed
2. 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		ATSDR	Physical activity survey will be modified in 2019. Retirement of other surveys is not common in epidemiology, required for ongoing analyses
3. Focus messaging about surveys to those more impacted	-Weight surveys -Display a thermometer showing % of survey(s) completed	ATSDR	Address after current revisions to Registry website are completed
4. Consider rating survey difficulty		ATSDR	Cannot estimate timeline due to OMB restrictions
5. Measure the impact of individual activities in Registry enrollment and survey completion.	-Identify spikes in enrollment monthly -Examine results of projects	ATSDR	Ongoing

Other Recommendations

Recommendation	Suggestions	Lead Organization	Status
6. Inform researchers about data/specimens available for research and encourage researchers in funding requests to use data/specimens	-Place paid journal ads in neurological journals -Consider inform/encourage with funding announcements -Exhibit at conferences attending by researchers	ATSDR	Ongoing
7. Discuss research opportunities with representatives of pharmaceutical companies	-Compare who talked to from year to year with pharmaceuticals	ATSDR	Ongoing

Discussion Points

Dr. Kasarskis asked whether for a single patient the order of the 17 surveys is randomized and is scrambled for the next patient so that everybody does not encounter the same surveys in sequential order. They saw a presentation earlier in the day pointing out that not everybody completes all of the surveys. If the average completion rate is 7 surveys and they are the same 7 surveys, perhaps they would get a more representative sample if the surveys are scrambled for each enrollee.

Dr. Mehta indicated that they do not and that on the dashboard, the surveys are not listed in order to avoid the creation of a bias with the survey names themselves. For example, someone may see a survey named "Military" and not take it because they were not in the military rather than opening it and checking that they were not in the military. The surveys are stagnant in terms of order 1 through 17 and are not scrambled. That is a good point. The first 6 to 7 surveys are the ones that are most often completed. There will be some revisions in the next OMB package. For example, race will now be captured when an individual first registers rather than when taking Survey 1. That way if someone registers but never answers any surveys, they at least will have that variable.

Dr. Thakur expressed appreciation for the tracking of feedback and suggestions, which he found to be very helpful. While he understood that they did not want to take a survey offline, he hoped that it was because there are specific period and cohort effects for which they are looking and they want to see how the responses change over time. Given that some surveys may seem less active or interesting at this point than when first initiated, they do have the opportunity to over-sample for some and under-sample for others. Even if they do not want to take them offline, he encouraged ATSDR to down-sample.

Dr. Mehta said he thought there potentially could be room for shuffling the surveys around, which they could discuss internally.

Communications and Outreach

ATSDR

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

Ms. Cory emphasized that they do not have a full-blown communication team or campaign. When people think CDC or ATSDR, they are thinking about national campaigns. Those cost a lot of money and feature more full-blown communication efforts. While she is very proud of a lot of the things they did and that they tried to be very responsive, she suggested that they think in terms of limited context.

In terms of ALS Awareness month, CDC and ATSDR try to focus their efforts by taking advantage of CDC or ATSDR vehicles such as the Twitter account. The Twitter account is somewhat small, but it can be used for awareness. Ms. Cory shared a few examples, and emphasized that they like to use photographs of real people rather than stock photos. To that

end, there was a professional photographer at the meeting and she encouraged participants to get their photographs taken so that they too could be featured on a CDC tweet. She gave a big shout out to the people in the room whose photographs they have blatantly used repeatedly. They also had a CDC home page feature in May 2019, which had over 700 independent views. People following CDC are generally looking for communicable disease outbreaks. Because this is competitive, it is great that a chronic disease got placement on the home page.

They also placed a "matte" article in community newspapers, which resulted in over 2500 placements in print in community newspapers and on websites. A lot of people pick up and respond to free newspapers. Last year they featured Ed Tessaro, and this year they featured Alan Alderman. They know that patient testimony is extremely compelling. It is one thing to think about a disease in abstract, but it resonates when a person has a name and a story.

One of the new items this year is that there now is a National ALS Registry Newsletter, which is very easy to sign up for. The newsletter features include a patient spotlight, updates for partners and patients, tools that are available, and news for researchers. Not surprisingly, the patient spotlight is the most popular element of the newsletter. The goal is to publish the newsletter quarterly, but they can feature news or other information as necessary. For example, they could feature an interview with a researcher. They need to show how research dollars are allocated and translate that. While the people in the meeting room understand a lot of the epidemiological factors and so forth, a lot of people do not.

In thinking about how to tell the story of the Registry, ATSDR held its first ever national training webinar for partners. The topic was how to talk about the Registry in a way that makes sense to people. The webinar had over 120 participants and offered people an opportunity to address very real issues of what works for patient outreach and education about the Registry. Summaries and additional information will be posted and emailed for those unable to join or get their questions addressed. The webinar emphasized the need for cross-cutting support across partner agencies.

One of the things they heard was that it is difficult to find things on the website. With that in mind, they have been thinking about how users enter the website and what they are looking for. They want to keep primary the idea of joining the Registry, so they want to make that an easy "Click Here" button. They also are thinking about their partners. There will be new groupings by target audience and portals for patients and caregivers, researchers, partners, and the general public. They are using a "Digital-First" platform to ensure that the site is scrollable whether someone is on their phone, tablet, or laptop. The Spanish website also is coming. That is not a complete 100% transfer.

One thing that their webinar presenter, Jennifer Hjelle, pointed out is that sometimes people are intimidated by online information. She made a concrete and practical suggestion of perhaps having a grandchild help someone from a generation that is not comfortable completing information online. That also is a great way to hear their story and have an intergenerational connection.

We try to listen and think about keeping materials patient-oriented. We heard loud and clear that people do not want to just be told that they contribute to research. They want examples to illustrate why it matters. The website needs to be accessible, not just in a 508 Americans with Disabilities Act (ADA)-compliant way, but also in the sense that a partner can find/print a handout that explains the difference in the kinds of Registries. There will be a partner portal that will have available items that are useful.

We are just starting to collect and analyze metrics such as who visited the website and how often, what the most popular are, et cetera. They can use some of that information to help guide them as well.

Discussion Points

Mr. Baker asked what possible changes they would implement after collecting some metrics about who comes from where, how many times they visited, et cetera.

Ms. Cory indicated that while these are not paid advertisements, they might have some paid placement in the future. That will make it a lot easier to track and have analytics. Right now, she can tell how many people and which pages are most popular. The changes will focus on regrouping and creating portals so that people can find what they are looking for. Part of the goal is to put things into more logical chunks. The metrics are currently pretty limited, but the plan is to broaden these to help guide what is working and what is not working, and to place some paid media to help track that better in the future.

Brunet-García Advertising

Francie Lefkowitz
Account Executive
Brunet-García Advertising

Ms. Lefkowitz indicated that Brunet-García was contracted by ATSDR in 2015 to support the National ALS Registry with communications and outreach. Each year, planning for the next year begins in the July to August timeframe. This year, development of the communications plan included four objectives, which were to: 1) increase awareness and engagement, 2) focus on under-enrolled populations, 2) increase online presence, and 4) coordinate with partner efforts. The communication plan was developed through a strategic analysis of materials, consistent communication with partner organizations, review of notes and action items from the 2018 Surveillance Meeting, and analysis of past efforts to determine what works best.

They researched impactful messaging and used with consistent branding across resources (e.g., testimonial quotes, social media, print materials, posters, handouts). One key focus is social media, which was used to lead people to the new website. They spent a lot of time trying to give the best support to the partners by creating new graphics, developing new posts, working close with them, and establishing a content calendar process.

Ms. Lefkowitz shared examples of all the marketing materials that have been developed this year. Marketing materials include these items:

- ❑ Appointment Reminder Card
- ❑ Poster for ALS clinics, chapters, and support groups
- ❑ New Registry Overview One-Pager
- ❑ Material to explain the importance of risk factor surveys
- ❑ Squeeze balls
- ❑ Material to explain the difference between partner organizations (in development)

The next steps are to finish the materials to explain the difference between partner organizations, share new materials with ALS chapters and offices in various cities, create a Spanish Overview One-Pager, and ensure that materials are relatable for people living with ALS.

Discussion Points

Mrs. Kennedy said she appreciated the need to distinguish between all of the organizations and emphasized that it is very confusing, especially for a newly diagnosed patient. She expressed concern that they seem to have blown right past branding the disease. For example, breast cancer has pink everything and diabetes and Alzheimer's have become branded. ALS has not become branded, which is a major problem. The international symbol for ALS is the blue cornflower, which she personally has promoted in her world and thought it made sense for ATSDR to promote it. However, the US does not embrace that. The Ice Bucket Challenge was a game-changer for ALS in terms of public awareness, but the disease needs to be branded.

Dr. Mehta pointed out that the colors for Alzheimer's are purple and that there are commercials for Alzheimer's, but he did not recall having seen any commercials for ALS. He agreed that there must be branding, more awareness, and more attention for ALS. ATSDR is not branding experts, so they must defer to their partners.

Ms. Lefkowitz added that one issue with branding is that there are different groups talking about ALS. The colors of the Registry are dark blue, maroon, and green. The ALS Association is red. They will talk about it more.

Ms. Backman said she completely understood where Mrs. Kennedy was coming from on this. She thought perhaps that the awareness piece was a different discussion, though she understood the point on that. She asked Mrs. Kennedy, as a person living with ALS, whether she personally felt that some of the materials coming from the Registry itself could be better clarified outside of colors and branding.

Mr. Kennedy emphasized that Mrs. Kennedy was already on board, so she was not the one they were trying to preach this to. He thought her frustration was that other than the Ice Bucket Challenge, a lot of people do not know about ALS or even who Lou Gehrig was. There just is not a marketing schtick anymore that everyone recognizes and associates in the right way.

Mrs. Kennedy pointed out that the incidence of ALS is essentially the same as multiple sclerosis (MS). The only difference is that people with MS survive and people with ALS do not. Everyone knows a lot of people with MS, while ALS remains an unknown.

Ms. Chalfant said that even though she is an ALS advocate, she also is confused about all of the associations. She agreed with Mrs. Kennedy that if they all had a similar color and branding, it would stand out for all of the patients, doctors, et cetera.

Ms. Jaffee agreed with the importance of raising awareness about ALS as a cause that needs attention. The pink ribbon is very recognizable with breast cancer, so there are probably ways to work in the blue flower such that it will grab people's attention. However, that is not what Brunet-García was specifically tasked to do for CDC/ATSDR. They want to be clear in communicating what the Registry is, what its goals are, and its importance. She thought what Mrs. Kennedy was referring to is a separate issue that is a problem across the country. Perhaps there are

ways to leverage some of the symbols and colors that have been used in other countries where people more immediately recognize it. That is a very important but separate issue.

Ms. Hernandez agreed that having the partners come together with a single brand around ALS would be great. Perhaps there is an opportunity for the Registry to incorporate something like that. She also noted that while she liked the appointment card a lot, one shortfall was that the Registry information is on the back of the card. If someone puts the card on their refrigerator, they will only see the appointment information and nothing about the Registry. Perhaps they could incorporate the information about the Registry on the part of the card the patient is actually looking at and seeing every day before they go to their appointment. She also is excited about the materials being developed to explain the difference between partner organizations, and thinks they need to be very specific about registering with MDA, MDA's MOVR Data Hub™ (neuroMuscular ObserVational Research), and the ATSDR National ALS Registry. Registering with MDA and going to an MDA care center ALS appointment is not the same as being in the MDA MOVR Data Hub™ registry. She also is very excited about all of the Spanish language materials being developed, but wondered whether the Registry tracks the primary language of people who are registered and if they know the breakdown. If the Spanish-speaking share is large enough, it could go a long way to garner more resources to develop more Spanish language information for patients and/or caretakers who speak Spanish.

Dr. Mehta indicated that while they could ask what language is spoken in the home, that is not currently asked by ATSDR. The Registry is all in English with the exception of the Spanish portion of the website.

Dr. Goutman said that they create the most handshakes and then it is the neurologists after the fact, but they do not get any feedback in terms of how well they are doing. Posters may be more of a challenge because in a hospital, they have to worry about fire codes. Certainly, the flyers would be very useful. What they like to do is present an iPad in the clinic to fill out as much as there is time for, and then be able to give them the materials that can facilitate the completion of either registering or completing surveys when they are not in clinic. The number of patients they see per month is variable, but it can be about 20 per month who are newly diagnosed.

Dr. Mehta asked at what point they provide the iPads. He also said that they could probably give them a percentage, although they cannot provide any PII pursuant to OMB and IRB regulations. Potentially they could discuss internally sharing some metrics that are at a much higher percentage level.

Dr. Goutman thought that any information would be better than no information. The way that he tries to do it is that the clinic visits can be busy, but as they are discussing some amount of information, the Registry may not be the number one topic that will come up. They have asked that somebody else be dedicated to helping facilitate the enrollment. He also asks the question in the intake information at each visit, "Have you registered with the National ALS Registry? Yes, No, and I don't know." "I don't know" comes up a lot, so he thinks there is registry confusion in terms of what people have registered for and what it means, speaking to the branding. One of the critical handshakes is the neurologist helping to influence their patients to register. There is just no metric to tell them how good of a job they are doing. If there is a way to get that through OMB to provide information, it would be useful.

Dr. Mehta said that ATSDR sends the information regarding the states and Tiers 1, 2, 3 to the partners as well. That is one way to communicate to neurologists and the ALS Association, MDA, and Les Turner what is occurring in the various states they are serving. Looking at the granular data Dr. Thakur was requesting is something ATSDR would have to consider on their end. It is not clear how they would differentiate between Henry Ford, University of Michigan, the clinic in Traverse City, and so forth. In terms of branding, ATSDR used Lou Gehrig's image for a long time and had licensure from the Rip Van Winkle Foundation (d/b/a/ The Lou Gehrig Society). They have moved away from that based on feedback that people no longer know who Lou Gehrig is, especially those who are newly diagnosed. Perhaps like Mrs. Kennedy said, it is time to have a new image or new branding campaign. The partners could get together, perhaps with some other groups, to figure out a national US symbol for ALS.

Dr. Horton thanked Dr. Goutman for what they are doing with iPads and recognized that Les Turner also is using iPads to help people enroll. He also thought this showed the discrepancy in how the message is getting out. He considered helping people enroll via laptop above and beyond the call of duty; whereas, he knows other clinics, for whatever reason, do not or will not mention the Registry. The challenge that ATSDR is facing regards how to get everyone to push out the message in the same way, or at least some kind of uniform way, so that everyone is hearing the message. This is challenging, and this is where he looks to the partners to help them with this challenge.

Ms. Backman recalled that earlier there was discussion about the difficulty in getting the information, especially some of the pamphlets, out in front of patients. Les Turner ALS Foundation does not give out everything at once. They assemble different folders for different visits. They put certain information that patients need when they present for an initial diagnosis or first-time visit to the clinic in a first visit folder, and then other information in a later visit folder. That is not just about the Registry, but also is about how they approach education about the disease. They are able to incorporate a lot of these elements. They do have an issue with the posters only because they are using the neurology outpatient clinic 2 days a week for ALS, but other days of the week it is used for other diseases. The feedback they received from the neurologists was that this may be confusing if someone is visiting for a different neurologic disease and is seeing ALS posters on the wall.

Dr. Mitsumoto noted that one study showed that only 20% to 30% of patients in ALS clinics are involved in clinical trials. If physicians tell patients, the influence is very strong. Just giving people a package of materials may not be as effective as they think. It is still very important for whomever is in charge, medical director or doctor, to emphasize the importance of the Registry. That will be very influential and helpful.

ALS Association

Neil Thakur, PhD
Executive Vice President of Mission Strategy
The ALS Association

Dr. Thakur provided a brief background on the ALS Association and presented an update on its Registry promotion efforts. He called out Adam Baker for doing a remarkable job working with numerous stakeholders within the ALS Association, including Ms. Embro and Dr. Dave. In terms of background, the ALS Association supports advocacy, research, and care services through a network of chapters around the country and a national office that coordinates these three areas

of support. 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.

He said he shared the ALS Association's mission to provide some context for why they were there and why they care about the Registry. The Registry is very important in terms of understanding how many people there are with ALS in a particular area so that they can think about the resources that people in that area might need. Clinics, transportation, and travel time are all very important because they are trying to provide services to people. They also are interested in and excited about the research that is facilitated through the Registry and the specimen Biorepository. The ALS research space is remarkably collaborative. One reason for that is because centralized resources make research efficient and fast. The work that is done on environmental risk factors is extremely important. In order to reduce the incidence of ALS, it is imperative to figure out what causes it. If there are environmental factors, it is important to figure out how to reduce exposures and manage risks for people, especially people who carry the ALS gene. No one is doing as much work in this space as the Registry, so it is vital for this work to continue.

Regarding some of the work the ALS Association has been thinking about in terms of the Registry, they have been trying to work systematically and in a structural way. They recognize that their chapter and clinic staff are major assets in shaping narrative around the Registry. The ALS Association holds walks, fundraisers, and other events that offer opportunities for the ALS community to gather and for promotion, registration, and some sample collection. Social media acts as a major force multiplier in spreading the word about the Registry. In terms of chapters and clinics, they have been engaging clinic staffs and directors in a series of surveys and focus groups. They have been engaging their staff in chapters who put together events to help them think about the Registry and how to incorporate that into their activities. In addition, they have been working on some materials they can use to promote the Registry on social media.

The evidence suggests that multidisciplinary clinics represent the single best intervention to improve length of life of people with ALS, and it offers a great opportunity to talk about the Registry. The ALS Association ran a focus group to determine what is working and what could be improved in how ALS clinics promote the Registry. This was done in a staged manner with a pre-survey activity in order to obtain some information about what to talk about. That was followed up with a focus group with clinic professionals during a meeting at the October 2018 Clinical Conference. They gathered the ideas from there and then validated those ideas through a survey.

About half of the people from the pre-focus group survey found that people with ALS hear about opportunities for clinical trial enrollment from their physicians. Clinical trial enrollment is known to be a very big incentive and value for being a part of the Registry. That is an opportunity to start to tie these together. Overall, those responses helped to understand what the clinicians thought were the reasons why people would want to sign up for the Registry. They were able to follow this through with a focus group comprised of 6 nurses, 3 physicians, 2 occupational/physical therapists, and 12 ALS Association chapter clinic staff and board members. They discussed the mechanics and logistics of getting materials and what materials are most effective.

They discussed the potential of including a general written summary description of the Registry when people receive their visit summaries. Overall, the best time to engage people in the Registry is when they start to ask why they have the disease. The answer is, "We don't really know, but we're trying to find out. Here is a tool we are using that you can help participate in." It is about waiting for people to be ready for the information rather than handing them a binder at the time of diagnosis. Another thing that was interesting is that a lot of the people who are tasked with engaging and recruiting people to participate in the Registry had never participated in a registry themselves. They do not have ALS and were not allowed to play with the interface, take the instruments, et cetera.

There was a strong request for what they are calling a "Practice Registry Module" to help clinic staff and caregivers understand the process through actual practice. They wanted to know what CDC materials are available. A lot has been developed over the years, some of which they are really excited about. However, the volume seems to be creating some challenges for them. Focus group attendees also pointed out that there have been challenges with passwords and tracking their progress through the modules, so it would be helpful to have some type of checklist. They also observed that people could be using clinic downtime to start the Registry modules and/or complete surveys. The amount of downtime does vary depending upon the clinic or perhaps the day of the clinic. Another suggestion that seems very feasible is that while the documents and materials are great, people need help walking through them. To that end, there was a specific suggestion to create a high-level document such as the two-page brochure with supplementary materials included in a different packet. In addition, focus group participants observed that messages and materials must be empirically tested. Different clinicians have theories about what works, but they are just hypotheses until they are tested.

The ALS Association assembled these ideas and sent them out to all clinic leads in July 2019 to test potential ideas with clinic directors who were asked to rank the ideas on a scale of 1 to 6, as reflected in the following table:

Item	Overall Rank	Score	No. of Rankings
Improve Document Awareness/Checklist	1	137	33
Registry + Biorepository Document Orders	2	125	33
Increased Education of Clinic Staff	3	121	34
Clinic-Specific Promotion Opportunities	4	118	33
Practice Registry Module	5	102	33
Take Advantage of Clinic Downtime	6	96	33

Part of the overall theme here is that there is a fair amount of complexity in dealing with the Registry. The clinic staff who are trying to convey this information are experiencing challenges with this complexity, and they recognize that the people enrolling in the registry are experiencing challenges as well. A lot of strong materials already have been created to help manage this, and there is a potential partnership in which the folks on the ground can help focus on some of those materials.

They also have been working with their walk staff, given that walks are an opportunity to engage new PALS, caregivers, and supporters. Each chapter does individual outreach, which can be standardized and supplemented with guidance from the national ALS Association office. One of the things that people really like about the Registry is the opportunity to contribute to the specimen Biorepository, so they have been able to collect specimens at some of these walks. Collaboration with the walk team generated three action items, which are to: 1) bolster table presence and repetition of Registry benefits; 2) familiarize staff with the most popular Registry documents; and 3) routinely discuss the Registry in regular webinars for chapter events staff. ATSDR would like to increase Biorepository collections at chapter events other than walks as well. ALS Association staff have functioned as a liaison between chapters and the CDC to determine the best place and time for collection, figure out materials needed for collection from the chapter and CDC, and walk chapter executives through the process and answer questions.

In terms of social media, the ALS Association has a video promotional campaign that was developed by its staff during the 2018 National ALS Conference. They are in the planning phase of developing a promotional campaign that includes social media, targeted emails to chapters, and advertisements on social media platforms. In addition, they have talked a lot about the Registry during some large ALS Association meetings. During the March 2019 National ALS conference, they updated over 35 chapter executives on current and future Registry initiatives and charted a possible path forward for working with clinic staff to increase the effectiveness of Registry promotion. During the June 2019 conference, a scholarship fund allowed some PALS to attend for the first time and CDC performed Biorepository sample collection and had two display booths.

Discussion Points

Dr. Mehta praised the video as being excellent and powerful from the patient perspective, and noted that ATSDR has a link to the video on its website. In terms of the suggestion about practice modules, ATSDR could create 40 unique user IDs and passwords for the 40 ALS Association chapters so that they can go into the surveys to see all of the questions and play around with them. This way, ATSDR will know where these are coming from so it can be sequestered later and not counted as an actual case.

Dr. Thakur thought this was a great idea that perhaps they could try as a first step. He clarified that it was the clinic staff who made the suggestion. There are more clinics than chapters and have turnover and more than one person working on this issue. If MDA would like the same ability, the numbers will likely be a few hundred and may not be feasible.

Ms. Hernandez indicated that this would be of interest to MDA as well to have mock sign-in IDs and passwords, and it would be beneficial to share the webinar that their staff participated in. This granular information would be good to share with MDA staff and the people who work in their clinics. It would have to be in an easily digestible, perhaps shortened version.

Dr. Mehta indicated that he would talk to ATSDR's communication team to determine whether there is a way to create something of this nature.

Muscular Dystrophy Association

Brittany Hernandez
Senior Director of Policy & Advocacy
Muscular Dystrophy Association

Ms. Hernandez gave an update on MDA's work as a partner with ATSDR on promotion of the Registry. She explained that MDA is an umbrella organization that covers 43 neuromuscular diseases (NMDs), one of which is ALS. They offer a number of support services to the community, in addition to the research that they fund. They have a network of over 150 Care Centers across the country that provide care to people with NMDs, fund a robust research grant program, have an Advocacy Department, provide support to families in a variety of ways, have a resource center where individuals with any of the conditions under the MDA umbrella can go to inquire about information that either MDA offers and/or can point them in the direction of other organizations or resources, and recently launched a new Medical Education Department. MDA has been in existence for over 65 years. From the beginning of the inception of the organization, MDA has been working on research for ALS. As noted, there are currently 150 Care Centers delivering care to patients with all of the conditions under MDA's umbrella. Of those, 48 are MDA/ALS Care Centers. MDA has contributed over $160 million to ALS research over time, with over $20 million in funding allocation to ALS research grants.

MDA's promotion of the National ALS Registry is a complicated and vast effort. Over the last year, MDA has increased its social media promotion of the Registry substantially. They make regular postings on the national site, including a lot of postings during ALS Awareness Month. MDA's local offices also regularly post about the Registry to share information. They are gathering metrics from these and sharing them back with ATSDR so that they can see the amount of impact MDA is having via its social media networks. In addition to social media, MDA has online and print publications with *Quest Magazine* that is published quarterly. They often have full-page advertisements in *Quest Magazine* that are dedicated to promotion of the Registry. *Quest Magazine* has tens of thousands of subscribers who receive the magazine by mail. They host a number of community gatherings and events. The new MDA Engage program is one of these, and they recently had an MDA Engage event in Boston focused on ALS during which they hosted about 80 patients and family members. This was a great opportunity for people to get together to share information with each other and for MDA to share information about the Registry.

MDA dedicated a booth to the Registry at their recent scientific and clinical conference in April, and were pleased to host ATSDR staff to share information. The MDA conference is geared toward clinicians and researchers, so it is not a patient-centered conference. However, being able to provide to the people delivering the care to the patients and clinics is very important and is a good complement to what MDA's partners across other organizations do to promote their conferences focused on patients. There is a blog on the MDA website called "Strongly Blog." A number of advocates with ALS have written blog posts for that calling attention to the Registry. MDA is always happy to promote people in their community and their experiences. There are links on the MDA website to the Registry, and MDA is undergoing an effort to overhaul a lot of the information on its site to ensure that this is more prominently featured on the top line ALS page on its website. MDA continues to be involved in distribution of materials during clinic hours. Printed materials from MDA and ATSDR are included in MDA's Newly Diagnosed Binder Toolkit that are given to new patients. MDA has information about ALS in its own materials, and shares the information with patients on an ongoing basis after their first visit with Clinic Care Specialists.

Direct communication with MDA staff is an ongoing effort. MDA's Clinical Care Specialists are generally working with patients for a few years at a time, so they do have a lot of turnover in that space. Thus, the ongoing education of people who are coming into MDA to ensure that they are aware of the Registry and the most appropriate way to message it to patients is a high priority. MDA also is working to summarize the outcome of its efforts, including its work on the under-enrolled states. In addition to routine outreach conducted across the country, MDA implemented a targeted strategy from July through December 2018 aimed at increasing National ALS Registry enrollment in areas identified by ATSDR as being under-represented (Hawaii, Mississippi, New York, Utah, West Virginia, and Wyoming). There have been numerous national and local outreach efforts.

Outreach strategies by local MDA personnel include two or more of the following:

- ❑ Engaging in outreach calls to individuals with ALS in under-enrolled health districts who are registered with MDA
- ❑ Posting monthly pre-approved announcements on Facebook pages of appropriate MDA District office(s)
- ❑ Discussing the National ALS Registry during one or more local MDA support group meetings, educational events, or community gatherings
- ❑ Meeting with Care Center team members or Care Affiliates regarding under-enrolled status and strategies for sharing information about the National ALS Registry during ALS visits
- ❑ Inviting families living with ALS to attend the National MDA Engage ALS Educational Symposia in May 2019 in Boston, Massachusetts

In addition to routine ALS Registry outreach conducted by MDA's National office team, support for efforts aimed at improving participation in under-enrolled health districts includes the following:

- ❑ Providing scripts for outreach calls from MDA staff to ALS families
- ❑ Providing approved posts for social media outreach on local MDA Facebook pages
- ❑ Having Regional Directors of Care and Clinical Services phoning Care Center directors in under-enrolled health districts to discuss ALS Registry
- ❑ Exhibiting the National ALS Registry at MDA's 2019 Clinical Conference in April 2019
- ❑ Inviting families living with ALS to attend the National MDA Engage ALS Educational Symposia in May 2019 in Boston, Massachusetts

MDA has recently undertaken a new effort to ensure that all of its staff are officially and adequately trained on the National ALS Registry. They are working to develop an internal training module for existing MDA staff so that everyone on the Innovations in Care Team, the team that oversees all of the MDA's clinical networks, is aware of how the Registry works, why it is important, and the top line priorities of MDA's contract with ATSDR. MDA promoted the first ATSDR webinar to its staff and are discussing making participation on these webinars a requirement, either live or by reviewing the recordings. MDA also is undertaking an overhaul of its onboarding training sessions for new MDA staff in the Innovations in Care Team, and this will be part of that.

Discussion Points

Ms. Cory inquired as to how the module used for training is delivered (e.g., handout, in-person, et cetera).

Ms. Hernandez indicated that MDA has an onboarding module for new staff that includes a number of webinars staff view, so it will be part of that. They also are developing an internal webinar training module that they will share with any staff who either come into contact with patients or oversee them. It is a major undertaking to develop a training program, so this is a long-term project for MDA. Nevertheless, they do have a very clear goal of getting this done as soon as possible.

Dr. Horton asked whether MDA has summarized and/or published the data from the MOVR Data Hub™ and how many ALS patients are enrolled.

Ms. Hernandez replied that they have not, because the MOVR Data Hub™ was launched in about the last year or so and is not fully rolled out in all of the MDA clinics yet. Because they are still in the launch mode, they do not yet have any data to share or a number of patients enrolled. Once they can, this is something they will be happy to share.

Les Turner ALS Foundation

Lauren Webb, LCSW
Director of Support Services and Education
Les Turner ALS Foundation

Ms. Webb expressed gratitude to individuals joining the meeting via webcast and those in the room, recognizing that they were the primary reason for this work. The Les Turner ALS Foundation is the leader in comprehensive ALS care in the Chicagoland area, with a focus on individualized support through local community support and scientific research. Their teams are in homes every 6 to 10 weeks engaging with families directly, with multiple points of conversation about the Registry. The Les Turner ALS Foundation's mission is to provide the most comprehensive care and support to people living with ALS and their families in Chicagoland so that they can confidently navigate the disease and advance scientific research for the prevention, treatment, and cure of ALS. Over the last 42 years, they have raised $73 million. About 84¢ of every $1 is spent on direct services.

The Les Turner ALS Foundation engages in comprehensive efforts with several organizations throughout the Chicagoland area, including the ALS Association, MDA, VA, home health agencies, hospices, community organizations, and the Les Turner ALS Center at Northwestern. They also help families confidently navigate insurance, financial options and grant programs. In terms of creating a local community of support, the Les Turner ALS Foundation has 31 clinicians at its multidisciplinary ALS center. There is a focus of promoting the Registry with the clinicians and engaging with them so that they understand the goals of the Registry. Last year, they served 233 PALS . They conducted 1670 home visits in the last year, during which nurses and social workers took the opportunity to engage with individuals with ALS and their families to help identify their challenges and creatively problem-solve. The Foundation Support Services Team use home visits as an opportunity to talk with individuals living with ALS about how the Registry can help them. This is all driven by patient needs and concerns. They also promote the Registry in 5 support groups in the Chicagoland area.

In terms of support services, the Les Turner ALS Foundation provides a personalized approach to treatment and care to prepare people living with ALS to navigate their difficult journey and supporting them each step of the way. They provide assistance with home and community services, augmentative communications services, equipment, respite, transportation grants, and support group meetings. Some of the National ALS Registry/Biorepository promotional efforts in the Chicagoland area have included the following:

- ❑ Home and clinic visits
- ❑ Support groups
- ❑ National ALS Registry Associate
- ❑ Print newsletters
- ❑ E-news and website
- ❑ Annual Education Meeting
- ❑ Education for Medical Professionals
- ❑ Abilities Expo, with over 4000 attendees, which offered a nice opportunity to talk with families and the overall community and discuss the registry
- ❑ Annual Research Symposium on ALS and NeuroRepair
- ❑ Community education and expos
- ❑ Social media: Facebook, Twitter, and LinkedIn

The Les Turner ALS Foundation has a dedicated National ALS Registry Associate who works in the clinic, Cara Gallagher. Ms. Gallagher enrolls people living with ALS at the clinic, in their homes, or on the phone. People living with ALS report significant ease of enrollment with personal assistance. She may begin the initial process during a clinic visit, but clinic visits can be somewhat overwhelming, so this is done in the home the majority of the time. The number of Registry discussions with people living with ALS increased 8% FY 2018 over 2017. This is somewhat of a decrease, given that Cara has engaged with most people living with ALS in their clinic in prior years. They estimate that about 85% of the individuals they serve are enrolled in the Registry, which they know because they engage with families in various settings.

They promote the Registry in the Les Turner ALS Foundation eNewsletter that is distributed to 45,000 constituents in the Chicagoland area and other parts of the country. The National ALS Registry is featured prominently on the Les Turner ALS Foundation website, and they use a variety of tools in their social media promotion efforts. Ms. Webb noted how amazing the transformation in the development of materials has been over the years. Having these materials makes everyone's jobs easier. Last year, over 400 individuals participated via web stream in the Les Turner Symposium on ALS and NeuroRepair Promotion. Of the participants, 200 were from the Chicagoland area and this symposium was very well-received. The board knows about the Registry and is actively engaged in the Les Turner Foundation work. The ALS Walk for Life is one of the largest ALS walks in the country, which ATSDR always attends. Approximately 6,000 to 7,000 individuals attend the walk, and there is a research tent where the work that takes place at Northwestern Medicine is promoted. This helps to make research accessible and drive conversations.

The Les Turner ALS Center at Northwestern Medicine hosted its annual ALS Clinical Conference for Medical Professionals in September 2018. This conference was geared toward medical providers in the Chicagoland area. The conference is a collaboration with Northwestern's Community Education Department, which is critical to reaching other provider communities that are not necessarily connected with the various multidisciplinary clinics across the Chicagoland area. Something unique to the Les Turner ALS Foundation is that they engage in community education specifically for providers in hospices, churches, community neurologists, home health agencies, et cetera to help raise awareness about ALS and the Registry. The overall purposes is to help people with ALS have better access to informed individuals in their community.

One of the key take home messages is the importance of continuing to engage with the community about why the Registry matters. It is critical for individuals to tell their story through participation in the Registry. Part of telling the story is by opening up the conversation in a very approachable way. One of the lessons that they have learned is that they should not assume that someone is overwhelmed. The Registry should be offered as an opportunity to engage with research. Providing care is co-produced with people living with ALS, their loved ones, caregivers, and providers. The Registry is an important part of providing patient-centered care and research. Having these tools to confidently navigate the various ways to participate in research is very important. Their key focus will be to continue to work with their key partners locally, MDA and the ALS Association, because the Les Turner ALS Foundation supports only one clinic in the Chicagoland area. They have solid saturation with engagement of their families with whom they work directly, but they need to widen support in their specific area. She concluded by thanking the families with whom they work every day, as they help to drive the research, push everyone to ask important questions, and engage in and support meaningful efforts.

Discussion Points

Dr. Horton inquired as to whether they have any insight as to why the other 15% of their patients are not enrolled in the Registry.

Ms. Webb acknowledged that they have to figure this out. She just had a lovely conversation with a woman who is in public health whose mother's disease happened so rapidly that they had started to register, but her progression was too fast to finish. She thinks she needs to ask this 15% of patients and their families what the barriers are for them instead of assuming. Perhaps there is something obvious that has not been addressed.

Dr. Mehta recognized that the Les Turner ALS Foundation model works very well in the Chicagoland area in that it is a very interactive and personal model of talking to patients to inform and educate them. He wished this could be translated in other parts of the country. Taking a concierge approach by having a National ALS Registry Associate seems to be key. He acknowledged that resources are limited and praised the excellent work they have done with what they have.

Ms. Webb said they are really proud of this and that she thinks this model of having a National ALS Registry Associate can be incorporated in specific ways with having a point person at each clinic. This does not necessarily have to be the clinician. The idea is to have someone to engage with patients to start that conversation.

Regarding the 8% increase in Registry discussions mentioned, Mr. Tessaro asked whether they have a metric on the number of patients who registered as a result of that increase.

Ms. Webb indicated that they had a huge spike in registration when Cara was initially hired, which has since decreased because of their multiple points of engagement with families and their high level of penetration. Now that this has leveled off, they are shifting the focus to addressing the 15% who have not yet registered and helping to promote completion of the risk factor surveys. They also will further consider how to engage families who want to participate in the Biorepository who were not initially consented. They will continue to increase total enrollment by working with their partners in the Chicagoland area.

Mr. Tessaro asked if Ms. Webb were to move to another organization she would do so with a shining light to hire a National ALS Registry Associate there as well.

Ms. Webb indicated that she moved from MDA to the Les Turner ALS Foundation. She recognized that one important MDA effort is the great work that Ms. Hernandez is doing with their team to implement training pieces and to focus on dedication. Having a point person is of tremendous benefit. It takes the burden off of the multidisciplinary team when partners are utilized in the appropriate way. She does think the shining light is to help guide families in a personal way and truly engaging them.

Regarding branding ALS, Dr. Mitsumoto emphasized that this country is so big. He has been working in ALS since the early 1980s. He had a harder time working with the ALS Association initially 10 to 20 years ago. Then he moved to MDA because Columbia has MDA centers. The ALS Association and MDA are quite competitive. Competition makes everything better in this country, but sometimes working together is important. He went to some national conferences that were initially funded only by MDA, but then attended some funded by both institutions. The Les Turner ALS Foundation does a fantastic job, and now the ALS Association and MDA are working so closely together working together on this effort for one major purpose—the ALS Registry. Ms. Hernandez mentioned inviting the ALS Association to go to MDA to be educated. This took several years, but now they are working so closely. He commended Drs. Horton and Mehta for everything they do for the national patient-level Registry and support with all of these organizations working together. This country is so vast, but now there are approximately 50 ALS Association Clinics and 50 MDA clinics and they are doing a good job.

End of the Day Wrap-up / Questions / Open Discussion

Cherie Imam, Facilitator
Carter Consulting, Inc.

Before closing out the first day, Ms. Imam opened the floor for final questions, comments, and discussion.

Discussion Points

Ms. Backman recalled that an issue was raised earlier in the day in response to the presentations by Dr. Kaye and Ms. Wagner on the Biorepository pertaining to confusion due to the number of biorepositories. She wondered what next steps they could take to ensure that all of the biorepositories could all be accessed on a similar basis.

Dr. Mehta responded that one of the ways ATSDR is working with other groups such as NEALS is by using the GUID system. When patients register with ATSDR, they are provided with a GUID. This offers a way to collaborate with NEALS. NIH has their own GUID, so ATSDR also generates a second GUID for each patient who registers. The Clinical Research in ALS and Related Disorders for Therapeutic Development (CReATe) uses the NIH GUID. Provision of these unique identifiers allows them to track patients from one study to another. ATSDR's samples are available to anyone who wants to request them for scientifically meritorious reasons. ATSDR is not in competition with anyone, but sometimes there is a perception with researchers about not sharing samples unless there is something in it for those who possess the samples. That must change, especially with ALS being the rare disease it is. There needs to be more cross-collaboration among biorepositories. ATSDR is like Switzerland in that they will collaborate with almost anybody. Sometimes people do not want to collaborate with ATSDR for a variety of reasons, including because they are the government.

Dr. Bowser agreed that there are a lot of opportunities for sharing samples. The challenge is that sometimes the types of information that has been collected and are linked to the samples are often different. Researchers may be looking for certain types of datasets or clinical information that are linked to clinical samples that may be available in only one or another biorepository. In terms of biofluids, most of the ALS repositories use the same standard operating procedures (SOPs). That is good because at least all of the samples are collected, processed, and stored essentially the same way across the various biorepositories. The issue he raised earlier related more to the postmortem samples. Target ALS is generating the WGS and RNA sequencing from the tissues and then making that publicly available immediately online. Because that information is so readily available and people are looking at it, the number of sample requests are enormous. It would be great to partner with other biorepositories that already exist if they generated the same type of information. That would allow scientists to look across perhaps 3 to 4 repositories for samples that have the same genetic or RNA information. That type of information would allow for even greater utility of all samples across all repositories. As someone who has been collecting samples for a very long time, he does not want to leave them in his freezer forever. He would rather give them out for people to use, and he thought everyone in this business is probably of the same mindset. Obviously, there has to be a scientific rationale for wanting the samples. But if so, he certainly is not going to tell someone something is not going to work. They should do the experiments to find out.

Dr. Gubitz agreed with that point. In her view, the various repositories are in a collaborative not competitive mode. All of the samples are finite, so they realize that more samples are a good thing. NIH has tried to promote the concept of data harmonization so that samples and associated clinical data are comparable. They have common data elements for ALS, although not everybody is adopting them. However, they have engaged in calls with NEALS to compare and take notes. She thinks things are very manageable in the ALS space, but that what is perhaps missing is one website that lists all of the repositories. That is difficult for NIH to do because they could not share all of the information of the non-profits, but perhaps this would be a useful service to the scientific community. She does refer people to the other biorepositories if they do not have what someone is looking for. Everyone has been extremely collaborative and it has been very positive. For example, she has been able to hook people from Northwestern up with samples. Nevertheless, more can be done.

Dr. Mehta indicated that ATSDR also is doing WGS on the National ALS Biorepository as well with Dr. Traynor's laboratory in the upcoming fiscal year. Hopefully, this will continue successfully throughout the coming years. These data also will be available for researchers.

Ms. Webb appreciated the conversation they were having, because when they are having discussions with families about end-of-life care and what their wishes are, it is very important to present them with options and choices. Some families want to give back in that way as part of their plans. Continuing to offer families choices along the way and informing them about the process would be really helpful. She expressed gratitude for the families who have contributed in that way.

Ms. Hernandez suggested that perhaps it would be beneficial to develop a publication with information about each of the various biorepositories. For people who want to take part in this, it is important to make it as easy and non-confusing as possible.

Dr. Mitsumoto suggested that perhaps a conference could be convened for those who have biorepositories to discuss these issues amongst themselves. For example, they could discuss how Dr. Bowser could distribute his samples rather than having them just sit in his freezer. Based on the conversation, it seemed that this could be very helpful.

Ms. Lefkowitz clarified that the materials Brunet-García is creating is to show that there are differences between registries and organizations. The way they are positioning the National ALS Biorepository is that it is a component of the National ALS Registry and by enrolling in the ALS National Registry, patients will then have the opportunity to donate to the Biorepository. They are trying to explain that when someone joins the ALS Association, for example, it is joining an organization not a registry. However, there are places members can go to join places like the National ALS Registry.

Dr. Kaye pointed out that the National ALS Biorepository postmortem specimens are collected the same way as the VA and the same neuropathologist is processing them. The ATSDR and VA collections live in the same freezers, which makes it easier for people who need samples to obtain a lot that would be equivalent. The VA has many more samples because they have been doing this so long, but they all have been handled the same way and have the same neuropathology report.

Dr. Agnese noted that they would be hearing a presentation the next day on the REFINE-ALS study, which is Mitsubishi's edaravone biomarkers study. Over the past two years, they did their due diligence looking at all of the different biorepositories, including very early discussions with Dr. Kaye. It was a tedious but very fruitful learning that came out of that meeting with each of the biobanks to understand truly the pros and cons of each. For example, some of the biobanks have more longitudinal data that might be needed for certain assessments. From an industry perspective, they felt very lucky that there is a variety of options. However, it took a lot of effort to fully understand and appreciate what is sitting in each of the biobanks and everyone was very receptive to the collaboration with industry. They look forward to collaborations moving forward. Having a basic understanding of where to start would be very helpful, and industry would be very supportive of this.

To close the loop, Ms. Backman suggested that two areas of navigation are needed. The first pertained to where to point researchers seeking data and samples, and if there is a portal, to place that on everyone's website that can be shared or linked in some way. The second audience for whom they need to navigate is the patient population. It sounded like Mitsubishi Pharma was taking care of that, but found it to be a fairly heavy lift. Perhaps one goal should be focused on how to find navigation efforts for researchers and patients to obtain the information that they need.

July 24, 2019

Update from Pharma

Biogen

Sunny Cho, PharmD
Associate Medical Director
Global Medical Neuromuscular Disease
Biogen

Dr. Cho expressed her gratitude for the opportunity to present Biogen's product portfolio in ALS. She noted that over 50 randomized clinical trials have failed to demonstrate efficacy including their own EMPOWER Phase III study with dexpramipexole. Biogen re-evaluated its approach to its ALS development program. What they learned with dexpramipexole was that despite no clear mechanistic rationale, early studies demonstrated some encouraging results. While the Phase III study failed to meet the prespecified efficacy, this provided an opportunity to examine the rich datasets that were generated from the EMPOWER study with over 800 patients. Key learnings from EMPOWER and previous ALS studies led to evaluating genetically validated targets in defined patient populations, pursuing the most appropriate modality for each target, implementing biomarkers of target engagement and disease activity in early-stage studies, and employing sensitive clinical endpoints.

They are now focusing on evaluating genetically validated targets in defined patient populations, including: 1) mutations in superoxide dismutase 1 (SOD1), the first identified genetic cause of ALS and the most advanced clinical program that Biogen has; and 2) expansions in C9orf72, the most common genetic cause of ALS. The aim is to apply learnings from these genetic targets in order to target sporadic ALS and pursue complementary approaches for muscle strengthening. Biogen currently has a broad pipeline in ALS reflected in the following table:

SOD1 ALS	BIIB067 (SOD1 ASO) Phase III
C9ORF72 ALS	BIIB078 (C9orf72 ASO); Phase I Dipeptide repeat-targeting approaches; Preclinical
SPORADIC ALS	BIIB100 (XPO1 inhibitor); Phase I Additional preclinical programs
MUSCLE STRENGTHENING	BIIB110 (ActRIIA/B ligand trap); Phase I

During this session, Dr. Cho focused on Biogen's products that are in Phase I and Phase III development. Tofersen is an antisense oligonucleotide (ASO) targeting SOD1 mRNA. Tofersen mediates the RNase H-dependent destruction of SOD1 mRNA to reduce SOD1 protein levels. The hypothesis is that if the SOD1 protein levels are reduced, this may slow disease progression. In order to evaluate this hypothesis, Biogen conducted a Phase I multiple ascending dose (MAD) study. These results were presented by Dr. Timothy Miller at American Academy of Neurology (AAN) in May 2019. The objective of this study was to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and exploratory efficacy endpoints of tofersen in people with SOD1-ALS. The study population included individuals 18 years of age and older with a documented SOD1 mutation, weakness attributed to ALS, and forced vital capacity (FVC) ≥ 50% of the predicted value. A total of 50 participants were randomized 3:1 to tofersen 20, 40, 60 or 100 mg or placebo. The primary endpoints were safety, tolerability, and PK measures of tofersen in plasma and CSF. The secondary endpoints were CSF levels of SOD1 protein to ensure that there was target engagement. Some exploratory endpoints also were assessed including ALSFRS-R scores, slow vital capacity (SVC), hand-held dynamometry (HHD) megascore, and CSF levels of phosphorylated neurofilament heavy subunit (pNfH). A total of 5 doses of study treatment was administered intrathecally, and the total study dosing period was 12 weeks.

Overall, tofersen was well-tolerated for all of the doses up to and including the 100 mg dose. There were 3 deaths during the study, one of which occurred in the 20 mg group due to a pulmonary embolism, 1 in the 60 mg group, and 1 in the placebo group due to respiratory failure. However, all were considered by the investigators to be secondary to ALS or comorbidities and not drug-related. Most of the adverse events (AEs) were mild to moderate in severity, and the most common AEs were headache, procedural pain, and post-lumbar puncture syndrome (PLPS). In terms of the PK and PD results, the plasma concentrations were dose proportional. CSF tofersen exposure levels were less than dose proportional. CSF SOD1 concentrations were substantially reduced at the higher 100 mg tofersen dose. The maximal reduction of SOD1 CSF levels occurred at Day 85 with a 37% reduction in the tofersen 100 mg group compared to no reduction in the placebo group, with a p-value of 0.002. The exploratory efficacy endpoints were evaluated with the 100 mg dose, which showed a slowing of decline across clinical measures as assessed by ALSFRS-R, SVC, and HHD megascore.

It is known that disease progression among patients with SOD1 ALS can vary, so a post-hoc analysis was done to assess faster-progressing patients. The fast progressors were identified by their genetic mutations or the slope of decline based on their baseline ALSFRS-R measures. Overall, the trends between the patients who were fast progressors and the overall population were similar for all of the clinical measures. There was a greater decline in the placebo group for those patients identified as fast progressors compared to the overall placebo group.

In summary, administration of multiple doses of tofersen was generally well-tolerated at doses up to and including 100 mg. Plasma concentrations of tofersen were dose-proportional. CSF concentrations showed a less than dose proportional response. A statistically significant reduction in CSF SOD1 concentration was observed in the tofersen 100 mg group (37% reduction) as compared to placebo (no reduction). Interim exploratory analyses show a slowing of decline in functional, respiratory, and strength measures. Differentiation from placebo was most apparent in participants with fast-progressing disease. This first report of tofersen in participants with SOD1-ALS supports its continued development. A Phase III study with tofersen has been initiated called VALOR, which is currently enrolling patients with SOD1 mutations who demonstrated weakness attributable to ALS. The treatment duration for VALOR will be 6 months.

It is known that hexanucleotide repeat expansions in C9orf72 are the most common genetic cause of ALS. Biogen is looking at two potential targets. The first is with an ASO that will try to reduce the production of toxic repeat RNA. The second approach will be more targeted to the dipeptide repeat proteins themselves. The lead investigational candidate in C9orf72 ALS is BIIB078, which selectively targets the expansion-containing C9orf72 transcripts with the hope of reducing the risk of on-target toxicity. A Phase I MAD study is currently ongoing in patients with confirmed expansion of C9orf72. There are 6 BIIB078 dose cohorts, and the primary endpoint will be safety and tolerability. Treatment will be administered by intrathecal injection of either BIIB078 or placebo, with 3 loading doses followed by 2 maintenance doses. Patients will be followed for approximately 8 months.

Biogen is applying some of their learnings from genetic ALS to examine sporadic ALS. It is known that the accumulation of cytoplasmic inclusions in motor neurons is a pathological hallmark of ALS, which is hypothesized to be caused by deficits in nucleocytoplasmic transport. BIIB100 is a selective inhibitor of exportin 1 (Xpo1).Xpo1 is a nuclear transport factor that mediates the nuclear export of many proteins containing nuclear export signals. The hypothesis is that Xpo1 inhibition may reduce nuclear protein export and prevent the formation of neuronal cytoplasmic inclusions like TDP-43 and fused in sarcoma (FUS). A Phase I study with BIIB100 in sporadic ALS is ongoing.

Next, they will assess a potential complementary therapy for muscle strengthening with BIIB110. Myostatin signaling is a validated target for muscle strengthening. Myostatin is a loss-of-function mutation that is associated with muscle hypertrophy. BIIB110 acts as a ligand trap to bind and inhibit signaling of both myostatin and activin, while sparing BMP9. Sparing of BMP9 is hypothesized to reduce off-target toxicity previously observed with other myostatin inhibitors. BIIB100 is currently being studied in a Phase 1a study in healthy volunteers. The initial development will be in in spinal muscular atrophy (SMA) with an aim to expand into other neuromuscular disorders, including ALS.

In conclusion, Biogen is building a neuromuscular disease franchise focusing on targets with validation from human genetics and pathology. Following their failure with dexpramipexole, they have focused on monogenic disease like SMA with SPINRAZA® and SOD1-ALS with tofersen. The aim is to take a rational and systematic approach to sporadic ALS.

Discussion Points

Dr. Mehta indicated that ATSDR helped to recruit for Dr. Timothy Miller's study called "Determining the Half-Life of SOD1 in CSF." He did not recall tofersen being mentioned in his application, but he was thinking that might have been a linked study and endpoint. Dr. Cho said that would be a separate study from the phase l MAD study presented and that she was not aware of the half-life study.

In terms of the 37% reduction in the tofersen 100 mg group, Mr. Tessaro pointed out that everyone in the room works on very incremental changes and are happy for those. However, that seemed like a remarkably large number. He inquired as to whether she could say more about what they read into that 37% improvement.

Dr. Cho indicated that the 37% reduction is the reduction of SOD1 protein levels and a Phase III study of tofersen is ongoing to assess the efficacy and safety of tofersen. The efficacy assessment in the Phase l MAD study was an exploratory analysis.

Persons Living with ALS Perspective on the Registry

Alan Alderman

Mr. Alderman said that he has been at this a long time. It has been 18 years since his diagnosis in 2001. He would like to be able to say that because of what they have done, he is still alive. He expressed his gratitude to everyone in the room—the clinicians, researchers, ALS scientists, patients, analysts, and the people at ATSDR. He thanked them all for all that they do and emphasized how grateful he is. Seeing and watching people who have had a hand in their lives and in working to find a cure for ALS is keeping him alive. The Registry is one of the most important tools they have, which he tells patients in Utah all of the time. Even with all of the preaching he does, he has no idea why Utah is still a Tier 3 state. He does believe that the Registry is very important. He thanked Dr. Horton, Dr. Mehta, and everyone involved with the Registry. He encouraged everyone to continue working together, collaborating, and helping those living with the disease. In closing he said, "Keep up the good work and together we will find a cure!"

Madeline Kennedy

Mrs. Kennedy said that she was very happy to have the opportunity to be present, and that she now has a much broader view of the Registry and its collaboration with many communities in her ALS world. It is important that those who live with this terrible disease 24/7 be heard in such a critical endeavor. She realized that three of the participants in the room have ALS, and that she felt a significant responsibility to speak for the many PALS who were not there. When she accepted this invitation, she reached out to the ALS patient community for comments—good, bad, experiences, recommendations. Requests for input went to Facebook, NEALS ALS Research Ambassadors, and 5 active support groups in Florida and New York. She reached out to fellow PALS and conferred with as many as she could personally. She said that her comments would be based on those inputs, and she will respond back to all who took the time to reach out to her.

She has read the 2016, 2017, and 2018 annual reports—the Executive Summaries at least. The community hoped that some details of data crunching of ALS patient histories, environmental exposures, and occupational stories would lead research in new directions to effective interventions. Much of the concerns communicated to her regarding the registry had been discussed in detail during this meeting already. She understands the limitations of log-ins; time required for survey participation; and confusion over the Registry versus signing up with the ALS Association, MDA, and other repositories. She believes that much of the frustration she hears from the ALS community is exacerbated by the perceived slow pace of progress. The reporting of the final scrub of 2015 data in 2018 may be routine in the scientific community, but it is the remaining lifetime for many ALS patients.

The primary goals of the Registry have been well-documented. She could think of nothing more essential than the incidence and prevalence determinations. She noted that she certainly does not have the extensive reach of the CMS, Social Security, and VA data. Yet, she has met many PALS on her journey who have continued to work who are not Veterans and/or who are not over 65 years of age. She is concerned that the acceptance that 60% or more of ALS cases will be found in those government databases may blind them to the true ALS population in the US. She applauded the new ability to access the Medicare C and is anxious to see what it contributes to

the big picture. She expressed hope that the capture-recapture data will result in better projections. It should be reviewed critically.

At this point, with 9 years and $90 million invested, she had hoped for better results. She is excited by the emphasis on outreach to the under-represented communities' PALS. The urban studies and ethnic outreach may require changes in some assumptions and estimates as to where PALS are and how many there are. The financial pie charts are visually effective and Mrs. Kennedy is confident that they are accurate. However, for a $10 million annual enterprise, they do not go very far into the weeds. Are resources being allocated effectively in the direction to best meet the goals? Are they focused on previous assumptions at the expense of flexibility and agility to adjust to new findings? Can they do better?

The number of organizations providing a biorepository of PALS' tissues, not post-mortem, increases each year. Some of the research entities are utilizing PALS' tissues and serum to support their efforts in research. Is there room for more efficiency and less duplication of efforts? She has concerns regarding the Registry's entry into clinical trials outreach to PALS. Clinicaltrials.gov and the NEALS site certainly have a lot more in this arena. In retrospect, the match-up of a particular trial to a potential patient can be done more efficiently by the profile in the Registry. This could save much patient time and frustration in reviewing many trials where he or she fails to meet the inclusion criteria. Great potential. The Registry is the only one that has all of that data.

Mrs. Kennedy remembered back to her diagnosis and reviewing the accepted facts that there is a 90% death rate in 2 to 5 years. Indeed, most of her fellow patients she met in the beginning are no longer here. She is approaching 8 years since her symptoms and 7.5 years since her official diagnoses. She now understands the mean survival rate from symptom onset to be over 4 years. She wondered how many of them are out there. The previous day there was a comment about tracking the deaths and where people are at that point. She thought about that overnight and was not sure that it was valid to track. Certainly, that they are dead is important. However, she thinks that what is more important is where they lived, especially around the time of the diagnosis. She has a friend who lived about 3 blocks from her when they both were diagnosed. Mrs. Kennedy spent 90% of her life in Upstate New York. Her doctor is in Massachusetts. Currently, she is a resident of Florida where she will die. Her friend who lived so close to her at the time of diagnosis will die in Colorado. However, she did not think that where they will die is nearly as important as the fact that they both lived so close together when diagnosed.

In closing, Mrs. Kennedy stressed that the Registry is the best hope for the most comprehensive endeavor in determining the number of patients living with this disease in the US. The good news is that there are good people trying to do what is right and working to make a difference. She thanked Dr. Horton, Dr. Mehta, and everyone working on behalf of PALS and expressed how honored she was to be a part of this meeting.

Ed Tessaro

Mr. Tessaro said that his thoughts fell into three categories: 1) gratitude; 2) the sense of collaboration, sharing, and open data so many spent time on the previous day; and 3) the group of people that he thinks are doing remarkable work and are deserving of a little exposure. First, gratitude. The psychology of disability obviously is pretty complex. Adding fatal disease with no cure into that, it is clearly an animal of its own type. He is amazed after so long with this disease

with the benefit he receives from the kindness that is innate in all of us. It is not necessary to read too much news to know that kindness is not innate in the great swath of human nature. In his perspective oddly, because nobody would choose it, he sees people at their best every day. He receives from perfect strangers what could be called in a stretch "love" or at least "compassion" for what they sense they have that he does not. It might be a 10-year old breaking loose from her mother's hand to open a door for him. That has been one of the great benefits and strength issues that he gets from the disease. The version of gratitude that had to do with this day, which Madeline Kennedy said very well, was what everybody does in this conference. He expressed appreciation for Dr. Horton, Dr. Mehta, and everyone else for putting on this conference for so long. He emphasized how much he really appreciates the people who have dedicated their lives to something that is not curable. This tells him something about their nature as doctors, researchers, and scientists that he is in awe of because in his career, nobody died unless somebody shot them. He said that he is so impressed that they bring some ability to talk to people like Alan, Madeline, and himself knowing that they are dying. But somehow, they come to work and get charged about trying to find something that is meaningful in the face of all of the bad news. He does not understand how they could be built that way. Dr. Jonathan Glass at Emory spends an average Friday talking to 4 families with second opinions, everybody collapses, and then Dr. Glass goes home to his family. How does he do that? How do each of you do that? Mr. Tessaro said he really does not know how he and each of the other doctors, researchers, and scientists do that. Thus, his gratitude is in general due to the way people react to disability and he stands in awe of the way that the people working on this bring such fresh mind, matter, and enthusiasm to their work. That is gratitude.

In terms of collaboration and sharing, there are so many silos, Mr. Tessaro does not think they are going to break down just by the platitudes they spoke of the previous day. He expressed his hope that Drs. Horton and Mehta could really drive the attempt to share and collaborate more. A student of human nature would know immediately that humans' nature is to be proprietary. Human beings are hard-wired to survive and self-interest is premium. This work is counter to that a little bit. Sharing data is hard and it is going to take real leadership. He cannot imagine how many people are doing the same thing, on the same samples, and on the same issues. Is it ever going to come together? At this point, that answer was not clear to him even though such good thoughts were offered the previous day on how they have to work together. While he did not know the answer, he stressed that somebody has to own that. He hopes it is the Registry. He recognized that it is hard since they do not have line authority. He was not suggesting that it is a light lift, but whoever can play that role would be very important to the science.

Last was an example of a group of people who do this better than anyone, Answer ALS. While Mr. Tessaro acknowledged that he is not a professional and that others may have 10 ideas better than his, Answer ALS was founded in 2014 after a Steve Gleason effort and now has 8 clinics. They have 27,000 samples of blood, serum, and CSF that are already publicly available. Their app gets anybody to anything. He had the privilege of honoring Ed Rapp and Peter Warlick who serve on the Answer ALS Board and are patients who, like Mr. Tessaro, have raised millions of dollars for this cause. They are really putting their money where their mouth is, or their disease is. Answer ALS looks like their whole purpose is to share what they do. Everything is open and he does not think it is just marketing. They are not just 1 of 50 organizations that are doing something. Answer ALS is only 5 years old. That is an example that he would love to make a project out of next year. Like any project in his long career, he posed these questions: What has been accomplished? How did it work there when it has not worked elsewhere? Who does it great? How do we model our own efforts after those who have been really successful? How do we get our self-interests out of the way? Of course, the hard part is the last question.

In closing, Mr. Tessaro said he would end where he started by emphasizing how much he appreciates and gains strength from everything that everyone brings to this effort and that it is a privilege to know them, listen to them, and go to bed at night knowing they are working so hard for PALS' selfish interests.

ATSDR Funded Research Update

Environmental Risk Factors for ALS: Critical Time Periods and Genetic Interactions

Walter Bradley, MD, DM, FRCP
Professor of Neurology and Chairman Emeritus
Department of Neurology
University of Miami

Dr. Bradley presented an update on the study titled, *Environmental Risk Factors for ALS: Critical Time Periods and Genetic Interactions*. He began by emphasizing that the three most important questions with regard to non-familial sporadic ALS are:

1. What are the environmental causes of the disease?
2. At what time points in one's life did the exposures occur?
3. What are the genetic factors that underlie the interactions of those exposures to cause the disease?

These questions form the topic of the grant that CDC provided for them that they are now 9 months into running. During this session, Dr. Bradley presented a 30,000 feet overview of that grant. Obviously at 9 months, they do not have any results other than a collection of the beginnings of the databases that they are starting to work on. However, he wanted to share some of the excitement that they have with this project. They feel that they are now at the stage where, at the end of the 3 study years, they hope that there will be the beginnings of the breakthroughs to understanding what causes the syndrome of ALS. They all now think that the syndrome of ALS is not just one disease, but that many different factors produce this disease manifestation and the individual interactions of what, in the end, they are going to have to approach with many different treatments they are going to need to design in partnership with pharma.

Many people have told them that their quest to find the critical epochs when exposure to environmental risk factors, such as smoking and cyanobacteria, carry the greatest risk for later development of ALS, and the genes with which these environmental factors interact to trigger motor neuronal degeneration leading to ALS is "tilting at windmills." That may be true. Nevertheless, this is what they have to do:

Many people say that "it takes a village." It certainly does take a village. This project is being conducted by a consortium of people who are clinicians, geneticists, geographical information specialists, geographers, limnologists, people who have collected databases of patients for decades, satellite remote sensing experts who are looking at cyanobacteria, and people who are looking at the sources of environmental pollutants. Dr. Bradley said he never thought he was going to learn anything about all of these specialties over the years, and he is still learning. He especially never thought he would learn anything about machine learning.

The specific aims of the study are to: 1) investigate the time periods when exposures to environmental risk factors carry the greatest risk for later development of ALS in Northern New England, Ohio, and the Piedmont Region of Italy; 2) investigate the time periods when exposures to cyanobacteria and to pesticides carry the greatest risk for later development of ALS in the US, with a timeframe of exposures over the last 30 years; and 3) identify genetic variants conferring susceptibility to lifestyle factors and residential exposures to cyanobacteria and to pesticides as ALS risk factors.

In terms of the first specific aim, for the three areas (Northern New England, Ohio, and the Piedmont Region of Italy) they have very large databases of patients that are available. In the Piedmont area, for about the last two decades Dr. Adriano Chio has been collecting extensive demographic information, exposure data, and biosamples on over 1000 patients with ALS and at least 1000 control individuals. Approximately 700 of those individuals so far have been genotyped by Dr. Brian Traynor at NIH. In Northern New England and Ohio, in collaboration with Drs. Erik Pioro and Elijah Stommel, they will have collected together about 750 ALS patients and about 550 random population control subjects with questionnaire data and biosample data for performing the analyses of the exposome and genomes with Dr. Traynor using the Genome-Wide Association Study (GWAS) NeuroChip. These are the databases that they have collected in Northern New England and Ohio and are beginning to collect now in Piedmont:

- Databases by end of project 2021
  - Geocoded sources of environmental toxins and toxicants
    - Environmental pollutants: landfills, National Priority List (NPL) sites, municipal incinerators
    - Pesticide applications
    - Air quality datasets
    - Cyanobacteria content of waterbodies >8 hectares

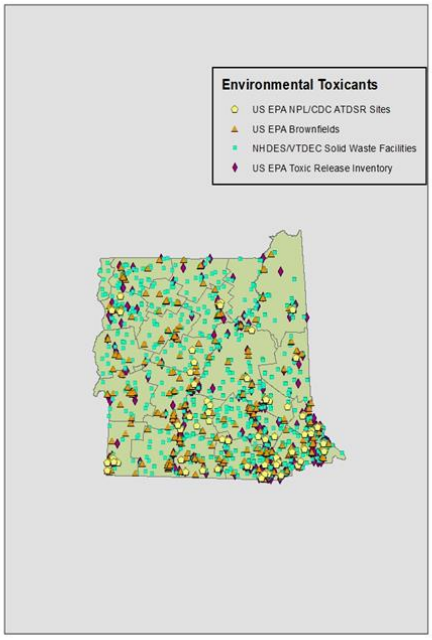
- Quantitation of toxins and toxicants
  - Air, soil, ground water,
  - Pesticide applications
  - Air quality datasets
  - Cyanobacteria content of waterbodies from direct calibration of satellite remote sensing databases

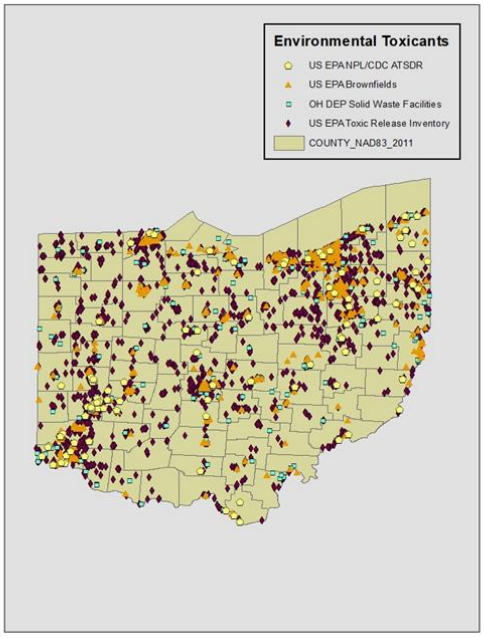
- Temporal epochs
  - Questionnaire-based exposures going back 30 years
  - Residential history analyzed for 30 years before diagnosis of ALS or enrollment of control subject
  - Quantitated data of sources of environmental toxins and toxicants going back 30 years

Because the temporal data go back 25 to 30 years, they will have quantification of the amounts of cyanobacteria in the water bodies and landfill exposures.

The Piedmont ALS Registry, Piemonte and Valle d'Aosta Register for ALS (PARALS), has been remarkably productive over the last 20 years. They have published approximately 45 papers from PARALS. PARALS is an epidemiologic prospective register that covers 2 Italian regions (population of 4.5 million inhabitants according to the 2011 Census) since 1995. From 1995 to 2014 (20 years of follow up) a total of 2702 patients (mean age at onset, 65.7 years) received a diagnosis of ALS, corresponding to a crude annual incidence rate of 3.03 per 100,000 population. During the 20 years of follow-up, the crude incidence rate of ALS progressively increased in the Piemonte and Valle d'Aosta regions by 14%, even if the APC model revealed that the increase of ALS incidence is attributable to a birth cohort effect in women, with a peak in the 1930 cohort.

Aim 1 involves a two-step process. Step 1 involves analysis of a broad category of environmental risk factors at the time of diagnosis. The second step involves an analysis of epochs of greatest effect for each environmental risk factor in the 25 to 30 years prior to diagnosis. These illustrative maps show the geographic distribution of the Superfund Site landfills and incinerators in New Hampshire, Vermont, and Ohio:



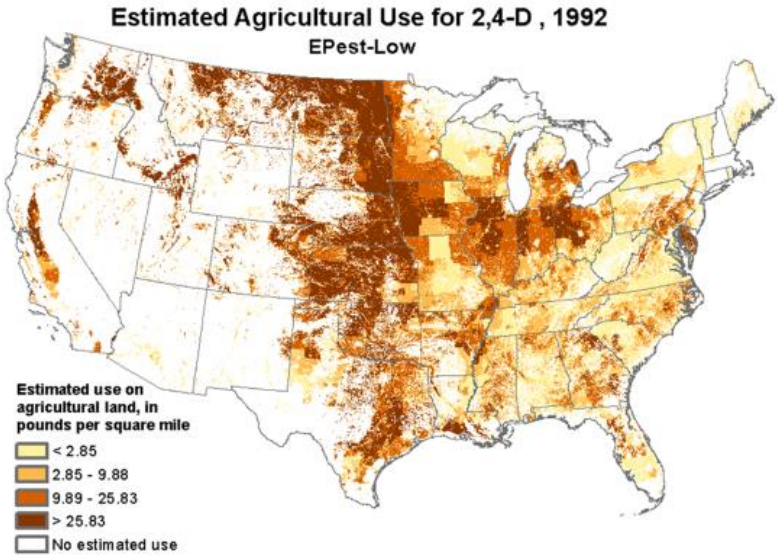


Patients and controls can then be mapped in relation to their proximity to these various sources of environmental pollutants and the water bodies that contain cyanobacteria.

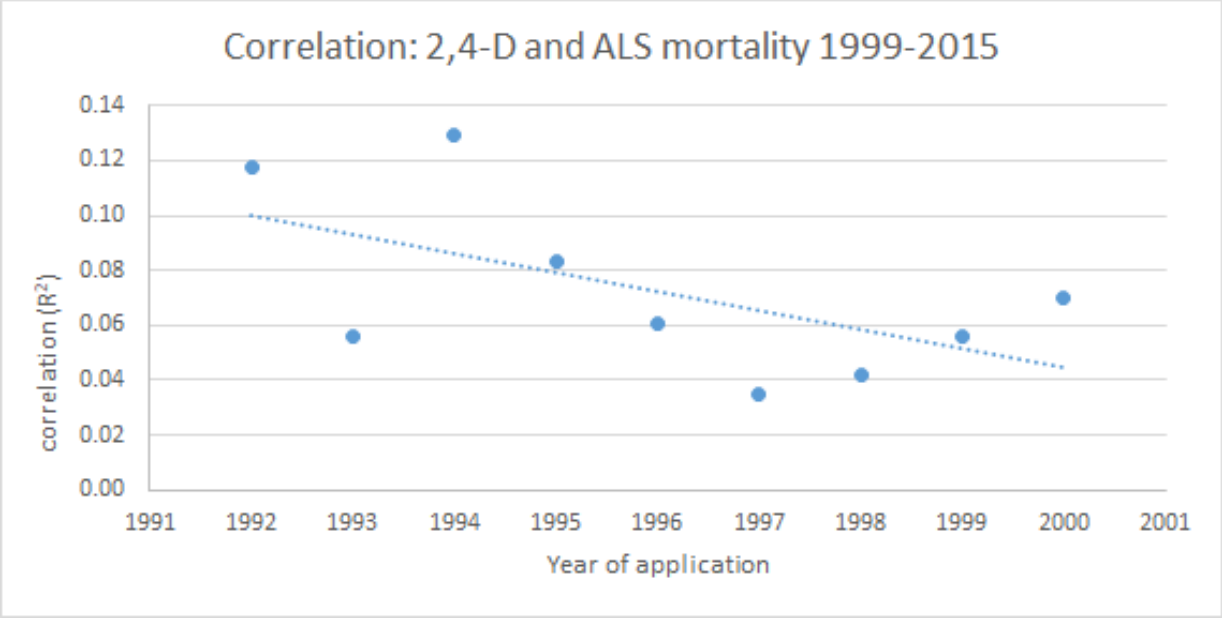
Specific Aim 2 is to analyze the distribution of patients in the whole US to assess their relationships to pesticides and cyanobacteria. The databases for this aim include the following:

- ❑ The National ALS Registry, which currently has full residential history on approximately 6000 patients and other more limited environmental risk module data on approximately 2700 self-enrolled patients with ALS from the continental US
- ❑ A collaboration with HVH Precision Analytics to use residential history of a national database of 34,000 ALS patients and about 340,000 control subjects for comparison case-controls from the continental US
- ❑ Maps of national annual applications of pesticides database going back 25 years
- ❑ Maps of national waterbody cyanobacteria map going back 25 years (exploring national air quality databases, particularly $PM_{2.5}$)

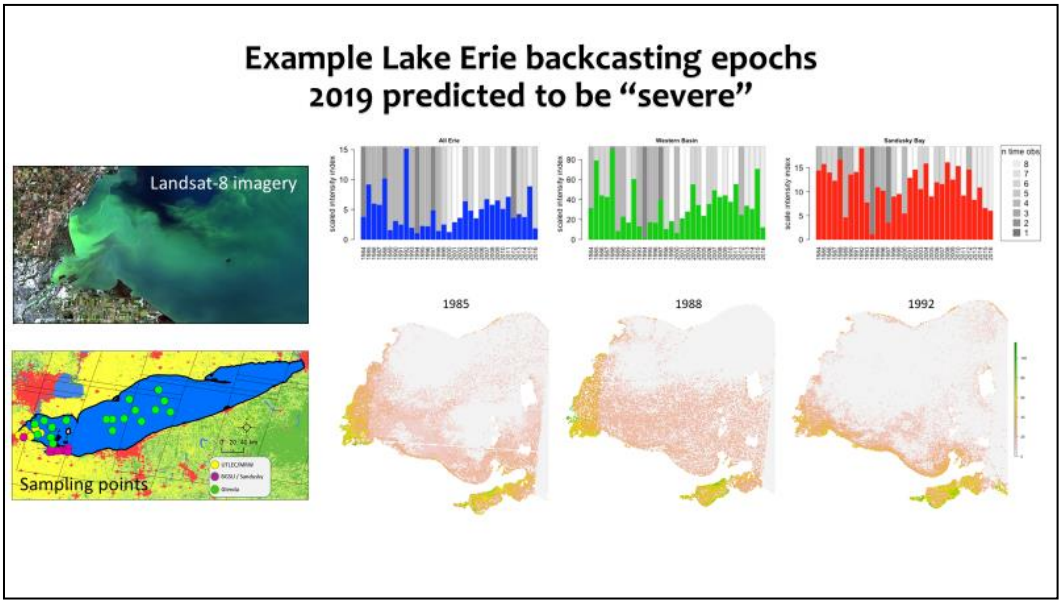
Here for comparison or illustration is a map for the year 1992 showing the pounds per square mile of 2,4-D that was applied in counties across the US, across which they can examine the distribution of patients versus controls:



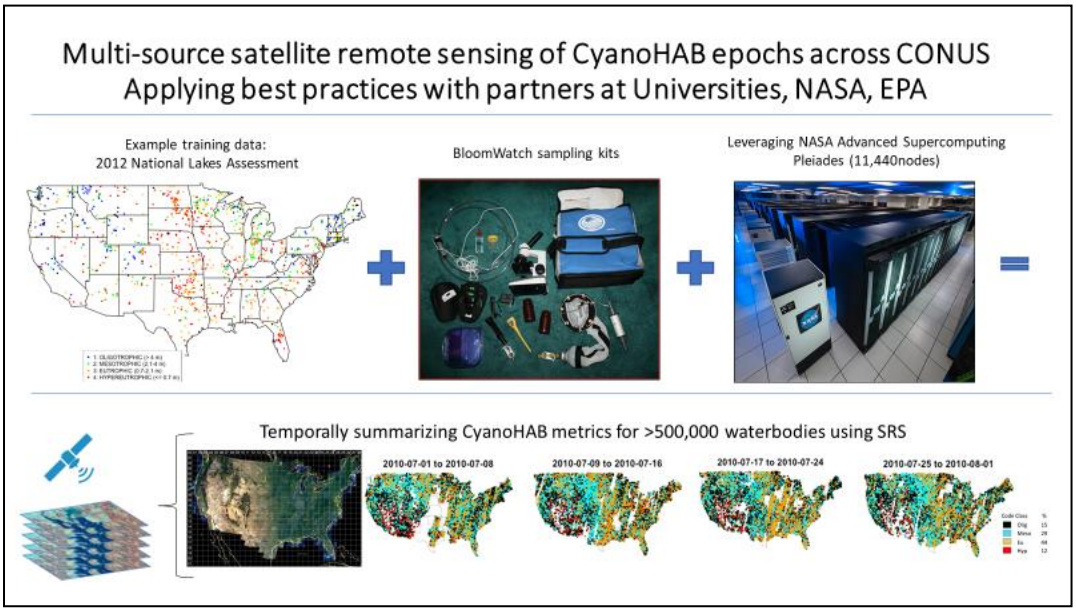
A preliminary assessment was done of county-level ALS mortality rates in relation to county-level pesticide application levels. Their preliminary analysis of the cases in the US NDI who died from ALS in the period 1992-1999 suggested that there was a correlation between the risk of developing ALS and 2,4-D pesticide application levels. In a very preliminary analysis of this, it appears that the earlier someone was exposed to 2,4-D, the higher the risk of developing ALS as illustrated below, with the caveat that there is a lot more to be done in regard to this aim:



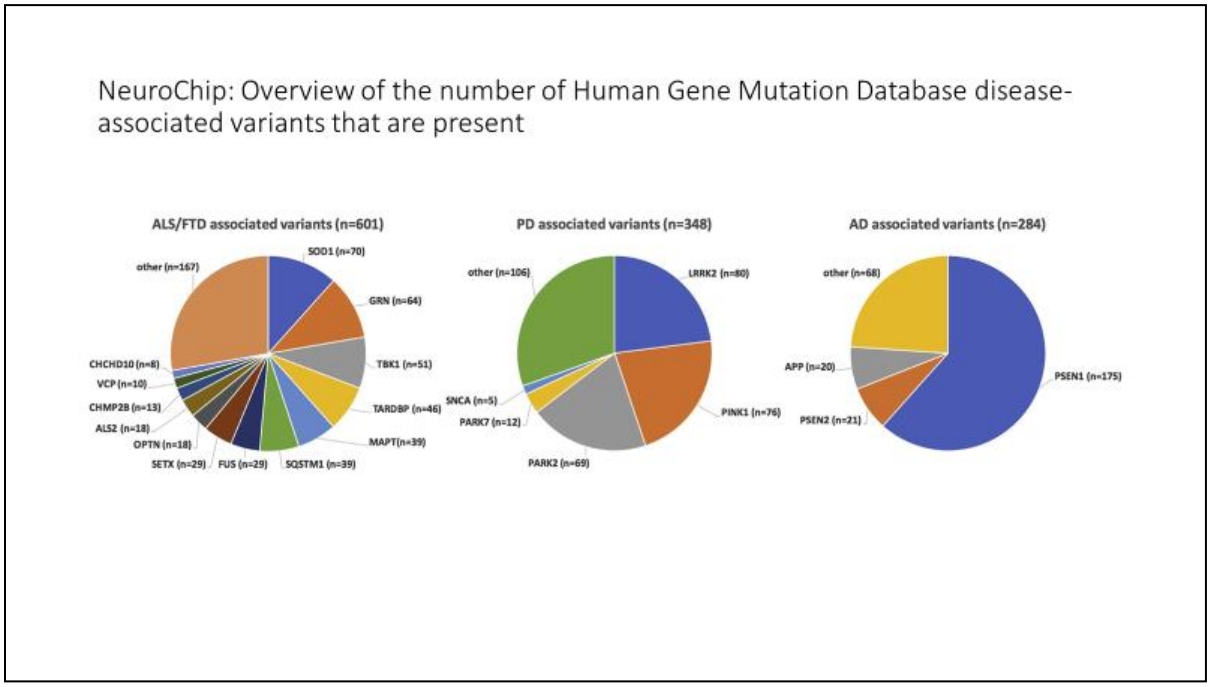
This is the amount of cyanobacteria blooms in Lake Erie from 1984 onward and then the different areas of Lake Erie, which can then be applied to the patients who are living in the different areas:



This is construction of the same sort of geographical map with the distribution of cyanobacteria content of water bodies across the US for doing the same comparison about the ALS subject-control population:



Turning to environmental factor-gene interactions, the intent of Specific Aim 3 is to analyze the gene-environment interactions using machine learning techniques. The genetic factor studies are done with Dr. Traynor with the GWAS NeuroChip, which has about 1200 individual single-nucleotide polymorphism (SNP) that are related to human neurodegenerative diseases. Here it is illustrated that there are about 600 ALS-associated variants for the SNPs, about 348 Parkinson's-associated variants, and about 280 Alzheimer's-related variants:



These 1200 variants produce on each individual subject, which can then be correlated with each of the individual exposome factors that come from both the residential exposure data that relates where the patient lives and how close they live to the environmental exposure features of interest, and also from questionnaire data about whether they were smokers and/or were working in industries that exposed them to lead, mercury, or whatever else. These can then be cross-correlated using machine learning.

Dr. Bradley and colleagues published a paper last year titled *Gene-Environment-Time Interactions in Neurodegenerative Diseases: Hypotheses and Research Approaches* that illustrated what they were trying to use as the basis for this research grant. Dr. Jiang Gui, the leader of the machine learning group from Dartmouth, has published a series of papers. Dr. Gui is producing a series of advanced algorithms to try to understand how machine learning can be used to advance the mechanisms by which the machine can produce an answer that the mind simply cannot get at of these terabytes of interactions.

Cancer research is well-ahead of research in the neurodegenerative disease areas. The following figures depict smoking and lung cancer and shows that if one has a SNP that predisposes them to having lung cancer, they will get lung cancer at an earlier age. If someone has the breast cancer gene, they will get it earlier. Those who have a combination of predisposing SNPs will get the addition of gene-gene interactions that will build up one's predisposition, which is probably what occurs in the neurodegenerative diseases as well:

Effect of various SNP markers of predisposing genes for lung cancer

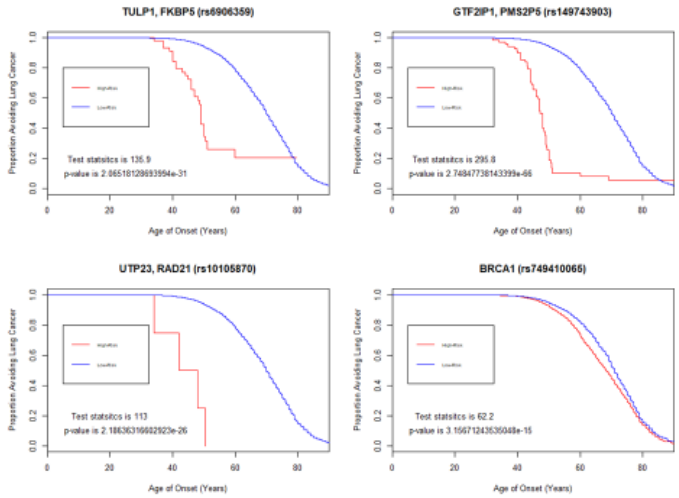
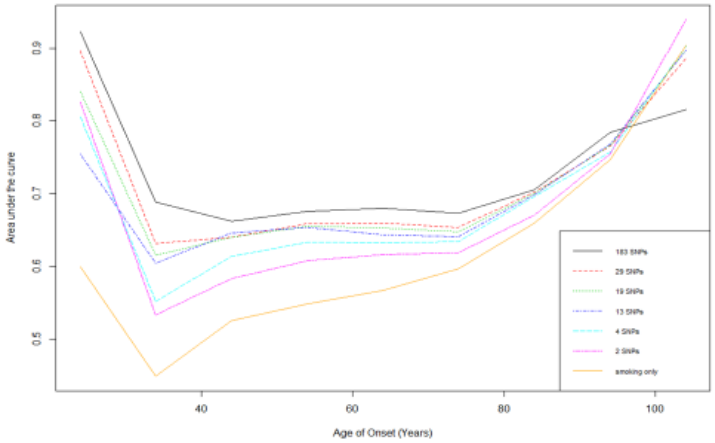


Figure 2. Lung cancer age-of-onset in relation to SNPs. Kaplan-Meier plots show the proportion of individuals avoiding lung cancer (y-axis) versus lung cancer age-of-onset in years (x-axis) by TULP1, FKBP5 (rs6906359) genotype, GTF2IP1, PMS2P5 (rs149743903) genotype, UTP23, RAD21 (rs10105870) genotype, and BRCA1 (rs749410065) genotype.

Combinations of SNP markers of susceptibility genes have additional effects in combination with smoking on the development of lung cancer



Area under the curve (AUC) plots. Each line corresponds to a different combination of smoking only or smoking plus SNPs. Here we compare the AUC when using a smoking only model or a model with both smoking and SNPs for lung cancer age-of-onset from 15 to 100.

Dr. Bradley concluded that he thought he had provided enough information to demonstrate where they think they are going. These attempts to find the epochs of greatest importance for individual environmental risk factors and to link individual environmental risk factors with individual genetic variants are daunting tasks, but not ones that are beyond the Don Quixotes of this collaborative consortium.

Discussion Points

Dr. Thakur posed a clarifying question about tracking the epochs of importance. It looked like they were proposing to look at the year of the exposure, not the year of exposure related to the year of symptom onset. He was trying to figure out why and how they would deal with looking at this as a period effect.

Dr. Bradley replied that in Guam, the evidence indicated that it was both ways. The Filipinos who immigrated into Guam and adopted the Guamanian way of life did not begin to develop the increased incidence of ALS until they lived there 10 or 15 years. Similarly, those who left Guam and went to California went on developing ALS with an increased frequency for at least 20 years after they left Guam. That was an indication of the long time period, or incubation period, before ALS occurred. There is a similar story in terms of arsenic and cancer. This is something that has been thought of as the same with regard to neurodegenerative diseases without evidence other than what he just quoted. That is what the consortium is trying to examine in terms of this research. The first evidence there is that a patient has the disease is when they are given the diagnosis. They will be looking at each of these hypothesized risk factors to determine the concentration of that risk factor 1 year before, 2 years before, 5 years before, 10 years before, 15 years before, 20 years before, and so forth. The concentrations are not the same each year. They occur higher and lower. This is an attempt to make that comparison.

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

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

Dr. Talbot provided an update on the study titled *Identification and Characterization of Potential Environmental Risk Factors for ALS Using ATSDR ALS Registry Cases and a Control Population*. She indicated that they are in the second year of the project, which she reported on during the previous ALS meeting. She thanked Drs. Mehta and Kaye for working with them to address some of the data management questions to keep moving the project forward.

The overall goal of this study is to examine environmental and occupational risk factors for ALS by conducting a case-control study of cases from the National ATSDR ALS Registry and population-based matched controls. The specific aims are as follows:

- Specific Aim 1
  - 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 from the Environmental Protection Agency (EPA) Air Quality System (AQS). This has been modeled for the whole country at the Census Tract level from 2001 through 2015.
  - Specific Aim 1c: Download, link, and examine ambient air toxics using the EPA National Air Toxics Assessment (NATA) data, which EPA has been working on since 1996. Every three years, this system models 187 air toxicants. They have been able to extract 35 of the 187 that are known or suspected to be neurotoxic, which they will be assessing.
- Specific Aim 2
  - Measure exposures to pesticides and solvents in samples with a battery of tests using blood concentrations of persistent environmental pollutants (pesticides and solvents) in cases and 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.

At this point, they have the individuals who were in the pilot project for the Biorepository, as well as the ALS Registry individuals in the ongoing Biorepository. This occurred because they determined that they wanted the best information on the surveys. There are now 17 surveys total, and they were basically targeting at least 8 of them with the most complete data. They have been very lucky to work with Drs. Kaye and Mehta and Ms. Raymond to make sure that they have the most complete data possible and the best cases. Therefore, they have 80 cases from the National ALS Biorepository Pilot collected from 2013 to 2015. They will recruit 80 controls matched on age, gender, and geography. This will be augmented with an additional 200 cases from the ongoing National ALS Biorepository from 2017 and 2018 and recruitment of

200 matched controls. The controls will be matched on age, gender, and geography. The two groups will be combined for a total sample size of 280 cases and 280 controls.

Individuals from the ALS Registry will not be contacted by University of Pittsburgh researchers. This was done through the ATSDR Registry. CDC is providing the following data and materials for the study:

- ALS Registry survey data (demographic, employment, military history, smoking, residential history, occupational exposures, home pesticide exposure, and hobbies)
- ALS Biorepository results from analyses of the blood specimen for organic pesticides and metals
- ALS Biorepository genetic material for analysis, which is ongoing with the NeuroChip that Dr. Traynor is in charge of

In terms of progress to date, they have obtained survey data from CDC on individuals in the Biorepository pilot study (n=80) and a portion of those from the ongoing National Biorepository (n=44). They assume they will be getting the remainder of the 200 from Ms. Raymond when those are approved. In addition, they have received the genetic material for further DNA testing and analysis of ALS cases. The next steps are to obtain the remaining survey data and the results of the pesticide analyses of the blood specimens. Obviously, they need to do their part to obtain the controls. While they have test values for cases, they have to be able to compare it to something. That is where the power is of Dr. Walters' case-control study and this case-control study.

The two parts of the study are the survey of the matched controls and a blood draw to be analyzed for pesticides, which has been challenging. Dr. Talbott said she figured she would be going on *Good Morning America* for every possible TV catchment area, and that she would be doing Chicago while Drs. Kaye and Mehta were going elsewhere. Recruitment actually has gone very well. They created a very nice brochure, website, video, a personal letter to share for recruiting controls. It has been heartening to her that that they have gotten such a wonderful acceptance and approval rating and consent to be involved. They only had one person who completed the survey who declined to complete the blood draw, which is very impressive. There are a lot of very good people in this country who know about the Bucket Challenge and ALS and know people with the disease who are willing/want to help. She has been very impressed by the individuals who have come forward.

Recruitment is ongoing. They have completed about 75 surveys and about 60 blood draws. They have sent their first batch of blood to SGS AXYS Labs in British Columbia for measurement, and will continue to send them in batches of 20 to 30. They figured out how to send them safely to British Columbia without being stuck on the tarmac, which is an ongoing concern in Phoenix. Tables 1 and 2 and Figure 1 below reflect the characteristics of ALS cases from the National ALS Biorepository Pilot Study and the controls, self-reported environmental and occupational exposures by case status, and self-reported longest industry work by North American Industry Classification System (NAICS) Supersector for ALS cases (n=79) and controls (n=54), respectively:

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Table 1. Characteristics of ALS Cases from National ALS Biorepository Pilot Study and Controls

Characteristic	Cases (n=79), n (%)	Controls (n=54), n (%)
Male	45 (57.0)	32 (59.3)
Year of birth		
≥1970	6 (7.6)	3 (5.6)
1960-69	18 (22.8)	10 (18.5)
1950-59	29 (36.7)	19 (35.2)
1940-49	21 (26.6)	18 (33.3)
<1940	5 (6.3)	4 (7.4)
White race	78 (98.7)	54 (100.0)
Education*		
High school diploma/GED	10 (12.7)	6 (11.1)
Some college, technical/trade school diploma	18 (22.8)	9 (16.7)
College graduate or higher	50 (63.3)	39 (72.2)
Age at ALS diagnosis, mean (SD) years	57.2 (11.0)	---
Member of Armed Forces	20 (25.3)	16 (29.6)
Smoking status		
Never smoker	41 (51.9)	29 (53.7)
Ever smoker (≥1 cigarettes/day for 6+ months)	38 (48.1)	25 (46.3)
Current Smoker	5 (6.3)	---
Not current smoker	33 (41.8)	25 (46.3)

*Other education was reported by one case

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Table 2. Self-reported Environmental and Occupational Exposures by Case Status

Work Exposure	Cases (n=79)	Controls (n=54)
Handled insecticides	3 (3.8)	3 (5.6)
Handled herbicides	4 (5.1)	2 (3.7)
Handled fungicides	2 (2.5)	1 (1.9)
Applied chemical soaps, shampoos, dips, powders (kill fleas, tick, other insects on pet)	---	---
Handled fumigants	1 (1.3)	0 (0.0)
Used glues or adhesives	4 (5.1)	2 (3.7)
Used solvents and degreasers	18 (22.8)	6 (11.1)
Worked with unleaded gasoline	9 (11.4)	5 (9.3)
Worked with leaded gasoline	9 (11.4)	4 (7.4)
Used unleaded paint	3 (3.8)	1 (1.9)
Used lead paint	4 (5.1)	1 (1.9)
Used formaldehyde	1 (1.3)	3 (5.6)
Soldered	11 (13.9)	2 (3.7)
Welded, brazed or flame cut metals	9 (11.4)	5 (9.3)
Metal dust or metal fumes	9 (11.4)	5 (9.3)
Any other chemical	21 (26.6)	4 (7.4)
Any other chemical (2nd chemical reported)	11 (13.9)	1 (1.9)
Home Exposure	**Cases (n=79)**	**Controls (n=54)**
Handled insecticides	49 (62.0) in home 48 (40.8) on lawn/garden	42 (77.8) in home 32 (59.3) on lawn/garden
Handled herbicides	50 (63.3)	35 (64.8)
Handled fungicides	9 (11.4)	8 (14.8)
Applied chemical soaps, shampoos, dips, powders (kill fleas, ticks, other insects on pet)	41 (51.9)	25 (46.3)

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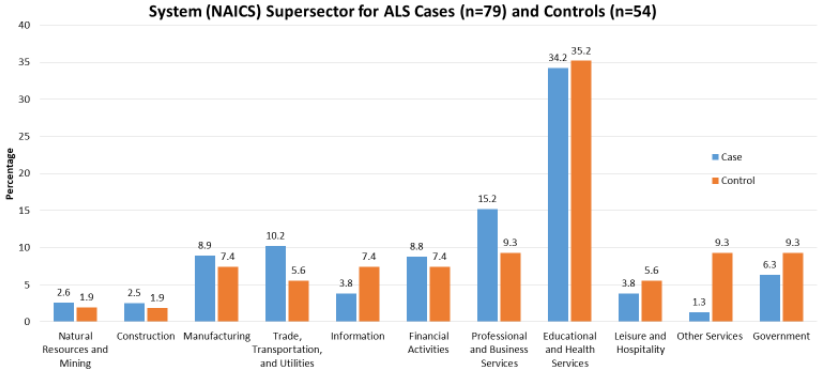
Figure 1. Self-Reported Longest Industry Work by North American Industry Classification System (NAICS) Supersector for ALS Cases (n=79) and Controls (n=54)



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This provides an example of the kind of information that will be compared between cases and controls and the wide gamut of people, occupations, and industries to be included to ensure that the sample is not biased. In addition, self-reported environmental exposures from hobbies will be included for remodeling projects, woodworking, plastic model glue, gardening, outdoor hunting and shooting, and fishing with lead weights/sinkers.

In terms of exposure to ambient air pollution $PM_{2.5}$ and ozone, the EPA will be providing 24-hour average estimates of $PM_{2.5}$ and 8-hour maximum ozone estimates. EPA uses a Bayesian space-time downscaler model to "fuse" daily ozone and $PM_{2.5}$ monitoring data from the National Air Monitoring Stations/State and Local Air Monitoring Stations (NAMS/SLAMS) with 12 km gridded output from the Models-3/Community Multiscale Air Quality (CMAQ) model. Daily predictions are available at the 2010 US Census Tract centroid locations for 2002-2015. They feel pretty confident that these data have been collected in a very consistent manner and that this is probably one of the better databases to use.

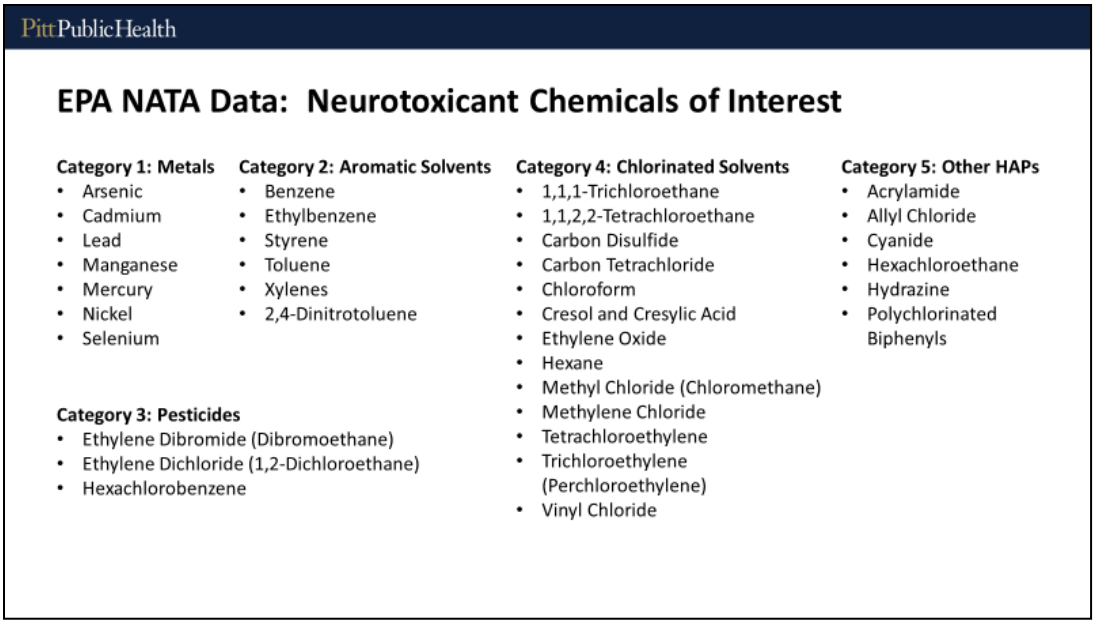
Regarding progress to date, daily estimates of $PM_{2.5}$ and ozone from 2002-2015 at each Census Tract Centroid were downloaded from the EPA website. For each year from 2002-2015, average annual pollutant estimates of $PM_{2.5}$ and ozone were calculated for each Census tract from the daily predictions. Air pollutant estimates for each ZIP Code Tabulation Areas (ZCTA) was assigned using two methods: 1) calculating the nearest distance Census Tract centroid to each ZCTA centroid (SAS); and 2) determining the Census Tract which contains the ZCTA centroid (ArcGIS). The next steps are for CDC staff to link the ambient air database to zip code at residence of blood draw for each ALS case, delete the geographic data (Census tract and zip code), and send the file to the investigators who will compare the ambient air NATA-based estimated exposures between cases and controls.

The last element of the exposure component is to examine exposure to air toxics using NATA data. As noted earlier, the EPA NATA uses emissions data nationwide to estimate health risks from 187 toxic air pollutants. NATA offers open data on model-estimated concentrations of air toxics at state, county, and Census Tract levels. Ambient air concentrations include background concentrations and total concentrations, and risk estimation are provided for cancer and neurological diseases. Air toxic data estimates are available for every 3 years since 1996, except 2008 with which there were some problems. They currently have data for 1996, 1999, 2002, 2005, 2011, and 2014 and believe that 2017-2018 data may be coming. These estimates are very sophisticated. Estimates are based on data from point, non-point, on-road, and non-road source groups as well as monitored data, reports, models, etc. These have been used in other studies, so the investigators feel that they are on solid ground to use these data.

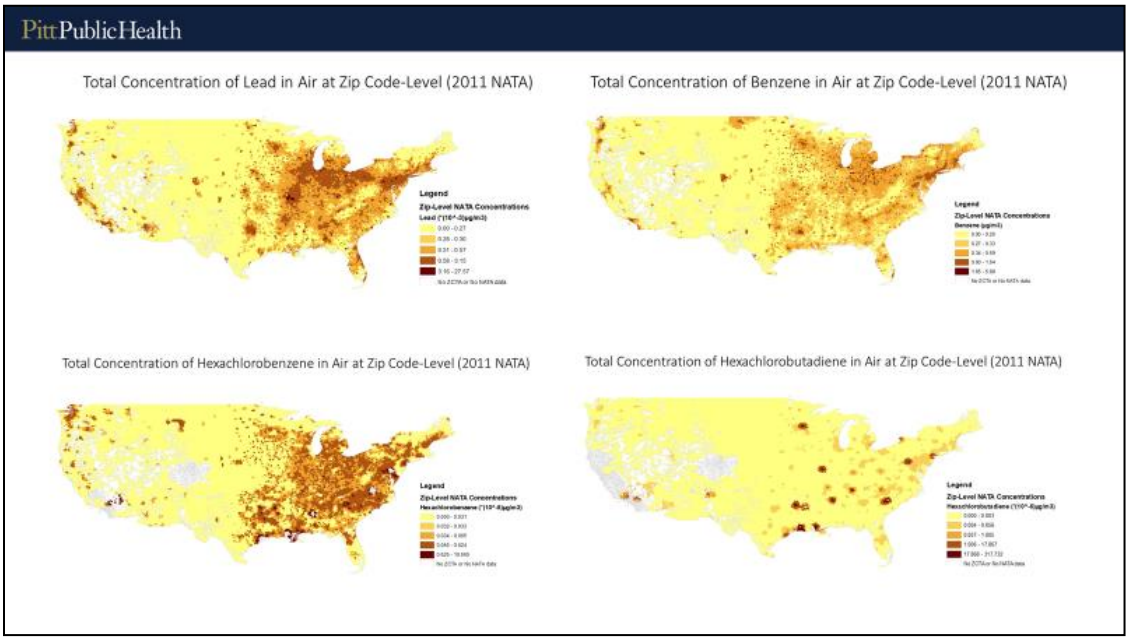
These are the pesticides of interest that they were able to glean from the EPA NATA model data:

- ❑ 1,4-Dichlorobenzene
- ❑ 1,2,4-Trichlorobenzene
- ❑ 1,2,3,4,5,6-Hexachlorocyclyhexane (Lindane)
- ❑ Chlordane
- ❑ DDE (1,1-Dichloro-2,2-Bis(p- Chlorophenyl) Ethylene)
- ❑ Heptachlor
- ❑ Hexachlorobenzene
- ❑ Hexachlorobutadiene
- ❑ Methoxychlor
- ❑ Toxaphene (Chlorinated Camphene)

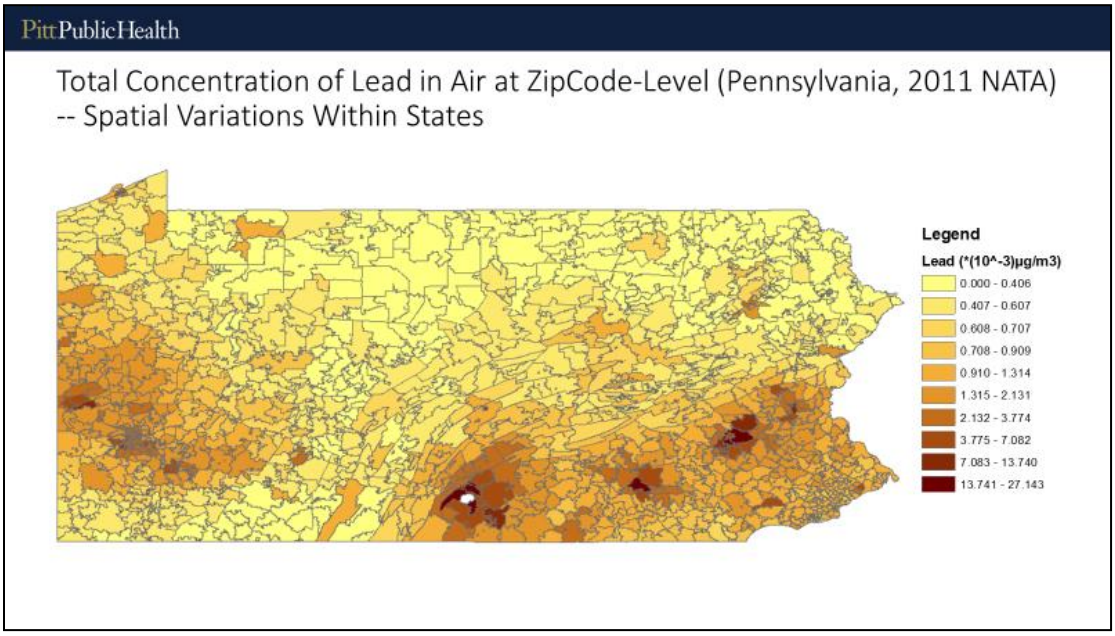
These are the same pesticides that SGS AXYS Labs in British Columbia is measuring in the 28 analytes they are examining. It was an extra bonus that they discovered this. The EPA NATA data neurotoxicant chemicals of interest are categorized below:



The progress on this is that they have downloaded the NATA data and EPA website for estimates of concentrations for the chemicals of interest, created a combined database for 2011 and 2014 NATA data (2010 Census Tract), working with CDC to assign the zip-level NATA data. They selected the Census Tract Centroid as a surrogate for the exposure within the Zip Code and they have 33,000 Zip Code-level exposures for 2011 to 2014. They have created the database and the next steps will be to estimate the air toxic exposures of cases and controls using the assigned Zip-level NATA data, and compare the NATA-based estimated exposures between cases and controls. This is what it looks like for the whole country for Zip Code-level lead, benzene, hexachlorobenzene, and hexachlorobutadiene to illustrate that there is heterogeneity of the exposures—it is not just one exposure:



There are spatial variations within states. This map shows total concentration of lead in the air at the Zip Code-level for just the State of Pennsylvania based on 2011 NATA data:



For Aim 2 to measure pesticides in blood specimens, the following two groups of pesticides will be analyzed:

E1 Pesticides to be Analyzed

- ❑ Hexachlorobenzene
- ❑ HCH, alpha
- ❑ HCH, beta
- ❑ HCH, gamma
- ❑ Heptachlor
- ❑ Aldrin
- ❑ Chlordane, oxy-
- ❑ Chlordane, gamma (trans)
- ❑ Chlordane, alpha (cis)
- ❑ Nonachlor, trans and cis
- ❑ 2,4'-DDD
- ❑ 4,4'-DDD
- ❑ 2,4'-DDE
- ❑ 4,4'-DDED
- ❑ 2,4'-DDT
- ❑ 4,4'-DDT
- ❑ Mirex
- ❑ Toxaphene

E2 Pesticides to be Analyzed

- ❑ HCH, delta
- ❑ Heptachlor epoxide
- ❑ alpha-Endosulphan
- ❑ Dieldrin
- ❑ Endrin
- ❑ beta-Endosulphan
- ❑ Endosulphan sulphate
- ❑ Endrin aldehyde
- ❑ Endrin ketone
- ❑ Methoxychlor

They have sent the first batch of 40 control serum specimens to SGS AXYS labs for pesticide analyses, with another 20 to be sent in the next week. They will continue to obtain blood specimens for controls and send them to the laboratory for analyses, and hopefully will be working with CDC on a joint venture to compare the cases and controls.

The ALS genetic laboratory analyses for Aim 3 will be conducted by Chris Donnelly, PhD who is a Neuroscientist in the University of Pittsburgh Department of Neurobiology. Dr. Donnelly trained at Johns Hopkins, is a cutting-edge ALS researcher, and knows Dr. Traynor very well. He has start-up funding to create a state-of-the-art genetics laboratory at the University of Pittsburgh. He will be measuring the length of the C9orf72 repeat expansion, and considering newly identified genetic polymorphisms for Familial ALS (FALS) in those individuals who reported a family history but for whom no ALS gene was identified. In terms of progress, the genetic information was recently received from the CDC/ATSDR Registry for the C9orf72-positive cases for both the pilot DNA analyses and the 200 newly identified National ALS

Biorepository participants. They have 50 or so C9s and will be looking at the additional genetic markers. Dr. Talbott asked Dr. Donnelly to send her the genes that have been identified or linked since 2015. For the ALS genetic analysis, the genes to be tested for include:

- ❑ KIF5A (2018)
- ❑ NEK1 (2016)
- ❑ TBK1 (2015)
- ❑ GLT8D1 (2019)
- ❑ ARPP21 (2019)
- ❑ C21orf2 (2016)
- ❑ CCNF (2016)
- ❑ TIA1 (2018)
- ❑ ANXA11 (2017)

The goals for the coming year are to: 1) complete recruitment, consent, and surveys of matched controls; 2) acquire permission for obtaining serum samples of matched controls and ship them to the SGS AXYS laboratory for testing, processing, and analysis; 3) perform the matched pair analysis and conditional logistic multivariable analysis for presentation of preliminary results at professional meetings; and 4) develop manuscripts on environmental and occupational risk factors associated with ALS, exposure to ambient concentrations of air pollutants and air toxics and risk of ALS, and the functional relationship between environmental toxicants in human biological samples and key biological pathways and common genes for ALS.

Discussion Points

Dr. Goutman asked how they are doing their NAICS coding to the cases and controls and whether people did that or if they used any automated methods.

Dr. Angela Malek indicated that Dr. Jeanine Buchanich used the Registry and assigned the codes for both cases and controls.

Dr. Talbott added that CDC did a lovely job with a drop-down menu that had every occupational area and the industry in which people worked. Her impression is that there is a very good coding system within the survey that CDC developed. The investigators have a Job Exposure Matrix (JEM) Coding Manual and the industry and occupation from the Census. They have the listing that CDC created and she has worked with industry and occupation and knows there is a coding manual that goes along with that.

Dr. Goutman indicated that they have a lot of jobs to code. CDC and NIH have automatic coding systems as well, which they are exploring, but these are not perfect. NIH has the Standardized Occupation Coding for Computer-assisted Epidemiological Research (SOCcer) and CDC has a different system, so he wondered whether the Pittsburgh team had something automated that provides numbers in terms of the likelihood of a title matching or whether one needs to review it. He has not done the drop-down himself and Registry, so he did not know if individuals could select a job code. There can be disagreement between coders.

Dr. Talbott indicated that the cases are self-report, but when they call the controls they do not want to put words in their mouth. They read the controls a list of the basic exposure/occupation examples and then let them speak. There is a text field, but often the examples do not fit and there is a degree of error involved.

Dr. Mehta indicated that ATSDR is currently in the process of assigning those NAICS codes to the occupations as well, but it will not be automated. He suggested that perhaps they should get together once theirs is finished in order to compare and contrast.

Dr. Talbott emphasized that it is tricky when the cases are self-reported. They do have control over the degree of agreement between what one person says and what another person says, so it sounded like perhaps they should have some adjudication.

Dr. Wright pointed out that ATSDR is particularly interested in military service history and traumatic brain injury (TBI) and wondered whether among the controls they were seeing the same representation of military service.

Dr. Talbott indicated that they are.

Novel Extracellular Vesicle and Molecular Biomarkers of Environmental Exposure and Disease Progression in ALS

Nicole Comfort, M.Phil.
PhD Candidate
Department of Environmental Health Sciences
Columbia University, New York

Ms. Comfort indicated that she was presenting during this session on behalf of Dr. Neil Schneider and Dr. Diane Re who were unable to attend. She provided an update on their ATSDR/CDC-funded R01 examining novel extracellular vesicle and molecular biomarkers of environmental exposure and disease progression in ALS. Before beginning, she expressed what a privilege it was to be there and thanked all of the PALS for sharing their perspectives.

To give a brief overview, the focus of the research is toxicant levels that are reported for peripheral ALS specimens. Changes in blood and urine are unlikely to actually reflect toxicant load in the central nervous system (CNS), so CSF is considered a better surrogate biospecimen for CNS levels of exposure. However, obtaining CSF is invasive and difficult to obtain. Autopsy is the only direct measure of toxicant levels in the CNS, but this terminal endpoint is not informative about longitudinal exposure, and tissue donations are rare. Thus, these are precious samples. Ideally, biomarkers should be specific, minimally invasive, reproducibly measured, and easily implementable. The goal of this project is to develop novel potential biomarkers of exposure and disease progression that combine all of these features. Ms. Comfort noted that due to time constraints, she might not be able to fully describe all of the aims.

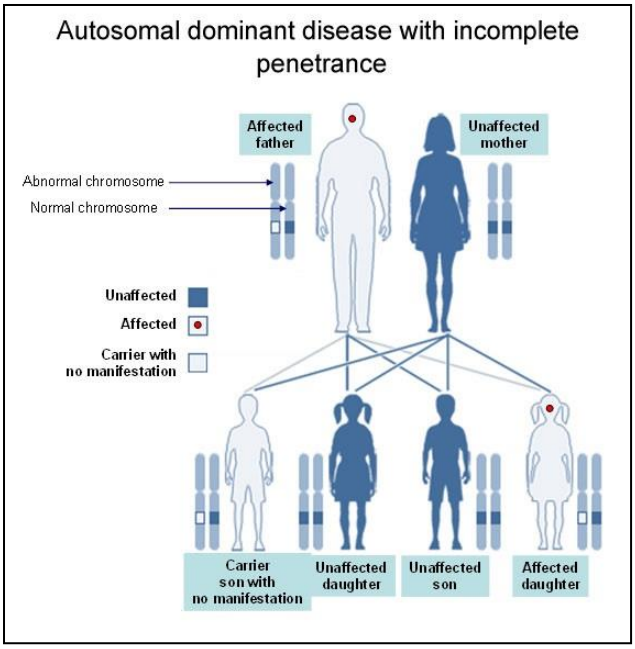
As noted, the overall idea of the study is to look for novel biomarkers of environmental exposure and disease progression. Aim 1 seeks to validate hair as a useful biospecimen in ALS for pesticide measurements. To do this, they will measure pesticides in 180 ALS patients at two different time points spaced 6 months apart to test a total of 360 hair samples. This will be measured by liquid chromatography-mass spectrometry (LC-MS) by the collaborator Dr. Beizhan Yan at the Columbia Earth Institute. And as of right now, they are just starting to process the actual samples from the Registry after a long time of methods optimization. What is really novel about this aim is that most ALS epidemiological studies that look at individual exposure will assess persistent organic pollutants (POPs) because they are persistent externally and internally as they can accumulate in fat. The choice of looking at these persistent neurotoxicants is to increase the odds of exposure and also internal detection. However, they

think that chronic or repeated exposure to non-persistent pesticides such as organophosphates or pyrethroids still can have a critical role in triggering ALS. That is because even though they are metabolized so quickly by the human body, they are very ubiquitous and found in food, water, and household products. A 2011 study by Kanavouras et al found that they could measure in-hair organophosphate pesticide metabolites up to the time of diagnosis. The goal of this aim is to examine these non-persistent pollutants or pesticides.

In Aim 2, they will pilot the use of circulating CNS-derived extracellular vesicles (EVs) to measure metal exposure in that same set of patients from the Registry that will measure the pesticides in hair. EVs are nanoscale membrane-bound vesicles that are released virtually by every cell type. EVs have been found in every biofluid that has been tested (urine, blood, tears, saliva, semen, etcetera). They are aiming to measure lead, mercury, manganese, arsenic, selenium, and copper in extracellular vesicles. Something that also is unique about EVs is that when they are released from the cell, they retain some of the cell specific proteins from the membrane providing a "tag" of the cell type of origin. Therefore, in blood they can actually do immunoprecipitation for neuron or astrocyte membrane markers to pull down the CNS-derived EVs. This is very novel because it will be a peripheral measure that can tell something about actual CNS metal load. They are looking at metals because they have been associated with neurological disorders. They also have been found in EVs, which carry a lot of proteins for metal metabolism.

Aim 3 seeks to examine concordant signatures of the messenger RNA profiles between ALS patients brain motor cortex and spinal cord and that of toxicant-exposed mice. Ms. Comfort focused on this aim in more detail, given that it is the furthest along in this project. The scientific premise for this aim comes from a study published in 2012 titled *Concordant Signaling Pathways Produced by Pesticide Exposures in Mice Correspond to Pathways Identified in Human Parkinson's Disease* by Gollamudi et al. These investigators found that the signaling pathways correspond with those of human Parkinson's disease in the ventral midbrain and striatum of these mice. That provided the rationale to look at this for ALS patients. They have done RNA-seq on 100 ALS patients and 20 controls so far from the motor cortex in spinal cord, which was analyzed by Dr. Harms. Now they will chronically expose control and TDP-43 G298S mice to a vehicle (water), a metal (manganese), and a pesticide (chlorpyrifos). They chose manganese and chlorpyrifos because these were found to interact with TDP-43 G298S in their pilot studies.

Ms. Comfort acknowledged that she was talking to a group of ALS experts, so she would not go too far into the etiology of ALS. To provide some rationale for why they selected TDP-43, it is known that causative genetic mutations, primarily C9orf72 and SOD1, explain about 68% of familial ALS and 10% of sporadic ALS. However, there is still an unknown contribution. They think that environmental exposures might also play a role, even in inherited ALS. These gene mutations are often incompletely penetrant, which complicates genetic counseling and also indicates that additional factors may be determining risk. TDP-43 shows incomplete penetrance, meaning not all individuals with the mutation will exhibit clinical symptoms. For example, this figure illustrates an example of an autosomal dominant disease with incomplete penetrance:



Of the 4 offspring, 2 have unaffected chromosomes and are phenotypically normal. One daughter carries the abnormal chromosome and shows clinical symptoms; whereas, her brother has the abnormal chromosome and carries that but does not show any signs of disease. This represents an incompletely penetrant mutation.

TDP-43 is a mutation in the TAR DNA-binding protein (TDP-43). There are many variants of this gene of which 26% are clearly pathogenic, 15% show minimal segregation, 47% show no segregation, and 10% are also found in controls. What is very striking is that even within the same TDP-43 family, disease onset can vary by up to 35 years. In addition, TDP-43 aggregates are found in 90% of ALS patients post-mortem. This is the rationale for assessing TDP-43. The study's overarching hypothesis is that what causes ALS is not just the environment or just genetics, but a combination of these individual susceptibility variants. For example, mutations and TDP-43 with exposure to neurotoxins, metals, and pesticides have been implicated the most with neurodegenerative diseases in the literature and together, these can interact to cause disease. Their group is looking only at metals and pesticides.

Ms. Comfort pointed out that unlike Drs. Bradley and Talbott, the Columbia Team studies this using different models. They use cell models, either primary cultures or iPSC models and animal models, to study the exposures and different windows of susceptibility to examine gene-environment interactions. The mouse model for this study is a TDP-43 knock-in mouse model. It has a missense mutation converting glycine to serine substitution at position 298, hereinafter referred to as TDP-43 G298S. The beauty of these mice is that TDP-43 is expressed at the right locus in a cell-specific and temporal-specific manner. These mice were created by Neil Schneider's Doctoral student, Sarah Ebstein. There is a recent paper on this published in *Cell Reports* for those who want further details.

Thus, they use the mouse that is heterozygous for this mutation in humans. This is an incompletely penetrant mutation. Those that do show clinical symptoms typically have an earlier onset and more rapid rate of disease progression. On the other hand, the heterozygous mice are asymptomatic. They do not show any motor phenotype and or neuropathological features. However, the mice homozygous for the mutation do show these neuropathological features and

degeneration of muscles, particularly the first muscles that typically degenerate in ALS but at a very late age. They chose to study the heterozygous mouse model because it provides an opportunity to study gene-environment interactions and environmental exposures that might push the clinical phenotype to show, and also to be more relevant to the human experience because it is very unlikely to be homozygous for the mutation.

To provide an overview of the study design, 48 male mice are evenly distributed across 8 groups. The mice will be exposed to the metal manganese via drinking water, which is formulated as manganese chloride. For chlorpyrifos (CPS), the pesticide, the mice will be exposed via biodegradable pellets. Exposure starts at postnatal day 80 and continues for either 6 months or until there is a motor deficit and some apparent paralysis. This is because at that point, whichever comes first, they will sacrifice the mice and collect their tissues for the comparative RNA transcriptome analysis. The reason they want to sacrifice the mice as soon as they start to see a motor deficit is because they want to look at what is involved in the initiation of the disease. They will be submitting the mice to motor assessment using the accelerated rotarod paradigm. They also will collect blood longitudinally to look for acetylcholinesterase inhibition.

The mice will be exposed to manganese at 400 parts per million (ppm). The reason they chose this metal and this dose was because it is the most prominent metal in their preliminary studies. They exposed their cultures to 6 different metals. They tested 200 and 400 ppm because mice exposed to 400 ppm of manganese start to show a slight reduction in grip strength. The rationale was that with these mice that are genetically silent to ALS but genetically susceptible, perhaps they would see the gene-environment interaction. They tested the mice on the accelerated rotarod, but saw no difference in the mice exposed to the 200 ppm manganese chloride and those mice exposed to water in the pilot study. However, the wild-type exposed to the 400 ppm did start to show some deficit. This is measured in latency to falling off of the accelerated rotarod. Falling off sooner is a sign of less motor coordination and balance, so they decided to use 400 ppm.

Because they are exposing the mice via drinking water, they had to make sure there was no difference in water consumption across the different groups and no exposure effects or any difference in water consumption between the two mice. They also have to look at weight across the 4 groups, because any decrease in weight would be a sign of the beginning of the clinical manifestation and disease. They did not see any difference. Ms. Comfort indicated that the data she was presented went up to 18 weeks because they did not have time to transfer all of their data up to 21 weeks. However, she assured everyone that there was no difference in weight so far. In terms of the results up to Week 21 of the rotarod, the mice all started at the same percent at baseline. The wild-type mice exposed to water experienced steady improvement in the accelerated rotarod. That was expected. However, in the wild-type mice exposed to manganese or in the heterozygous mice exposed to water, they did not see the improvement expected or a decrease. In the heterozygous mice exposed to manganese, they started to see a drop. While they rebounded at Week 18, a more progressive decline in motor coordination has been observed thereafter. Thus, the heterozygous mice exposed to manganese appear to start decreasing in performance compared to the mice exposed to vehicle (water).

In terms of examining gene-environment interactions with exposure to pesticides, they are using CPS. For this, they are using biodegradable pellets. This is a pretty novel route of exposure because this is the first time that these pellets are being used in a toxicology study. Usually, they are used only for drug delivery purposes. The pellets are administered subcutaneously between the shoulders just as any subcutaneous shot would be administered. They can stay in

for 60 days and then a new pellet is inserted. Subcutaneous exposure in mice most closely mimics human dermal exposure, and it is more controlled than wrapping the mouse tail in something soaked in CPS. This is the novel aspect of this aim. In choosing the dose of CPS to use, they conducted a pilot study going from placebo 0.1 mg/kg/day, 0.05 mg/kg/day, and then 0.2 mg/kg/day. They wanted to have an acetylcholinesterase inhibition target of about 40% to 70% to model an Egyptian farmer cohort study by Pam Lein et al at the University of California Davis. However, even at the highest dose that they tested, there started to be some rebound in the inhibition. They really wanted to make sure that they could keep this inhibition stable, because they were not sure whether these pellets would be stable subcutaneously at the physiological temperature in the mouse. They ended up selecting a dose even higher than this testing 0.5 mg/kg/day and reached the target level of acetylcholinesterase inhibition, which remained stable across weeks. Therefore, they will use 0.5 mg/kg/day.

Regarding the work plan for the rest of the budget period, they will order the 0.5 mg pellets and will start the exposure with CPS and placebo pellets. They will continue exposure to manganese and vehicle via drinking water with the weekly motor behavior assessment via the accelerated rotarod and the neuroscore to look for signs of paralysis. For both of these studies, upon any deficit in performance or clear sign of paralysis from the neuroscore or until the end of the exposure at the end of 6 months, they will sacrifice the mice for the transcriptome analysis.

ATSDR Funded Research Update

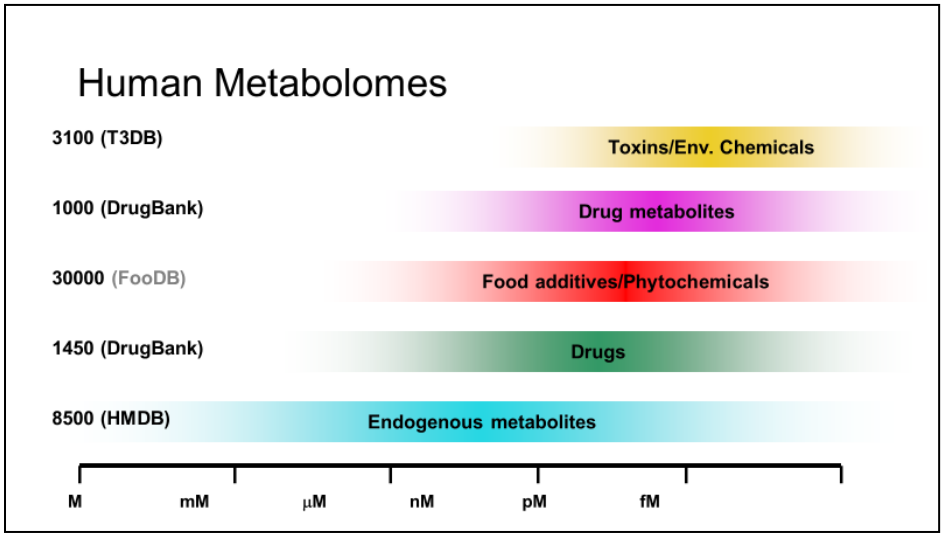
Metabolomic Signatures Linking ALS to Persistent Organic Pollutant Exposures

Eva Feldman, MD, PhD
Director, ALS Center of Excellence
Russell N. DeJong Professor of Neurology
University of Michigan

Dr. Feldman thanked CDC and their colleagues for inviting her and Dr. Goutman to present their work. She explained that it would be presented in two parts in that she would be presenting the back end of what Dr. Goutman would be presenting later, which would be the front end. She acknowledged that they were very fortunate to have been funded by the CDC from 2013 to 2017 and that, based on their quantitative measurements of pollutants in blood, allowed them to assign ALS patients a risk and correlate that risk with each patient's phenotype. She indicated that Dr. Goutman would be talking about that in detail in a later presentation.

Is the second part of their CDC funding that began on September 30, 2019, they will be linking metabolomic signatures with environmental pollutants to increase the understanding of ALS pathogenesis. Like many investigators, they are interested in understanding the pathogenesis of ALS in context with the environment at the gene, proteomic, and metabolomic levels. They are currently examining the metabolome, which is the complete collection of small molecule metabolites in a cell, organ, or tissue, or organism. It includes endogenous metabolites and exogenous molecules, as well as transient or even theoretical molecules. Because it is defined by different detection technologies, metabolome size is always somewhat ill-defined. A specific metabolite is actually defined as any organic molecule detectable in the body with molecular weight less than 1500 Daltons (Da). This includes pesticides, oligonucleotides, sugars, nucleosides, organic acids, ketones, aldehydes, amines, amino acids, lipids, steroids, alkaloids, foods, food additives, toxins, pollutants, drugs, and drug metabolites. It also includes many human and microbial products. The concentrations are usually detectable at about the 1

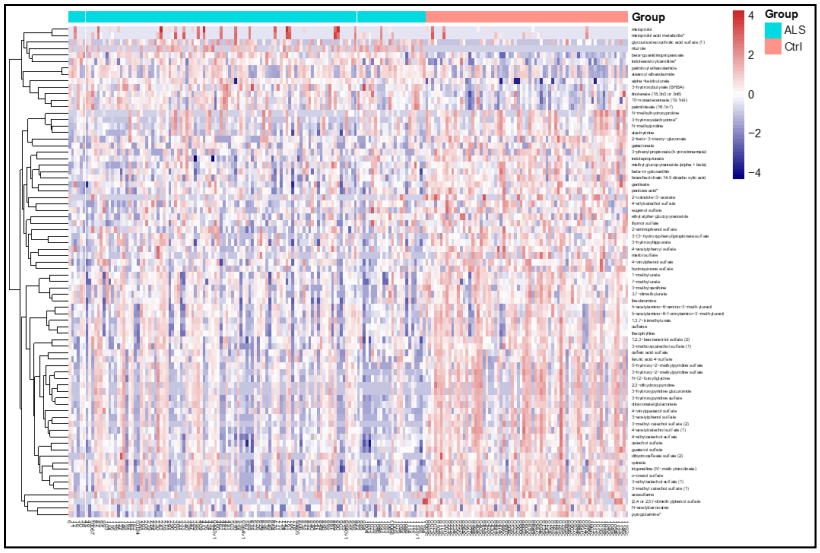
picaMolar (pM) level. Human metabolisms are varied and not complete. There are many more unknown metabolites than known metabolites in the Human Metabolome Database (HMDB) as depicted in this illustration:



The idea of linking metabolomics with exposures is one that is of growing interest, as evidenced by numerous recent articles in which metabolomics has been used as a readout to better understand what the environmental exposure has done quite simply to one's body and how the body is reacting to the environmental exposure. Metabolomics can serve as a biomarker; increase the understanding of ALS pathogenesis; and even take a step back further to show how one's genetic make-up can impact how different toxicants, pesticides, and pollutants will influence susceptibility to the disease and disease progression.

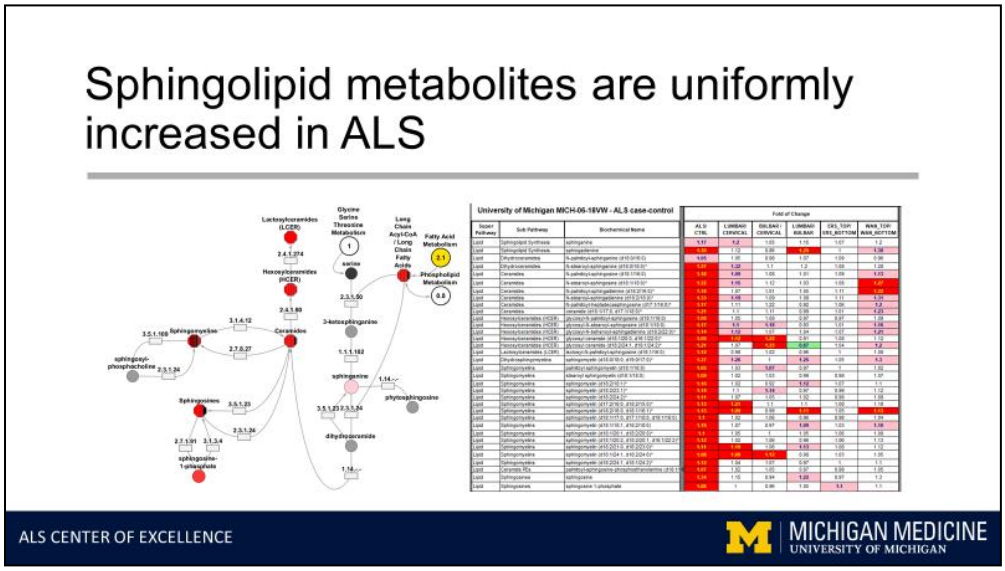
The hypothesis for this current CDC grant is that persistent organic pollutants (POPs) and other exposure types will lead to unique metabolite signatures detected in both plasma and central nervous system tissue in ALS subjects. This will: 1) yield novel biomarkers of ALS; 2) inform us of past exposures; and 3) increase our understanding of disease pathophysiology. Dr. Feldman reported on Year 1 of the study. Michigan Medicine began a patient biorepository a little over a decade ago. They currently have 350 cases and 280 controls in this biorepository. All of the ALS cases are finely phenotyped and blood is drawn every 6 months from the 350 cases. They have 100 autopsies and complete brain and complete spinal cord, so they have a very robust biorepository to address their questions of interest.

Dr. Feldman focused this presentation on the initial metabolomic profiling they were able to accomplish. The current unpublished data from this period includes 134 cases and 72 controls with completed untargeted metabolomics. They know the occupational or environmental exposure risks of those patients, although she noted that she would not be discussing that in great detail due to time. Between the cases and controls, there was no statistical difference in age, body mass index (BMI), or race. For a snapshot overview, this heat map comparing the metabolites of ALS to control participants offers a visual of untargeted metabolism of the ALS patients, which are in blue, and shows a clear robust difference in the signature:



There are multiple accepted methods to analyze metabolomics. Dr. Feldman briefly discussed three of these and shared some highlights of what they are finding using these three different methods. She emphasized that what was important to note was the congruence of these methods at the end in terms of their similar results. Using T-test and false discovery rate (FDR) approaches, they can create a random forest analysis (RFA) classification. The RFA was 85% accurate in determining case versus control status. She was really surprised by how different the metabolome is between cases and controls. They found many important biomarkers that are associated with case status, including creatinine metabolism, alpha-ketobutyrate and 2-hydroxybutyrate, aromatic amino acids, compounds derived from phenylalanine, and dietary phenolic compounds.

Looking at some of the data, the class of aromatic amino acids and compounds are decreased in ALS. Metabolites maps show the interconnection of all of the metabolites in order to better understand pathogenesis. Here is an example of the sphingolipid metabolites shows that they are all uniformly increased in ALS:



Dr. Feldman said she found this to be one of the most fascinating pieces of data, given that the other hat she wears in her research world is studying the complications of diabetes. It is actually the lipid biosynthesis going awry that is likely causing a lot of the neurologic complications of diabetes neuropathy. Dr. Traynor recently published a paper showing what is known as serine C-palmitoyltransferase 1, which is the first enzyme needed to make sphingolipids in a case of juvenile familial ALS in which there was a mutation in that gene. A mutation in that gene is also known to cause neuropathy and a fairly severe neurodegenerative problem. In that ALS patient, there were high levels of sphinganine, which is a very toxic sphingolipid by-product. A lot of these sphingolipid by-products they are seeing as well are extremely toxic. Therefore, she believes that looking at sphingolipid metabolism is going to turn out to be very important.

There is a paper by Daniel Carrizo et al titled *Untargeted metabolomic analysis of human serum samples associated with exposure levels of persistent organic pollutants indicate important perturbations in sphingolipids and glycerophospholipids levels* that found important changes in sphingolipids. This group looked at dichlorodiphenyldichloroethylene (DDE), which is the first metabolite of dichlorodiphenyltrichloroethane (DDT). An orthogonal partial least-squares discriminant analysis (OPLS-DA) was used to separate low and high DDE groups. Then loading plots are used to show the compounds responsible for variation between the two groups. The sphingolipid by-products that are associated with high exposure are the ones that are clearly known to be the more toxic sphingolipid metabolites. Medium-chain fatty acids and acylcarnitines were decreased in the top quartile of the ERS group (survival) compared to the bottom quartile, even though they were elevated in the ALS group compared to controls. There is again an analogy with diabetes and its complications in that the same thing occurs in patients with diabetes and severe neuropathy.

There are many ways to examine the data to have it become even more informative, such as using regression-based models. These are just models that are adjusted for age, sex, and BMI. In this case, the sample size is a 125 cases and 61 controls. With regression-based models, they can look at super pathways to see which are significantly different between cases and controls, and then among these super pathways they can look at sub-pathways. This is one approach the Michigan team is taking for this research. In terms of ALS pathogenesis, another method that can be used is an adjusted case-control using sub-pathways. Dr. Feldman was very excited to see these data because the fatty acid metabolism, which is quite well-documented in the complications of diabetes and neurologic complications of diabetes to be disorganized and working poorly, is showing the same thing in ALS. The inability to use fatty acids for energy is likely part of this disorder, which has never been shown before. Neither have these sphingolipid findings that they are now seeing been shown in detail. They can also adjust the differences in metabolites. Patients also can be regressed for the presence of the metabolites, such as guaiacol sulfate, creatinine, and catechol sulfate.

Using bioinformatics approaches also can be extremely informative. Dr. Feldman shared the following two examples with ERS and POPs versus metabolites:

- Example 1: Comparing metabolites of ALS subjects in the top quartile of exposure (n=33) versus those in the lowest quartile of exposure (n=27) based on the ERS scores from the survival analysis

- Example 2: Comparing metabolites of cases and controls selected from groups of pentachlorobenzene concentrations, divided into quartiles, quartiles 3 (n=96) and 2 (n=61) had the most overlap between cases and controls

In conclusion, the Michigan team is very excited about what they have and what they are discovering. Dr. Feldman emphasized that this is one of the most important pieces of work she has done in this field. They are identifying unique signatures as hypothesized, and identifying the metabolomic signatures of POP exposures in ALS patients. They can then correlate these metabolomic signatures with residential and occupational exposures histories to yield insights into causal ALS mechanisms. They have a fairly robust 30-page survey that their patients complete. Based on their first CDC contract, they now have an infrastructure to use these new data to seek answers. As mentioned earlier, they have 100 autopsies that can be used to determine whether metabolomic signatures in ALS subject plasma are present in post-mortem brain and spinal cord tissue and correlate with exposures. They are currently doing this on 9 cases.

To close, Dr. Feldman again thanked CDC for the previous funding that allowed them to set up the infrastructure for Dr. Goutman to receive his K23 award and for her and Dr. Goutman to receive the new grant to begin to explore the metabolomic signatures.

Discussion Points

Regarding an inquiry about whether the investigator were surprised that the ALS patients have a slightly higher BMI than the controls, Dr. Feldman indicated that the difference is not statistically significant, but Dr. Goutman has requested that patients provide weights 6 months prior to their diagnosis. What he has discovered is very interesting.

Dr. Goutman added that he would talk about this further in their second presentation, but they have now requested that individuals provide their weight 5 years and 10 years before diagnosis. They adjusted the ERS analyses for these changes in weight over time to help reflect the concern about whether there would be differences in concentrations of POPs and blood due to weight loss.

Dr. Feldman said that he also had discovered that a decrease can be seen in a patient's weight. If someone tells them what they weighed a year previous to the diagnosis, they we can track it. Not unsurprisingly, patients lose weight prior to their diagnosis.

Dr. Goutman added that the reason they were exploring these regression based methods was because they have to think about high dimensional data and selection of targeted metabolites. In the literature, there has been a focus on using approaches such that covariate adjustment cannot be done with the analyses. One of the things that they have been working on with these data is to investigate the ways that they can adjust for covariates, because one of the aims of this grant is to look at the metabolomics over time in order to have longitudinal metabolomics. They hope to combine that with other longitudinal datasets of their exposures, but the current methods to do metabolomics do not allow for longitudinal covariate adjustments. One of their statisticians is currently doing some least absolute shrinkage and selection operator (LASSO)-based approaches and running simulations right now that they hope to see. As Dr. Feldman mentioned, they are seeing very nice concordance between the top metabolites that are coming up with in each of these methods, which gives them a lot of comfort that they all work. As they start to perform some of the longitudinal analyses, they can fall back on the high-dimensional data reduction techniques that they need to use.

Dr. Feldman reiterated that they have blood from every 6 months, but are going to do a longitudinal analysis at Year 1 and Year 2.

In terms of a question about whether they stratified on treatments participants were on, Dr. Feldman indicated that they have not but can do that. That is part of the plan.

Dr. Pioro posed a question regarding the similarities Dr. Feldman mentioned about diabetes and wondered if she had any additional thoughts about that in terms of the kind of mechanistic involvement. Given that they are looking at serum in both patient populations, it is a reflection of what is going on in the nervous system presumably, at least to some degree, and probably in the body in general. He wondered whether they were seeing changes in the ALS patients that may be more downstream to the actual disease mechanism. Presumably, the diabetic population does not have any upper motor neuron dysfunction. He wondered whether they had separated out upper and lower motor neuron predominant ALS patients, given that presumably the peripheral nerves are contributing to some of those changes in the metabolites.

Dr. Feldman indicated that these plasma metabolites mirror, at least for diabetes, how the nervous system utilizes fatty acids and triglycerides for energy. When there is poor utilization (dysfunction of beta oxidation in the nervous system, liver, muscle), which has been shown in diabetes, there is an accumulation of some of the fatty acids. They accumulate because they cannot be properly metabolized, which is what they are seeing in the ALS study. She thinks that what this points out, just as a broad stroke, is energy misutilization and the inability to use at least lipids well. They are currently doing a deep dive into the glycolytic intermediates. In parallel, they are now taking a lot of these findings into the basic science laboratory. They have human iPS cell-derived neurons and rat and mouse primary motor neurons, so they are starting to look at energy utilization at a very basic level. At a high level, she thinks these data point to a lack of the ability of the nervous system in this disease to properly utilize or make energy.

Dr. Pioro noted that if they have enough samples, it would be interesting to look at fast progressors versus slower progressors.

Dr. Feldman indicated that they are going to be able to do that, which Dr. Goutman would be discussing in their second presentation. He just published looking at the difference in how ERS scores actually accelerate progression. They are now going to call those patients out to look at their metabolites.

Dr. Wright congratulated Drs. Feldman and Goutman on this amazing amount of work. Sometimes fishing expeditions can be risky, but this is really great.

Dr. Feldman emphasized how excited they are and expressed gratitude for the opportunity to be able to do this work.

A Population-Based Ohio ALS Repository and a Case-Control Study of ALS Risk Factors

Elijah Stommel, MD, PhD
Dartmouth College
Dartmouth-Hitchcock Medical Center
Geisel School of Medicine

Dr. Stommel indicated that their original 3-year application for the grant period 9-30-2015 to 9-29-2018 was not funded. Initially, this grant was supposed to be for 3 years and include Northern and Central Ohio. Given that CDC did not have the funds for 3 years, adjustments were made for the grant to be 2 years and include all of Ohio. The specific aims of the original study were to: 1) assess ALS incidence by developing the Ohio ALS Repository, a comprehensive, population-based ALS registry for newly diagnosed residents of Northern and Central Ohio; 2) identify ALS risk factors by comparing questionnaire data on exposure to environmental toxins and toxicants between ALS patients and population controls; and 3) perform geospatial analyses of potential environmental exposures to toxins and toxicants in relation to the risk of developing ALS. The revised 2-year application was funded for the period 9-30-2016 to 9-29-2018 with Specific Aim 1 revised to assess ALS incidence by developing the Ohio ALS Repository, a comprehensive, population-based ALS registry for newly diagnosed residents of Ohio. They had to project a target to try to reach, so they projected 200 ALS patients per year based on incidence of ~1.7/100,000 and a total Ohio population of 11.7 million. Dr. Lorene Nelson wrote an interesting paper in 2010 showing that to get a clear idea of incidence, it is necessary to have multifactorial data and use the capture-recapture method mentioned earlier. His team has been attempting to do that type of thing as well.

In terms of Specific Aim 1 to building the Ohio ALS Registry, as of September 30, 2018, they had collected 227 ALS cases out of an anticipated 400 cases based on the incidence of approximately 1.7/100,000. Another 19 cases were reported outside of the diagnostic period. They have collected 98 questionnaires from ALS patients diagnosed within the study window, and 2 from patients outside of the study window. Including those 2 questionnaires outside the study period, a total of 100 questionnaires have been completed by Ohio ALS patients. Random questionnaires were mailed to population controls, of which 342 have been completed in Ohio. Adding the Northern New England population control data, they have received 557 questionnaires out of an anticipated 550 questionnaires for the study duration. They do plan site visits to hospitals, clinics, and neuromuscular centers July through September 2019 with the hope of obtaining an additional 120 ALS cases. They have obtained mortality records from the Ohio Bureau of Vital Statistics for all cases identifying G122 as the underlying or contributing cause of death. These hopefully will be used as some kind of control to look at incidence. Mortality data have been received from 2016 to early 2019 for 906 ALS cases. These data represent about 3.4 years, so the incidence may be higher than they thought. As of June 17, 2019 they had collected 167 biosamples (blood and saliva) from ALS patients and 160 biosamples (saliva) from population controls. The saliva kit is much easier to mail to the controls. Given that blood samples are not required from controls, they simply have to mail back the saliva sample.

They still have some large medical centers that are IRB-approved but have not yet provided cases, including Neurology and Neuroscience Associates, Inc.; University of Cincinnati; University Hospitals; and the VA System (application pending). They recently received approval to access one university hospital in Cleveland, but are not sure exactly how many cases they have. The University of Cincinnati is also a relatively large medical center, so they are hoping to receive some cases from there as well. They expect a fair amount of ALS patients through the VA system once they are approved. They also will look at the VA system in Northern New England. Here is a list of sites that declined to participate, although Dr. Stommel did not know why they did not want to participate other than perhaps they thought it was too much work:

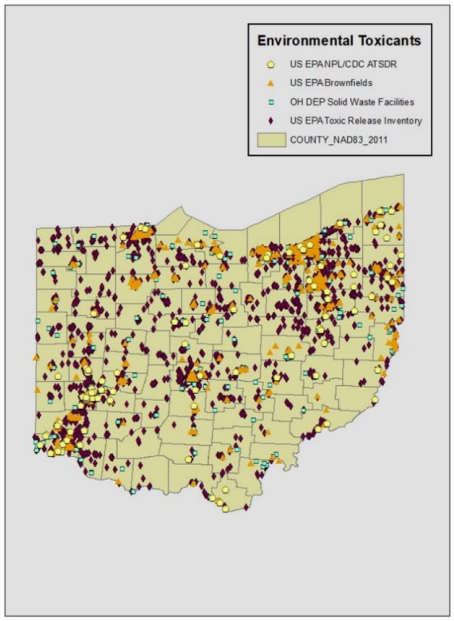
- ❑ Neurosciences Center: ProMedica
- ❑ University of Toledo
- ❑ Advanced Neurologic Associates, Inc.
- ❑ Mercy Health: St. Elizabeth/St. Joes/Belmont
- ❑ Mercy Health Toledo: Neuroscience Institute
- ❑ The Toledo Clinic, Inc.
- ❑ Neuro Health and Wellness
- ❑ UPS Neurology Center

Regarding Specific Aim 2 to identify ALS risk factors by comparing questionnaire data on exposure to environmental toxins and toxicants between ALS patients and controls, in addition to the Ohio population-based case-control analysis, they have analyzed the Northern New England questionnaire data from New Hampshire and Vermont and they found some interesting results. Solvents, lead, and pesticides all seem to have significant p-values. Occupations such as construction, manufacturing, mechanical, military, or painting seem to be associated with ALS with a high odds ratio of 3.95 (95% CI 2.04-8.30). Water skiing has a relatively high risk odds ratio of 3.89 (95% CI 1.97-8.44). Chemotherapy has an inverse odds ratio of 0.46 (95% CI 0.22-0.89). They have published on cancer patients and their risk of developing ALS. Looking at the results in the combined group of patients from Ohio and Northern New England, one finding that stands out is that for those with a family history of ALS, the p-value is going to be very low. This is not surprising, and they did not see much in terms of education and smoking. In the combined Northern New England and Ohio data, they have seen a continuing trend of lead being an important exposure substance with an odds ratio of 2.69 (CI 1.32-5.33). Some of the types of exposures to lead vary the p-value, but apparently casting lead bullets and using stained glass techniques seem to be important. In the combined data from Ohio and Northern New England, they still see that water skiing and swimming are risk factors for ALS, which is important in terms of their interest in cyanobacteria.

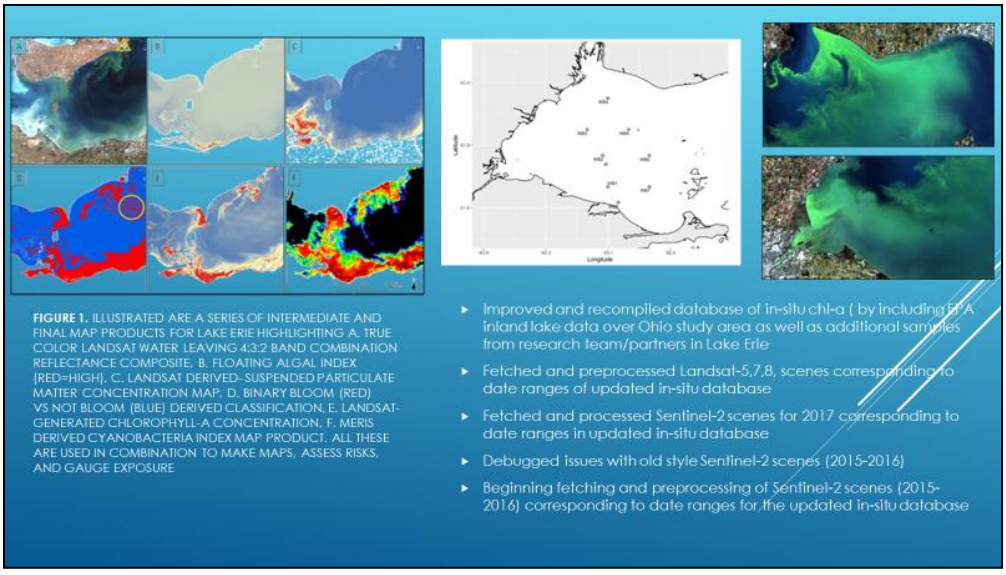
Pertaining to Specific Aim 3, they have mapped out all of the environmental risk factor databases of sources of environmental pollutants in Ohio for the following (this task has been completed for Northern New England for Vermont and New Hampshire as well):

- ❑ Individual sites (n=2551)
- ❑ Individual items (n=282,502)
- ❑ Total number of chemicals (n=~10,000/site)
- ❑ Cyanobacteria compound metrics for all lakes >8 hectares in Ohio, including Lake Erie and Grand Lake St. Marys, and including county pesticide applications 1992-2012

The kilograms per county of pesticides being applied throughout Ohio is alarming, especially in the Northwestern part of the state. Pesticides are known to have a very strong link to Parkinson's disease and probably have a link to ALS as well. Some of the variables that they are looking include National Priority List (NPL) sites, brownfield sites, coal fired power plants, solid waste in landfills, and major highways. This is just an overlay of Ohio with all of the potential exposures on one map:

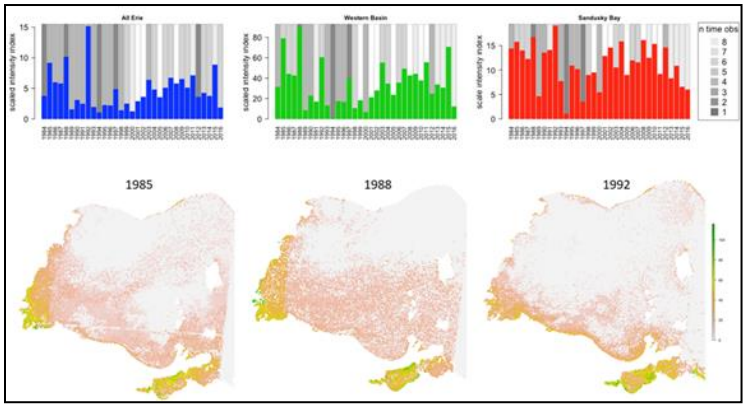


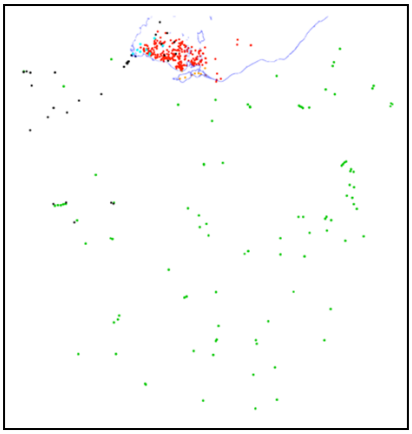
This is the sensing work that Dr. Nathan Torbick and Dr. George Bullerjahn did. The upper left is a true color Landsat imaging technique. This allows them to look at things like the Floating Algae Index (FAI) and particulate matter in the water, all of which correlate with cyanobacteria. On the far right are the Landsat images of the Western Basin of Lake Erie, and the middle image is the sampling sites that were taken at the same time that the Landsat images were taken:



Thus, field measurements that can be correlated with remote sensing. This is just to demonstrate that it is possible to look back in time as there are historical records on cyanobacteria over 20 to 30 years, which may be very important in terms of when people were exposed.

Dr. Stommel indicated that an example of another technique they are using to try to look for clusters in their ALS populations is of time series backcasts of satellite remote sensing models of bloom extent and intensity across Lake Erie, Western Basin, and Sandusky Bay and an ALS patient population from a Florida ALS surveillance project that was conducted between 2009 and 2011:





A similar technique will be used in the Ohio and the Northern New England states. In the [1]Florida example for detecting clusters, the locations of the cases were dithered by the Florida DHHS to conceal the real locations of patients. The cluster detection was conducted using the ArcHealth method kernel-density method (Shi [2]2009, [3]2010) in which a rate is calculated within a neighborhood defined by a circle (the kernel). This calculation is performed for each and every location within the study area. The statistical significance of each rate value is evaluated through a Monte Carlo process. If the p-value at a location is < 0.001, the location is considered to be part of a cluster (hot spot). The neighborhood (the kernel) can be defined in different ways, such as: 1) fixed bandwidth, which applies the same size of circle to all locations; and 2) adaptive bandwidth, which applies different circles to different locations based on local population. The rates for age-sex categories have a jump at age 60. The rates for the categories of age 60 and above are fairly similar. Also, most cases are in the categories of 60 and above. Thus, they first lumped all cases in those categories of age 60 and above for each gender and ran cluster detection for the lumped cases. They then added cases from younger categories to the lumped cases and ran the analysis again to detect the difference caused by younger cases [[1]Freer C, Hylton T, Jordan HM, et al. 2015); [2]Shi, X., 2009, A GeoComputational Process for Characterizing the Spatial Pattern of Lung Cancer Incidence in New Hampshire, *Annals of the Association of American Geographers*, 99(3): 521-533; [3]Shi, X., 2010, Selection of Bandwidth Type and Adjustment Side in Kernel Density Estimation over Inhomogeneous Backgrounds, *International Journal of Geographical Information Science*, 24(5): 643–660].

In terms of the results they are seeing, they received some funding through CDC to continue the Florida work. Definite, probable, and probable-lab supported ALS cases were mapped out in Florida. An interesting finding with the clustering is that it seems to change somewhat when males 60 years of age and above are included versus when males 45 years of age as included. This same phenomenon occurs with females as well. Dr. Stommel said that while it was not completely clear how to interpret these data yet, he thinks it may have to do with genetics. Perhaps younger patients are more prone to getting ALS because of their genetic make-up, or it could be that the younger patients have higher or different exposures than patients who are over 60 years of age.

The plan is to apply this type of clustering technique to the populations of Ohio, Northern New England, and Florida in terms of overlapping these with all of the environmental toxins that they have mapped out.

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

Hiroshi Mitsumoto, MD, DSc
Director, Eleanor and Lou Gehrig MDA / ALS Research Center
The Neurological Institute of New York Columbia University Medical Center

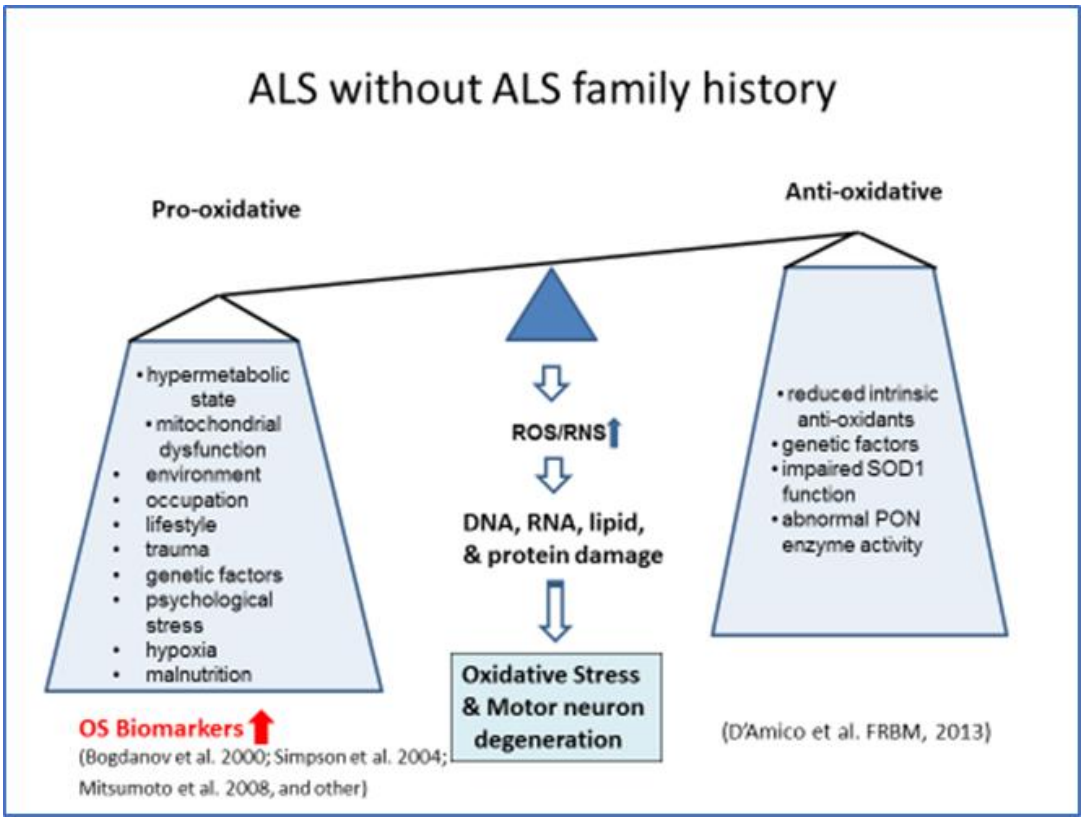
Dr. Mitsumoto began by emphasizing what incredible progress has been made and expressing his gratitude to Drs. Horton and Mehta for their leadership. He recalled that when this started and Dr. Horton talked about establishing the National ALS Registry, he was hit by a lot of negative comments from ALS experts. Because they persisted, the progress has been incredible. Dr. Mitsumoto said that he is so positive now about this effort, and that hearing presentations on all of the inspiring and various types of research renewed his commitment.

During this session, he discussed the project titled ATSDR Risk factors Epidemiologic Studies in ALS (ARREST ALS), which is an epidemiology study of ALS that is based on the ALS Multicenter Cohort Study of Oxidative Stress (ALS COSMOS). ALS COSMOS is a large, prospective, multisite longitudinal (24 months) study assessing clinical, cognitive, epidemiological (environmental risks, military, hobbies), psychological, and dietary risk factors in 355 patients with ALS within 18 months after symptom onset. ALS COSMOS includes DNA, plasma, skin fibroblasts (165 patients), and urine biorepository data. They now have collected almost all survival data. The ALS COSMOS study provides Class II evidence.

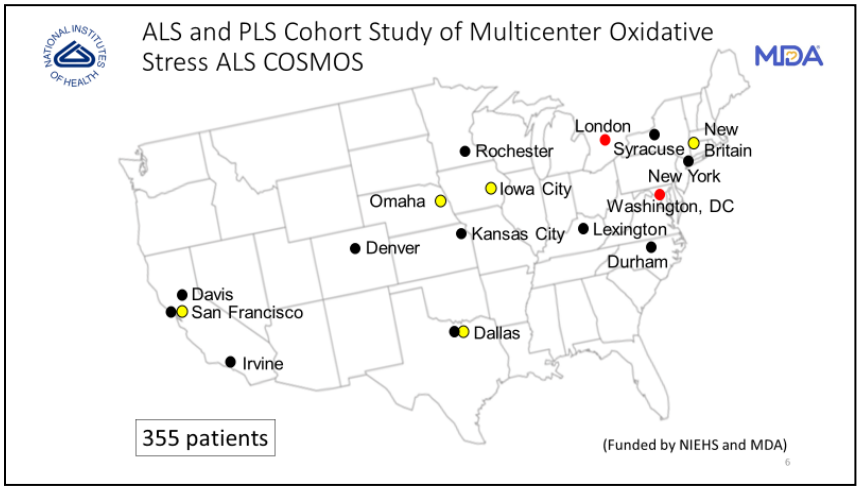
The National Institute of Environmental Health Sciences (NIEHS)-funded ALS COSMOS 16-center cohort study is based on the hypothesis that for patients with more oxidative stress, disease progresses faster. The hypothesis for the ALS COSMOS study was that oxidative stress (OS) is associated with the progression of sporadic ALS without ALS family history. There are a tremendous number of exposures, internally and externally, that result in oxidative stress. The principle hypothesis of the ALS COSMOS study is that OS may be associated with the progression of sporadic ALS. The specific aims of ALS COSMOS were to determine:

- ❑ If increased OS (combined environmental exposure) biomarkers are associated with the progression of ALS
- ❑ If OS biomarkers and the OS index (combined environmental exposure is associated with survival in ALS)
- ❑ If a variety of environmental, psychological and lifestyle factors are associated with increased levels of OS biomarkers at baseline
- ❑ If lipid profiles have any association with ALS progression
- ❑ If baseline OS biomarkers are associated with subtypes of ALS

The following depicts the pro-oxidative and anti-oxidative states:



The study centers are shown in the following map. The black dots are original sites, yellow dots are new sites, and red dots are PLS-only sites:



The study was completed in April 2018, and a number of papers have been funded as shown in the following table, with a number of major papers to be published in the coming months with very interesting results:

Publications from ALS COSMOS Study

Paper (Personnel)	Paper Status
ALS COSMOS Structure and Methodology (H. Mitsumoto et al.)	Published in ALS/FTD Journal
Mitochondrial Markers in ALS Fibroblasts (G. Manfredi et al.)	Published by Annals of Neurology
Depression and Wish to Die in ALS Cohort (J. Rabkin, et al.)	Published in ALS/FTD Journal
PLS, Clinical and Molecular Characterization (H. Mitsumoto et al.)	Published in Neurology Genetics
Cognitive and Behavioral findings at Baseline (J. Murphy, et al.)	Published in Neurology
Nutritional Analyses at Baseline (J. Nieves, et al.)	Published in JAMA Neurology
Cognitive, Behavioral, Depression, Wish to Die (J. Rabkin, et al.)	Published in Neurology
Telephone based cognitive-behavioral screening for frontotemporal changes in patients with amyotrophic lateral sclerosis (ALS) (G. Christodoulou et al.)	Published in ALS/FTD Journal
Longitudinal Cognitive and Behavioral Changes (S. Woolley, et al.)	Published in Behavioral Neurology
Plasma Creatinine and Oxidative Stress Biomarkers in Amyotrophic Lateral Sclerosis (H. Mitsumoto, et al)	To be submitted

(A study report of epidemiological and oxidative stress is still pending)

Based on those multi-center studies in ALS COSMOS, the National ALS Registry became an important way to reach out to the entire nation. Dr. Mitsumoto and his team wondered how they could increase the number of patients. Since 355 was trivial, they wanted to increase the numbers. The plan was to recruit an additional 420 patients for the ARREST ALS project. Essentially, the protocol was exactly the same as for COSMOS. The specific goals for ARREST ALS were to:

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

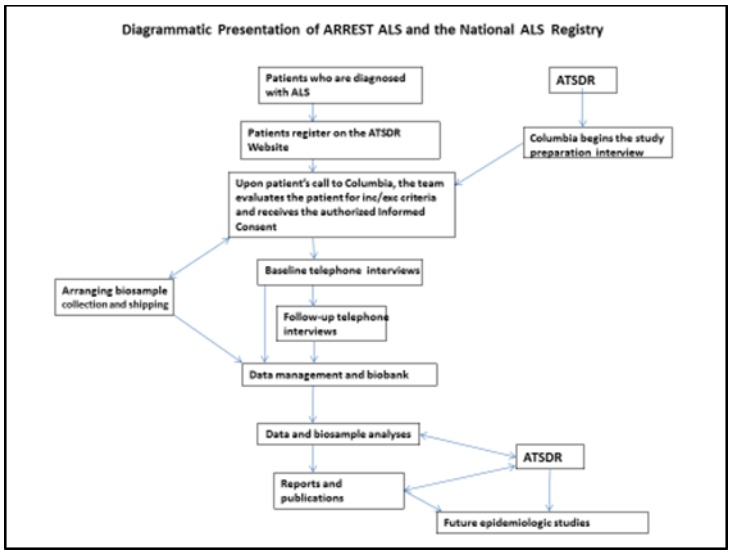
- ❑ Have patients participate voluntarily by enrolling themselves into the National ALS Registry and initiating their participation

The key is to increase awareness of this project for potential patients through a national campaign. Patients diagnosed with ALS register under the National ALS Registry and then initiate a call to Columbia's ALS Center at 1-855-STOP ALS. Everything is done over the phone (obtaining informed consent, medical records, all interviews, et cetera). Cognitive testing was done over the phone as well. A pilot study showed the equivalency of most in-person and telephone cognitive screening tests. DNA and urine samples are obtained. Patients' follow-up schedules are similar to the ALS COSMOS study at baseline, 3, 6, 12, 18, and 24 months. The aim was to enroll 420 subjects from 50 states. Also collected were general items within the categories shown on the following table:

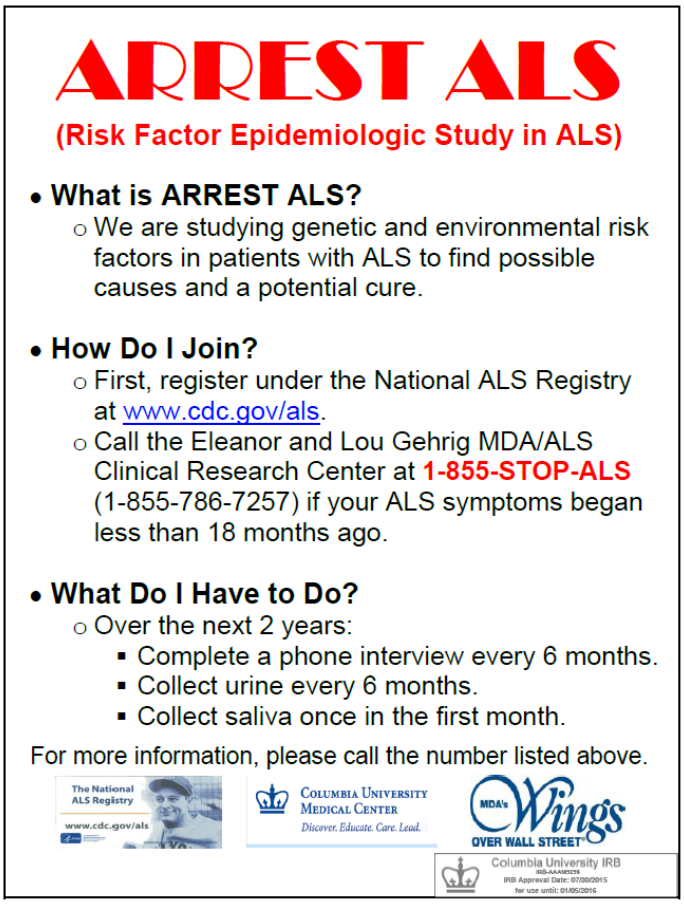
Description of Questionnaire Data Collected: Items Related to Oxidative Stress

Assessment	Min – Max	Assessment	Min – Max
Demographics	9 – 13	Occupational	17 – ∞
Case Ascertainment	26 – 70	Military	2 – ∞
Family Pedigree	28 – ∞	Physical Activity	1 – ∞
Health Review / Current Physical Condition	12 – ∞	Hobbies	1 – ∞
Early Life	23 – 36	Tobacco and Alcohol	4 – 29
Adverse Childhood Experience	11 – 11	Caffeine	4 – 26
Stressful Life Events	12 – 73	Psychological Measures	95 – 106
Head Trauma	6 – ∞	Sleep	24 – 25
Residential	16 – ∞	Fatigue	10 – 10
		Diet	89 – 237

The following diagrammatic presentation illustrates the process:



This piece was created to advertise the project, with a goal to generate enough publicity to encourage newly diagnosed ALS patients to register and call Columbia University:



Those who registered are called and if deemed eligible received telephone-based cognitive testing. Diagnosis is determined through medical record information. Basic physical data (weight, FVC, et cetera) and biosamples (urine and DNA) are acquired. The following cognitive scales are utilized:

- ❑ 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 tests were modified so that they could be used over the phone. Equivalence Testing was performed for in-person and telephone tests that had the same scales (ALS-CBS, WVFT, COWAT, FBI-ALS, CNS-LS). These statistical methods are rigorous alpha-level analyses used by the FDA to compare generic drugs to standard drugs. For tests with different scales (MMSE/TICS, ALS-CBS Caregiver Portion), percent of total values were used for analyses.

Intraclass correlation coefficients (ICC) were calculated as secondary analyses. Sequence effects also were analyzed. The findings are shown in the following table:

Table 1: Results from equivalence testing across visit types. Equivalence is claimed with 5% significance (*) when the 90% confidence interval on the mean ratio is completely contained within the equivalence bounds of **[0.80, 1.25].** For comparison, 80% confidence intervals are displayed for a test of equivalence with 10% significance (#) for those not significant at the 5% level.

Instrument	ICC	Asymmetric 90% Conf Int on ratio	Asymmetric 80% Conf Int on ratio
ALS-CBS	0.50	**[1.00, 1.11] ***	
COWAT_A	0.71	[0.79, 1.05]	**[0.82, 1.01] #**
COWAT_F	0.75	**[0.87, 1.01] ***	
COWAT_S	0.51	**[0.90, 1.12] ***	
CNS-LS	0.79	**[0.94, 1.09] ***	
FBI-ALS	0.54	[0.72, 1.14]	[0.76, 1.08]
WVFT	0.76	[0.95, 1.32]	[0.99, 1.27]
MMSE_TICS (%)	[b]	**[0.84, 0.93] ***	
ALSCBS-CG (%)[a]	0.79	**[0.95, 1.00] ***	

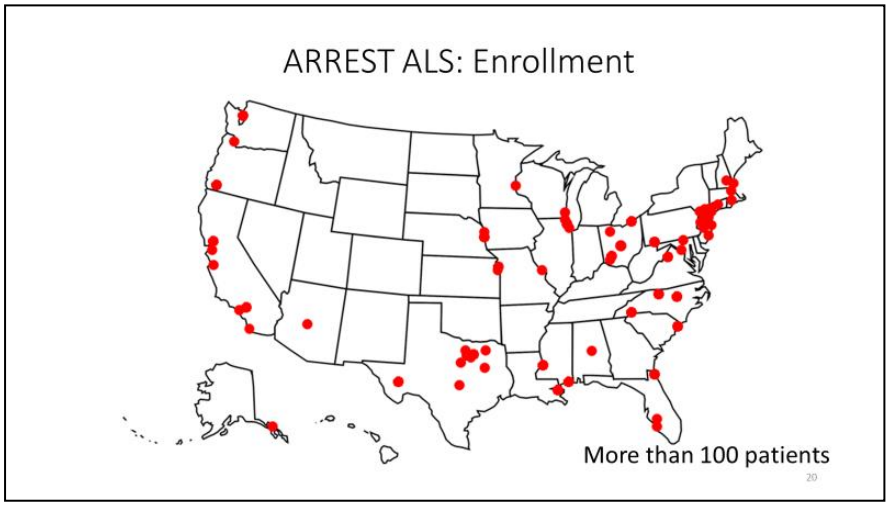
a: A constant value of 1 was added to accommodate the 0s in log transformed values.
b: The ICC could not be estimated due to ill-conditioning of the covariance matrix of the random effects.

In terms of conclusions from the pilot study, the ALS-FBI and WVFI 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 were found across testing. The study suggests that the telephone-based version 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. Development of telephone-based cognitive testing for ALS could become an integral resource for large population-based research in the future [Christodoulou G, Gennings C, Hupf J, Factor-Litvak P, Murphy J, Goetz RR, Mitsumoto H. Telephone based cognitive-behavioral screening for frontotemporal changes in patients with amyotrophic lateral sclerosis (ALS). Amyotroph Lateral Scler Frontotemporal Degener 2016; 7-8:482-488. PMID: 27121545].

The ARREST ALS goals are to:

- ❑ Expand the ALS COSMOS study
- ❑ Conduct a multisite study that reaches the entire nation
- ❑ Generate enough publicity to encourage newly-diagnosed ALS patients to register and call Columbia University
- ❑ Conduct all interviews by telephone, which they have shown they could do
  - ➢ Diagnostic certainty through medical record information
  - ➢ Basic physical data: weight, %FVC, etc.
  - ➢ Developed telephone-based cognitive testing
  - ➢ Psychological status
  - ➢ Epidemiological information
  - ➢ Diet Questionnaire
- ❑ Obtain needed biosamples (urine and DNA) through the mail

In terms of enrollment, a total of 227 patients have been screened and 105 of those were deemed eligible and were enrolled. Regarding the source of the 227 patients screened, 165 came from the National ALS Registry, 21 from the brochure, 35 from CUMC, and 7 from other (e.g., ALS forums, ATSDR conference). ARREST ALS enrollment by state is shown in the following map:



With regard to comparisons between ALS COSMOS and ARREST ALS, there are no differences in gender ratio, ethnicity, and region of onset. Patients in ARREST are more likely to be white, use Medicare/Medicaid, show a trend of higher educational attainment, have distant family members who had ALS (although this is marginal), and have more non-ALS symptoms such as progressive muscular atrophy (PMA) based on El Escorial criteria. They did this comparison based on about 80 patients, and then they continued. They have not analyzed the difference between the ALS COSMOS population and the ARREST ALS population combined, but will soon do this to increase the power.

In terms of the comparison of clinical features, there are some differences in the ALSFRS-R total scores which are significantly lower in ARREST ALS. The onset of screening and enrollment time is longer in ARREST ALS because they had such a hard time recruiting patients, which took 18 months initially. This may be the reasons ALSFRS-R scores might be more. Based on the telephone interviews, finger tapping was much slower than foot tapping. Dr. Mitsumoto does not think this is accurate. He asked the interviewers how they did it, and he thinks they need to use a smart phone for tapping and foot tapping for more clear and rigorous tapping. He would not rely on these data at this point. Cognitive testing was essentially the same except for a few things. Behavioral screening done by caregivers showed no difference, which is very important in terms of comparing the ALS COSMOS patients and the ARREST ALS patients. Some are clearly showing some differences, such as the Verbal Fluency Index. They also looked at the C9org72 hexonucleotide repeats. In ARREST ALS patients, 5.0% of cases tested were positive. Among COSMOS patients, 6.2% of cases tested were positive. While Dr. Mitsumoto said he did not know whether this was significant, he did not think so. They looked at urinary OS biomarkers normalized by specific gravity for 8-isoprostane, 8-oxodG, and creatinine and compared previously and newly analyzed data and there was a significant difference. Urinary OS markers showed isoprostane, which was significantly higher in the ARREST ALS group.

With respect to epidemiological studies in ALS with the National ALS Registry in comparison with the ALS COSMOS study, the first patient was enrolled in December 2014. At the end of the CDC contract in June 2018, more than 100 patients were enrolled. The pace of enrollment was much slower than anticipated, despite several adjustments and modifications. Data entry and analyses of all environmental (occupational, military, hobby, residential), dietary, and psychological risk factors are currently underway. This project established the reliability of novel telephone-based frontotemporal cognitive testing to evaluate cognitive impairment among ALS patients for ARREST ALS. The molecular test results of C9orf72 gene was slightly lower in the ARREST ALS patient group (5%) compared to ALS COSMOS (6.2%). Urinary oxidative stress markers showed isoprostane, which was significantly higher in the ARREST ALS group. The investigators will confirm this finding when they complete the ARREST control study. They demonstrated that extensive epidemiological studies can be conducted entirely over the telephone. Finally, minimal differences in clinical characteristics between study samples will allow them to combine the two study groups (ALS COSMOS and ARREST ALS) to increase power for future analyses.

In terms of ARREST controls, ALS COSMOS and ARREST ALS are cohort studies. Appropriate controls are needed to determine the significance of environmental risk factors. They proposed another study to include controls and proposed to do everything the same way in terms of interviews and so forth. They decided to use sibling controls because most siblings share the same exposures, lifestyles, et cetera. Information from sibling controls will provide control data for environmental health risks during early developmental ages. Population-based controls are based on Zip Code, age, and using the Federal Information Processing Standard (FIPS) country code, race, and ethnicity. This information provides control data for environmental, dietary, and psychological risk factors. They hoped to get 2 controls for every 1 patient originally. Instead, 50 sibling controls were screened and 41 were found to be eligible. Of those, 39 completed interviews. Of the patients, 30 never consented for sibling contact as they died or withdrew before ARREST controls were up and running and 24 patients either do not have siblings, have unwilling siblings, are estranged from their siblings, or their siblings speak other languages. For the population controls, 177 patient cases were sent by RTI to date. Of those, 175 were screened, 71 were deemed eligible and enrolled, 4 of 5 deemed eligible that are pending have consented, and 21 were ineligible. Of the 71 enrolled subjects, 64 have completed interviews, 65 have submitted urine specimens, and 61 have submitted saliva samples. Immediate future plans are to:

- ❑ Enter all data into a large database

- ❑ Analyze urinary isoprostane and 9-oxod-G (urinary OS) biomarkers for:
  - ➢ ALS COSMOS
  - ➢ ARREST ALS
  - ➢ Sibling controls
  - ➢ Population controls

- ❑ Decide on the most effective comparisons:
  - ➢ Can ALS COSMOS+ARREST ALS patient populations be combined?
  - ➢ Comparisons between ARREST ALS population and sibling controls
  - ➢ Comparisons between ARREST ALS and population controls
  - ➢ Comparisons between all ALS patients and all controls

In closing, Dr. Mitsumoto again expressed his gratitude to ATSDR and CDC for their continued support and to RTI for their assistance with population controls.

Discussion Points

Ms. Comfort inquired as to whether they already piloted and had success with the 9-oxo-dG assay to look at OS.

Dr. Mitsumoto that they published on that some years ago in 2004. They did 8-isoprostane and 8-oxo-dG. Initially, they normalized by creatinine levels. It turned out that creatinine is increasing with disease progress. Therefore, they are now using specific gravity and have published that. Clearly, ALS cases and controls are very different.

Ms. Comfort noted that the 8-oxo-dG kit has changed the enzyme that they used in the kit, so they have had trouble reproducing some of their results, at least for the 8-oxydG. She was not sure about 9-oxo-dG.

Dr. Mitsumoto indicated that Regina Santella is conducting all of those studies and knows all of those changes very well.

Ms. Backman observed that about 80% of the individuals who were screened for ARREST ALS came from the Registry. Because the enrollment rate was about 50% of the screening rate, she wondered if they looked at whether there was a higher percentage of those who actually enrolled if they came from the Registry. The Registry is a notification tool, so given the extent that they continue to promote it as such, it is important to know that those people who are enrolling are actually making it to the final cut.

Dr. Mitsumoto indicated that while they have looked at this in a number of ways, he could not answer that offhand. This may have been done and he acknowledged the importance of knowing. They have a conference call monthly with Drs. Horton and Mehta who have raised the question. The ALS Registry is an internet-based questionnaire, and ARREST ALS is using the telephone interview process for risk factor exposure. They do want to know whether the internet-based surveys are getting the same results as the telephone interviews. A major problem is the Columbia University IRB. It took one year to solve a disagreement between RTI and Columbia University to get approval to look for control participants based on patient information. Confidentiality is important without any doubt. However, for future studies they need to somehow modify to facilitate IRB's rigid barriers to sharing confidential information.

Identification and Validation of ALS Environmental Risk Factors

Stephen Goutman, MD, MS
Associate Director, ALS Center of Excellence
Russell N. DeJong Professor of Neurology
University of Michigan

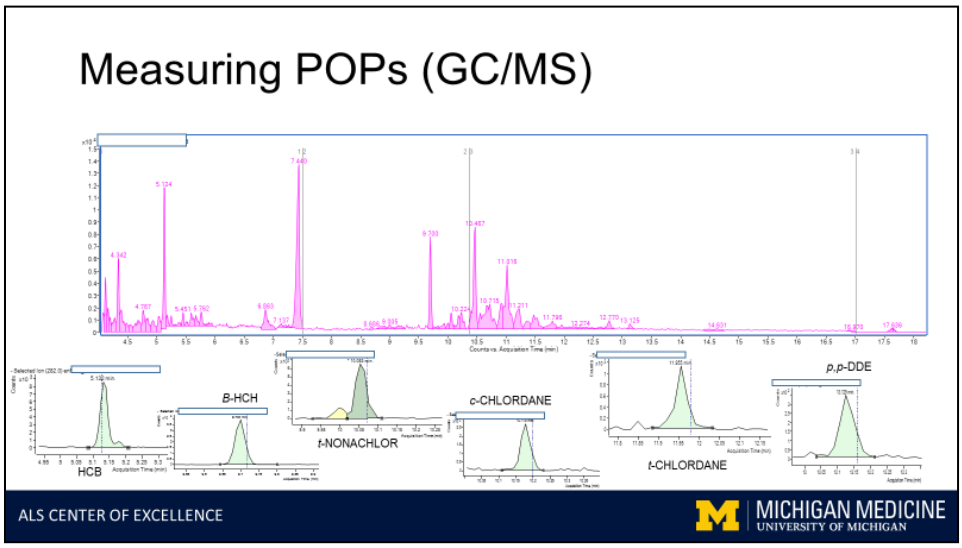
Eva Feldman, MD, PhD
Director, ALS Center of Excellence
Associate Professor of Neurology
University of Michigan

Dr. Goutman emphasized what an honor it was to be presenting on behalf of the University of Michigan and expressed gratitude to Drs. Horton, Mehta, Wright, and everyone else at ATSDR for all of the support they have provided. During this session, he provided an update on their last contract to give some background on what Dr. Feldman discussed earlier. In terms of the project background, the study goals for the project that just ended were 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. While the initial project has been completed, they continue to learn a lot from the data that have been collected and that will support work moving forward in many directions. They are very excited about the types of data that have been collected, what they can learn from it, and what can be done with it to help solve this disease.

The University of Michigan has a very robust ALS patient biorepository comprised of individuals with ALS and controls. The repository collects demographic data, clinical data, biofluid samples, fibroblasts, and autopsy tissue (brain, spinal cord, teeth). They have published on this in the last couple of years. The demographics for the cases and controls are similar in terms of the numbers of individuals, gender, age, and non-smokers. There is some difference between the cases and controls in terms of the distance people live from the University of Michigan, which is a challenge in terms of generating a good control population. Clinical data and biospecimens are collected from patients about every 6 months during their clinic visits, so they get a nice coverage of the patients they see and have good participation rates. They are collecting information from people with all types of ALS.

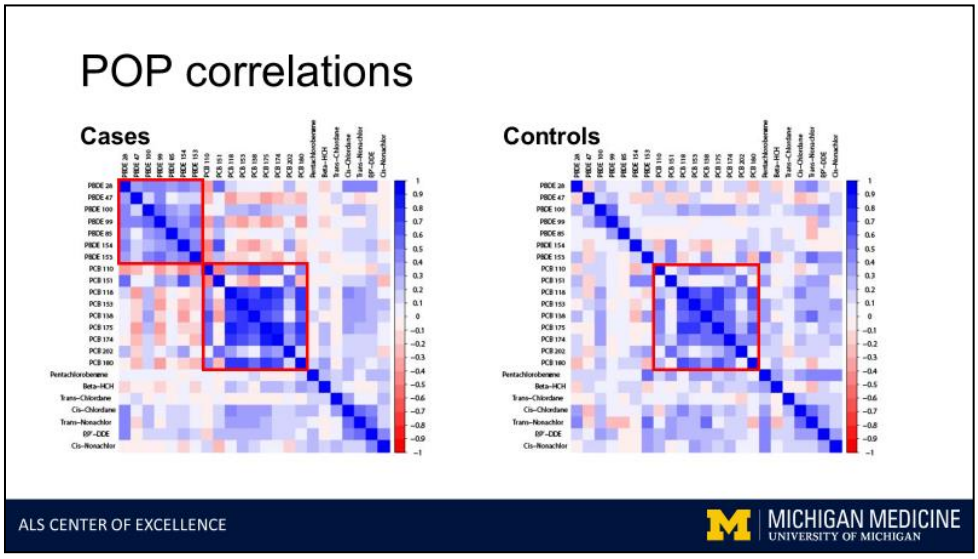
One of the major efforts they have undertaken is to measure POPs using gas chromatography-mass spectrometry (GC/MS) methods as shown in this chromatogram:



This chromatogram shows the masses that are displayed over their retention times. Through this targeted approach and targeted extractions, they can see the different organochlorine pesticides in this case that are appearing in their subjects. They have done this on a large number of individuals and currently have about 150 samples that are fresh off of the machine that they have not looked at yet. A few years ago, they published on the association between POPs and the risk or odds of having ALS. What they noted was that as a whole, each of the pollutants has a small risk in terms of having an association with ALS. Of particular note is that organochlorine pesticides have a strong risk for ALS. Looking at the effects of combined exposures, they found that pesticides were strongly influencing the risk of ALS.

In the original publication, they combined plasma and whole blood measurements. Because of a protocol change, they now focus totally on plasma measurements. They now have new unpublished data, which do not include the samples that are just coming off of the machine yet, so they are going to add to this number considerably. What they see between their 167 cases and 99 controls is that there is no difference between age, sex, military service, or smoking status for the most part. There is a difference in the baseline BMI and the BMI slope at the time of enrollment in the study. These variables have been adjusted for in the models because of that difference. There also is an educational difference. There have been some recent publications that support educational status as either a risk factor or protective factor for ALS. While it is not clear whether this cohort is necessarily proving that, it is something to keep in mind.

In terms of assessing the correlations of these pollutants, it is very important to understand how they act together. They may have additive risks, synergistic risks, or no interaction whatsoever. In their models, they have to consider how these pollutants interact with one another and how they are correlated to one another. Here are the cases and controls:

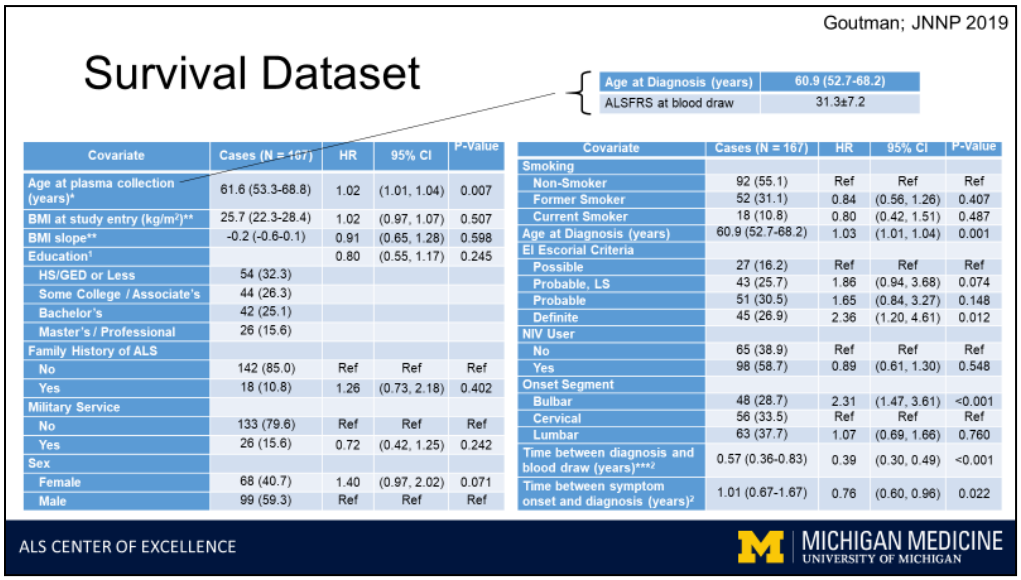


In the ALS cases, the categories of polychlorinated biphenyls (PCBs) are correlated to one another and so are the polybrominated diphenyl ethers (PBDEs). The PBDEs are flame retardants. In the controls, the correlations are with the PCBs. When considering the combined effect of multiple exposures, it is important to use the correct statistical methods to account for that. Therefore, one of the things their group is interested in is developing an environmental risk score (ERS). An ERS is essentially a summary score to characterize the disease risk from exposures to mixtures of pollutants:

- $ERS_i = \widehat{\beta_1}E_{1,i} + \widehat{\beta_2}E_{2,i} + \cdots + \widehat{\beta_p}E_{p,i}$
  - ERS_i is the environmental risk score for each case (i)
  - $\widehat{\beta_1} \ldots \widehat{\beta_p}$ are the regression coefficients for the given environmental pollutant (1 to p)
  - $E_{1,i} \ldots E_{p,i}$ are the standardized concentrations of the given environmental pollutant for each case

When they assessed these data, they found that multiple pollutants are associated with a higher risk of ALS. When they combined these into ERS scores, they see that of particular importance is that PBDE 153, cis-Nonachlor, and pentachlorobenzene were strongly influencing this risk. The other thing to point out is that the combined ERS odds ratio is around 7.5, so the combined effect of the ARs is stronger than individual effects. This provides some additional statistical power as they do some of the associated studies with these data. Looking at cases versus controls, they found that when an individual moves from the 25th percentile of exposure to the 75th percentile of exposure, they have a 7 times greater risk of having ALS when the effect of these pollutants combined is considered. This is a pretty amazing risk to consider. Essentially none of the other covariates included in the model were significant. These data indicate that the mixture of pollutants are strongly driving the risk of ALS.

They also wondered whether these exposures alter the progression of ALS or the survival of ALS. For the 167 individuals who have ALS, they considered some important covariates in ALS models, including: age, sex, El Escorial criteria, onset segment, non-invasive ventilation (NIV) use, time between symptom onset and diagnosis, BMI and BMI slope, education, family history of ALS, military service, and smoking history. All of these covariates have shown to have some effect on prognosis and survival of ALS, so they wanted to make sure they adjusted for all of these in their models. In terms of the demographics of their survival dataset, the median age at collection of the plasma was 61.6. The associated hazard ratio of each of these variables individually is shown in this table:



Goutman; JNNP 2019

Survival Dataset

Age at Diagnosis (years)	60.9 (52.7-68.2)
ALSFRS at blood draw	31.3±7.2

Covariate	Cases (N = 167)	HR	95% CI	P-Value
Age at plasma collection (years)^	61.6 (53.3-68.8)	1.02	(1.01, 1.04)	0.007
BMI at study entry (kg/m²)**	25.7 (22.3-28.4)	1.02	(0.97, 1.07)	0.507
BMI slope**	-0.2 (-0.6-0.1)	0.91	(0.65, 1.28)	0.598
Education[1]		0.80	(0.55, 1.17)	0.245
HS/GED or Less	54 (32.3)			
Some College / Associate's	44 (26.3)			
Bachelor's	42 (25.1)			
Master's / Professional	26 (15.6)			
Family History of ALS				
No	142 (85.0)	Ref	Ref	Ref
Yes	18 (10.8)	1.26	(0.73, 2.18)	0.402
Military Service				
No	133 (79.6)	Ref	Ref	Ref
Yes	26 (15.6)	0.72	(0.42, 1.25)	0.242
Sex				
Female	68 (40.7)	1.40	(0.97, 2.02)	0.071
Male	99 (59.3)	Ref	Ref	Ref

Covariate	Cases (N = 167)	HR	95% CI	P-Value
Smoking				
Non-Smoker	92 (55.1)	Ref	Ref	Ref
Former Smoker	52 (31.1)	0.84	(0.56, 1.26)	0.407
Current Smoker	18 (10.8)	0.80	(0.42, 1.51)	0.487
Age at Diagnosis (years)	60.9 (52.7-68.2)	1.03	(1.01, 1.04)	0.001
El Escorial Criteria				
Possible	27 (16.2)	Ref	Ref	Ref
Probable, LS	43 (25.7)	1.86	(0.94, 3.68)	0.074
Probable	51 (30.5)	1.65	(0.84, 3.27)	0.148
Definite	45 (26.9)	2.36	(1.20, 4.61)	0.012
NIV User				
No	65 (38.9)	Ref	Ref	Ref
Yes	98 (58.7)	0.89	(0.61, 1.30)	0.548
Onset Segment				
Bulbar	48 (28.7)	2.31	(1.47, 3.61)	<0.001
Cervical	56 (33.5)	Ref	Ref	Ref
Lumbar	63 (37.7)	1.07	(0.69, 1.66)	0.760
Time between diagnosis and blood draw (years)***[2]	0.57 (0.36-0.83)	0.39	(0.30, 0.49)	<0.001
Time between symptom onset and diagnosis (years)[2]	1.01 (0.67-1.67)	0.76	(0.60, 0.96)	0.022

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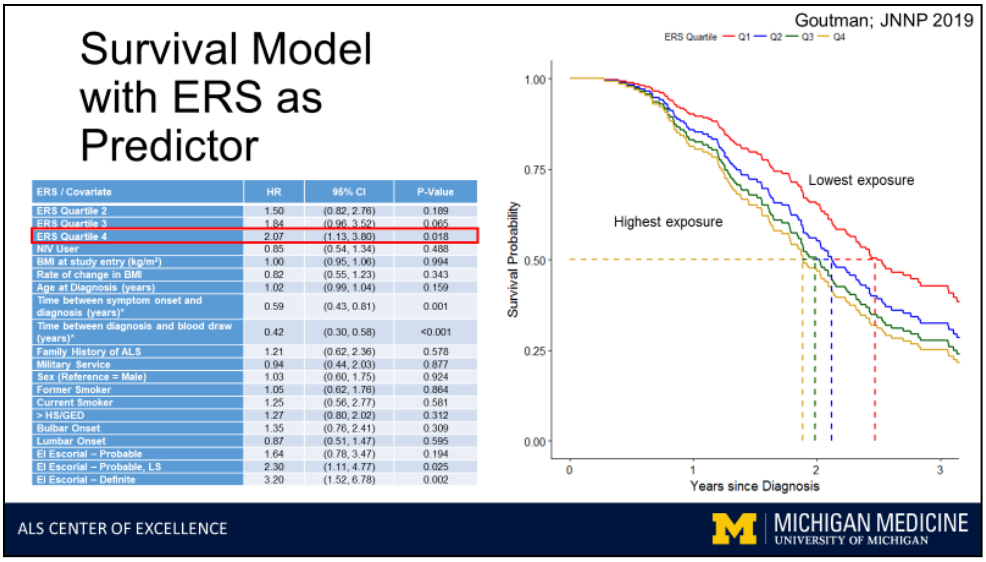
Looking at each of these pollutants in terms of their individual contribution to the hazard ratio and how they individually impacted survival, many of these pollutants alone have a small effect on influencing the survival of the cohort. However, the combined effect of these pollutants results in a statistically significant ERS of about 1.5. They grouped the cohort into quartiles to look at individuals with the highest quartile of exposure versus those in the lowest quartile of exposure, shown below:



ERS / Covariate	HR	95% CI	P-Value
ERS Quartile 2	1.50	(0.82, 2.76)	0.189
ERS Quartile 3	1.84	(0.96, 3.52)	0.065
ERS Quartile 4	2.07	(1.13, 3.80)	0.018
NIV User	0.85	(0.54, 1.34)	0.488
BMI at study entry (kg/m²)	1.00	(0.95, 1.06)	0.994
Rate of change in BMI	0.82	(0.55, 1.23)	0.343
Age at Diagnosis (years)	1.02	(0.99, 1.04)	0.159
Time between symptom onset and diagnosis (years)*	0.59	(0.43, 0.81)	0.001
Time between diagnosis and blood draw (years)*	0.42	(0.30, 0.58)	<0.001
Family History of ALS	1.21	(0.62, 2.36)	0.578
Military Service	0.94	(0.44, 2.03)	0.877
Sex (Reference = Male)	1.03	(0.60, 1.75)	0.924
Former Smoker	1.05	(0.62, 1.76)	0.864
Current Smoker	1.25	(0.56, 2.77)	0.581
> HS/GED	1.27	(0.80, 2.02)	0.312
Bulbar Onset	1.35	(0.76, 2.41)	0.309
Lumbar Onset	0.87	(0.51, 1.47)	0.595
El Escorial – Probable	1.64	(0.78, 3.47)	0.194
El Escorial – Probable, LS	2.30	(1.11, 4.77)	0.025
El Escorial – Definite	3.20	(1.52, 6.78)	0.002

This is a Cox Proportional-Hazards Model, not a Kaplan-Meier Plot. The lowest exposure group is in red and the highest exposure group is yellowish gold. The group that has the highest exposure has a hazard ratio that is 2 times that of the lowest exposure group. This accounts for about a 6-month period of survival difference between these two groups, which is a pretty significant interval when considering the survival time of ALS. There does appear to be a dose response effect. The individuals in ERS Quartile 2 had a hazard ratio of 1.50, those in Quartile 3 had a hazard ratio of 1.84, and those in Quartile 4 had a hazard ratio of 2.07. Some of the other typical factors that are important in a survival model show up, including time between symptom onset and diagnosis. Bulbar onset had a higher hazard ratio but was not statistically significant.

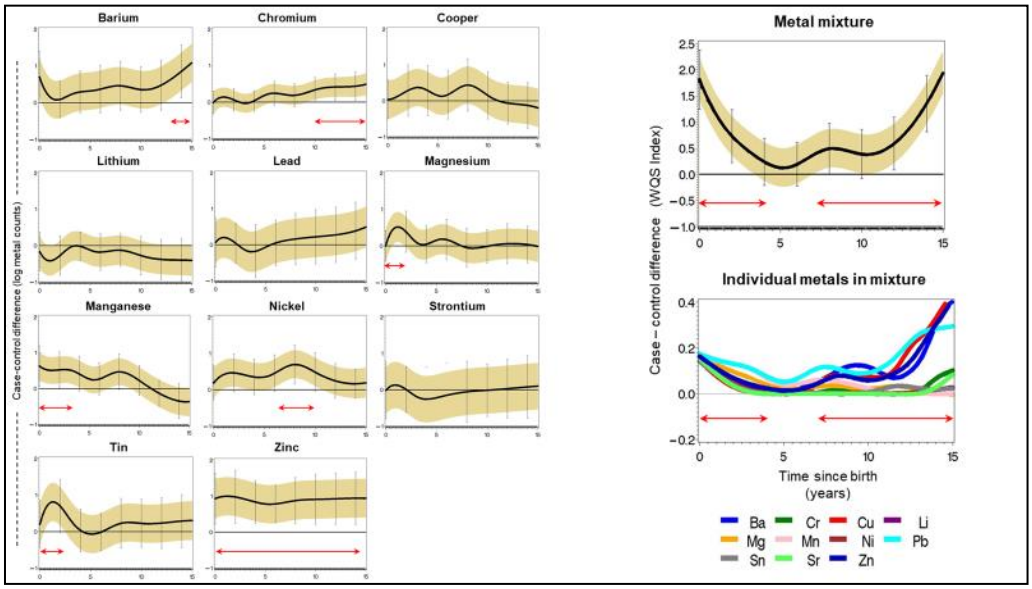
They also have been collecting surveys from individuals who enter this cohort. This is a detailed survey asking about their occupational history, residential history, hobbies, lifestyle factors, military service, and head trauma to try to understand what insights can be gained on prior exposures. Questions from each survey are categorized into different exposure types, including: Pesticides, Metals, Particulate Matter (PM), Volatile Organic Compounds (VOCs), Biologicals, Combustion Products, Radiation, Corrosives, and Thermals. These are all preliminary data. They are working to finalize the scores and categorizations.

In terms of PM exposure score development, PM is defined by the EPA as "A mixture of solid particles and liquid droplets found in the air." Emission sources include construction sites, fires, power plants, automobiles." Essentially what they have done is developed a PM exposure score based on about 120 variables from their survey based on the residential and occupation history questions to better understand the characteristics of jobs and homes that would drive one's likelihood of being exposed. They are collecting very detailed information on the use of kerosene or wood stoves or fireplaces in the home; scraping paint or demolition activities in the home; use of gas-powered equipment in an attached garage; and the presence of nearby emission sources (major roads). They assigned all of the questions in the variables a risk to try to figure out which are the most relevant questions that are influencing the score. They also are looking at the performance of this score versus survey completeness. This is of interest because it is known that some people work tediously to complete their whole survey and others fight through it. They want to understand if certain questions are driving the PM score in order to reduce it down. Perhaps this would be applicable for other researchers who are using different surveys. They are continuing to work on these scores, which can then be applied to other

datasets. This is particularly relevant to the metabolomics dataset to understand whether there are metabolomic signatures of PM, reported PM exposure, reported exposure to pesticides, and some of the other categories listed.

One of the newer datasets that they have brought online is an evaluation of urinary metals that includes 136 cases and 24 controls. They have not been funded to do this, so they used internal funds in these cases and controls in order to get a sense of what is occurring. They sent urine to a company called NSF International in Ann Arbor, Michigan. Water filters usually are certified by NSF International, and they also do a lot of environmental monitoring. To date, the following have been analyzed: Antimony, Arsenic, Barium, Beryllium, Cadmium, Cesium, Chromium, Cobalt, Copper, Lead, Manganese, Mercury, Molybdenum, Nickel, Platinum, Thallium, Tin, Tungsten, Uranium, Vanadium, and Zinc. They have seen no significant differences between cases versus controls and the National Health and Nutrition Examination Survey (NHANES) data, no significant association with current water source (well versus city), no significant association with geography, and no significant association with onset segment. The plan is to send more control samples, longitudinal samples, and perhaps samples to check for metals in the blood.

The reason they are not willing to give up on this is that they are very interested in understanding the windows of susceptibility to disease in terms of exposures to metals. This work is driven by Dr. Figueroa-Romero in Dr. Feldman's laboratory and Dr. Manish Arora at Mount Sinai, who is a dentist by training. They have been able to look at the metals in teeth, which are really interesting for understanding exposure. The tooth can be thought of as rings on a tree, which can be cut open to see the rings. Teeth become a permanent marker of one's exposure to metals exposure from 0 to 15 years of age. Dr. Arora's laboratory uses laser ablation to drill into a tooth and pick up the metal particles via mass spectrometer (MS) techniques to look at the uptake or absorption of metals at 2-week intervals from 0 to 15 years of age. What they have found is shown in the following illustration in which the red arrows indicate a period of time where there was a statistically significant difference in the absorption of metals in cases compared to controls:



For example, for barium a case was more likely to be absorbing barium between the ages of 12 and 15. For chromium, there is a period of time between 10 and 15 years of age. With barium, chromium, magnesium, manganese, nickel, tin, and zinc there are windows of time during early childhood and early development where the cases are absorbing more metals. They are collecting teeth post-mortem and the permanent marker does not change. They are able to get controls from people who are losing their teeth for other purposes. The combined effects of these mixtures of metals also must be taken into consideration. Using a lagged weighted quantile sum (WQS) method shown in the right side of the illustration above, the cases are more likely to be absorbing metals as a mixture between the ages of 0 and 3 and 7 to 15. They believe that metals, even in early development, may be playing a role in terms of one's susceptibility to ALS.

Their conclusions are that higher concentrations of POPs measured from plasma are associated with increased odds of having ALS. PBDE 153, cis-nonachlor, and pentachlorobenzene are of particular interest in driving this risk. Pentachlorobenzene is the group Dr. Feldman mentioned in the presentation of metabolomics in which they are seeing unique metabolites in terms of the grouping of the pentachlorobenzene. The ERS is a powerful method of summarizing exposures to multiple chemical mixtures. Lower concentrations of POPs measured from plasma in ALS subjects are associated with a longer survival. Survey-based responses can yield insight into prior exposures. While they have not seen any changes in urinary metals in cases versus controls and NHANES cohorts, early childhood exposure to metals does associate with ALS risk.

In terms of future directions, they want to expand their longitudinal exposure measurements to examine changes in POPs, metals, and organophosphates at multiple time points. They are anticipating some National Institute of Environmental Health Sciences (NIEHS) R01 funding for that. They also want to understand the genetic and exposure interactions and have submitted an application for grant funding to determine how the measurements they are collecting are interacting with genes. They want to continue to develop survey-based exposure measures and test these against their other datasets (exposure biomarkers and metabolomics) to determine how they yield insight into disease pathophysiology and mechanisms. In addition, they want to examine the influence of these exposures on disease risk, progression, and phenotype.

In closing, Dr. Goutman expressed their gratitude to ATSDR and the National ALS Registry for funding the key work that was needed for them to continue their program.

Discussion Points

Dr. Kuldip inquired as to whether organic pollutants are metabolized on their own throughout the years. For example, would PCB 174 be excreted or metabolized. If not, he wondered how they would know whether a person has a certain level because they had a little exposure a year ago or were exposed to a lot of it 20 years ago. That seems like a confounder that must be dealt with.

Dr. Goutman replied that organic pollutants are metabolized. These are halogenated compounds that were developed because of their stability. The goal of these chemicals was that they would persist in whatever application they were used, such as a pesticide application or flame retardant. When they are applied, their half-lives are decades and longer and they have the same half-lives once inside humans. Once someone is exposed to them, they persist. They are enrolling individuals with ALS in the State of Michigan, which is relevant because Michigan is surrounded by the Great lakes. There has been a lot of work trying to understand how these

toxins may or may not accumulate in the Great Lakes, such as bioaccumulation through fish, and then drive that exposure to humans. Once they get into the environment, they last and people continue to get exposed. All of these compounds are now banned, but they continue to be persistent. The exception perhaps is DDT. They think it is no longer made in India and in China, but there is some concern that it could still be under production in North Korea. Because these toxins get into the atmosphere, they can travel some distance. They have even been picked up in the Arctic, so they can be measured in polar bears that have never otherwise come in contact with them. While based off of a measurement he could not say whether somebody was recently exposed or exposed 20 years ago, they are hoping to fill in that gap by using longitudinal measurements to help understand the change in these exposure levels over time. If they take a measurement at Time 0 at 1 year, at 2 years they can get the trend. They have done some preliminary work looking at these measurements over time in a handful of cases and a handful of controls from a different study. What they see is that some people stay the same, some increase, and some decrease. They really need to roll this out now to a large sample size to determine what is happening with these pollutants over time. Dr. Feldman added that they are funded to do that by the CDC.

Ms. Comfort asked whether calcium is measured in teeth and, if so, how they control for calcium levels. For example, perhaps the greater uptake of metals in teeth is due to a lack of calcium in the diet during childhood development.

Dr. Goutman indicated that there is a control for calcium.

Dr. Nelson said she wondered about the fact that the ALS cases are losing fat and the controls are not, given that fat is where these POPs are stored. Perhaps controlling for that is not really controlling for that, given that the controls are not emancipating these products into their blood.

Dr. Goutman replied that they do not fully know. This is one of the reasons they want to look at the longitudinal measures. One thing they noticed when they preliminarily looked at controls longitudinally they saw the same changes. Some of the control measurements stayed the same, some increased, and some decreased. They have to understand what factors may be driving the changes. Is it just fat loss effect? Is it not fat loss effect? Is it something different? They are going to have to gain some insight with the longitudinal measurements as well as the metabolites of these pollutants and how they affect the metabolism, which should offer some sense of what is happening biologically.

Antecedent Medical Conditions and Medications: Associations with the Risk and Prognosis of ALS

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Dr. Nelson thanked ATSDR for providing the opportunity to study the association of antecedent conditions and the medications used to treat those conditions with the risk of developing ALS, on which she presented an update during this session. This was a true population-based study using Medicare data from 2006 to 2013 in individuals 65 years of age and above. This was a nested case-control study which identified ALS cases and appropriate controls in that time period using the Medicare claims data. The specific aims were to: 1) investigate the association

between antecedent medical conditions and the risk of developing ALS to determine whether metabolic conditions (diabetes, hyperlipidemia), cardiovascular diseases (CVD), or autoimmune disorders are associated with the risk of developing ALS; 2) investigate the association between medications used to treat antecedent medical conditions and the risk of ALS to determine the association between several classes of medications (diabetic medications, statins, lipid-lowering medications; cardiovascular medications (ACE inhibitors); and immunosuppressants and the risk of developing ALS; and 3) determine whether medical conditions or medications present at diagnosis of ALS adversely or positively affect survival with ALS.

In terms of the first aim, previous studies that have investigated the association of diabetes with ALS risk have not been able to study diabetic medications and their association with risk. Therefore, it is not clear if it is the condition itself that is inversely associated or apparently protective for ALS, or if it might be one of the classes of drugs that is used to treat ALS that is lowering the risk of the disease. Dr. Nelson's group is still analyzing data regarding statins and lipid-lowering medications. They are planning to specifically evaluate ACE inhibitors, which have been inversely associated with ALS in some past studies of interest. ACE inhibitors are used in diabetic patients, especially those who have kidney disease. Therefore, it will be important to adjust for diabetes and make sure that if there is an inverse association and ACE inhibitors appear to be protective, that it is not due to just the presence of diabetes. However, Dr. Nelson indicated that she would not be presenting those results during this session. In this presentation, she focused largely on antecedent medical conditions with the newest results on diabetes medications.

A very intriguing picture is developing about ALS. Some studies in the past have shown that increased engagement in vigorous physical activity increases the risk of ALS. The studies have been inconsistent, probably because of the difficulty in measuring this ubiquitous fact of life, physical activity, and its relationship with risk of disease, and not really knowing exactly which time periods to look at or which aspects of physical activity might be most associated. The studies associating BMI and increased risk of ALS are very consistent, especially if the BMI is measured 10 or more years prior to the clinical onset of the disease. Diabetes has been consistently associated with risk in an inverse direction in recent studies, meaning that people who develop ALS are less likely to have had diabetes. When considering a question like this, it is important to make sure that the presence of diabetes and antecedent conditions before the actual clinical onset of the disease may have affected those factors. That is, they do not want to be measuring something that is an effect of the disease. They want to make sure to look at a period of time that actually could have causal significance. There is an excellent publication that goes exhaustively through all of the various changes in energy balance and altered metabolism after disease onset in ALS patients [ZA Ioannides et al. Altered Metabolic Homeostasis in Amyotrophic Lateral Sclerosis: Mechanisms of Energy Imbalance and Contribution to Disease Progression. Neurodegenerative Diseases 2016; 16: 382–397].

The Stanford collaborators used an ambidirectional study design. They are interested in the factors that precede ALS onset in the first aim, while the third aim is looking at the factors present at onset that are associated with a shorter survival. The first two aims were addressed using a nested case-control design in which they look at the previous history captured by Medicare records of the antecedent conditions and comparing the cases with age, sex, and geographically matched controls. They ultimately ended up with 3714 ALS cases and five controls per case for nearly 19,000 controls. Later, they will conduct a retrospective cohort study looking at the association between those factors present at onset that may affect survival with ALS (e.g., diabetes, hyperlipidemia, autoimmune conditions, and medications used to treat

conditions). This session covered association of medical conditions themselves with ALS, as well as diabetic medications.

The study time period was 2006 to 2013 and included all Medicare beneficiaries who were captured in Parts A, B, and D Medicare, meaning that all of their claims data was captured. They are not in Medicare Part C or Medicare Advantage. If people are captures who are continuously enrolled in Parts A, B, and D for both cases and controls, it is possible to get an exactly matched time period for each person and their age-matched controls. Not examining differing lengths of previous history for the two groups is a critical study design feature. They have to have equal opportunity for assessing that exposure and determining whether it was there. They identified ALS cases that occurred in 2008 to 2013 because they required at least a 2-year prior antecedent medical history. They matched them to controls on sex for year of birth +/- 1 year and the county of enrollment, because it is important to have a geographic match due to geographic differences in medical care.

The case definition criteria used by the National ALS Registry was used, adapted for the fact that there is only one source of data in which they were looking for ALS cases:

- One or more encounters coded for ALS in ≥ 1 year, and one or more prescriptions for Riluzole

  Or

- One or more encounters coded for ALS in ≥ 2 years, one of which must be a neurologist visit

  Or

- One or more encounters coded for ALS in 1 year, with ≥ 5 neurologist visits during that year

After applying the criteria to the Medicare utilization record for those years, they identified 3714 subjects who met the eligibility criteria in that they met one or more of the ALS case definition criteria. Most of them met several, either all three or at least two. About 81% met Criterion 3 that required 1 or more encounters coded for ALS in at least 1 year of their utilization with 5 or more neurology visits during that year. Another 45% met the criteria of having 1 or more encounters for ALS in 1 or more years and they had at least 1 riluzole prescription. About 9% met only Criterion 2, which is 1 or more encounters coded for ALS in greater than 2 or more years, 1 of which must be a neurologist visit. That means that in total, 90% of the cases identified either satisfied Criterion 3 and/or had been treated with riluzole, so this is a pretty robust set of cases in terms of misclassification.

The other thing that must be done when conducting this kind of study is to establish the appropriate antecedent period in which exposures will be assessed. They were interested in everything before ALS onset, but ALS onset must be defined. They know from examination of the records the date at which they first met the case definition criteria. However, there may be a lag between the first show of codes for ALS or MND. They know from their records what the date was of the first ALS/MND code that later resulted in a confirmed case definition. They call that index data or reference date. They know that anything that might be causally contributive has to occur before that, but presumably much before that. Most studies in the past have counted all exposures up until the time of diagnosis, but she and Dr. Kasarskis spoke and

decided that they should be very strict about that. A couple of rigorous studies excluded the 1-year period prior to the first clinical recognition of ALS in the record. While that is better, they decided to exclude the whole 2-year period prior to the clinical recognition of ALS. The reasoning was that that is probably the etiologically relevant period, and that they are looking at antecedent chronic conditions that probably present during a lifetime that should be in the record more than two years prior to the index date.

They constructed antecedent medical variables based on recommendations of the Chronic Conditions Data Warehouse (CCW) within Medicare. The CCW has algorithms for 27 chronic conditions that have been well-validated, so they used these recommended algorithms for identifying the various conditions of interest in the medical utilization data. They had to construct their own for autoimmune diseases, which they modeled after the rheumatoid arthritis algorithm. The claims were from outpatient clinical care, inpatient hospital care, skilled nursing facilities, home health care services, hospice care, prescription data, and mortality data.

Dr. Nelson presented the results for demographic characteristics, hyperlipidemia, diabetes, CVD, and autoimmune diseases. There was an exact match on the number of males and females in the ALS cases and controls and in age for the groupings of 67-74 years of age, 75-79 years of age, and 80+ years of age. There were slight differences in race/ethnicity in that 93% of the cases were white versus 86% of the controls. Of the cases, 3% were black and 1% were Hispanic, while 6% of controls were black and 2% were Hispanic. They adjusted for race/ethnicity, age, sex, and county in all of the analyses.

In terms of the association between hyperlipidemia and the subsequent risk of ALS, the period of interest excludes the 24 months prior to the diagnosis or the index date of cases. There was an identical prevalence of hyperlipidemia in the medical claims data prior to that point, with an odds ratio of .99 (0.91-1.07). They performed a sensitivity analysis to determine whether that changed at all if they counted up to 12 months prior to the index date. There was still no difference. There also was no difference when they counted up to index dates. At least in this dataset, hyperlipidemia is not associated with the risk of developing ALS. They did look at duration of hyperlipidemia as well, and there was just a flat line. There was no association between how long hyperlipidemia had lasted and the risk of ALS.

Regarding the association of antecedent diabetes with ALS counting all diabetes of Type 1 and Type 2, in the time period up until 24 months prior to index data, 23% of cases and 30% of controls had evidence of diabetes in their records. The odds ratio was .68 (0.63-0.74). Any odds ratio below 1 indicates an inverse association or a possible protective effect. The way to interpret an odds ratio of .68 is that that is associated with a 32% reduction in risk. No risk is at one, so.68 is subtracted from 1, which is a 32% reduction in risk associated with diabetes when you count diabetes up to the 24 months prior to the index date. The association did not change much actually. It was still highly statistically significant and inverse when looking at the other two time periods as a sensitivity analysis.

To put this into context with the rest of the literature, the Stanford study had an odds ratio of .68 and is the only study that examined individuals 65 years of age and above so their prevalence of diabetes was much higher than in the other studies. Dr. Mariosa in Sweden, Dr. Weisskopf from Harvard, and a group in the Netherlands all found in case-control studies an inverse association between diabetes and the risk of ALS. These were very consistent ranging from .59 to .79. A cohort study done in Italy showed an even stronger inverse association with a relative risk of .30. There was a curious outlier study in Taiwan that had a positive association of 1.35. That study was interesting in that the only group that had the increased risk associated with

diabetes was men under the age of 65. Therefore, it could have been due to more Type 1 diabetics perhaps causing that. Among women above the age of 65, the odds ratio was inverse at .84. She has not reviewed all of the features of that study designed to figure out why it would be so inconsistent with all of the other studies, but it is curious.

When they examined whether the association varied according to type of diabetes since Type 1 diabetes is an autoimmune condition and Type 2 is a metabolic condition, the odds ratios for those two disorders were virtually identical. Interestingly, the previous studies done in Sweden and Denmark both identified stronger inverse association of diabetes in older individuals with a significant trend. The Stanford team observed the same thing in that the individuals above age 75 at diagnosis had a stronger inverse association with risk for Type 1 diabetes and Type 2 diabetes. These are highly statistically significant effects. With such large sample sizes, this is very precise and very gratifying to analyze. Looking at the duration of Type 2 diabetes, there was no significant dose response. People that had diabetes longer did not have greater protection. It was just that having diabetes conferred a continuous reduction in risk of about 20%. They then looked at the medications associated with treating diabetics, counting those up to the period of 24 months prior to the index date.

About 10% of cases versus nearly 15% of controls have been treated with metformin. The associated odds ratio is .66 and the confidence limits exclude 1 significantly, so this is highly statistically significant. When they restricted that association to diabetics, it was still highly statistically significant. The odds ratio was .78, but it did move a little closer to unity once they restricted it to the diabetics. Sulfonylureas showed the same thing with a significant inverse association, movement toward unity, and still highly statistically significant after adjustment for diabetes. The same was true with thiazolidinediones. For the incretins that are a newer class of diabetic medications that are more rarely used, there was a significant inverse association looking at them by themselves. When they looked among diabetics and adjusted for that, it was no longer significant. They looked at insulin by combining both Type 1 and Type 2 diabetics because they both get treated with that. The odds ratio there was the strongest inverse association they saw with any diabetic medications. It was highly statistically significant, and was still highly significant after looking at the effect among diabetics.

This just shows that all of the classes of diabetic medications except for incretins still had a significant inverse association with risk even after adjusting for diabetes, so these are two independent risk factors that appear to be inversely associated or protective for ALS. It is also important to point out is what happened to the effect estimate for diabetes once the medications were adjusted for. Even after adjusting for the diabetic medications, the presence of diabetes was still strongly inversely associated with the risk of ALS that is highly statistically significant, suggesting that there is a 20% reduction in risk if someone has diabetes.

Thus, their conclusion about metabolic conditions is that antecedent hyperlipidemia was not more common among ALS cases than controls. Nevertheless, because there has been a lot of interest in statin medications and their possible association with ALS risk, they are going to analyze the medication data about that. With respect to diabetes, both Type 1 and Type 2 diabetes were associated with at least a 20% reduced risk of developing ALS, even after adjusting for medication use. The inverse association was strongest among the individuals aged 75 years and above, and was observed for all diabetes medication classes in terms of the inverse association with medications.

There is a growing body of evidence that shows that dysregulated energy metabolism in animal models of ALS exist with metabolic abnormalities that proceed onset and can hasten disease progression, both in the mutant SOD model where caloric restriction has detrimental effects and causes earlier symptom onset and shortened lifespan. In the other direction, high energy diets actually protect mutants against MND progression. With the TDP-43 over-expression model, it can lead to elevated TBC1D1 in skeletal muscle, which itself is associated with defective insulin-mediated glucose uptake. Protective effects of high sugar intake have been observed in the C. elegans model of ALS that expresses mutant TDP-43. There are increasing publications regarding the disease-associated genes in ALS and their contributions to glucose regulation or dysregulation and energy metabolism. This body of evidence is summarized in a recent paper by Wade in 2018.

In the Stanford study, they want to adjust for obesity. However, they do not have BMI measures from the claims data so they have to use ICD-9 codes as surrogates for being obese. The Demark study by Dr. Weisskopf et al showed that obesity status by itself was inversely associated with ALS with an odds ratio of .69 or .72. When they adjusted for diabetes, it was no longer statistically significant. It was still inverse, but the confidence limits encompassed 1, so that was not statistically significant. However, diabetes was associated with an odds ratio of .59. It was not materially affected after adjusting for obesity, so it looks like diabetes is a strongly associated inverse factor, even after taking into account the fact that patients with ALS are less likely to have been obese, which itself is a risk factor for diabetes.

One of the most interesting studies is one done by the group in Sweden. Dr. Mariosa's dissertation was done in this area. They had a Swedish cohort from whom serum samples had been stored on individuals, so they were able to conduct a follow-up nested case-control study to identify those who developed ALS and those who did not over an average of 20 years after the serum were collected. They found that there was a statistically significant inverse association of high glucose levels. Levels of ≥6.1 milliliters per liter were associated with a 38% reduction in risk, and this was statistically significant. This is evidence that while high glucose levels might be deleterious for diabetes development, they may be protective for ALS.

In terms of cardiovascular conditions, hypertension, acute myocardial infarction, ischemic heart disease, heart failure, and stroke, any CVD had a modest inverse association of any cardiovascular disease with risk at 0.85. This is the exact odds ratio that others have reported for cardiovascular conditions. They saw a slightly increased association of stroke with ALS in that 8% of cases versus 6.3% of controls had ICD-9 codes for stroke in their medical records. They thought that might be due to early clinical consideration of the symptoms of ALS, and perhaps ascribing them to stroke and subsequently reclassifying them as ALS. They are not sure. The other three conditions that were inversely associated with risk were hypertension, ischemic heart disease, and heart failure. When they looked at the whole class of autoimmune diseases, there was essentially no association with any of them (asthma, RA, systemic AID, thyroid AID, cardio AID, skin AID, non-neuro AID, or all AID). The confidence intervals overlap 1, which means that they could find no evidence that having had autoimmune conditions in one's past medical history was associated with ALS.

To summarize, there was a modest inverse association with several of the cardiovascular conditions associated with about a 15% reduction in the risk of ALS. This has been observed in a couple of other studies. They want to conduct additional analyses to control for obesity and cigarette smoking. Some studies have shown that cigarette smoking is more common among cases than controls. If that were the case, this would drive the odds ratio further away from unity and would make it seem more protective. Despite the fact that they might be more likely to be

cigarette smokers, they still have a lower prevalence of those cardiovascular conditions. They are also going to look at the association with ACE inhibitors and other CVD medications with ALS. There was no association found between ALS and antecedent autoimmune conditions. The remaining work to do is to complete the examination of medications as they relate to the risk of developing ALS, and examine all of the antecedent medical conditions together to assess their association with the length of survival with ALS.

In closing, Dr. Nelson thanked everyone who worked on this study and Drs. Mehta and Wright for their ongoing support.

Discussion Points

Dr. Talbot asked whether they think that the statins can lead to muscle wasting. They published a paper in *JAMA Neurology* two years ago with the Women's Health Initiative (WHI) cohort of 193,000 women 50 to 79 years of age with 256 cases. Women who exercised moderately to heavily had a 1.5 increased risk of ALS. They did not look at statins, but it does go with the keeping of the reduced diabetes.

Dr. Nelson indicated that there have been studies linking statins to myopathy, muscle weakness, and even rhabdomyolysis. There has been a keen interest in whether exposure to statin medications may increase the risk of ALS. They plan to study that as well as other lipid-lowering medication.

Dr. Agnese expressed appreciation for the methodology used in defining index data and looking at the time leading up to that, and suggested that perhaps they could discuss this further offline. This is something that they have tried to tackle to develop an algorithm for early diagnosis by looking at the 5 years leading up to the index data. They defined it slightly differently, but it is interesting that by the time these patients enter trials, they are at the tail-end of the lengthy disease process. For their research, they did not categorize specific therapeutic areas or diseases. They cast a wide net and looked at the Truven Health MarketScan® database that has 180 million lives, among which they were able to identify 14,000 ALS patients and look at the 5 years leading up to diagnosis. They were able to see different patterns in their CPT, ICD-9, and ICD-10 codes for at least 5 years leading up to the time of diagnosis, which supports some of the comments made during their discussions about there being a very long process leading up to the time a patient actually gets diagnosed. They have now developed an algorithm using that mutual information to identify these commentarial features that would predict which patients, based on their coding, would get diagnosed. She emphasized the challenge and importance of interpreting what is occurring in the pre-diagnosis period. The common features they saw were connective tissue disease, fatigue, hypertension, resource utilization, et cetera. Using machine learning, they are not going in with any biases per se. Interpretation is an entirely different skill set.

Dr. Nelson pointed out that the 1 or 2 years prior should be excluded because of the increased medical surveillance and increased recognition and coding of other conditions.

Dr. Oskarsson asked whether they were able to assess the severity of diabetes and whether that had a connection. Someone with poorly controlled or difficult to control diabetes would be more likely to be put on insulin. He wondered whether other diabetes complications such as neuropathy or nephropathy would give them dose information and show an even stronger association.

Dr. Nelson indicated that they could look at those data and thought it was a good suggestion, but it is a big programming load to do because there are 18 or so associated diabetes complications codes.

Dr. Mehta asked whether they examined A1c.

Dr. Nelson said that they do not have the ability to look at A1c because it does not show up in the Medicare claims data.

In terms of the study design and finding some autoimmune diseases that are known to increase the diagnostic odyssey, Ms. Webb asked whether they could help inform future directions for medical education to help identify ALS earlier in order to get people into multidisciplinary clinics and trials earlier.

Dr. Nelson indicated that when they looked at the other autoimmune diseases in the year prior to first recognition of a MND, several conditions were observed more commonly among cases than controls just as suspected: myasthenia gravis (MG), multiple sclerosis (MS), and chronic inflammatory demyelinating polyneuropathy (CIDP). If those occurred in the record, consideration should be given to considering those diagnoses on the way to the true diagnosis of MND.

Dr. Kuldip asked whether they looked at lipid storage diseases, recalling that Dr. Feldman discussed sphingolipids earlier.

Dr. Nelson said that because they have large sample sizes, they could look at that to see if there is any kind of signal.

Dr. Pioro asked whether they looked at patients who may have had cervical radiculopathy or cervical myelopathy, which may be confusing the diagnosis. He often wonders whether previous trauma to a nerve root or that part of the nervous system could predispose one to developing ALS. There are some data from the VA in some older studies identifying that the onset of ALS was more frequent in a region where there had been trauma. He wondered whether Dr. Nelson could pull that out of some of their data to look at associations such as that.

Dr. Nelson indicated that they could. It was not in their class of conditions that they were looking at with CVD or autoimmune diseases. It is a matter of financial support and time. They still have a lot to do to finish even their basic analyses, but with enough time she would like to look at that.

Open Discussion on Research Challenges and Suggested Future Research

Cherie Imam, Facilitator, Facilitator
Carter Consulting, Inc.

During this session, Ms. Imam facilitated an open discussion focused on research questions, challenges, and suggested future research.

Discussion Points

In terms of plans to look for ALS frequency, Dr. Bradley recalled that Dr. Nelson mentioned the previous day that they were thinking about conducting capture-recapture studies. He also recalled that she published a paper in 2010 on capture-recapture with regard to ALS incidence, which was a rather negative study with regard to the benefits of capture-recapture. Capture-recapture in the animal population field is, in fact, a very well-validated method. It uses the same method of capturing and then recapturing the population. He thought most of the studies Dr. Nelson was looking at were really alternative ways of getting the cases rather than capturing and recapturing. He requested that she enlighten them with regard to what she is planning to do with capture-recapture, because he thought it would be a very valuable technique if they could design something that would actually be capture-recapture. In the animal field, they have to band the birds and then go back to find out how many are banded and how many are not banded. This cannot be done with ALS patients.

Dr. Nelson remembered conducting a study on the Registry data for the years 2002-2004 using the administrative data sources, but that was published more recently about 2 years ago. Perhaps he was thinking of Dr. Benatar's paper, who has an interesting and challenging clinical population. She just received notice of funding to do that work on the first year of the Registry and on 2014, which she will be able to report back next summer. One of the assumptions underlying capture-recapture is that each of the sources that is used to capture is operating independently of the others. With Medicare, Medicaid, and VA data, there is not necessarily that assumption of independence. However, that independence can be taken care of statistically by modeling it to still get a precise and robust measure of the degree of undercount.

Dr. Mehta mentioned that ATSDR hopes to expand the ALS research agenda for FY19 by funding a new award at the end of this year. He asked whether anyone had any ideas about areas on which they should focus. He knew that military veterans and ALS represent an important area of study on which they want to focus, potentially in collaboration with the VA. TBI and ALS is another area they feel needs to be explored.

It was noted that one source they are not getting is commercial claims data. They know that they are probably under-capturing individuals under 65 years of age and those who are still employed and have employer-based insurance. Dr. Nelson indicated that by examining Truven Health MarketScan® data, they found 13,000 cases.

Dr. Mehta indicated that ATSDR is doing the same thing as well. They have the Truven MarketScan® database internally at CDC, and they have given permission to a group at CDC to run ATSDR's algorithm on their dataset for MarketScan® to see exactly what sort of case numbers they get back. They are in the process of doing this. ATSDR is hoping to publish on that in conjunction with the 2016 report, if not separately. They just are not sure when that will be finished and what the timeline is. ATSDR is getting Part C data as well.

Ms. Backman clarified that the fact that Medicare data are loaded into the portal does not mean that those individuals are only over 65 years of age. Based on their numbers, 60% to 65% of individuals with ALS are in Medicare because of their disability, not because of their age.

Mrs. Kennedy added that there are also people who continue to work, which excludes them from Medicare for either disability or age.

Dr. Bradley pointed out that although Truven is a very extensive database, it does have geographical patchiness in that there are areas that it does not cover. Many of these databases must be overlapped.

Dr. Mehta added that a limitation for any paper is geographic coverage, so they want to make sure they are addressing pockets in the US that are not covered.

Dr. Pioro said that one of the things they have discussed briefly is the age range of patients who develop ALS. It might be interesting to examine the extremes of the age ranges. It is known that ALS tends to occur within the age range of 55 to 65 years of age, depending upon male/female. But by looking at the younger age group versus the older age group, it may be possible to identify risk factors that may predispose an individual to developing earlier disease in the very young if it is not familial. His hypothesis would be that the youngest ones are the most likely to be genetic. If they are not, then consideration should be given to what the sporadic cases are doing in that age group. What is driving the disease in earlier onset? Conversely, they could look at the older age group to determine why individuals are developing ALS over the age of 80. Are there protective genes or epigenetics factors playing a role? Examining these extremes could be very informative.

Regarding the focus for future research announcements and the broader goals, Dr. Thakur said he gets a little lost when he hears the details of the individual projects. If they could identify risk factors for ALS, that would be great. However, it was not clear what they would do with that information to find a cure or lower the incidence. While it was hard to keep that focus on a per project level, the part of their obligation as funders is to make sure that they are driving all of these individual projects toward the broader goal. First, that involves a clear articulation of what that goal is so that everyone understands it. Second, there has to be an understanding where each component of funding fits in with all of the other funding. None of the funders alone is going to be large enough to accomplish these goals, so there has to be some sense of who is going to fund the next leg of the journey—whatever that journey is. For example, he would like to have seen someone in attendance from NIEHS in order to understand how their RFAs are complementing the work that ATSDR is funding and vice versa.

Dr. Mehta emphasized that there is correlation, causation, and association in terms of epidemiology. They are seeing associations and correlation, but not any causation. The crux of ALS is that they are not sure what causes it. Obviously, there are risk factors. In public health, they cannot say what causes ALS because there are still studies being conducted. One study refutes another study and so forth. ATSDR feels that the Registry is promoting and supporting some of the most important research being conducted. At this point, no one can say what causes ALS other than familial ALS.

Dr. Thakur stressed that they did not have to answer that question to figure out what direction the funding should be in. If they want to go down the risk factor path to figure out what environmental exposures might be contributing to ALS, that is only an academic exercise unless there is some end-stage in mind. What is that end-stage? Is it that they want to reduce whatever the environmental exposures are for the whole population? Is it that they want to reduce the incidence of ALS, which is a different question? Is it that they want to reduce the risk for people who have genetic markers, which is a different question? Articulating those questions might help the entire scientific community orient toward whatever the goals are.

Dr. Bradley emphasized that the science has advanced a dramatic amount over the last 2 to 3 decades. They are seeing the beginning of the opening up of what Dr. Thakur is asking in terms of reducing environmental factors that they are now beginning to identify, for example. Such outcomes are going to influence the funders.

To close on this, Dr. Mehta stressed that his personal take is that he sees optimism and the glass being half full—not half empty. He thinks more progress has been made and more attention has been made from everyone's efforts, especially in terms of care and pharma. He is certain that patients are frustrated because progress is not fast enough. His mother died of breast cancer two years ago and he sees the commercials every day on all of the drugs for breast cancer, and he wonders why those drugs did not help him mom. But he has to be positive and optimistic. ALS is a very tough field and it is frustrating, but they are in it for the long game. They want to make sure they find what causes this damn disease and have treatments for it to potentially stop it, prevent it, reverse it, and cure it ultimately.

Dr. Bradley noted that during the break, he and Dr. Nelson were discussing the breakthrough that they have witnessed in the last couple of years for spinal muscular atrophy. He was lucky enough to chair all of the Data Safety Monitoring Boards (DSMBs) that watched the effectiveness of SPINRAZA®, the gene therapy that turned around the ability to be able to stop the progression of spinal muscular atrophy. It was amazing to be able to see for the first time, as someone who has taken part in something like 30 different failed ALS trials, to suddenly see a drug that is working. That is what they are looking for in ALS and is what they hope maybe is going to come down the pike.

Next Steps Discussion: Recommendations/Strategies

Wendy E. Kaye, PhD
Senior Scientist
McKing Consulting Corporation

Dr. Kaye reminded everyone that each year, they take notes on what they think participants are making as recommendations and group them into categories. She used the same group of categories as last year to develop this year's list:

Outreach
- ❑ Create universal branding for ALS (e.g., consider using the international symbol and colors)
- ❑ Consider how to better engage minority populations
- ❑ Provide more guidance to neurologists on the most effective engagement strategies
- ❑ Provide registration information at multiple time points
- ❑ Have someone or information available at the doctor's office

Communication
- ❑ Have more materials about how to sign up for the Biorepository after registration
- ❑ Have more materials explaining importance or risk factor surveys and encouraging Registrants to complete them

Analysis
- ❑ Consider whether state enrollment expected numbers need to be adjusted to account for the North-South gradient

Miscellaneous

- ❑ Randomly order surveys for each participant
- ❑ Place information about the Registry on the same side of the appointment card as the appointment information
- ❑ Have a checklist or card for Registry participants to note user ID and password
- ❑ Have a practice site/test account for partners and clinic staff or alternatively, have a webinar that steps partners/clinic staff through registration and a sample of surveys
- ❑ Have a central location for information on all ALS Biorepositories

Discussion Points

Regarding a central biorepository, Dr. Mehta indicated that ATSDR cannot put up a website with everyone's information because it could be construed as them endorsing or promoting these biorepositories. That will probably need to be done by one of the partner organizations.

Dr. Thakur indicated that the ALS Association will look into this to determine what is feasible.

Dr. Kuldip suggested that it might be helpful if ATSDR takes charge of at least creating the central information on not just what each of the repositories has, but the ways to get access to them such as eligibility requirements, whether there is a full application, a letter of intent (LOI) is required, a steering committee needs to approve requests, typical timeframe, if a cost is involved, et cetera.

Dr. Mehta agreed that having that type of information someplace would be beneficial.

Ms. Backman thought that would be a wonderful resource and suggested that they need two audiences for this resource with a separate portal for each: 1) for researchers to access the data and samples; and 2) for patients to make donations.

Dr. Thakur wanted to make sure that they did not miss what the value and impact of the outreach are. Increased outreach is very important to improve the survey response rate, but he was not sure whether it would be sufficient to capture the right number or total number of people with ALS. Perhaps they did the work years ago and he was new enough to have missed it. He wondered if bringing the under-enrolled states up to the median and increasing enrollment by 30% through outreach, which seems like an ambitious goal, would get them up to the number that ATSDR feels is the right number. It would be good to have an answer for that, because his guess is that given the success of in-person outreach versus the electronic data capture, the electronic data capture seems to be working much better. Perhaps they need to think about figuring out the electronic side and putting a lot of resources and energy into that as opposed to outreach. On the other hand, the electronic data capture does not fill out surveys. He did not think they should randomly order surveys. His suggestion would be to look at the survey response rate, figure out which ones have been under-responded to relative to the others, and somehow weight those so that they come up first and more frequently.

Dr. Kaye said that her opinion is that the ones that are not answered the most are the ones that are the most difficult. If the first one someone gets is the most difficult, they are unlikely to complete any of the others. From a survey design perspective, it is important to start out slow and work up to the difficult surveys. For example, the residential history could be extremely difficult for someone who has moved around a lot and has to list every address where they lived for 6 months or more their whole life along with all of the details about each.

Dr. Thakur said he appreciated that, but he thought there was a difference between how to get the best response from people versus just randomizing. He emphasized that they should not give up the opportunity to have a more targeted strategy.

Dr. Mehta indicated that the response rate overall for the surveys is over 50%, which is higher than typical for federal surveys.

Dr. Kaye added that the Behavioral Risk Factor Surveillance System (BRFSS), National Health and Nutrition Examination Survey (NHANES), and National Health Interview Survey (NHIS) call people on the phone to get the answer; whereas, the ALS National Registry is dependent upon people going to a website themselves and being motivated to complete surveys. With that in mind, it is even more impressive.

Ms. Webb said it had been lovely to see everyone's progress over the years. Something that she keeps thinking about with regard to the website re-design is that it would be great every time the Registry data are utilized to be able to encompass a brief one-minute video with quick information about news about what has happened. It should be simple, accessible, and patient-friendly and allow for people to drill down further if they want to read the full paper. It would be helpful so that they are constantly demonstrating value. There is a lot of turnover at various organizations, so different ways to engage them such as a quick video update would help the partners. It does not have to be a heavy lift.

Dr. Mehta indicated that they do tweet about new clinical notifications, funded work, et cetera. Of course, tweeting is only as good as someone having Twitter and reading the tweet. The newsletter is certainly a way to disseminate information, and the partners can put this on their sites as well.

Regarding an inquiry about whether they could color code the surveys or give a caveat to the person who is going to complete them so that they know how long each one will take, Dr. Kaye indicated that they cannot include the time. They give an average amount of time that is designated by OMB. They do provide a caveat on the residential history survey suggesting all of the items they may need to gather before they try to complete the survey.

Dr. Agnese asked whether there could be a quid pro quo approach to this. For example, a webinar might be free but completion of a survey might be required to register for it. Industry might be able to support the content of webinars once a month to some extent.

Dr. Kaye indicated that this would not be acceptable because an IRB would view it as coercive. There might be a way to structure an incentive for people who complete surveys, but they could not make it such that someone could have X if they do Y. They have been trying to figure out various places to put messages about going to the website to complete surveys. This is why they got permission to revise the Biorepository "thank you" letter so that it now says something to the effect of, "Thank you for your blood donation. If you haven't already done so, please consider completing the surveys because it makes your blood more valuable for research." She has not assessed whether more people have been completing surveys because of that, but is to offer encouragement to do so.

Mr. Baker wondered whether it would be considered coercive if once someone clicked into a survey to have a notice at the top saying something like, "Hey, if you complete this survey it is particularly valuable for us because we have under-response in this area."

Dr. Kaye said this would not be possible. They have to treat them all the same way. Even if that was not a problem, there is an issue from a scientific point of view in that what is valuable for one study is not necessarily valuable for another. For the Biorepository, they tried to determine whether there is a set of questions they should get approval to ask separately so that everybody who gives blood answers certain questions even if they do not complete the surveys. The problem was that they could not come up with a short standard list.

Ms. Backman asked about the timing on the sports history survey that Dr. Mehta mentioned would be coming out. Her thought is that since they have not had a new survey in 2 to 3 years, this would be a great opportunity to re-energize the idea of survey completion with the rollout of the 18th survey and why it is so important.

Dr. Kaye indicated that if it is approved by OMB, it is unlikely to be available before the first of the year and most likely would be in the second quarter. Some emails go out when new surveys are launched to encourage people, but she liked the idea about using it as an opportunity to get people jazzed.

Dr. Mehta added that after approval, they have to do some user testing. Ideally, it would be good to launch it on January 1, 2020 if at all possible. In terms of the overall list of recommendations and strategies, a progress update will be provided around the first of the year.

Closing Remarks / Adjourn

Paul Mehta, MD
National ALS Registry Principal Investigator
Environmental Health Surveillance Branch
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Dr. Mehta first thanked everybody for attending in person, especially the persons with ALS. He thanked the Kennedys for coming up from Florida and expressed appreciation for all of their input and insight. He thanked Mr. Alderman for his courage and bravery, especially in sailing across the ocean last December. He emphasized that all of the PALS are all very brave, their input is vital, and they are greatly appreciated. The ALS Registry belongs to the PALS and ATSDR staff are the caretakers of it. ATSDR's objective is to improve it and make it better as it matures. He invited feedback anytime, and stressed that he is only a phone call or email away. He also thanked their partner advocacy group representatives for their attendance and the important work they are doing at the ground level in helping talk to patients, attend to their needs, provide care services, and so forth. The partners see a lot of things ATSDR does not see. He thanked all of the researchers, practitioners, and Pharma for their attendance and the important work they are doing. He expressed gratitude for the hard work of the ATSDR ALS and Carter teams, as well as Brunet-García for their work in communication and social media. He recognized Mr. Tom Hicks from Carter, who soon would be retiring, and emphasized how much he would be missed. He thanked everyone again for traveling to Atlanta, said he looked forward to seeing them at the next annual meeting, and bid them farewell.

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