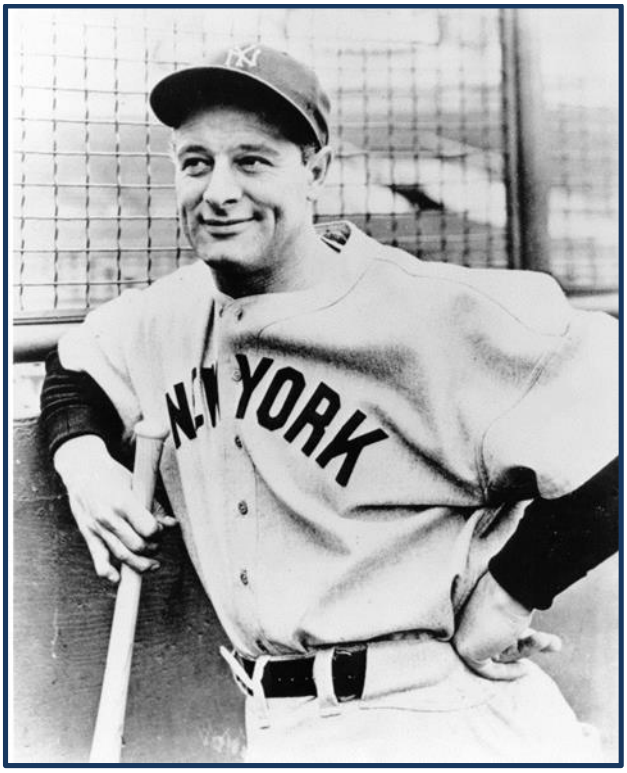
Department of Health and Human Services
Centers for Disease Control and Prevention
Agency for Toxic Substances and Disease Registry

ATSDR's Annual Amyotrophic Lateral Sclerosis (ALS) Surveillance Meeting



July 22-23, 2015
Summary Report

This document has not been revised or edited to conform to agency standards. The findings and conclusions in this report are those of the meeting presenters and attendees and do not necessarily represent the views of the Agency for Toxic Substances and Disease Registry.

2015 Annual ALS Surveillance Meeting Executive Summary

Due to the limited information on the unknown cause(s) of Amyotrophic Lateral Sclerosis (ALS), the Agency for Toxic Substances and Disease Registry (ATSDR) established the National ALS Registry in 2010. The primary purpose of the ALS Registry is to describe the incidence and prevalence of ALS, to describe the demographics of ALS patients, and to examine the risk factors for the disease. In 2014, the ALS Registry published their first report on the prevalence of ALS in the United States in CDC's *Morbidity and Mortality Weekly Report* (*MMWR*). In addition, ATSDR has published/supported publication of over two dozen journal articles relating to a number of ALS topics including, but not limited to, incidence and prevalence findings in three states and eight metropolitan areas, demographics of those living with the disease, selected potential risk factors for ALS, and recruitment for ALS research through the National ALS Registry.

ATSDR organizes the Annual ALS Surveillance Meeting to update stakeholders on the progress of the National ALS Registry, the Registry data and its implication, and to discuss strategies to further enhance the Registry for all of the stakeholders. In 2016, the National ALS Biorepository will be initiated with the primary goal of providing the largest bank of ALS blood and tissue samples in the US.

Overview of the National ALS Registry

The US ALS Registry Act, passed in October 2008, directs CDC/ATSDR to establish and maintain the National ALS Registry. The purposes of the Registry, launched in October 2010, are to describe the incidence and prevalence of ALS, describe the demographics of ALS patients and examine the risk factors for the disease. The Registry ALS data is derived from national databases (e., Medicare, Medicaid, VA Health Administration, and the VA Benefits Administration) in addition to the information about persons with ALS retrieved from the web portal.

The web-based portal allows person with ALS to enroll in the Registry and answer questions regarding their disease and possible risk factors for the disease. During 2014, approximately 150 patients enrolled in the web portal per month. With the advent of the Ice Bucket Challenge, Registry enrollment spiked in August 2014. In addition to registering, ALS patients can also complete any or all of 17 risk factor surveys available on the Registry web site. With approximately 46,000 surveys complete, these surveys will help to answer questions about the potential risk factors for ALS. ATSDR is currently in the process of analyzing the risk factor data collected so far.

ATSDR has also implemented several initiatives to strengthen the Registry including:

- The State and Metropolitan-Based Surveillance Project
- The Research Notification System
- The Biorepository Pilot Study
- Outreach to PALS attending non-referral clinics, and

- ATSDR supported ALS research

These initiatives will help strengthen the work of the National ALS Registry by providing information about PALS, their health status and risk factors. ATSDR also works closely with its partners and collaborators, which provide invaluable insight into how the Registry can facilitate the efforts to defeat ALS. Being the first and only population-based ALS Registry in the United States, the research being done provides data on incidence, prevalence, demographics, and risk factors for ALS and is serving as a recruitment tool for research.

National ALS Biorepository Update

The National ALS Biorepository Pilot Project began in 2013. The primary goals of the pilot study were to assess the feasibility of gathering biological specimens from a sample of participants enrolled in the National ALS Registry and to use the information from the study to determine whether a biorepository could be integrated into the National ALS Registry. The objectives of the pilot study were to:

- Maximize the scientific potential of the specimens,
- Maximize cost-efficiency,
- Make recommendations for long-term sustainability, and
- Recommend a process for providing access to the specimens to researchers.

An expert panel meeting was held in March 2012 meeting, to obtain input on the draft protocol for the project. This discussion yielded recommendations for the pilot project, which resulted in decision to collect specimens such as blood, urine and cerebrospinal fluid from 300 participants. Those enrollees of the National ALS Registry who agreed to be contacted about research projects would be primary participants for the biorepository. Primary recruitment began in April 2013 and a total of 330 participants were drawn for biological specimens. The national sampling methodology used included participation of PALS from all 50 states. Some recommendations from the pilot study include educating participants about the biorepository during the enrollment process in the Registry and collecting additional information such as phone number and mailing address.

Research Notification Mechanism: Update and Future Challenges

During enrollment in the National ALS Registry, PALS, have the option to consent to be notified about opportunities to participate in research studies. The Research Notification Mechanism connects researchers to PALS, facilitating their interactions and advancing the process of recruitment. The process involves researchers submitting research proposals to ATSDR, with prior approval from their institution's IRB, which are reviewed by ATSDR. If the research proposal is approved, eligible PALS are notified about the research project. Interested PALS can contact the researchers to be part of their research project. On average, over 95% of PALS who enroll in the web portal of the Registry elect to receive notifications. The Research Notification Mechanism has been extremely successful, with considerable increases in the number of notifications sent to PALS each year since its inception. Additionally, a large pharmaceutical

company recently approached the Registry for clinical trial recruitment, which would provide benefits such as being an established ALS Registry with available national recruitment.

Capture/Recapture: Methodology for Estimating True Prevalence of ALS in the United States

The first report of the National ALS Registry was used to calculate the prevalence rate of 3.9 ALS cases per 100,000 people in the population. However, in an effort to better estimate the prevalence of ALS cases in the US, the capture/recapture method was introduced. The purpose of the capture/recapture method is to help estimate a corrected count of PALS in the US and to address the number of PALS who are missing from the capture approaches. The capture/recapture approach is not regularly used in epidemiological research, but the concept aims to capture, mark and recapture the data. By using an algebraic formula, the capture-recapture methodology estimates the cases of ALS that are missed by the independent sources of data. Some additional goals of the capture-recapture method are to determine whether the degree of undercount differs based on age, sex, race or geographic distribution and whether additional case-finding methods are needed.

The capture-recapture method concludes that those under the age of 65 are undercounted in ALS cases, while approximately 23% of both male and female cases are missing from each data source. Additionally, capture-recapture established that when only federal databases are used, 22% to 23% of ALS cases are missed. However, the undercounting does not differ based on gender, but differs according to age, where the younger population will be missed if only federal databases are used. Thus, the Web portal of the National ALS Registry is crucial to include cases of ALS amongst the younger population. The next step is implementing the capture-recapture method with the 2010-2011 data to better understand possible missing cases and provide prevalence rates that best match the ALS population in the US.

Registry Promotion and Outreach

National ALS Registry

ATSDR presented the marketing strategies being used to increase awareness of the National ALS Registry to gather data and encourage PALS to participate in the Registry. The marketing strategy includes traditional and online, digital media, with digital media being the primary focus. While working with partners, ATSDR focuses the marketing initiatives toward PALS, family members and caregivers, health care providers, researchers, and ALS support organizations and entities. Advertisements and articles about the National ALS Registry are posted on media such as MDA's *Quest* Magazine, along with CDC's website and blogs on ATSDR's website. During ALS Awareness Month in 2015, a feature article was posted on CDC's website, which describes the Registry and encourages PALS to enroll in the Registry and take the risk factors surveys. Another key marketing strategy focuses on using social media, with ATSDR having approximately 13,400 followers and CDC's Facebook page having 472,000 followers. With these marketing initiatives, the views of the Registry have been steadily increasing annually since 2011.

Brunet-Garcia

One of the recent partnerships of ATSDR has been with Brunet-Garcia, an agency focusing on 100% social impact. The agency was contracted to increase awareness and engagement with the National ALS Registry through developing a communication outreach plan. The primary objectives of the plan include raising awareness of the National ALS Registry with PALS, targeting and informing PALS about the latest updates from the National ALS Registry and increasing completion of the risk factor surveys among self-registered PALS.

The outreach plan identifies communication goals including:

- Developing champions of the ALS Registry to carry the message of the Registry through word of mouth,
- Using technology to engage stakeholders,
- Creating and distributing digital and print content, and
- Increase the online visibility of the ALS Registry.

Les Turner ALS Foundation

The Les Turner ALS Foundation was founded in 1977, when the family and friends of Les Turner, an ALS patient, aimed to provide resources for ALS research and share the findings of this research. With the first ALS Research Laboratory opened in 1977, the foundation currently has three dedicated ALS research laboratories. In addition to the laboratories, Les Turner supports other patient service programs such as in-home consulting, support groups, and community educational programs to over 90% of the ALS population in the Chicago region.

The Les Turner ALS Foundation described how in addition to being a champion of community outreach, their efforts also focus on promoting the National ALS Registry. Les Turner promotes the Registry through a dedicated Registry page on their website, monthly features on the foundation homepage, social media announcements and inclusion of links in e-newsletters. Additionally, because PALS may have challenges with enrolling in the Registry, Les Turner hired a summer associate to promote the Registry. By visiting the patients in their homes, this helps to overcome access and mobility challenges and motivates patients and their caregivers to dedicate time to joining the Registry and completing the risk factor surveys, which provides valuable information to the National ALS Registry.

The Muscular Dystrophy Association

For the past 50 years, the Muscular Dystrophy Association (MDA) has been working to save and improve the lives of people fighting muscle disease through research and treatments. MDA includes over 40 diseases, including ALS, the Muscular Dystrophies and Spinal Muscular Atrophy (SMA). In the past five years, MDA has contributed $46 million for ALS research through grants and awards. MDA also promotes the National ALS Registry through MDA clinics and MDA/ALS centers, legislation and healthcare policy, support groups and educational seminars, home visits, fundraising events, and outreach and emotional support.

Additionally, out of the 180 MDA nationwide clinics, 44 are ALS Centers which provide support to PALS and promote the National ALS Registry. In addition, MDA has created the MDA National ALS Registry toolkit, which is distributed throughout all MDA clinics and provides educational materials about ALS and the importance of the registries. MDA also collaborates with the ALS Association to educate the community on the importance of participating in the Registry and the advantages to those who participate.

The ALS Association

With 39 chapters across the United States, the Amyotrophic Lateral Sclerosis (ALS) Association organizes listening tours twice each year. One of these tours focuses just on the National ALS Registry and enrollment. The ALS Association discussed an important issue of PALS not being connected to the internet and how this issue impacts Registry enrollment and communication. The ALS Association also mentioned the top performing states and described the outreach practices used by these chapters to reach the high rates of enrollment. Some key factors mentioned were volunteers being part of the outreach, neurologists being advocates, direct outreach by PALS, and even promotion of the Registry through Minor Lead Baseball teams, which particularly target rural areas and smaller cities. The challenges for underperforming states include difficulty in identifying ALS cases, enrollment issues and lack of access to the Internet.

Furthermore, with the establishment of the Continuous Improvement Program, the chapters can improve their programs over time by using a Chapter Scorecard to communicate information. A section of this program focuses on the Registry. The ALS Association's new partnership with MDA will include outreach efforts which focus on the National ALS Registry. Through the new Public Policy Association Program, there will be increased "boots on the ground" to enroll more PALS in the Registry and expand their services. Increased use of infographics will provide a better way of telling the National ALS Registry story, including enhancements such as the Research Notification System, updates on Registry-funded research, and other information from the Registry.

Promotion of the National ALS Registry in Non-Referral Centers

In conducting the ALS Surveillance Projects it was discovered that most neurologists were not practicing in ALS referral centers. In addition, the race, gender, and age at diagnosis were slightly different for case reports from non-referral centers. These demographics indicate an enrollment gap in the National ALS Registry. Therefore, there is a need to reach out to non-referral centers to encourage enrollment. An education outreach program was created using a four-group approach. The initial component of the program was phone outreach to neurologists (in Groups 1 and 2) to identify neurologists who care for PALS. The calls would also confirm contact information, size and providers of the practice. Following the phone calls, neurologists in Group 3 would receive mailings, circulated ATSDR materials and information on the National ALS Registry. Follow-up calls would be made one week and three months after the mailings to determine use of the materials.
The second component of the program would include train-the-trainer presentations. Additionally, neurologists from Group 1 would be trained to help their patients and conduct qualitative interviews to assess their knowledge, beliefs and attitudes about the Registry. The

program will be evaluated based on the frequency of communication, Registry self-enrollment and common themes through the qualitative interviews. The data will be analyzed and a manuscript will be prepared in 2016.

Georgia Registry Enrollment Pilot Project

The Georgia Registry Enrollment Pilot Project was established to improve target outreach activities for the National ALS Registry. The primary goals of the Georgia Pilot Project are to: 1) Identify an area smaller than a state that is reproducible in other states and meets the restrictions imposed by OMB; 2) Provide qualitative assessment of Registry enrollment; and 3) Test the methods using Georgia data. Some limitations of this program include cities not directly coding to a county or the time periods of the available data do not match. The results of the Pilot Project indicate that the highest enrollment in the Registry is in Health District 3, metropolitan Atlanta. Additionally, the lowest rates of enrollment were in Health District 1, 6, 7 and 9. Because Georgia is a state with enrollment in the Registry below the national average of expected enrollment, this Georgia Pilot Project will be used as a test case to utilize more targeted information from ATSDR regarding under-enrolled regions in Georgia and to develop best practices for improvement.

One approach includes targeting ALS Clinics to distribute information on the National ALS Registry, by distributing flyers and having tablets available to enroll patients. An additional approach includes establishing support groups to increase buy-in from ALS patients and increase individual follow-up. By focusing on existing patients in under-enrolled areas that were identified by ATSDR, the Georgia ALS Association chapter enrolled 20 patients in the first quarter of 2015 and was removed from the under-enrolled states. However, due to staff turnover at the Georgia ALS Association chapter, there was a decline in patient enrollment and Georgia was back in the under-enrolled category, indicating the importance of reminders and follow-up. The Georgia Pilot Project provides several takeaway lessons, which are included in the final report. The outreach approach used in Georgia can be adjusted and used in other states to increase individualized follow-up and enrollment in the Registry.

ATSDR Funded Studies

Research is a critical component in learning more about the etiology of ALS and its risk factors. 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. ATSDR has funded 10 ALS studies. The ATSDR-funded studies listed below are in progress and were presented by their principle investigators during the 2015 Annual ALS Surveillance Meeting. More detailed information about each study can be found on the National ALS Registry website.

A Prospective Study of Biomarkers and Risk Factors for ALS Incidence and Progression

Identification and Validation of ALS Environmental Risk Factors

Cognition, Behavior, and Caregiver Burden in Amyotrophic Lateral Sclerosis

Ecologic Study to Evaluate Spatial Relationships between ALS & Potential Environmental Risk Factors

A Prospective Comprehensive Epidemiologic Study in a Large Cohort in the National ALS Registry: Identifying ALS Risk Factors

End of the Day Questions

During this session, the floor was open for meeting attendees to ask questions and to provide expert advice and guidance to Registry staff pertaining to challenges encountered by the Registry, strategies and recommendations to maintain and further enhance the Registry.

Table of Contents

Acronyms Used in this Document

Acronym	Expansion
ACA	(Patient Protection and) Affordable Care Act
AJPH	American Journal of Public Health
ALS	Amyotrophic Lateral Sclerosis
ALSA	Amyotrophic Lateral Sclerosis Association
ALS COSMOS	ALS Multicenter Cohort Study of Oxidative Stress
ARREST ALS	ATSDR Risk Factors Epidemiologic Studies in ALS
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	Area Under the Curve
BFR	Brominated Flame Retardant
BiPAP	Bilevel Positive Airway Pressure
BMI	Body Mass Index
BMAA	Beta-N-Methylamino-l-Alanine
CDC	Centers for Disease Control and Prevention
CME	Continuing Medical Education
CMS	Centers for Medicare and Medicaid Services
CPS-II	Cancer Prevention Study II-Nutrition Cohort
CSF	Cerebrospinal Fluid
dbGaP	Database of Genotypes and Phenotypes
DME	Durable Medical Equipment
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
GIS	Geographical Information System
GUID	Globally Unique Identifier
HHS	(United States Department of) Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HMO	Health Maintenance Organization
HMORN	Health Maintenance Organization Research Network
HPFS	Health Professionals Follow-up Study
ICC	Intraclass correlation coefficients
ICD	International Classification of Diseases
iPS	Induced pluripotent stem (cell)
IRB	Institutional Review Board
MARCH	Michigan ALS Research Consortium of Hospitals
MDA	Muscular Dystrophy Association
MEC	Multiethnic Cohort Study
MMWR	*Morbidity and Mortality Weekly Report*
MND	Motor Neuron Disease
MOU	Memorandum of Understanding
MS	Multiple Sclerosis
NCEH	National Center for Environmental Health
NDI	National Death Index
NEALS	Northeast Amyotrophic Lateral Sclerosis Consortium
NHANES	National Health and Nutrition Examination Survey
NHS	Nurses' Health Study

NIEHS	National Institute of Environmental Health Sciences
NINDS	National Institute of Neurological Disorders and Stroke
OMB	Office of Management and Budget
PALS	Persons with Amyotrophic Lateral Sclerosis
PCB	Polychlorinated Biphenyl
PI	Principal Investigator
PII	Personally Identifiable Information
PLS	Primary Lateral Sclerosis
PPE	Personal Protective Equipment
PPO	Preferred Provider Organization
QC	Quality Control
RFP	Request for Proposals
RIN	RNA Integrity Number
RNA	Ribonucleic Acid
SES	Socioeconomic Status
SMA	Spinal Muscular Atrophy
SOD-1	superoxide dismutase 1
SOP	Standard Operating Procedure
TDP-43	Transactivation Response (TAR) DNA binding protein-43
VA	(United States Department of) Veterans Affairs
VABBB	(United States Department of) Veterans Affairs Biorepository Brain Bank
VBA	Veterans Benefits Administration
VHA	Veterans Health Administration
WGCNA	Weighted Gene Correlation Network Analysis
WHI	Women's Health Initiative

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

Minutes of the Meeting
July 22 - 23, 2015

Theme / Purpose

Theme: Registry Results and Next Steps for the National ALS Registry

Purpose: Update stakeholders on the progress of the National ALS Registry, the Registry data and its implications, and discuss strategies to further enhance the Registry for all stakeholders.

Welcome and Introductions

Robert Kingon, MPA, Facilitator
Carter Consulting, Inc.

Mr. Robert Kingon, meeting facilitator, called the meeting to order at 8:35 am. He described ground rules for the meeting and went over housekeeping items. He noted that much of the meeting would be live-streamed on the Internet. The meeting participants introduced themselves. An attendance roster is appended to the end of this document.

Opening Remarks

CAPT William Cibulas, PhD, MS
Senior Advisor to the Director
Agency for Toxic Substances and Disease Registry /
National Center for Environmental Health

Dr. William Cibulas introduced himself to the group and welcomed them to Atlanta. He remarked on the history represented at the meeting, with agency representatives from the early days of the Agency for Toxic Substances and Disease Registry (ATSDR).

Federal agencies have learned that they cannot develop and maintain programs by themselves. The collaboration and support of the Amyotrophic Lateral Sclerosis (ALS) experts, federal partners, outside experts, and Congress is critically important with an endeavor as large as the ALS Registry. ATSDR was without a permanent director for over two and a half years, and it was challenging to initiate a national program without a leader to support it at all levels of the federal government. A new permanent director of ATSDR, Dr. Pat Breysse, joined the agency the previous winter. He is passionate about public health and translating the results of research into practice. He understands and recognizes the value and necessity of developing partnerships. He sent apologies for not attending the meeting in person and has conveyed his commitment to the ALS Registry.

ALS is a devastating and fatal disease. It not only impacts persons with ALS, but also is a tremendous strain and drain on family, friends, and loved ones. ALS has affected Dr. Cibulas and his family personally. No cause for ALS has been identified. The National ALS Registry is

a groundbreaking effort as scientists work toward a cure for ALS. The Registry is making progress, with the help of partners and supporters. The Registry published its first-ever report on the prevalence of ALS in the United States (US) in 2014. Additional manuscripts and data analyses are underway currently, including work on prevalence and mortality for 2012 and 2013.

Since going live in October 2010, the Registry's web portal has collected demographic and risk factor data on thousands of persons with ALS (PALS) in all 50 states, and more PALS are enrolling every day. In addition, thousands of PALS have been detected in the large administrative datasets maintained by the Centers for Medicare and Medicaid Services (CMS) and the US Department of Veterans Affairs (VA).

The National ALS Biorepository will be initiated in the fall of 2015. When it is fully operational in 2016, it will have the largest bank of ALS blood and tissue samples in the US. These samples will be paired with risk factor survey data. Many other new initiatives are on the horizon, including projects to link researchers with PALS and efforts to promote the Registry in non-referral centers.

CAPT Ed Murray, PhD
Deputy Director
Division of Toxicology and Human Health Services
Agency for Toxic Substances and Disease Registry

Dr. Ed Murray welcomed the group and noted that he is now the Deputy Director of the Division of Toxicology and Human Health Services at ATSDR. This was his third meeting, and he intends to return on a yearly basis. The meeting achieves many objectives as the National ALS Registry moves forward. At about this time in 2014, the "Ice Bucket Challenge" caused the visibility of ALS to skyrocket. He is encouraged by the Registry's progress.

The Registry will continue to move forward with the full support of the division, ATSDR, and the Centers for Disease Control and Prevention (CDC). ATSDR is developing external partnerships, including international partnerships as they expand the Registry. He noted the work of the ALS Association (ALSA), the Muscular Dystrophy Association (MDA), the Les Turner Foundation, and other partners, as well as the efforts of PALS. He emphasized that these partnerships must continue.

Overview of the National ALS Registry

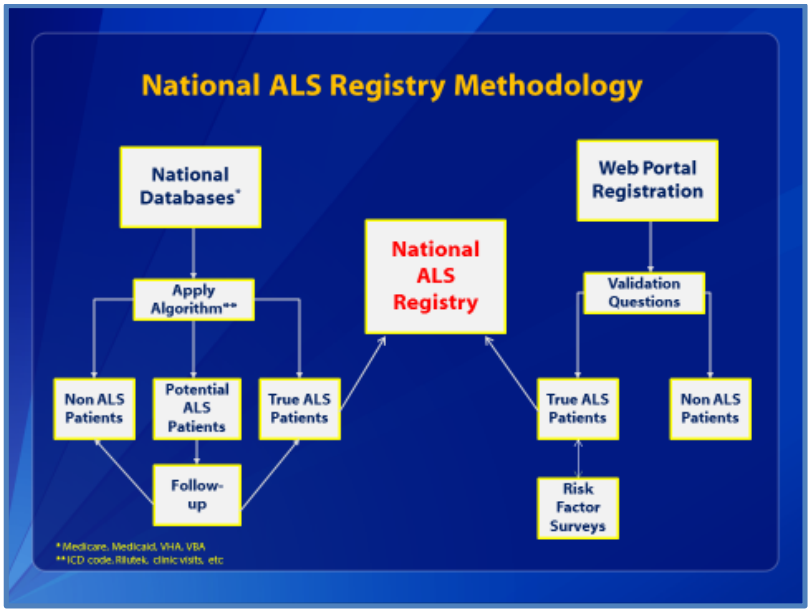
D. Kevin Horton, DrPH, MSPH
Chief, Environmental Health Surveillance Branch
Division of Toxicology and Human Health Services
Agency for Toxic Substances and Disease Registry

Dr. Kevin Horton welcomed the group and thanked them for the effort that it takes to attend the meeting and to help build and improve the National ALS Registry. He described recent changes in ATSDR leadership, which is the nature of business. Despite recent leadership changes at ATSDR, it is important to note that a core group of people at ATSDR has worked on the Registry since its inception, and they are passionate about ALS and other public health issues. He thanked viewers of the meeting via the Internet live stream.

Dr. Horton offered background and methodology of the National ALS Registry. The US ALS Registry Act was passed in October 2008. The law put CDC/ATSDR on the path to creating a population-based ALS Registry for the US, which had not existed previously. The National ALS Registry launched in October 2010, after pilot-testing and development. The Registry purposes, as specified by the Act, are largely to:

- ❑ Describe the incidence and prevalence of ALS
- ❑ Describe the demographics of ALS patients, and
- ❑ Examine risk factors for the disease

Because ALS, like most non-communicable diseases, is a non-notifiable disease, the Registry needed novel approaches to identify ALS cases. The Registry has a two-pronged approach for identifying cases of ALS as depicted in the following graphic:



The pilot-testing phase from 2008 – 2010 created an algorithm for identifying ALS cases from large national databases from federal agencies. The algorithm includes elements such as the International Classification of Diseases (ICD)-9 code for ALS, RILUTEK® prescriptions, and frequency of visits to neurologists or healthcare providers. The algorithm separates people into three categories: Non-ALS Patients, Potential ALS Patients, and True ALS Patients, the latter of whom are automatically added to the Registry.

The other aspect of the Registry methodology is the registration through the Web portal. This approach is successful through engagement with ALS patients, ALS support groups and organizations, and other sources for telling the story of why it is important for patients to enroll in the Registry. 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. Records are matched by Social Security number so that there are no duplicates from the national database and web portal approaches.

The web-based approach gives patients the chance to tell their stories, particularly about risk factors for the disease. ALS patients who are enrolled in the Registry via the national

databases are encouraged to enroll through the web-based portal as well to share that information.

During 2014, approximately 150 patients enrolled in the web portal per month. There was a spike in enrollment in the month of August, when the Ice Bucket Challenge raised awareness of ALS. There were also increases in website hits during that month. The portal includes 17 different risk factor surveys. They were not all deployed at the same time. Patients can take the surveys at their convenience. Almost 46,000 surveys have been completed, and the number grows every day. It is important for patients not only to enroll in the portal, but also to complete as many surveys as possible. All but one of the surveys are to be completed only one-time., The one exception is the disease progression module, which is taken at several points over time to chart the progression of disease. Patients receive auto-generated reminder emails to take the surveys.

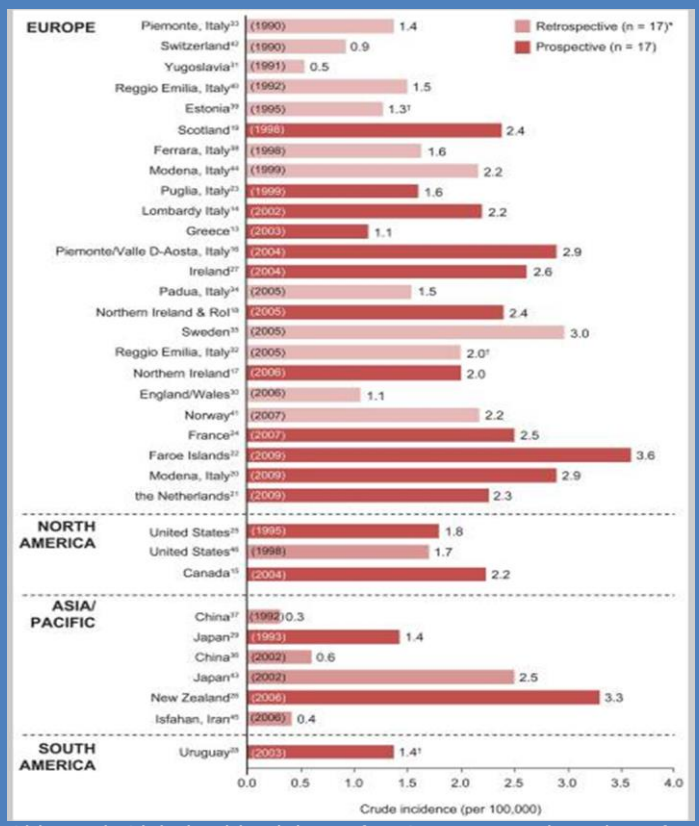
The first National ALS Registry report was published in CDC's *Morbidity and Mortality Weekly Report* (*MMWR*) in 2014. It included data from the Registry's launch on October 19, 2010 through December 31, 2011. During that period, 12,187 PALS were identified either through the national administrative databases and/or via the Web portal. The prevalence rate was 3.9 cases of ALS per 100,000 population. ALS was more common in Whites, males, non-Hispanics, and persons aged 60 through 69. Males had a higher prevalence than females. The lowest number of ALS cases was in the 18 through 39 year old age group. The findings were consistent with expectations. As the Registry grows and progresses, the data will be stronger and more robust.

The next report will include updated prevalence rates, and selected incidence rates. It is slated for release in the spring of 2016. ATSDR plans to release annual reports, but in this case decided to release data from 2012 and 2013 in a consolidated report. One of the Registry's goals is to be a "one-stop shop" for ALS epidemiology in the US.

Additional analyses are underway using Registry data. In order to assess the completeness of the Registry, capture-recapture analyses and comparisons of the active surveillance in the State and Metro project to the data from the National ALS Registry are being conducted. Some risk factor modules were presented in the first report of Registry data, and analyses of other risk factor modules will be published in late 2015 or early 2016.

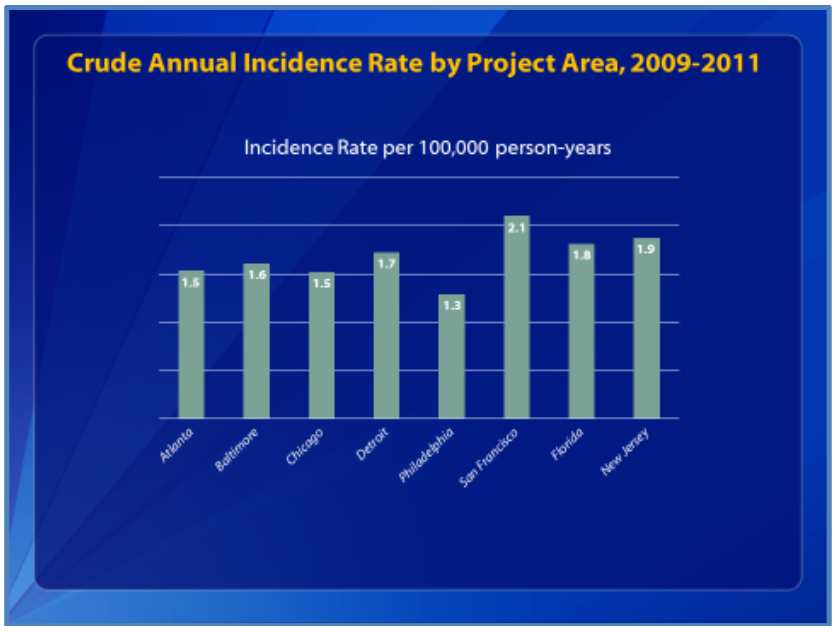
The State and Metropolitan Area Based ALS Surveillance Initiative was launched to help test

WORLDWIDE ALS INCIDENCE



Chio et al, Global epidemiology of ALS: a systematic review of the published literature. Neuroepidemiology, 2013

the completeness of the National ALS Registry and also to gather high-quality incidence and prevalence data in tightly-focused catchment areas: eight metro areas and three states. Data were collected from 2009 – 2011. The findings were consistent with the National ALS Registry, ALS registries in Europe, and other epidemiological studies. The prevalence rate was 3.8 cases per 100,000 population, while the incidence rate was 1.5 cases per 100,000 person-years. PALS were more likely to be white, male, non-Hispanic, and 50 through 79 years of age. The median age at diagnosis was 64 years. More males reported with the disease than females. Approximately 4% had a family member with ALS. There were significant racial and ethnic differences in incidence rates, with non-Hispanic whites having double the rates of African Americans and Asian Americans. Crude annual incidence rates by project area were as follows:



A number of papers using National ALS Registry data were published in 2015. ATSDR purchased open-access to all of the papers, which are available on the website and Registry stakeholders can read these papers free of charge. Other papers have been accepted, and more will be submitted in 2015-2016.

The National ALS Registry is not only designed to count ALS cases. In addition, it is designed to have maximum benefit for all stakeholders. The Registry can link PALS with researchers who are conducting clinical trials or epidemiological studies. A high percentage of patients in the Registry want to participate in research. The Research Notification System notifies patients about clinical trials or studies for which they might be eligible. Beginning in February 2013, patients participating in the Registry who have indicated their willingness to be contacted for research began receiving emails. To date, 18 different studies have been supported, mostly from universities in the US. Patients have been linked with 12 researchers in the past year. More than 63,000 emails have been sent. As word spreads about this system among patients and researchers, more studies are being supported. Information about these studies is available on the Registry website.

ATSDR has also created research funding opportunities, primarily for examining ALS risk factors and etiological issues. Eight studies have been supported, and five are ongoing.

Information about the studies is available on the Registry website. The research can shed light on risk factors for ALS. If new risk factors are discovered, ATSDR can create a new risk factor module for the National ALS Registry. A new funding announcement was posted in January 2015, and two to three awards are expected to be granted.

Other activities are designed to enhance the Registry. Information from these efforts will help ATSDR develop new outreach activities aimed at increasing the representativeness of the Registry enrollees. For instance, work is ongoing to improve outreach to PALS who attend non-referral clinics, especially in rural areas. All materials have been translated into Spanish and will be launched soon. The demographic data in the Registry will guide future directions and potential translations into other languages. The Registry is also enhanced by specialized statistical analyses and a pilot project on targeted outreach in Georgia, which is yielding information about barriers to participation in the Registry.

The National ALS Biorepository will launch in the fall of 2015. Survey data is important, but pairing biological specimens makes the data much stronger and richer. The pilot project for the biorepository began in September 2011 and will end in September 2015. Preliminary results indicate that the biorepository is feasible and warranted. There are other ALS biorepositories in the US, but the National ALS Biorepository is different because it collects epidemiological data. It will be nationally representative and user-friendly to PALS. Phlebotomists will be sent to participants' homes to collect samples. Participants in the pilot study have reported that the process was easy and quick. Information about donating samples will be shared on the website.

Because ATSDR and CDC do not interact with PALS as frequently as other groups and organizations, input and recommendations from clinicians, support groups, and other stakeholders are critical to the Registry's success. The Annual ALS Surveillance Meeting is an excellent opportunity to hear suggestions and recommendations. Some recommendations can be implemented immediately, while others may take more time or may not be feasible. All recommendations are taken into consideration, however. During this meeting, recommendations will be extracted during the presentations and discussion periods and then presented and discussed at a focused session at the end of the meeting.

The National ALS Registry represents a great deal of work from ATSDR and the constituents represented at the meeting. Dr. Horton thanked them for devoting time to educating Congress and telling the story of the Registry, which is the first and only population-based ALS Registry for the US. It is yielding data on incidence, prevalence, demographics, and risk factors for ALS and is serving as a recruitment tool for research. Research is being funded, and the biorepository will be another strong tool for the ALS community. ATSDR cannot do this work alone, and they are grateful for the partners who have made the group initiative possible and successful.

Discussion Points

Mr. Ed Tessaro observed that the demographic data from the Registry indicate that veterans are one of the largest groups. He asked about the cooperation between ATSDR and the VA.

Dr. Horton answered that all of the federal agency partners want to be cooperative. There are challenges associated with the bureaucracy that ATSDR must navigate to receive data from the VA and CMS. There are now Memoranda of Understanding (MOUs) or inter-agency agreements in place with the agencies so that the steady stream of data can continue.

Mr. Tessaro asked whether ATSDR needs help maintaining those relationships and communication.

Dr. Horton answered that the relationships with federal agencies are strong, but help is needed in telling the story of ALS and the National ALS Registry to as many people as possible.

Dr. Bryan Traynor commended ATSDR for the tremendous amount of work on the Registry over the years. Regarding the scientific methodology, he noted that the algorithm divides persons who join the Registry through the Web portal into ALS and non-ALS. He asked about the reliability of the data, as the scientific utility of the database relies on the patients who identify as truly having ALS. He wondered whether improvements should be made, or whether they are satisfied with the breakdown of patients.

Dr. Horton answered that the validation questions on the Web portal came from the VA ALS Registry that operated in the 2000s. The VA conducted a study in which 93% of the persons who answered the questions had ALS. That capture rate is very good, and ATSDR decided not to duplicate efforts. At this point, they are happy with the validation questions.

Dr. Paul Mehta noted that the bulk of the patients, approximately 80% to 85%, in the National ALS Registry come from the national databases. The rest come from the Web portal.

Dr. Wendy Kaye did not have the number of persons who did not pass through the validation questions on the portal, but it is possible to get that information. From the perspective of a surveillance system, a 93% accuracy rate is good. However, there is a dilemma associated with collecting a biological specimen from a person who is not an ALS patient. A good number of persons from the national databases also enter through the portal and match up.

Dr. Ed Kasarskis was involved with the VA ALS Registry. The questions were validated against personal chart review of records. At the time, the Institutional Review Board (IRB) was not constructed such that the researchers could determine what the 7% of people who did not pass through the ALS questions actually had. It would have been interesting to know more about the cases of "ALS mimics."

Dr. Christopher "Kit" Brady said that of the 155 specimens in the VA Biorepository Brain Bank (VABBB), one did not have ALS. Of their cases, 95% are from the Registry.

National ALS Biorepository Update

Wendy E. Kaye, PhD
Senior Epidemiologist
McKing Consulting Corporation

Dr. Kaye presented an overview of the biorepository pilot study. A biorepository is a collection of biological specimens stored for future use. In the past, biorepositories have been used in ALS research to identify genes associated with ALS, to monitor response to treatment, and to search for evidence of environmental causes. In the future, ALS biorepositories could be used to validate biomarkers, classify ALS subtypes for prognosis, and discover underlying pathobiology. Understanding the use of the biorepository helps influence the specimens that are collected, and how they are collected.

When the National ALS Biorepository Pilot Project began, there were a number of biorepositories used in ALS research. The two clinical biorepositories were the Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS) and the National Institute of Neurological Disorders and Stroke (NINDS) Motor Neuron Disease Collection. A population-based biorepository was housed at the VA. There were two brain banks, the VABBB and one in London, England.

The National ALS Biorepository is important for correlating biomarkers with extensive epidemiologic data collected by the National ALS Registry. It will enroll a nationally representative, population-based sample of participants who are not selected by geographic area, exposure, or clinical characteristics. It also increases the number of biological specimens available for research on ALS. The pilot study assessed the feasibility of gathering specimens from a sample within the National ALS Registry. That information was used to determine whether a biorepository could be integrated into the National ALS Registry. The objectives of the pilot study were to:

- ❑ Maximize the scientific potential of the specimens
- ❑ Maximize cost-efficiency
- ❑ Make recommendations for long-term sustainability
- ❑ Recommend a process for providing access to the specimens to researchers

An expert panel meeting was held in March 2012. The participants included ALS researchers, PALS, and representatives from biorepositories. They provided input into the draft protocol for the pilot project. The discussion included the sample size and follow-up, the types of specimens to collect, and the potential research uses of the biorepository. It was determined that the specimens should:

- ❑ Complement the National ALS Registry epidemiologic data
- ❑ Allow comparisons with other studies and other biorepositories
- ❑ Maximize scientific utility
- ❑ Be "future-proof" and amenable to emerging technologies and research opportunities and priorities

As part of the March 2012 meeting, a list of specimen types that would be desirable was shared from a paper by Otto [Otto et al, *Amyotrophic Lateral Sclerosis*. 2012 Jan;13(1):1-10]. The table to the right illustrates the specimen collections considered and their potential for being useful in ALS research:

NATIONAL ALS BIOREPOSITORY PILOT STUDY

Specimen consideration

Characteristic	Blood*	CSF	Urine	Saliva	Skin	Muscle
Proximity to CNS pathology	++	+++	+	+	+	+
Less molecular complexity	+	+	++	+++	++	++
Less invasive	++	+	+++	+++	+	+
Practicality of sampling	+++	++	+++	++	+	+
Ease of handling for storage	++	+	++	+	+	+
Resistance to exogenous drug contamination	+	+++	+	++	++	++
Candidate molecules to date	++	+++	+	+	+	+
Potential for DNA/RNA analysis	+++	+	+	++	+++	+++

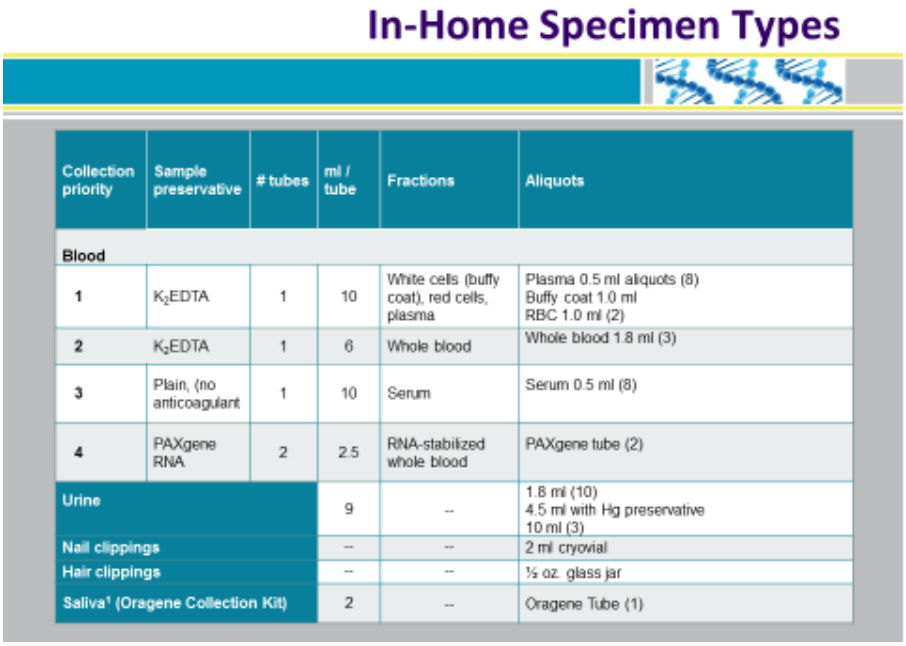
+++ high; ++ moderate; + weak

From: Otto et al, *Amyotrophic Lateral Sclerosis*. 2012 Jan;13(1):1-10.

The potential specimens were considered based on their usefulness for research, practicality of collection, invasiveness, storing and processing the samples, and other properties. The expert panel concluded that the pilot project would:

- ❑ Collect specimens from 300 participants
- ❑ Collect from each participant twice, approximately six months apart
- ❑ Collect some specimens in a "metals free" manner, such as blood, urine, and cerebrospinal fluid (CSF)
- ❑ Add a specimen processing form to collect some information necessary to process and interpret the specimen analyses

The collection included five tubes of blood for white blood cells, red cells, and plasma; whole blood, which was collected metals-free; serum; and two tubes for ribonucleic acid (RNA). The other specimens collected included urine, hair, nails, and saliva if participants were unable to give blood. The postmortem tissue specimens included brain, spinal cord, CSF, bone, muscle, and skin.



In-Home Specimen Types

Collection priority	Sample preservative	# tubes	ml / tube	Fractions	Aliquots
Blood					
1	K_2EDTA	1	10	White cells (buffy coat), red cells, plasma	Plasma 0.5 ml aliquots (8) Buffy coat 1.0 ml RBC 1.0 ml (2)
2	K_2EDTA	1	6	Whole blood	Whole blood 1.8 ml (3)
3	Plain, (no anticoagulant	1	10	Serum	Serum 0.5 ml (8)
4	PAXgene RNA	2	2.5	RNA-stabilized whole blood	PAXgene tube (2)
Urine			9	--	1.8 ml (10) 4.5 ml with Hg preservative 10 ml (3)
Nail clippings			--	--	2 ml cryovial
Hair clippings			--	--	½ oz. glass jar
Saliva[1] (Oragene Collection Kit)			2	--	Oragene Tube (1)

In order for in-home specimen collection, participants had to be enrolled in the National ALS Registry. When they signed up for the Registry, they had to have agreed to be contacted about research projects. Participants permitted phlebotomists to come to their homes. The participants could be in any stage of disease. Recruitment was proportional to the population in each state, and individuals were selected from the National ALS Registry based on state. The Registry sent an email describing the project, and up to four follow-ups were permitted. Outreach from MDA and ALSA was also part of the process, and there was an alert on the ATSDR website. Anyone expressing interest in the project received a packet of information and was contacted approximately one week later for follow-up and consenting.

Special collection kits were created for the pilot project. They were distributed by the laboratory and sent to the participants' homes. There were total kits as well as kits for collecting only blood, urine, or saliva. The kits were adjusted to add a sharps container, as some of the traveling phlebotomists did not have a means for disposing of sharps.

The collection form included information about when the specimens were taken and other details such as when the participants had had something to drink, whether they were wearing nail polish, and whether they dyed or used permanent solution on their hair. Participants indicated their preferred day and time for collection, which took place Monday through Thursday. Collections were performed in time for same-day shipping to the laboratory. Participants received a confirmatory letter and were contacted by the phlebotomist the day before collection.

A variety of outside phlebotomy vendors were used in order to ensure coverage in rural areas. Minimal standards were provided for the phlebotomists, and training materials for collecting and shipping specimens were provided. The tubes were collected in a certain order because of the metals-free requirements. Specimens were shipped to the laboratory overnight and logged in. Blood and urine samples were processed into aliquots and frozen. The PAXgene™ tubes were frozen as received, and the hair and nail samples were stored as received in small vials.

The project encountered some challenges. There was slow response to the recruitment emails. The only contact information that ATSDR has for PALS is their email addresses. The frequency of emails had to be increased, with the IRB's permission, in order to ensure that the PALS saw them. The sample size was increased to 330 in order to increase the number of paired samples. Of the participants, 15% to 20% were unable to complete their second collection due to death or illness. Some potential participants did not want a person to come to their homes, and there were challenges associated with finding reliable phlebotomists in remote areas. At least one person in every state contributed specimens. Because the summer of 2014 was very hot, changes were required to the packing and shipping procedures. Additional quality assurance measures were added.

In order to be eligible for postmortem collection, participants had to be enrolled in the National ALS Registry and agreed to be contacted about research studies. The participants were asked to sign a Health Insurance Portability and Accountability Act (HIPAA) authorization. Their eligibility was confirmed by their treating neurologist. Family authorization forms were also required, as families are heavily involved in postmortem donation.

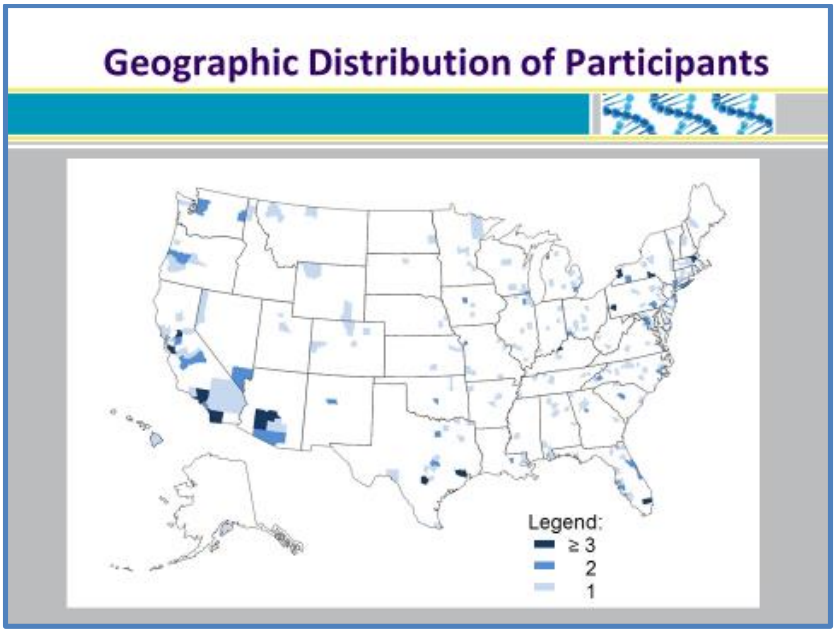
Potential participants in the postmortem collection aspect of the project were recruited if they had been diagnosed with ALS for a longer period of time. The outreach process was the same as for the specimen collection. A number of people who participated in the postmortem collection were volunteers from the National ALS Registry. Packages of information were sent to potential participants, and the neurologists were contacted upon receipt of the HIPAA authorization. The potential participants were also visited in their homes, with a family member present, to discuss the project and to obtain informed consent. The participants were contacted quarterly to assess their disease progression and to confirm their interest in postmortem collection.

Partway into the project, ATSDR added the collection of skin to be made into cell lines. The protocol was amended, and participants were re-consented. Of the 30 participants, 27 agreed to the skin collection. Of the three people who did not consent to have skin collected, two had passed away and their specimens had already been collected, and one declined.

Recruitment for the biorepository pilot project began in April 2013. ATSDR sent 1078 emails. Of those, 71 persons were deceased, 80 were not interested, and 464 received information packets. A total of 339 persons consented to be in the study. Of those, 9 withdrew after consenting, 3 passed away before the collection, 2 were too ill to participate, and 4 did not

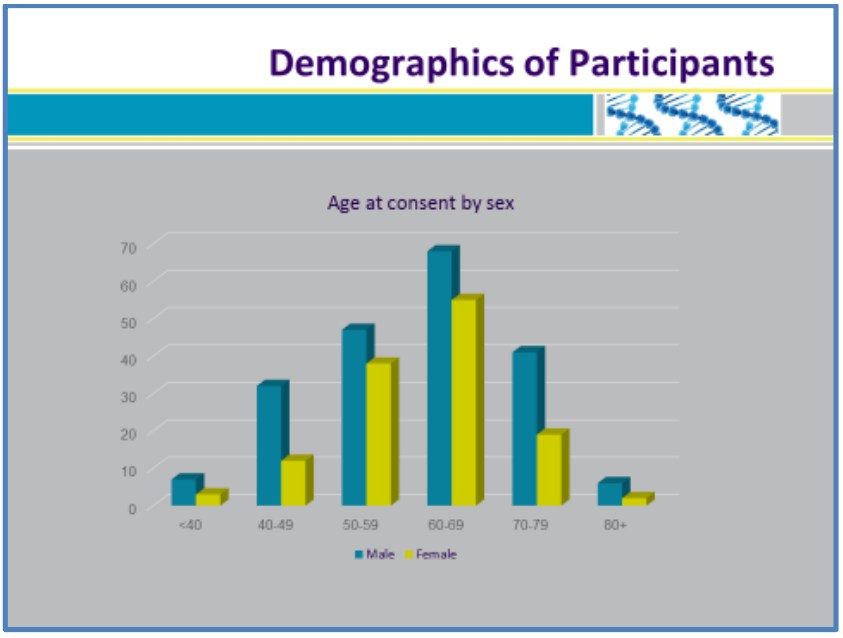
participate for other reasons. First draws of biological specimens were completed for 330 participants. Different approaches helped with recruitment, including advertisements and promotions through ALSA and MDA.

The geographic distribution and demographics of the participants are depicted in the following graphics:



The geographic distribution map has some clustering, but there is at least one person participating from every state. Not all participants are seen at an MDA or ALSA referral center. About 27% of participants recruited live more than 25 miles from a referral center. More than 50% of the population in the project lives 50 or more miles from a center.

The age and sex distribution of participants can be seen in the following graphic:



The second draws began in October 2013. Through June 2015, 265 second draws were completed. Of the 330 participants, 55 withdrew after the first draw, 36 passed away before the second collection, three were too sick to participate, three could not be contacted, 12 were not interested, and one person did not participate for another reason. Of the 330 participants, 281 completed at least one epidemiological survey and 91% completed all of the surveys.

Some challenges were associated with the specimen collection forms. For example, all of the dates were not filled in. In one instance, the forms were cut up and wrapped around the tubes. The answers on the forms did not always agree with the specimens received, and there was some misinterpretation of the questions. Some of the questions about hair and nails were not answered.

In some cases, the phlebotomist confirmed the appointment but did not fulfill it. The appointments would be rescheduled, sometimes at a day or time when next-day delivery to the laboratory was not possible. Specimens were left at facilities without calling for pick-up. One phlebotomist took the specimens home and stored them in the refrigerator. There were reports of phlebotomists who were not professional or not well-trained, and some phlebotomists did not complete the collection forms accurately. There was no way for ATSDR to provide direct supervision or observation of the phlebotomists. The tubes are labeled clearly so that they will be drawn in the right order, but there is no way to verify that they were. Only the materials provided in the kit should be used, because metals-free collection is required. In addition, there was some difficulty reaching remote locations.

Recruitment for the postmortem specimen collection began in April 2013 with 144 emails from ATSDR to recruit 30 participants. Of those recruits, 26 persons had already passed away and five were not interested in participating. Ultimately, 97 information packets were distributed, and 33 persons returned HIPAA forms and were deemed eligible. They were consented on a first-come, first-served basis, and 30 people participated. There were 15 men and 15 women in a range of age groups, and more than half of them lived 50 or more miles from a referral center. Nine persons declined participation in the postmortem collection, but provided biospecimens. All participants in the postmortem collection also participated in the biospecimen collection. As of the end of June 2015, 13 participants have passed away and donated brain, spinal cord, CSF, bone, and muscle. Eleven of them donated skin.

There have been several challenges associated with the postmortem study, including the following:

- ❑ Assessing eligibility and consenting quickly
- ❑ Re-consenting for the addition of a skin specimen
- ❑ Working with participants to make final arrangements
- ❑ Finding dieners and pathologists in remote locations
- ❑ Assuring diener coverage at all times
- ❑ Designing kits for additional specimen types
- ❑ Ensuring that specimens are shipped quickly
- ❑ Ensuring that specimens are received and processed quickly
- ❑ Ensuring that skin specimens are not contaminated with mold

The following recommendations emerged after the pilot study:

- In order to integrate with the National ALS Registry, learning more about donating specimens to the biorepository should be part of the enrollment process, and there should be an option to indicate interest in the biorepository as part of the Registry enrollment process.

- Collect additional information such as mailing address and phone number to facilitate contact.

- For in-home specimen collection:
  - Continue the selection of participants from those who express interest to maintain geographic representativeness
  - Consent and collect from 400 to 500 participants per year
  - Collect specimens only once, but potentially increase the amount of blood collected

- For the postmortem aspect of the project:
  - Consent and collect from 20 to 30 participants per year
  - Continue quarterly contacts

- Regarding in-home specimen types and processing:
  - Continue collecting blood and urine, extracting and freezing DNA from one blood tube during the processing and extracting and freezing RNA from the PAXgene™ tube
  - Stop collecting the metals-free blood tube until the demand for them is assessed; the tube could be added in at a later time
  - Stop collecting hair and nails until the demand for specimens is assessed. They are easy to collect, but there are costs associated with collecting and storing them.
  - Continue collecting saliva specimens from participants who cannot give blood. Process and extract DNA from them. Consider a model in which saliva kits could be administered to a different group of people to increase the number of DNA specimens available.

- Regarding postmortem specimen types and processing:
  - Continue collecting brain, spinal cord, and CSF
  - Assess the usefulness of collecting bone and muscle specimens, and whether they might be added for a limited time as necessary
  - Assess the usefulness of skin fibroblasts and consider only adding them for a limited time

- Regarding quality assurance and processing of existing specimens in-home:
  - Continue assessing samples as they are received
  - Extract the DNA immediately from blood and saliva specimens
  - Extract RNA from PAXgene™ tubes

- Regarding quality assurance and processing of existing specimens postmortem:
  - Continue calculating the RNA Integrity Number (RIN) and pH
  - Continue donation plans with pilot study participants

- General Recommendations

- Obtain IRB approval to continue with the pilot study participants after the study ends in September 2015, and re-consent participants as necessary or help them enroll in another project
- Integrate the biorepository into the protocol for the National ALS Registry
- Amend the IRB protocol to include the donation of specimens and the Office of Management and Budget (OMB) package to include specimen donation
- Update the National ALS Registry website with application materials for researchers to access the specimens
- Maintain the specimens in a private laboratory
- Integrate the distribution of specimens into the biorepository operation: Facilitate the review process of applications for specimens; maintain the inventory of available specimens, which is a difficult process; and retrieve and ship specimens to approved researchers
- Obtain approval to charge a minimal fee for retrieval and shipping as well as any custom dissections of brain or spinal cord tissue

Discussion Points

Dr. Kasarskis asked if a patient who wishes to make a tissue donation in the near future could sign up for the biorepository now.

Dr. Kaye answered that the project has reached its maximum number of participants per the IRB protocol, so no new patients can be enrolled. ATSDR is recommending modification of the protocol so that patients can be enrolled more quickly if they wish. All interested persons were placed in an alternative study if they could not join the biorepository pilot study.

Dr. Lucie Bruijn asked about the possibility of using a globally unique identifier (GUID) for persons who participate in the biorepositories.

Dr. Kaye said that ATSDR only collects two of nine variables required to create a GUID. OMB and IRB approval will be required in order to collect the other seven variables, and the security agreement will need to be modified to incorporate the additional personally identifiable information (PII) collected via the Internet.

Dr. Horton noted that ALS patients have provided feedback that they would like a GUID. Dr. Kaye said that the "menu" presented to patients when they enroll in the biorepository could include creating a GUID. In response to a question from Dr. Kevin Boylan, she said that the GUIDs would be for the National ALS Registry, not just the biorepository.

Dr. Bruijn said that ALSA has invested heavily into biomarkers and envisions sharing information about the resources that scientists could utilize from each of the biorepositories. There is value in not duplicating sequencing and sampling from the same patient. There are nuances associated with this work, such as different GUIDs. The more that these efforts can be combined, the better for everyone's investment.

Dr. Traynor asked whether the consent form allows for data generated from the specimens to be made publicly available.

Dr. Kaye said that de-identified data can be provided to individuals who have been approved to receive data and specimens from ATSDR. An approval process is required before the data can be shared.

Dr. Traynor said that if NIH generates genomic data, the agency is mandated to make the de-identified data available in the database of Genotypes and Phenotypes (dbGaP), a Web repository. They have experienced issues in cases where patients were consented under a different paradigm, and the data are not permitted to be made available. It is worth considering a mechanism for making the National ALS Biorepository data publicly available.

Dr. Kaye said that a new consent form would be required, and CDC would have to agree with the approach.

Dr. Traynor clarified that skin biopsies were being collected to make induced pluripotent stem (iPS) cell lines and said that the field is moving toward using blood samples.

Dr. Kaye agreed and said that the meeting in March yielded a recommendation for an additional tube for blood for that reason. That addition was also in the Request for Proposals (RFP) from ATSDR.

Dr. Robert Bowser congratulated Dr. Kaye and the team for getting the biorepository up and running. Reaching out to patients in distal locations and collecting samples and information from them is heroic and allows patients to participate in research studies in ways that they could not before. He observed that the phlebotomists note the time that samples are collected in the homes and suggested that the time that the specimens are stored and/or processed at the laboratory should also be recorded. Many research studies may not be able to use the specimens because of the time that lapsed between collection and storage of the specimens, but other studies may be able to use them.

Dr. Kaye said that a catalog of the specimens will be created so that researchers will understand how they were collected and the lag time before they were processed. This information will allow researchers to make an informed decision regarding whether the specimens will be appropriate for the analyses that they want to run.

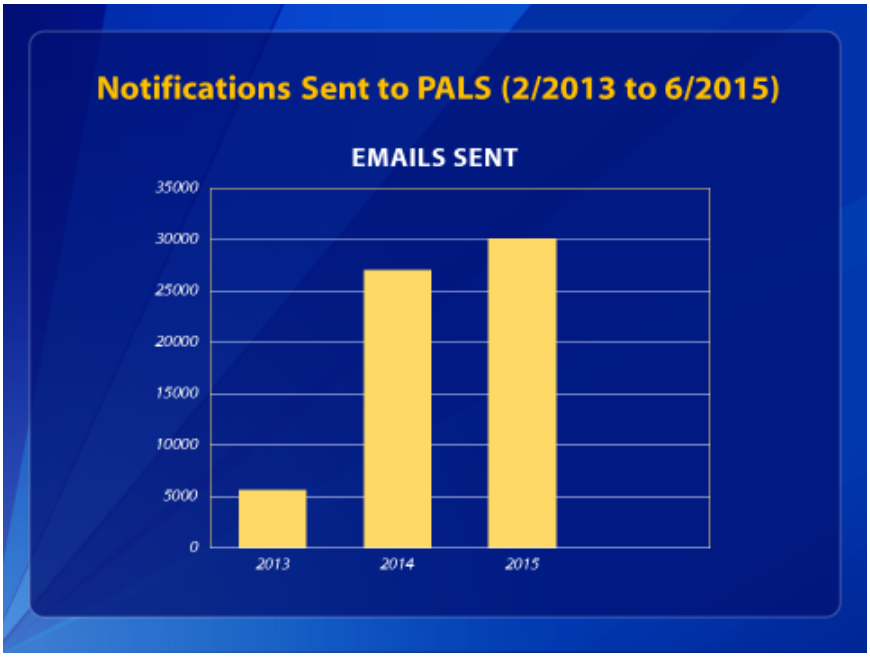
Research Notification Mechanism: Update and Future Challenges

Paul Mehta, MD
National ALS Registry Principal Investigator
Environmental Health Surveillance Branch, DTHHS
Agency for Toxic Substances and Disease Registry

Dr. Mehta provided an update on the research notification mechanism of the National ALS Registry, including focus areas, feedback, challenges, and access. When a patient enrolls in the National ALS Registry via the web portal, he or she is given the option to consent to be notified regarding opportunities to participate in research studies. When a researcher submits a proposal to ATSDR, it is first reviewed internally before being forwarded to an external committee for review. If the proposal is approved by the external committee, ATSDR notifies eligible patients in the Registry via email. The email includes information, recruitment materials, and contact information for the study's Principal Investigator (PI). Patient names and emails are not disclosed to the researchers. Instead, patients choose to contact researchers. The Research Notification Committee includes both internal and external specialists, including neurologists, epidemiologists, ethicists, and other experts. CDC IRB of the submitted project is not required, as the IRB approval of the applying institution is used. The search criteria in the

application form include participant age range, time since diagnosis, gender, and geographic distribution.

Over 95% of PALS who enroll in the web portal of the Registry opt to receive notifications. The Registry's system is simpler and less cumbersome than clinicaltrials.gov. To date, over 60,000



emails have been sent to PALS through the system. There have been increases in the numbers of notifications sent year over year. The notification system debuted in 2013, when approximately 6000 emails were sent. In 2014, approximately 27,000 emails were sent. Midway through 2015, 30,000 emails have been sent. When appropriate for the study, national recruitment is best for researchers. If a study requests nationwide notification, over 5000 emails are sent to PALS, which yields a larger pool of potential recruits. Local- or geographic-specific recruitment can be limiting. It is important for researchers to be prepared for the volume of inquiries from PALS after the email notifications are sent. The studies that have recruited participants from the National ALS Registry range from epidemiological studies to drug trials. ATSDR developed a Research Notification Brochure to distribute to PALS through neurologists, clinics, ALS organizations, and other stakeholders. It can also be downloaded from the National ALS Registry website.

The Registry has been approached by a large pharmaceutical company for clinical trials recruitment. The benefits for the pharmaceutical industry in using the Registry are significant as the Registry is already established, it is the largest ALS Registry in the country, and it can provide national recruitment. There is tremendous interest from PALS for any and all possible treatments and therapeutics. Help from neurologists, researchers, and ALS organizations to get the message out to the pharmaceutical industry about using the Registry for recruitment is appreciated.

Feedback from researchers regarding the Research Notification System has been invaluable, and has been positive overall. Recruitment for studies ranged from less than 5% to 80%. All of the researchers would recommend using the Registry mechanism to other researchers. Researchers have offered some recommendations for improving the mechanism:

- ❑ Send out more than one email reminder to PALS. This point may have IRB limitations, however.

- ❑ Advertise or inform PALS about the research studies. Link to recruitment materials on the website so that PALS can read about open or active trials and studies.

- ❑ Inform the research team about the notification prior to sending to PALS so that they are prepared for the influx of calls.

The National Biorepository Notification System will be similar to and will build upon lessons learned from the Research Notification System of the National ALS Registry. It will also be a web-based system. The applicant can request a certain type and quantity of sample as part of the submission process. Eventually, the sample information will be merged with the information in the Registry's online surveys. All applications will be reviewed by a newly-established research committee.

Some challenges lie ahead for the system. All necessary intra- and intergovernmental approvals are needed, as well as IRB, OMB, and security reviews. A new web portal interface will be established. External reviewers are needed for the new research committee, including statisticians, epidemiologists, laboratorians, geneticists, genetic statisticians, ethicists, and pathologists for solid tissue requests. Recommendations from the research community are needed for the committee.

ATSDR has received numerous requests from researchers and the public regarding access to National ALS Registry data. Two non-identifiable datasets will be developed. For public use, a web-based system will be created that the public can use to analyze ALS prevalence, mortality, and certain risk factor surveys. These data will have been published already. For researcher use, a web-based application system will be created. Requests will be reviewed internally, as the data may not be currently published or released. Access to these data will require additional staffing, as the effort is labor- and time-intensive and includes cleaning, merging, de-duplicating, and verifying the data. The timeframe for release is 2016.

Discussion Points:

Dr. Steven Reznick asked why the research committee does not include PALS.

Dr. Mehta answered that PALS could be considered for the committee.

Dr. Kaye added that all committee members submit information regarding conflicts of interest, but there is no reason why a person with ALS could not participate.

Dr. Mehta encouraged Dr. Reznick to submit his name for the committee. Dr. Reznick indicated that he would do so.

Capture/Recapture: Methodology for Estimating True Prevalence of ALS in the United States

Lorene Nelson, PhD, MS
Associate Professor
Division of Epidemiology
Center for Population Health Sciences
Stanford University School of Medicine

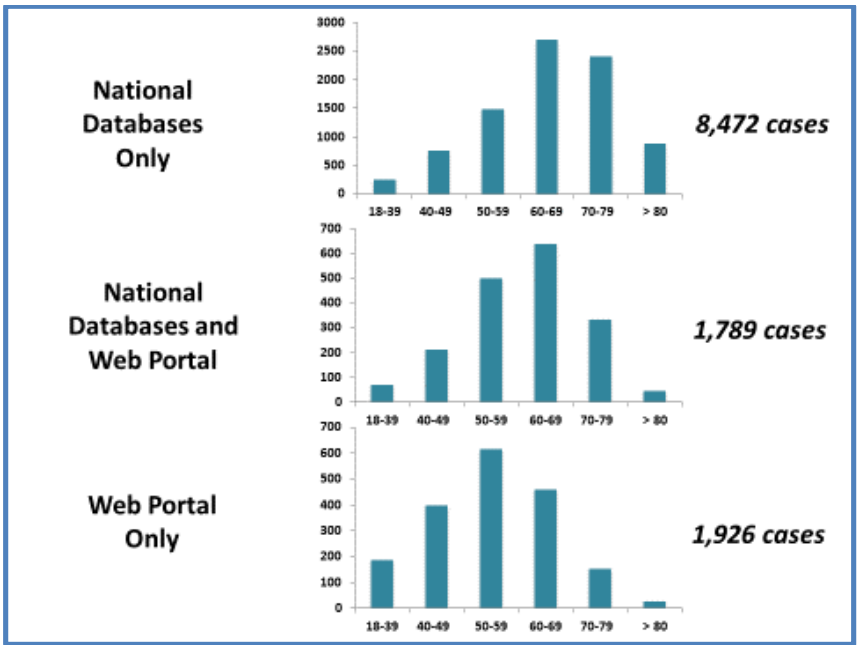
Dr. Nelson greeted the group and commented on the progress on the National ALS Registry. She presented findings from the first National ALS Registry report and introduced the capture-recapture method and its implications for the Registry. The report on the prevalence of ALS from 2010 – 2011 was released in *MMWR* in 2014. The methods used to identify individuals with ALS from that era include:

- Medicare, for which medication data are available as of 2006. Medicare covers 95% of the US population above age 65 as well as any PALS who have applied for Social Security disability.
- Medicaid differs by state, and each state has different timelines for compiling its data for the national dataset. Medicaid populations generally include persons of lower socioeconomic status (SES) and is an important source for capturing the prevalence of ALS.
- VA, which includes the Veterans Benefits Administration (VBA) and the Veterans Health Administration (VHA). VBA includes PALS with service-connected disability. VBA and VHA are combined for capture-recapture because of the overlap between them.
- The web portal, which became available in October 2010.
- The National Death Index (NDI) is used to identify individuals with ALS as an underlying or contributing cause of death.

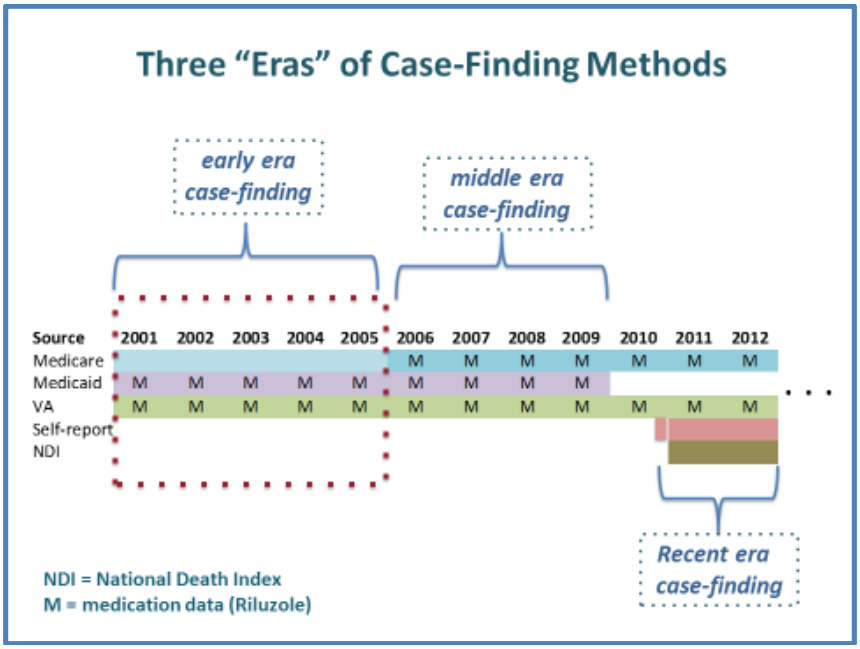
Prevalence is the best measure of disease burden in the US, as it is a best estimate of every person who lives in the US and has ALS at a given point in time. The first report from the National ALS Registry resulted in 12,187 PALS. The prevalence rate for the period of the report was calculated to be 3.9 ALS cases per 100,000 persons in the population.

It would not be possible to count all persons with ALS pathology, as they are not all readily identifiable. However, there is a subset of persons with ALS symptoms and a subset of those persons have sought medical care and been diagnosed with ALS. Of all the individuals with ALS identified in the two-year period of the first Registry report, 70% (n=8472) were uniquely identified through the national databases, 15% (n=1789) were uniquely identified by self-report through the Web portal, and 15% (n=1926) were identified by both methods. If only the Web portal were used to identify PALS, only 30% of them would be identified.

A combination of the methods is needed to assess prevalence. The types of people captured by each method should be considered. In particular, the age distribution of the patients in each method should be noted. The web portal only captures a segment of the age spectrum that is not as likely to be captured by the national databases.



The capture/recapture method helps address the number of PALS who are missing from all capture approaches and helps estimate a corrected count of PALS in the US. Three "eras" of case-finding methods are available for consideration:

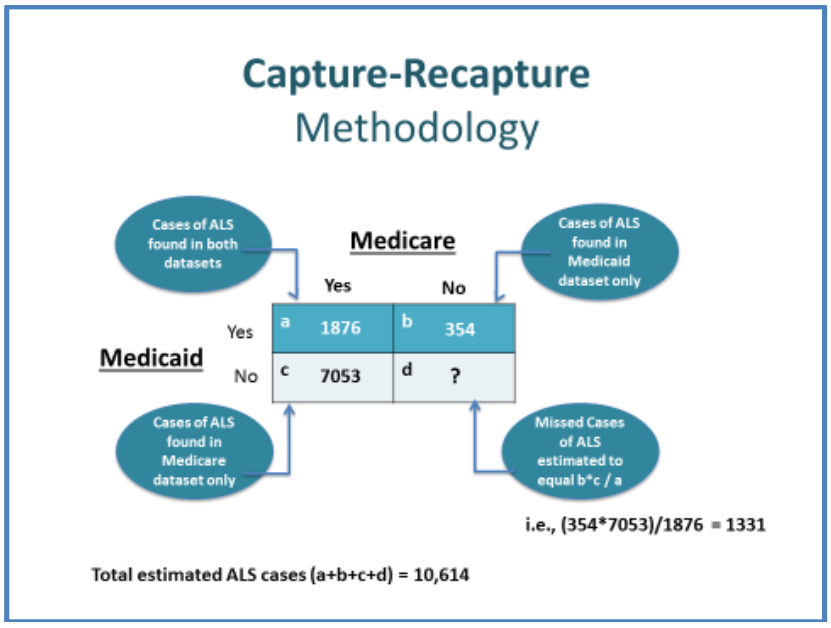


2006 was the first year that Medicare began capturing information about drug utilization, so the "middle era" of case-finding begins with that information. The data from 2001 – 2005, which includes Medicaid and VA data, can be compared to the data from the ATSDR State and Metro initiative. The data for this presentation are from 2002, 2003, and 2004. Data from 2001 and 2005 are not as good for estimating the total because part of the algorithm for identifying PALS requires two years of data with codes for ALS and a neurologist visit in at least one of those two

years. Therefore, including data from 2001 and 2005 would result in an under-count of ALS cases.

Using the data from Medicare, Medicaid, and VA, 8005 ALS cases were identified for the year 2003. Approximately two-thirds of them were identified solely by Medicare, 324 cases solely by Medicaid, and 422 solely by the VA. Overall, 92% of the sample was identified by Medicare, 23% by Medicaid, and 15% by VA. In general, the Medicaid age distribution includes younger parts of the age spectrum than Medicare and the VA.

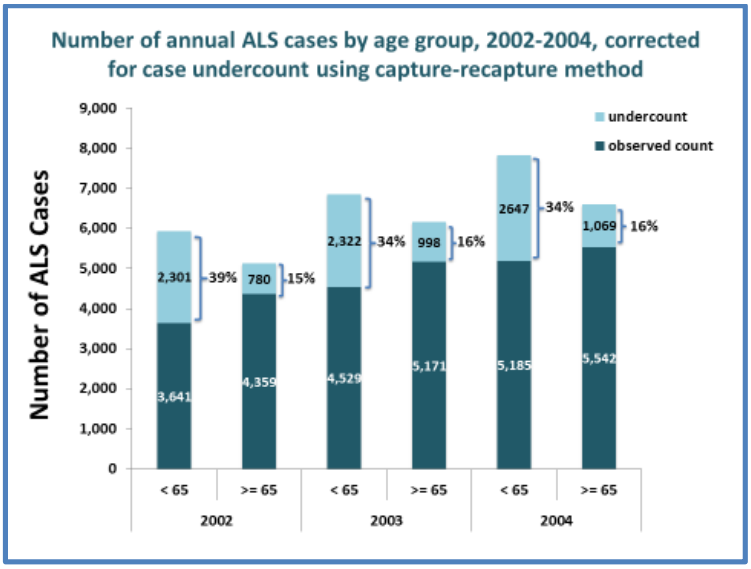
Capture-recapture methodology is not regularly used in clinical or epidemiological research. The idea, which comes from wildlife biology, is to capture, "mark," and recapture. For example, imagine a lake. Researchers want a valid count of the number of fish in the lake without dredging the lake and counting all of the dead fish. They can instead take samples and make inferences about the count of fish in the lake. One week, the researchers sample 100 fish and tag them so that they can be identified at the next capture. Those fish are released, and another sample of 100 fish is captured the next week. If 90 of the 100 fish captured the second week have tags, then researchers might infer that the total count of fish in the lake is not much more than 90. If the second capture yields only 10 fish of the 100 that have tags, then the fish population is likely to be much larger.



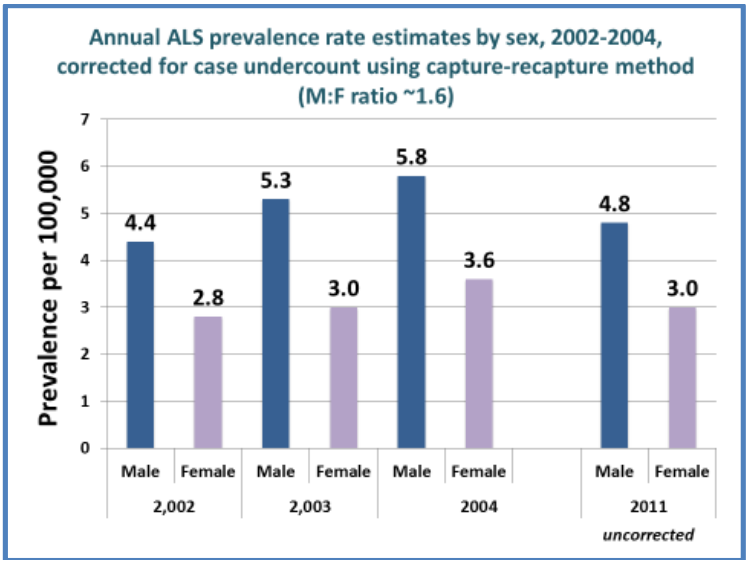
For estimating the prevalence of ALS, the capture-recapture methodology uses an algebraic formula to estimate the cases that are missed by the independent sources of data. It is difficult to determine whether the assumption of independent capture probability is met, however, without a third data source. Simple algebraic methods can be used to estimate the number of missing cases when there are only two data sources, but the estimation requires heavy assumptions. The probability of being captured by one source may be associated, either positively or negatively, with the probability of being captured by other source(s). Within a given source, the probability of capture should be the same across individuals, but it may vary by age, race, sex, or other variables.

The goals of capture-recapture are to: 1) estimate the number of cases that are missed by all capture methods in order to correct prevalence estimates; 2) determine whether the degree of undercount varies according to age, sex, race, or geographic distribution; 3) learn who is under-represented in the prevalence rates; and 4) determine whether additional case-finding methods are needed and/or whether one or more case-finding methods that are currently used might be duplicative.

A method called log-linear modeling allows for statistical analyses to estimate the number of missing cases even when assumptions are violated. Applying this method shows that the degree of undercount is greater for patients under the age of 65 than those above the age of 65. This finding is constant across the data years in the study and is not surprising, as 95% of the US population over the age of 65 is eligible for Medicare and should be captured by that method.



Across all of the data years, approximately 23% of both male and female cases are estimated to be missing from each of the data sources. When the prevalence ratios are corrected for the undercounts, the male to female ratio is approximately 1.6.



Overall, for the years 2002 through 2004, the number of ALS cases observed across case finding methods increased in a linear fashion, from 8005 in 2002 to nearly 12,500 in 2003 to nearly 14,000 in 2004. The case count increased still further in 2011, but the National ALS Registry web portal provided an additional data source for that year. If the undercount is applied to 2011, the corrected count would be closer to 16,000. Because the array of case-finding methods was different in 2011, however, the conclusions from the 2002-2004 capture-recapture analyses cannot be applied to estimate the undercount.

After securing the undercount estimates, it is ideal to use other means for checking whether the estimates are accurate. Data were available from 2001-2005 from studies conducted at Emory University as part of the Health Maintenance Organization (HMO) Research Network (HMORN), the Mayo Clinic, and South Carolina. The Emory University and South Carolina studies are applicable to the National ALS Registry. The estimate of individuals missed by the databases in both studies was 22%. This finding supports the conclusion that reliance only on federal databases for counting ALS cases results in missing 22% to 23% of total ALS cases for our data from 2002-2004.

The uncorrected ALS prevalence rates for 2002, 2003, and 2004 are 2.8, 3.3, and 3.7, respectively. When the rates are corrected using the capture-recapture method, however, the rates increase by nearly one point to 3.7 in 2002, 4.4 in 2003, and 4.8 2004.

The capture-recapture methodology established that 22% to 23% of ALS cases are missed when only the federal databases are used. The degree of undercounting did not differ according to gender, but it did differ significantly according to age. It is likely that individuals on the younger end of the age spectrum will be missed if only federal databases are used to capture ALS cases. The Web portal of the National ALS Registry is all the more important, as its case ascertainment is skewed toward younger individuals. The next steps are to repeat this methodology with 2010-2011 data, as well as with the intermediate era in which the case-finding methods are slightly different from the early and most recent eras.

The National ALS Registry has done a rigorous, careful, and thorough job. It represents the first effort, other than cancer, for a national, population-based Registry for a chronic disease that is not registerable. The Registry has reached different stakeholders who are all invested in the effort. The addition of biological samples is a significant development for the Registry. By the end of 2015, there will be 10 publications of ALS descriptive epidemiology in the literature. No other neurologic disease has seen an effort of this dimension. Dr. Nelson is on a national committee to estimate Multiple Sclerosis (MS) prevalence, which has not been done rigorously in many years. That group is relying on the findings from the National ALS Registry, which demonstrates that the Registry is contributing to the field even beyond ALS.

Discussion Points

Ms. Rebecca Kidd asked about the timeframe for conducting the capture/recapture analysis on data from 2006 to the present.

Dr. Nelson answered that the project would focus next on the data from 2010-2011, as it is important to understand how the recent estimates may need to be adjusted. Then they will work on data from 2012-2013.

Dr. Kasarskis asked whether the Patient Protection and Affordable Care Act (ACA) will be helpful for epidemiology in the future and when the new bolus of people covered by the ACA will be identifiable.

Dr. Kaye said that the individuals covered by the ACA may not be identifiable if they have private insurance. They can only be captured if they register on the web portal or are captured in national databases. Private insurance is not a data source for the National ALS Registry. The states that expanded Medicaid will have a substantially larger number of persons who may be identified for the Registry. There is a substantial time lag with Medicaid and with Medicare when PALS apply for Social Security and disability benefits.

Dr. Mehta noted that ATSDR considered the number of ALS cases in the published report (12,187) to be a baseline. That number and the prevalence rate are likely to increase. No surveillance system can capture 100% of cases. The capture/recapture method is important to assess the completeness of the system.

Dr. Benjamin Brooks commented that the capture/recapture project illustrates the importance of the web portal. The need and cost-effectiveness of the National ALS Registry is apparent. He asked about Medicare's information regarding the age distribution of persons who are prescribed riluzole and whether that information is available among other groups.

Dr. Nelson said that there has been some analysis of age and riluzole, but it is an area that could be examined formally. The only two sources in the early period of data that have information about riluzole are the VA and Medicaid. She recalled that approximately 50-60% of individuals who meet one or more of the algorithm criteria have had riluzole.

Dr. Brooks noted the importance of age in determining how knowledge is gathered about patients. An analysis of the age distribution of riluzole could provide important insight regarding missing cases. Dr. Kasarskis's point about the ACA also could contribute to knowledge regarding missing cases among younger persons.

Dr. Traynor asked whether mortality and death certificate data have been considered as another vector for the capture/recapture methodology.

Dr. Nelson replied that those data have not been considered yet because they were not available for the era of data in the project.

Dr. Kaye added that there are potential problems if there is only access to the code on the death certificate and not the text written by the physician. She examined more than 20,000 death certificates in a three-year time period. Consistently, 23% of them were not ALS and 17% were not even a motor neuron disease (MND), but rather a supranuclear palsy that was moved out of the Parkinson's group disease codes in ICD-9. Without the text from the physician, the code alone is not reliable. The National ALS Registry algorithm calls for another documentation of ALS along with the code on the death certificate.

Dr. Stephen Goutman commented on the importance of the riluzole prescription for capturing people; however, many patients in his practice choose not to receive a prescription. With the loss of patients in younger age strata, there is an accompanying potential loss of Registry members who can participate in research.

Mr. Ted Harada asked how the 22% of cases that are not captured by government databases compares to the completeness of the "deep dive" of the State/Metro Initiative studies.

Dr. Kaye answered that the process of matching the State/Metro data with the National ALS Registry for analysis is ongoing. This work is challenging because the Registry officially began on October 19, 2010, where the State/Metro project collected data from January 1, 2009 through December 31, 2011. Data regarding deaths in the time differential must be collected so that a person who died before the National ALS Registry began, and therefore could not have been counted, would not be determined as a missing case. There are cases missing from the Registry that were counted in the State/Metro project, however, and the results of the comparison will shed light on the demographics of missing cases in the Registry and will help target outreach activities.

Registry Promotion and Outreach

National ALS Registry: Marketing Update

Tom Hicks
Public Health Advisor
Carter Consulting, Inc.

Mr. Tom Hicks presented information regarding marketing objectives and strategies that the National ALS Registry is using, the target audiences of the efforts, the types of promotional media being utilized, and metrics for measuring interest in the Registry. The objectives of the marketing efforts are to increase awareness of the National ALS Registry and how the information gathered by the Registry is being used to defeat ALS; and encourage persons with ALS (PALS) to self-register and to complete the risk factor modules.

The marketing strategy utilizes both traditional and online, digital media. The focus is increasing on the digital side. The strategy also engages persons and organizations who interact with PALS to reach the largest number of potential Registry participants. The marketing includes close work with partners, including The ALS Association, MDA, Les Turner, and others, such as clinicians, neurologists, researchers, and caregivers. Contracts are in place with The ALS Association and MDA to help raise awareness of the National ALS Registry. The audiences for the marketing efforts are: PALS; family members; caregivers; specialized health care providers, including neurologists, physical therapists, and others; ALS researchers who work with patients; and ALS support organizations.

Several digital media channels are used. Articles are published in online magazines and E-newsletters. Advertisements about the National ALS Registry are posted in partner publications such as MDA's *Quest* magazine. Articles are featured on CDC's website and blogs are included on ATSDR's website. Articles and reports are posted online with findings from the Registry. Social media also is an important tool.

The most recent feature article on CDC's website was posted during ALS Awareness Month in 2015. The article describes ALS and the National ALS Registry and encourages PALS to enroll in the Registry and to take the risk factor surveys. The article also contained links to other sites where readers can find more detailed information. The ATSDR blog posts are brief and easy to read. The Registry blog focuses on highlighting accomplishments, increasing awareness,

encouraging PALS to enroll, and completing the risk factor surveys. The blog posts also include links for additional information and articles. The *American Journal of Public Health* (*AJPH*) published an article in June 2015 summarizing key points from the first report releasing data from the National ALS Registry, which described the prevalence of ALS in the US from 2010-2011.

Another major part of ATSDR's effort to market the Registry involves the use of social media. ATSDR has approximately 13,400 Twitter followers, and CDC's Facebook page has approximately 472,000 followers. There is often much competition regarding which messages are featured on CDC's Facebook page, and it can also be challenging to have messages posted in a timely manner. The social media messages build awareness about the importance of being counted by joining the Registry; urging PALS to help find the causes of ALS by completing the risk factor surveys; publications that use Registry data; research that uses Registry data; and initiatives such as the biorepository and data from the State and Metro ALS Surveillance project.

An infographic was published with the first National ALS Registry Report. Like other infographics, it relies on graphics to describe what the Registry is doing, how it works, and the Registry findings in an interesting, quick, and clear format. ATSDR has also created Web buttons that focus on populations that are under-represented in the National ALS Registry, such as minorities and rural populations. They also focus on caregivers. The buttons are included in articles and social media posts.

Several traditional media mechanisms are used to market the National ALS Registry. An article was published in *Today's Caregiver* magazine and E-newsletter in March and April 2015. The bimonthly print publication reaches approximately 100,000 people. Several brochures have been developed. The most recently developed Registry brochure focuses on the Research Notification System and describes how the Registry connects PALS who are interested in participating in clinical trials and studies with researchers. The intent of the brochure is to build awareness of the system among researchers. The following is a list of the distribution of Registry products by organization:

Registry Products Distribution by Organization

Product Type	ALSA	MDA	LES TURNER	Clinics, Physicians, Other	Total
Patient Guides	10,400	4,211	200	5,487	20,298
Provider Guides	1,710	1,737		1,694	5,141
Fact Sheets	3,535	6,061		3,027	12,623
Quick Start Guides	3,625	4,911		2,162	10,698
Continuing Ed. Guides	659	561		1,165	2,385
Doctor Office Posters	961	1,730		1,139	3,830
*Get The Facts Infographic	330	2,005		50	2,385
*Connecting PALS & Researchers	200	0	200	150	550
Total	21,420	21,216	400	14,874	57,910

As of June 30, 2015
*Infographic distributed starting in 2014, Connecting PALS & Researchers distributed starting in 2015

Nearly 58,000 copies of materials have been distributed since the National ALS Registry became active. The materials can be ordered online. It is important to note that views of the Registry have increased every year since 2011.

Discussion Points

Mr. Harada asked about efforts to measure the touchpoints and impact of the social media outreach or the traditional media outreach.

Mr. Hicks replied that work in this area is ongoing, and some of the information is available from the Cloud.

Mr. Harada expressed hope that the new marketing partner would help gauge improvement in the outreach. Regarding the distribution of 58,000 materials, he wondered how many of them represented re-orders from chapters as opposed to materials that were included in initial blasts to clinics and organizations. If the materials are not being re-ordered, groups may not be distributing them initially or may have stopped distributing when the initial materials were depleted.

Mr. Hicks responded that the distribution could be examined by year.

Mr. Patrick Wildman noted that the figures regarding distributed materials do not include materials that ALSA and other organizations have printed and distributed on their own. Initially, The ALS Association relied on ATSDR for materials, but in the past several years, they have printed and distributed them on their own. Chapters may not go to ATSDR for new materials, but to the national ALSA office. Across the board, materials have been resent continually since the beginning of the National ALS Registry. The ALS Association has developed additional tools as well, and some tools are more effective than others.

Dr. Mehta added that ATSDR has a limited printing budget, so they provide proofs to their partners for printing. ATSDR recently partnered with the *Rare Disease Report*, a major trade journal, to post articles.

Dr. Brooks asked what proportion of the hits on the National ALS Registry site was on the first report from the Registry.

Dr. Mehta said that the information can be accessed, as the "snapshot" of the website shows which pages are accessed, and how many times, per month or per year.

Dr. Brooks said that this metric is important. His center prescribes the National ALS Registry and the MDA ALS Outcomes Registry. Patients are educated regarding the differences between the registries. Even so, not all patients respond and enroll in the registries.

Brunet-García

Anna Jaffee
Account Brand Strategist
Brunet-García Advertising, Inc.

Ms. Anna Jaffee said that in the four months that Brunet-García has partnered with ATSDR, they have learned a great deal. She thanked ATSDR for their partnership and information-sharing, which has informed the development of the draft communications outreach plan for the National ALS Registry.

Brunet-García, based in Jacksonville, Florida, is 100% focused on social impact. The agency

was contracted to develop a communications outreach plan to increase awareness and engagement with the National ALS Registry. The plan has three objectives, which are to:

- ❑ Raise awareness of National ALS Registry among persons with ALS (PALS) and their family members and caregivers, as well as ALS clinicians and researchers.

- ❑ Target, inform, and educate PALS about the latest happenings and updates from the National ALS Registry. Communicate the benefits of the Registry beyond "counting cases" clearly.

- ❑ Increase self-registered PALS in the Registry and encourage the completion of risk factor surveys.

A draft communications outreach plan has been created and is in review with ATSDR. The development process included review of all of existing ATSDR and partner materials; strategic marketing session with ATSDR; partner conference calls; stakeholder calls with PALS and ALS strategic partners; review of notes and action items from 2014 surveillance meeting; a 90-day media scan and report to learn about the print and digital mentions of the Registry to develop a baseline for comparison when the communications plan is implemented; an Internet scan of content about the Registry; and an Internet scan of ALS support groups.

The plan identifies a series of communications goals, which are to:

- ❑ Develop champions of the ALS Registry across the nation to carry the message of the Registry through word-of-mouth
- ❑ Strengthen partnerships for enhanced communications
- ❑ Engage with stakeholders using technology to reach them with new methods
- ❑ Create and distribute digital and print content (Some materials already created by ATSDR will be updated. A cohesive, key messaging platform will be developed for partners to communicate the Registry benefits and encourage use of the Registry)
- ❑ Increase visibility of the ALS Registry online (Capturing people's attention while they are already online searching for information is the easiest way to lead them to the Registry)

Ms. Jaffee thanked the group for their input. They are early in the communication process, and the goals serve as "thought starters." She welcomed suggestions, questions, thoughts, and insights.

Discussion Points

Mr. Robert Goldstein noted that the National ALS Registry has a brand identity problem. The Registry is not about "counting" cases, but it is called the National ALS Registry. He suggested marketing the Registry as something else. Champions are an excellent idea, but people die of ALS quickly. It is important to think long-term about who the champions are, how they play a role, and how their loss is dealt with.

Ms. Jaffee said that PALS can be a huge resource for spreading the word about the Registry, but other stakeholders can also be champions.

Mr. Goldstein agreed and said that the most important aspect of capturing the missing cases is showing the Registry's value. Good marketing, branding, and communication can accomplish this goal. This work is likely to be one of the most important investments that ATSDR can make in the next few years.

Ms. Sarah Embro expressed excitement that the ATSDR materials are being updated and put into digital formats to capture that market, especially since the portal is web-based. There needs to be constant re-education and education in the strategic partner organizations because of natural turnover. New organization personnel are constantly educated about the National ALS Registry and how best to promote it. Regarding the communication plan, she noted that some organizations may assign the task of updating social media posts and other digital media to a person who may not be specialized in the National ALS Registry. If easy blasts are sent to the organizations as part of the communication plan, then the information will remain at the top of their minds.

Ms. Jaffee said that the plan considers not only making it easier for PALS to get to the Registry, but also how to make it easy for partners to talk about the Registry in a consistent manner.

Dr. Mehta added that one of Brunet-García's deliverables is to generate content, such as a newsletter that could be imbedded into partners' communications. ATSDR has been mandated by the US Department of Health and Human Services (HHS) to make the web design more

responsive. Currently, the design is not mobile-responsive. The US government is moving toward mobile design. In particular, it should be easy to enroll in the National ALS Registry on a mobile phone or tablet. In the future, it would be ideal to create an enrollment app.

Mr. Kingon asked about formative research with PALS and caregivers to ensure that the target messages will be effective.

Ms. Molly Walker answered that through the existing agreement, Brunet-García will distribute the communications plan through the ATSDR team, including a message platform. They are able to hold focus groups or surveys, if the budget will allow.

Ms. Jaffee said that the key messaging platform will be separated by audience so that the messages are tailored to PALS, researchers, and others.

Ms. Kidd recalled that the need for a marketing and communication strategy was identified as a top issue at the 2014 ALS Surveillance Meeting. She was pleased and encouraged to see it come together. She agreed that champions cannot just be PALS. Outreach organizations also need to have an investment in the Registry and in the communications plan. There should be a report card, because results come from what is inspected, not what is expected. When the champion model is defined, there should be measures associated with it to track progress.

Les Turner ALS Foundation

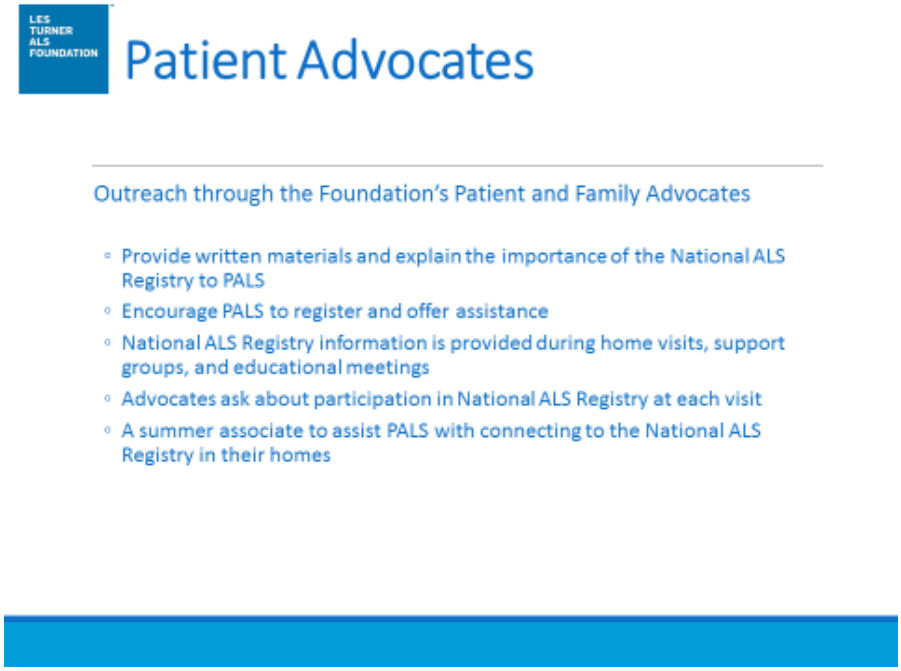
Jennifer Armstrong, RN, MSN/MHA
Nurse Coordinator
Les Turner ALS Foundation

Ms. Jennifer Armstrong indicated that the Les Turner ALS Foundation is based in Chicago, Illinois. The foundation supports the patient care and research activities at Northwestern University. The foundation began with grassroots efforts in 1977 when the family and friends of Les Turner, an ALS patient, wanted to provide resources for ALS research and share the results of ALS research.

The first ALS Research Laboratory at Northwestern opened in 1977, and the foundation started a clinic with Northwestern to provide patient services in 1986. Today, the foundation supports three dedicated research laboratories, a multidisciplinary clinic that meets two half-days every week, and other patient service programs such as in-home consulting, support groups, and community educational programs to over 90% of the ALS population in the Chicagoland region. In 2014, there were over 800 patient visits at the center. Of those, 155 were new patient visits. The foundation employs six patient advocates, who provided over 800 visits in homes during 2014. Over 360 participants attended support groups.

The Les Turner ALS Foundation has long been a champion of community outreach, promoting events throughout the international ALS community. Public awareness and promotion efforts for the National ALS Registry include a dedicated Registry page on the website; monthly features of Registry information on the foundation homepage; inclusion of links directing constituents to the Registry via e-newsletters; and routine social media announcements.

Timing is an important element of providing information about the National ALS Registry to persons with ALS (PALS). The clinic visit is not always the ideal time to discuss the Registry with patients, as there are other priorities during clinic visits. The average ALS patient clinic visit can be four to five hours long. Having patient advocates in homes can provide time to discuss



the National ALS Registry with PALS and their caregivers. The advocates can discuss how to register online and the information that will be needed, and help patients register in the comfort of their homes. The advocates provide this information through brochures and other written materials. The information is also provided in support group meetings, which often occur in evenings and on the weekends. PALS are encouraged to participate.

Not all PALS have access to computers or the ability or mobility to enroll in the National ALS Registry. It can be fatiguing for PALS to sit in one area to spend time enrolling. The Les Turner ALS Foundation has hired a summer associate to promote the Registry and to enable PALS to register. The associate is a volunteer medical student with a lifelong connection to ALS, as his father is a physician at one of the Les Turner centers. He has the knowledge and background to provide support for PALS and their family members as they enroll. He goes to the patients' homes with his computer, in case the patient does not have access. The patients and their caregivers are motivated to dedicate time to focus on enrolling. In his first two weeks, he helped over 10 patients start registering for the National ALS Registry and completing the risk factor surveys. The foundation has received positive feedback regarding his efforts. This approach is intended to help reduce the fatigue that PALS and caregivers experience in completing the Registry and to motivate them to encourage other patients at their support groups to utilize the associate to help them as well. The approach is also helping the associate become expert in helping other families complete the online registration.

Muscular Dystrophy Association

Kristin Stephenson
Vice President, Policy & Advocacy
Muscular Dystrophy Association

Ms. Stephenson shared information about how MDA promotes the National ALS Registry. MDA's mission is to save and improve lives of people fighting muscle disease. They have been engaged in this work for over 50 years. Over 40 diseases are within MDA's purview including ALS, the Muscular Dystrophies, and Spinal Muscular Atrophy (SMA). MDA has been working for decades to fight ALS, beginning when Lou Gehrig's widow, Eleanor, was searching for a way to fight the disease that took her husband's life. She served for more than a decade as MDA's National Campaign Chairperson.

MDA provides many essential services, including:

- ❑ Clinical care
- ❑ Public policy initiatives
- ❑ Support through outreach, support groups, and home visits
- ❑ Educational seminars and events at the national and local levels
- ❑ Equipment loan program
- ❑ Assistance with Durable Medical Equipment (DME) repair
- ❑ Influenza shots
- ❑ Print and online resources
- ❑ Improving care and understanding the progress of various diseases under its umbrella through the NMD Registry

MDA supports ALS families in many ways, such as through the MDA Registry and by promoting the National ALS Registry. MDA is committed to awarding research grants, holding support groups, engaging in public policy and advocacy initiatives, and providing care in more than 44 MDA ALS Centers. In the last five years, MDA's ALS research efforts have contributed $46 million for ALS research, including over 140 research grants and 18 awards to incentivize young scientists to pursue ALS research.

MDA's promotion of the National ALS Registry takes several forms. MDA's nationwide clinic network includes over 180 clinics, 44 of which are ALS Centers. Each clinic promotes the National ALS Registry. MDA also generates print and online publications, including the quarterly *Quest Magazine*, which reaches about 120,000 households. Each issue includes a full-page infographic about the Registry that encourages readers to participate. *Quest* is also published online and received over 1 million page hits in 2014. MDA's online *ALS News* magazine received over 220,000 page hits in 2014.

The MDA National ALS Registry toolkit is distributed at all MDA clinics. A webinar will be held for all staff and clinic directors to discuss the Registry and answer questions. Additionally, an ALS-focused "Lunch and Learn" was held in 2015 to discuss "all things ALS," including the Registry and the importance of achieving as much enrollment and participation as possible.

The toolkit includes additional materials, such as a pamphlet titled "The Power of Disease Registries." The pamphlet addresses the importance of registries and makes distinctions between the MDA NMD Registry and the National ALS Registry.

MDA also promotes the National ALS Registry via social media and at various events, clinical and scientific conferences, and educational seminars. These events reach beyond persons with ALS (PALS) to scientists, industry, and other relevant partners. They have international attendance. Additional regional and local opportunities for promotion of the Registry include muscle summits, regional education events and seminars, muscle walks, and support groups.

MDA works collaboratively to promote the National ALS Registry, particularly with ALSA. The two organizations will work together cohesively to communicate to the community the importance of participating in the Registry and the advantages to those who participate. MDA and ALSA will kick off the collaborative effort in Salt Lake City, Utah on September 1-2, 2015. They will focus on states with lagging enrollment in the Registry to identify future locations for similar events.

MDA is collecting information from its locations in states with high enrollment and states with lagging enrollment to determine activities and promotional activities that the higher-enrollment states may be utilizing, as well as opportunities for states that are lagging. This ongoing process will build best practices as the Registry moves forward.

Discussion Points

Mr. Goldstein said that MDA has a long history and a strong system. He asked what percentage of ALS patients seen at MDA clinics have enrolled in the National ALS Registry. It may be useful to have a goal to work toward full enrollment.

Mr. Steve Gibson said that in 2014, ALSA reported 13,000 patients and MDA reported 13,000. However, comparing the two is "comparing apples and oranges because the 13,000 patients counted by MDA included persons beyond ALS, such as those with Primary Lateral Sclerosis

(PLS). Also, some patients are served at several ALSA chapters. Some individuals live in New York and spend the winter in Florida, for example. The comparisons are not good because the datasets are not the same.

Dr. Brooks added that these numbers have been considered at the clinic level and published in abstract form. At a given MDA ALS Center, 62% of patients were enrolled on the first pass, and an additional 22% were enrolled on the second pass. The figure was never 100%.

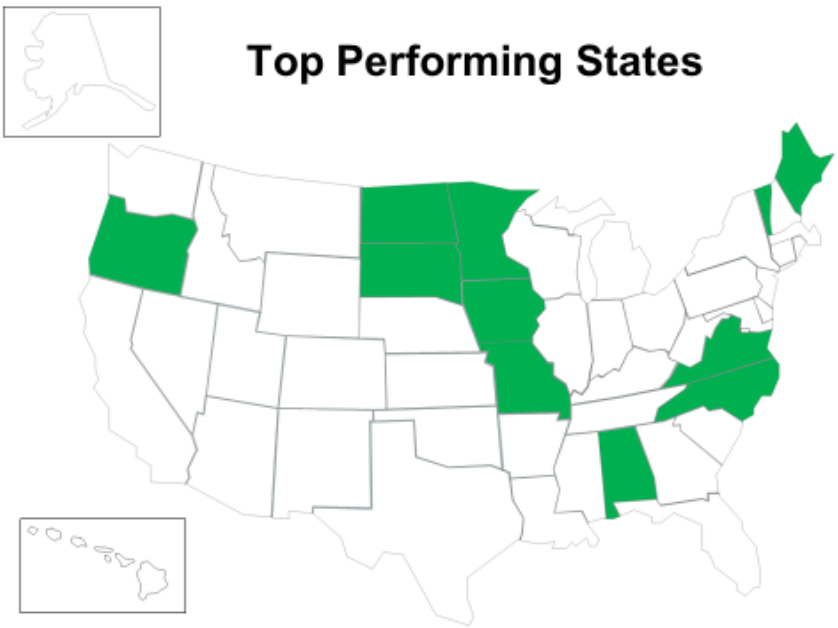
Amyotrophic Lateral Sclerosis Association

Steven Gibson
Chief Public Policy Officer
The Amyotrophic Lateral Sclerosis Association

Patrick Wildman
Director, Public Policy
The Amyotrophic Lateral Sclerosis Association

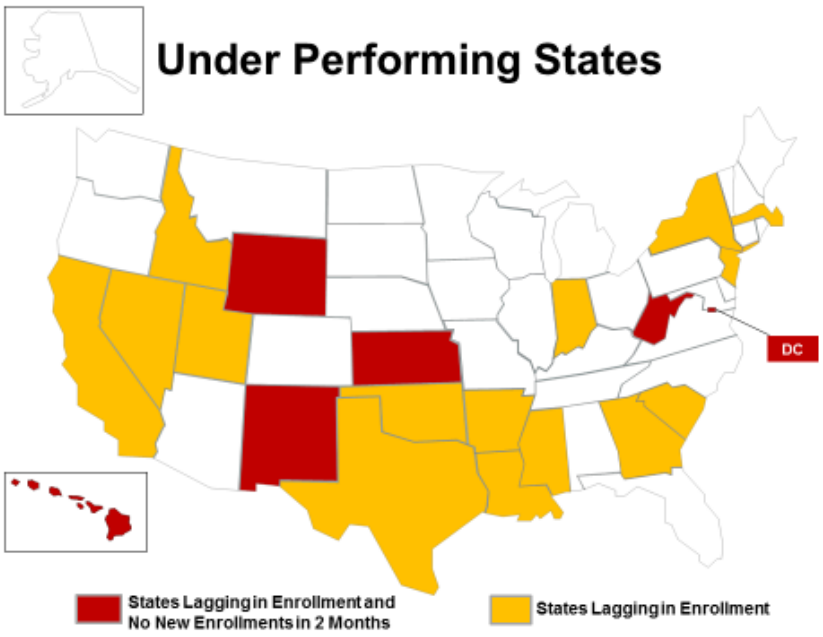
Mr. Gibson and Mr. Wildman presented information regarding ALSA. ALSA has 39 chapters throughout the US. ALSA reaches out to those chapters for input regularly. A listening tour is conducted twice per year. One of the tours focuses just on the National ALS Registry. Chapters are asked about what works and what does not work regarding Registry enrollment and other issues.

An important issue to consider is the number of people who are not connected to the Internet. For instance, 50% of the patients enrolled in the Georgia chapter of ALSA do not have an email address. What about PALS who ALSA does not know about? In terms of messaging and communication, it is important to remember that some people do not have access to the Internet. Further, people might have access to the Internet but do not feel comfortable using it due to a lack of familiarity, generational issues, cultural issues, or irregular access in rural areas.



The top-performing states are Minnesota, North Dakota, Iowa, South Dakota, Maine, Missouri, North Carolina, Oregon, Virginia, Vermont, and Alabama. Alabama is not one of ATSDR's top-performing states, but it has never been on the under-enrolled list and has taken important steps to ensure that it is never on that list. The Iowa Chapter is a good example of starting from the beginning. When a person is diagnosed with ALS, he or she is told about the National ALS Registry. Staff who visit PALS in their homes share information about the Registry and the link to it. Throughout the case management process, care service staff help PALS enroll in the Registry and help with completing the risk factor surveys. The experience is rewarding for the staff members because they get to know PALS on a different level. Each month, ATSDR sends ALSA a list of states that are lagging in enrollment in the National ALS Registry. This list helps to target additional outreach efforts.

Neurologists have been leaders in enrollment in the National ALS Registry in other states. They talk to patients at visits and at various symposiums, and they are active on social media as they communicate the importance of the Registry. Volunteers are also an important part of outreach. At the Oregon ALSA chapter, a volunteer felt that the National ALS Registry was so important, he traveled to each of the support groups and clinics in the state and personally helped to enroll every patient in the Registry. In Alabama, a newly-diagnosed PALS toured the entire state and enrolled patients in their homes who were newly diagnosed.



In Mississippi, Minor League Baseball has been a strong part of communication efforts. Minor League Baseball had an attendance of 42 million people in 2014, and most of them are not in large cities, but in rural areas and smaller cities. Not every ALS patient goes to a large ALS referral center in a large city, so this outreach effort may capture audiences who are not reached in other ways. The Mississippi Braves held three National ALS Registry events at games last year, promoting why it is important and why people should enroll.

In Idaho, another under-enrolling state, ALSA is putting "boots on the ground" to bring Registry information to PALS, caregivers, and families. Symposia are held to bring together PALS and their caregivers and families to educate them about the National ALS Registry and to give them

opportunities to ask questions. There is also information about spreading the word about the Registry to their patient and family networks. It is also important to meet with neurologists and others who have contact with PALS so that there are multiple touchpoints and continuous communication in multiple ways.

The ALSA chapter in Washington, DC, has historically had a difficult time identifying ALS cases. It is not clear why, but the reason may be that PALS are receiving support from community groups, such as church groups. In DC, ALSA has engaged with the local Department of Aging and specific advocates to make people aware about the National ALS Registry and of ALS.

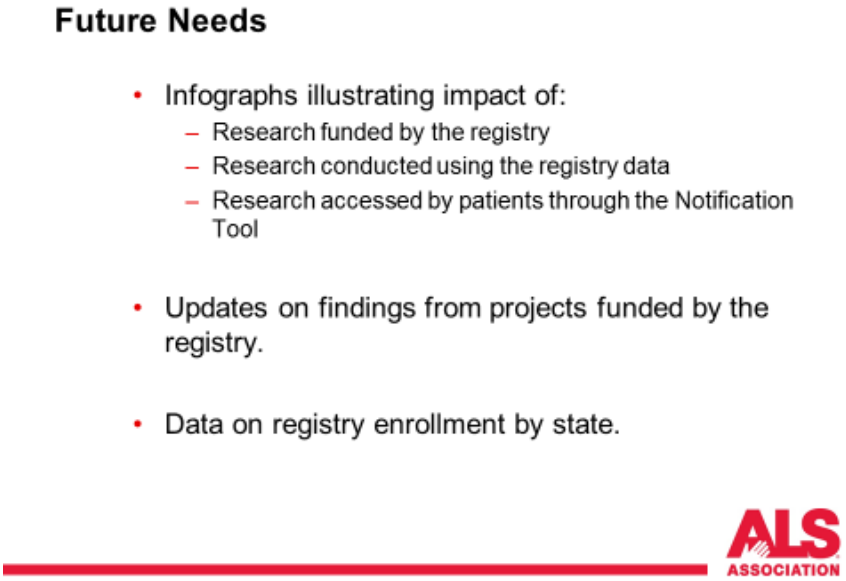
ALSA participates in a number of conferences and meetings with a range of partners and audiences. It is important to reach many different constituencies associated with ALS to communicate the value and utility of the National ALS Registry. ALSA also provides chapters with resources, such as print materials and online resources to help them communicate the value of enrolling in the Registry to PALS. To address the issue of lack of access to the Internet, ALSA chapters have been provided with tablets to take on in-home visits, support groups, and clinics to help enroll PALS.

ALSA has instated a Continuous Improvement Program with its chapters. This program helps chapters grow and improve all of their programs over time. A section of this work focuses on the National ALS Registry and chapters' efforts to improve their outreach and promotion efforts. A Chapter Scorecard provides metrics for communicating Registry information through various channels and for measuring activity. It is important to learn whether these efforts are having an impact on enrollment. Currently, the only way to measure impact is through the under-enrollment list from ATSDR, but additional detail is needed about enrollment and impact in specific areas to help guide outreach and to measure success.

ALSA is excited about the new partnership with MDA. The two organizations have worked together previously for a number of years, and the National ALS Registry is now their primary focus. They have identified some states where they can focus to make a difference.

Outreach efforts in Salt Lake City, Utah include support group and clinic events and a collaboration with MDA outlets. In April 2014, the Collaboration for a Cure meeting focused on how organizations can work more closely on advocacy activities, including the Registry. ALSA and MDA are co-chairing a task force to consider ways to work together and with other groups from the Collaboration for a Cure meeting, and to reach out to other groups to encourage them to communicate about the Registry.

ALSA is launching a Public Policy Association Program in all of its chapters. The program will roll out over four years and will bring more "boots on the ground." The job description will include enrolling PALS in the National ALS Registry. Some ALSA chapters have expanded their service areas with additional resources from the Ice Bucket Challenge. For instance, the Rocky Mountain Chapter in Denver, Colorado will now serve Utah. The national ALSA organization is considering ways to serve people in Oklahoma and West Virginia, which do not have chapters.



Future needs include more "boots on the ground" and a better way to tell the story. Infographics are a strong tool for storytelling about the Research Notification Tool and about information coming from the National ALS Registry. Sharing infographics among the patient community builds support and empowerment. Regarding sharing best practices, it is important to remember that each state, like each member of Congress, operates differently. The ALSA chapters and clinics are also different. Practices may change based on their resources, the types of PALS they work with, and other factors. It is helpful to have an a la carte list of strategies that can be used to engage PALS from all walks of life.

Discussion Points

Dr. Kasarskis expressed surprise that Massachusetts is one of the under-performing states, despite ALS being a reportable disease in that state. He asked how their under-reporting squares with the prevalence estimates.

Dr. Mehta answered that ALS is reportable in Massachusetts, but there is no agreement with the state to provide the ALS numbers to CDC.

Dr. Horton clarified that ALS is reportable in Massachusetts, but not notifiable on the national level to CDC/ATSDR.

Dr. Kaye added that by law, ALS cases in Massachusetts are reported to the state health department. The state health department will not share those data by name.

Dr. Horton said that ATSDR has been in discussions with Massachusetts. They were invited to the meeting but could not attend. They are in the process of assembling their first dataset, and ATSDR hopes to compare it with their data to determine any differences.

Mr. Wildman noted that there is confusion in Massachusetts, as people there think that when they enroll in the state Registry, they are automatically included in the National ALS Registry. The ALSA chapter works to educate PALS about the differences between the registries.

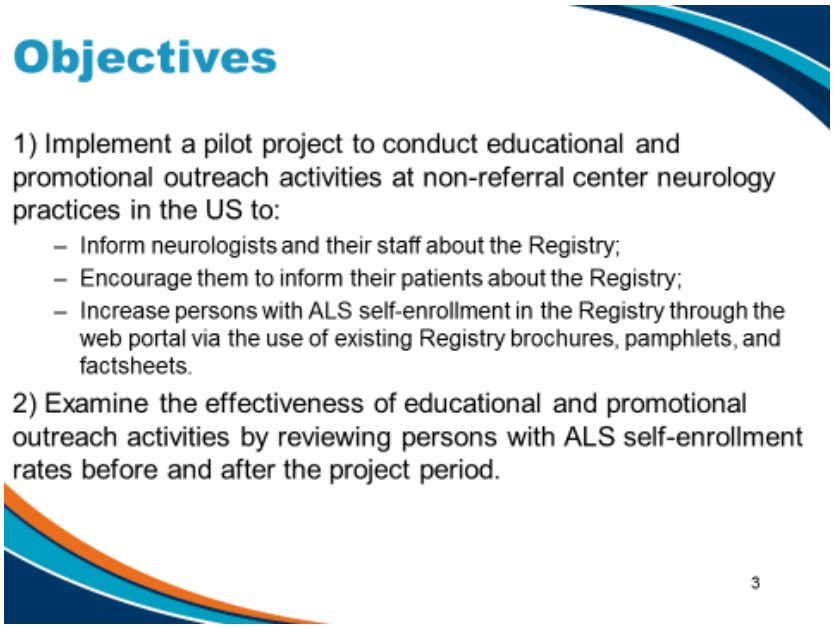
Dr. Brooks praised the collaborative effort between MDA and ALSA. Many studies have been conducted regarding how to enhance participation in registries in other diseases. He suggested that MDA and ALSA create an academic paper describing their process. It could be submitted to *Journal of the Patient*, as it will address the issue of increasing patient enhancement and participation.

Promotion of the National ALS Registry in Non-Referral Centers

Lindsay Rechtman, MPH, MCHES
Program Coordinator
National ALS Registry Promotion Project
McKing Consulting Corporation

Ms. Lindsay Rechtman explained that when the ALS Surveillance Projects were being conducted, the research team discovered that the majority of neurologists were not practicing at ALS referral centers. The projects found that of the 480 practices identified in Florida, 9 were referral centers. Similarly, of the 221 practices in New Jersey, only two were ALS referral centers. Of the case reports in both states, 25% were reported by non-referral centers and 1 in 5 cases came only from non-referral centers. These patients were more likely to be nonwhite, male, and slightly older at diagnosis. These demographics represent an enrollment gap in the National ALS Registry. Therefore, there is a need to reach out to non-referral centers to encourage their enrollment and ease the process of enrollment.

The objectives of the project to promote the National ALS Registry in Non-Referral Centers are as follows:



An educational and promotional outreach program was created, and its effectiveness will be assessed. The project design consists of a four-group approach:

- ❑ Group 1: New Jersey and Florida, which previously participated in the ALS Surveillance Projects
- ❑ Group 2: New York and Virginia
- ❑ Group 3: Ohio and Washington
- ❑ Group 4 (Comparison): Remaining 44 states

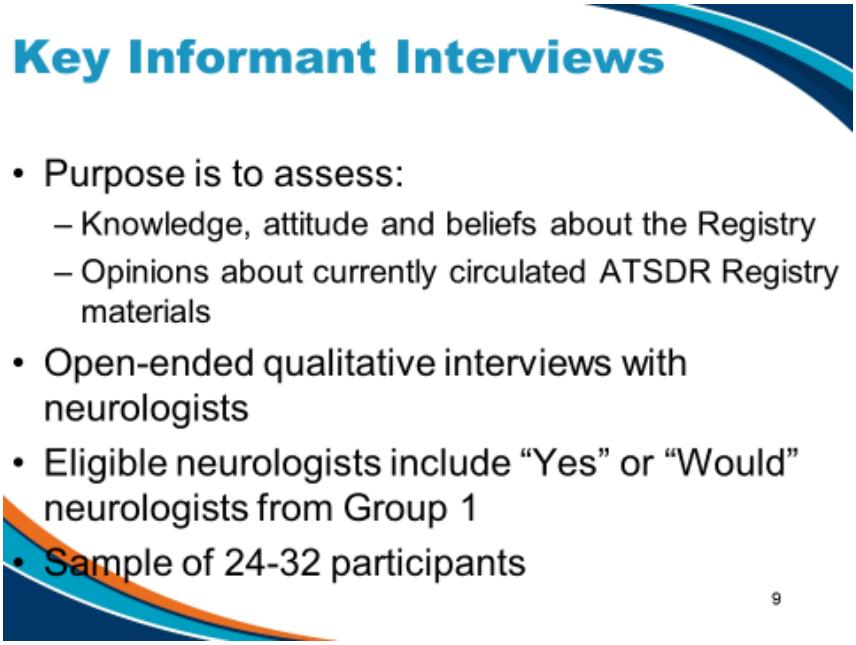
New Jersey and Florida previously participated in the ALS Surveillance Projects. Groups 2 and 3 include states that did not participate in the ALS Surveillance Projects, but are similar in population size and current enrollment levels in the National ALS Registry. They are also similar in demographics.

One of the first components of the project is initial phone calls to all neurologists in Groups 1 and 2, using proven methodology from the ALS Surveillance Projects to identify neurologists who care for PALS. They will be grouped into three categories:

- ❑ Yes: Those who currently have ALS patients in their practice
- ❑ Would: Those who do not have ALS patients presenting at this time
- ❑ No: Those who would refer ALS or suspected ALS cases to another physician

The calls will also confirm contact information, the size of the practice, and the providers in the practice. Using that information, mailings will be sent to "Yes" and "Would" providers in Groups 1 and 2. All neurologists in Group 3 will receive mailings. The mailings, currently-circulated ATSDR materials, will provide information about the National ALS Registry. One week later, follow-up phone calls to the neurologists will confirm that the mailing was received and encourage the use of the materials. Three months after the mailing, the neurologists will be contacted to determine whether they used the materials.

A second component of the project is a train-the-trainer presentation. A small sample of "Yes" or "Would" neurologists from Group 1 will be provided with information about the National ALS Registry and be trained on how to help their patients access it. The third component of the



project is key informant interviews, using a small sample of "Yes" or "Would" neurologists from Group 1. These open-ended, qualitative interviews will assess their current knowledge, attitudes, and beliefs about the Registry. They will also collect feedback and opinions about the current materials.

The analysis of the project includes:

- ❑ Process evaluation, assessing the frequency of calls, faxes, and mailings to assess the feasibility of the project and the Continuing Medical Education (CME) registration and completion rates;

- ❑ Registry self-enrollment rates will be examined monthly for each of the states in each of the groups to assess whether there is a dose-response relationship associated with more interaction; and

- ❑ Key informant interviews will be analyzed for common themes and studied for recommendations regarding future promotion activities and material development.

The protocol has been completed, and an IRB exemption has been secured, as no identifying information will be collected. The OMB 60-day and 30-day notices have been published. The lists of neurologists in Groups 1, 2, and 3 are being cleaned. The mailings and some interviews will begin by the end of 2015. The data will be analyzed and a manuscript will be prepared in 2016.

Discussion Points

Mr. Harada commented on the challenge of enrolling PALS in the National ALS Registry. He asked whether the Registry could include a question regarding whether the individual enrolling was diagnosed at a clinic: If yes, which clinic? If no, who is the diagnosing neurologist? It might be possible to capture patterns of diagnosing neurologists in each state so that there can be targeted outreach of practices.

Dr. Horton said that the National ALS Registry uses questions that already existed from the VA ALS Registry. That questionnaire was proven to capture a high percentage of patients; however, it might be possible to revisit the questions. There would be significant logistical challenges with OMB and IRB, so it would not be a quick process.

Mr. Harada said that ALSA is conducting specific outreach to patients who are not seen at a clinic, reaching out to as many practices as possible. It might be faster to gather that information directly from patients. The patients who are not seen by clinics may be seen by a common set of practices, especially since not all neurologists diagnose and treat ALS. It is likely that a top group of practices could be targeted in each state.

Ms. Rechtman said that this project hopes to reach neurologists who are not talking to their patients about the National ALS Registry.

Mr. Harada said that the approach assumes that patients learn about the Registry from their neurologists.

Dr. Kaye added that the State and Metro Project showed that many neurologists reported one case of ALS, and many indicated that they would treat a PALS but had not had an ALS patient within a three-year timeframe. The neurologists who see an ALS patient in a given year is almost random.

Dr. Brooks reflected on the issue of 22% missed cases of ALS. He noted that a certain percentage of ALS patients live at a distance from an ALS referral center and asked how to determine the distance between those centers and patients.

Dr. Kaye said that the majority of cases in metropolitan areas were reported from ALS referral centers. People in the Atlanta area, for instance, go to Emory University. But the story is different in the entire state of Georgia.

Dr. Traynor commented on the comparison of rural and urban areas. One of the major differences between the two is Internet usage. He asked about looking at overlapping incidence or the number of cases observed in a particular region with Internet availability.

Dr. Kaye said that it would be possible to consider that relationship.

Dr. Nelson asked whether systematic outreach to HMOs is possible. Cases in HMOs are likely to be under-ascertained, as they do not report their claims to Medicare or Medicaid. In states like California, which is 45% HMO, the under-counting could be dramatic. A campaign to that group could increase patient enrollment.

Dr. Mehta said that ATSDR has considered how to reach providers who see patients through HMOs and Preferred Provider Organizations (PPOs). It may be possible to work with the large companies that capture information for them.

Georgia Registry Enrollment Pilot Project

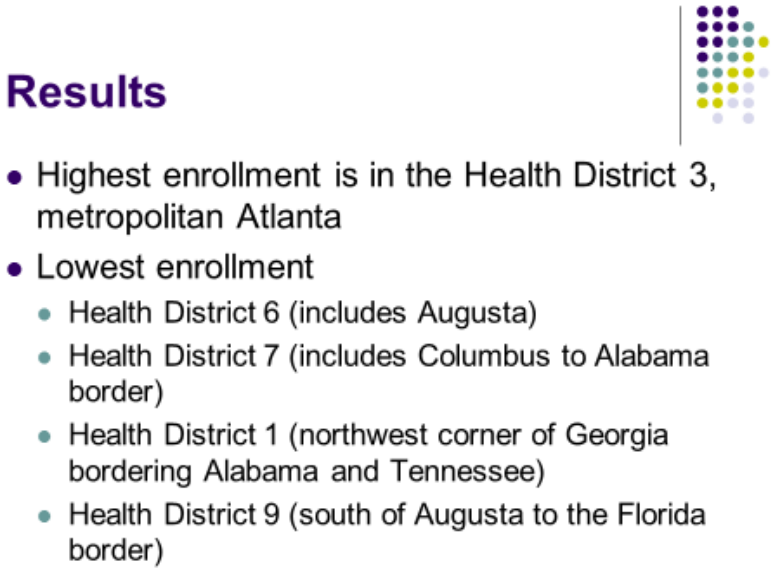
Wendy E. Kaye, PhD
Senior Epidemiologist
McKing Consulting Corporation

Ted Harada
Patient Advocate/Board Member
The ALS Association, Georgia Chapter

Dr. Kaye said that because of OMB restrictions related to data collection, it can be challenging to do outreach and provide qualitative information without quantitative information. It is important to find a better way to target outreach activities for the National ALS Registry. To that end, the Georgia Pilot Project goals are to: 1) Identify an area smaller than a state that is reproducible in other states and meets the restrictions imposed by OMB; 2) Provide qualitative assessment of Registry enrollment; and 3) Test the methods using Georgia data.

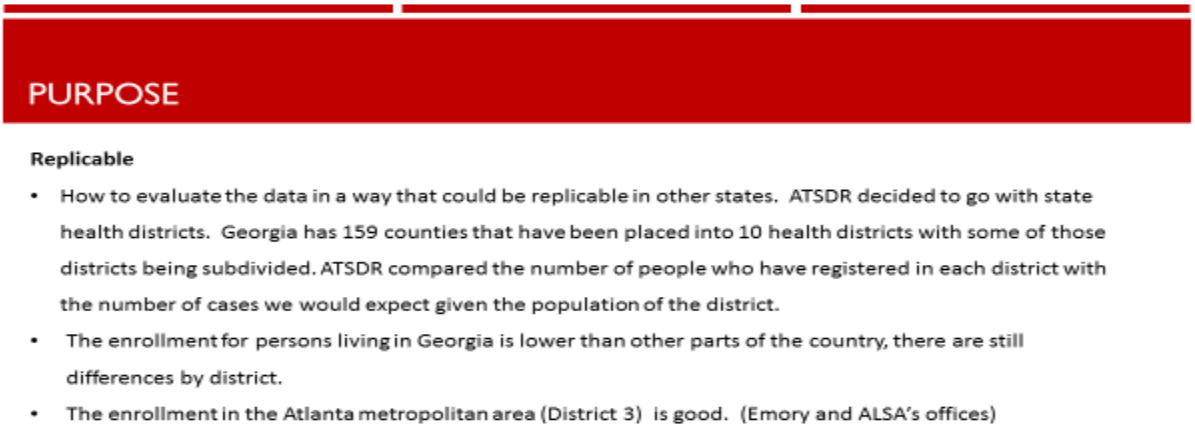
Georgia has 159 counties and 10 health districts. Some of the districts have been subdivided. The available data for the project includes: 1) Registration with the Georgia ALSA Chapter by county as of November 2014; 2) Enrollment in the National ALS Registry by county from October 19, 2010 through December 31, 2013 that were geocoded, although the only information available is city and state; and 3) Census data for 2010.

There are some limitations associated with the project, as the time periods of the available data do not match. The cities do not always directly code to a county; for example, the City of Atlanta lies in both Fulton and DeKalb counties. The health district is the same, however, so working at the health district level eliminates this problem.



In terms of the results of the project, the highest enrollment was in the Health District 3, the Metropolitan Atlanta area. The lowest enrollments were in Health District 6, which includes Augusta, and there is a referral clinic in Augusta; Health District 7, which includes Columbus to the Alabama border; Health District 1, the Northwest corner of Georgia bordering Alabama and Tennessee; and Health District 9, south of Augusta to the Florida border.

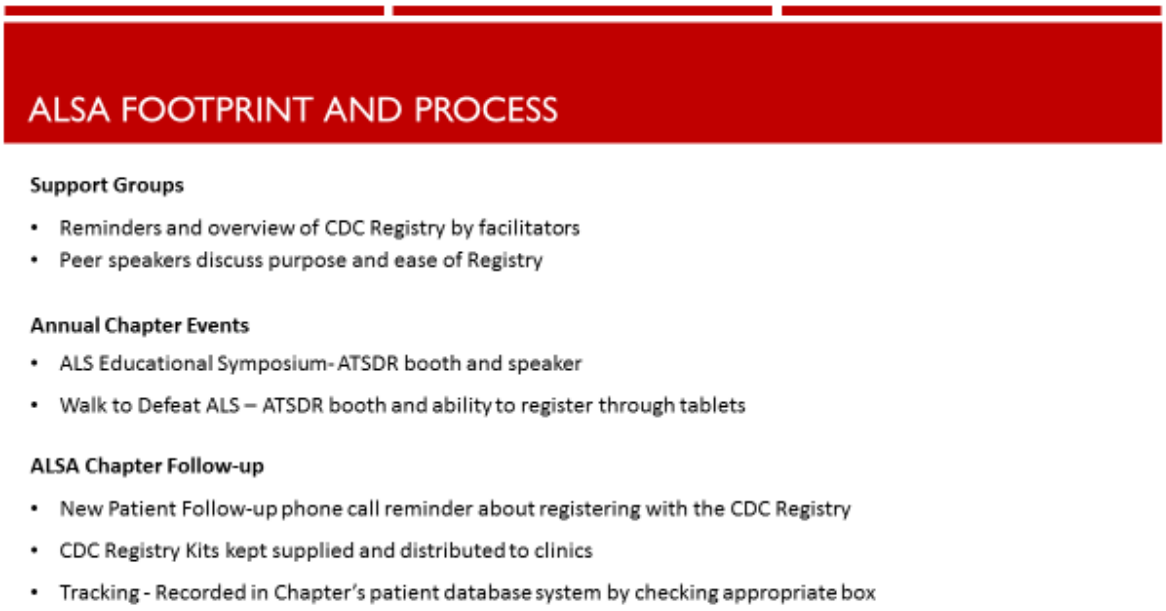
Mr. Harada thanked Dr. Kaye and her team as well as other people associated with the Georgia ALSA chapter who helped with the project. He pointed out that Georgia has been labeled as "red" in expected enrollment in the National ALS Registry since the start of ATSDR enrollment measurements. Chapters are measured against national expected enrollment levels. The objective of the Georgia Enrollment Pilot Project was to determine whether Georgia could be used as a test case to utilize more targeted information from ATSDR regarding under-enrolled regions in Georgia and to develop best practices for improvement.



The project is restricted not only by IRB limitations, but also OMB restrictions regarding information that can be shared. It is also important to learn whether the methodology is replicable in other states.

The enrollment in District 3, metropolitan Atlanta, is good. The ALSA chapter's footprint is largest in Atlanta, were the population is concentrated. District 6, which includes Augusta, is under-enrolled, but there is a clinic there. This under-enrollment shows the importance of clinic and staff buy-in into the National ALS Registry.

ALS Clinics are located in Atlanta, Augusta, and Macon. Information about the National ALS Registry is given to all patients initially and at follow-up care clinics, but giving them the information is not enough. Flyers are distributed at clinics and support groups, and tablets are taken to the clinics to assist with enrolling patients, but patients' clinic time is precious. Patients do not have 25 minutes to allot to enrolling in the Registry when they are in the clinic. These approaches represent a minimum set of strategies for Registry enrollment.



Support groups also include reminders about the National ALS Registry. Peer speakers often come to support groups. These peers have strong buy-in from ALS patients and are an important resource. It is frustrating for Georgia not to be "green," especially given that CDC and ATSDR are in Atlanta. ATSDR participates in symposia and walks, sharing information about the Registry and providing opportunities to enroll. Communication is occurring regularly at a macro level, but that level is not enough. Individual follow-up and contact bring greater levels of success. Staffing is an important element of follow-up and tracking. When the Georgia ALSA chapter was fully staffed, follow-up and tracking was more consistent than when the staffing levels were low.

By focusing on existing patients in under-enrolled areas that were identified by Dr. Kaye and her team, the Georgia ALSA chapter enrolled 20 patients in the first quarter of 2015 and was removed from the "red" states. Much of the focus was on individual follow-up phone calls and emails from Care Services Coordinators to patients. The contact made patients aware of the National ALS Registry and offered enrollment assistance.

After the first quarter of 2015, the Georgia ALSA chapter experienced staff turnover, losing two of three of its Care Services Coordinators. There was then a decline in patient enrollment follow-up, and Georgia was back in the "red" category. This loss illustrates the importance of reminders and follow-up. Just telling patients about the Registry at high-level touchpoints is not enough. As of April 2015, two full-time Care Services Coordinator positions have been filled, and two part-time positions are in transition.

Ms. Kidd created a Survey Monkey to reach out to patients on the ALSA Georgia Chapter's and Emory's email distribution list. There were 60 respondents, which represents approximately 15% of the current patient base. The results follow:

- Are you aware of the National Amyotrophic Lateral Sclerosis (ALS) Registry within the CDC?

  77 % Yes
  23% No

- Are you registered on the CDC ATSDR Registry?

  62% Yes
  27% Don't know
  11% No

- Why aren't you registered? Only two responses:

  Don't know how
  Don't see the benefit

- How did you hear about the Registry? They could write in their responses. The two overwhelming top responses were:

  Emory ALS Clinic
  The ALS Association

- What made you decide to register? The typical responses were:

  I have ALS and want to support any project that will help in stopping this disease
  Hoping that registration will help with a cure
  Was told that I should

- Have you participated in any Registry activities such as taking a survey, being notified of research, et cetera?

  60% Yes
  28% No
  12% Not sure

- Have you attended Clinic?

  80% Yes
  20% No

- Would you be interested in learning more about the ALS ATSDR Registry?

  85% Yes
  15% No

The number of people who do not know whether they are registered with the National ALS Registry indicates a branding concern. There is confusion about the Registry and also about ATSDR. There is general buy-in from the community of ALS patients, who want to help stop the disease and/or find a cure. The majority of respondents also expressed interest in learning more about the Registry.

There are a number of takeaway lessons from this project:

- This is not "Field of Dreams." If you build it, they won't just come. Individual follow-up is essential. Georgia experienced a lapse in enrollment when there were gaps in staff to conduct individual follow-up.

- Clinic staff education and buy-in is necessary, as evidenced by the difference between enrollment in the district with Emory versus Augusta and Macon. The clinics do not have time to enroll patients, however, except perhaps in the waiting room. MDA and ALSA can educate providers, and providers can also share information with each other at their professional meetings.

- Confusion: 27% of respondents are not sure if they have enrolled.

- Health District mapping is essential for targeting outreach efforts.

- Collaboration with other ALS organizations must be a priority. These collaborations at the national level are important, but they should also occur at the state and regional levels. Each group has finite resources and should work together to maximize, and not duplicate, efforts.

- Ongoing communication through multiple platforms, such as email, direct mailings, support groups, and others, will tell the story of the Registry.

- Peer patient education and encouragement is the most effective tool.

- Better measurements/metrics are needed, as the current methodology of "red" and "green" states is confusing. It may be preferable to set a goal: 80% and above enrollment based on ATSDR expectation equals "green," and below 80% equals "red." This approach will make it easier to track enrollment at clinics and to hold chapters accountable for the goals. ALS organization leaders must actively manage the metric. If the goal is 80%, then they must track new patient diagnosis versus confirmation of enrollment while simultaneously addressing under-enrolled area recovery plans.

- Interest exists based on the fact that 85% of patients want more information. Following up with them will raise enrollment.

The methodology used in Georgia may be replicable in other states. Georgia experienced a varying degree of success with it, but the basic plans can be implemented elsewhere. The most

surprising result of the project was that there is not a problem with awareness of the National ALS Registry. Individual follow-up is critically important, and a large portion of people are not sure whether they are signed up for it.

Discussion Points

Mr. Tessaro commented on the number of states that are doing well with enrollment, and how many are not. In large business organizations with multiple operations, an approach that works with one section of the business is made "mainstream" and brought to a larger perspective. They have discussed some individual success stories in some states, but it would be helpful to learn best practices from other states that are doing well.

Mr. Harada agreed and noted that one of the project goals was to generate best practices. He has not seen a "silver bullet" in other states' success, but in Georgia, individual follow-up appears to be the key to success. It is important to learn how many new ALS patients register with ALSA, as well as how many of them enrolled in the National ALS Registry. Regular tracking and follow-up with these patients can be measured, and chapters can be held accountable.

Ms. Kidd commented that the presentation from the Les Turner Foundation illustrated the best practice of an individual providing a one-on-one connection. The individual does not have to be paid. Volunteers will be happy to contact patients.

Dr. Mitsumoto noted that education and marketing are important. Mr. Gibson also mentioned the benefits of enrolling in the National ALS Registry. He wondered if it is possible to query patients enrolling in the Registry about the benefits that they expect from it. The individual follow-up and contact can provide benefits, showing indirect benefits such as the social network. There are also challenges associated with persons who do not have email; enlisting a volunteer to help them enroll could be beneficial.

Mr. Harada focuses on the research aspect of the Registry when talking to patients. Many ALS patients want to participate in research, but find clinicaltrials.gov to be cumbersome.

Dr. Reznick said that during lunch, the ALS patients discussed their disease progression. It would be beneficial to understand the risk of ALS and to develop a cure, but each patient faces the challenge of how the disease changes them over time. They learn from talking to each other. If the National ALS Registry put more emphasis on progression, and if participating in the Registry produced information that could be used for research on progression, it could help individual patients and their expectations. Some patients have trouble swallowing and talking, others have trouble walking, and others have trouble with their hands and arms. Thus far, the only mention on the Registry of progression is the Functional Rating Scale, which is not a clear metric. It also does not differentiate different patterns of progression. He clarified that the scale has some value and has been a useful tool, but it can be improved.

Best Practices

Paul Mehta, MD
National ALS Registry Principal Investigator
Environmental Health Surveillance Branch, DTHHS
Agency for Toxic Substances and Disease Registry

Dr. Mehta asked the group to reflect on the following discussion topics:

- ❑ Is it feasible to use the GA Enrollment Pilot Project in other states?
- ❑ How do we promote the Registry in states without a clinic or chapter?
- ❑ Why do some states have better enrollment than others?
- ❑ How do we increase awareness of the Registry?

Discussion Points

Mr. Wildman said that ALSA would be interested in expanding this approach. They have challenges with their outreach, as the data that they currently receive about states lagging in enrollment is not very informative. The kind of information from the Georgia pilot project will help them target outreach and identify best practices. This work is best conducted in collaboration with MDA to assess their collective footprint and determine which states would be best for the next implementation of the project.

Ms. Embro said that other measures are being put in place in the Georgia ALSA chapter as a result of lessons learned from the project. They are now examining their data on a quarterly basis, not just an annual basis or when they are answering a survey or participating in the listening tour. They are regularly tracking a set of data points such as new patient diagnoses, new patients registering with the chapter, and the number of those patients enrolling in the National ALS Registry.

Ms. Stephenson agreed that it makes sense for ALSA and MDA to work together on expanding the Georgia pilot project ideas into other areas. They are in close communication regarding how to promote the Registry, and this initiative flows naturally from that work.

Dr. Bowser commented on the presentations about branding, marketing and direct interaction with patients to enhance enrollment in the Registry. He asked about the target enrollment goal, given that it will never be 100%. Without a basic target, it is difficult to determine how to get there.

Ms. Kidd added that the goal should be realistic.

Dr. Mehta said that ATSDR has baseline prevalence data that can serve as a basis for a goal, but like any surveillance system, 100% of the cases are not captured. The question of a benchmark is a good one.

Mr. Goldstein said that the first report from the National ALS Registry is a baseline. Additional data points are needed in order to determine an enrollment goal. He suggested that they agree to set a goal after collecting a certain number of years of data.

Dr. Mehta concurred and noted that the next report, which will include data from 2012 and 2013, will answer more questions. He suspected that the number of cases and the prevalence rate would be higher for those years.

Mr. Harada agreed but noted that a goal could be adjusted as more robust data become available. It is not possible to hold people accountable without a goal, so a goal could be set based on the information that is currently available.

Dr. Mehta said that there are OMB restrictions associated with releasing the prevalence rate per state.

Mr. Goldstein emphasized that the American taxpayers are paying for the Registry, and patients want to see results. When a paper is released with a number of ALS patients, the number is interpreted literally, and it may be assumed that the Registry has 100% enrollment of patients.

Mr. Harada clarified that he was focused on the number of patients enrolled through the Web portal. The number of ALS cases published in the report includes cases from the administrative databases. The patients enrolling through the Web portal actively provide robust information through the risk factor surveys.

Dr. Mehta said that awareness and constant communication come into play in increasing enrollment in the Registry. Follow-up and contact, without being overburdening, are important. There could be a mechanism, such as a single point of contact, for assessing enrollment progress.

Ms. Kidd said that the branding, marketing and communications components will be strengthened by sharing strategic goals of the Registry beyond active participation. Information about how the Registry data will be used will encourage PALS to participate and tell an exciting story.

Dr. Mitsumoto asked about the frequency of email reminders to ALS patients to enroll in the National ALS Registry. He commented on the peak enrollment numbers after 2014's Ice Bucket Challenge. The enrollment numbers are fairly good, and it might be helpful to share those numbers. He asked about the number of states that report ALS cases to ATSDR.

Dr. Mehta answered that ATSDR does not receive any state data regarding ALS cases. ALS is not a reportable disease. They receive information through the national administrative databases. ATSDR does not know where a newly-diagnosed patient is at any time. ALSA and MDA have that information at the clinic level. Incidence is therefore difficult to capture. The date of diagnosis is self-reported on the Web portal, but is not available in the national databases. The State and Metro projects are building a case to collect information at those levels.

Regarding benefit to patients, Dr. Kasarskis asked whether ATSDR reports this meeting, including the attendance, to the patient community so that they are aware that their participation, experience, and contribution are valued.

Dr. Mehta answered that a page on the ATSDR site is dedicated to this meeting and includes reports and meeting notes going back five years. The live stream will also be available on the site. He hoped that the site could be more user-friendly, with more data and information about healthcare available to PALS.

Dr. Nelson suggested that the meeting reports could be included under the "For Patients" section of the website. She noted that some of the "red" states that are under-reporting data have a high percentage of patients who receive care through HMOs, such as Hawaii and Washington, DC. Focusing on those areas will be critical for outreach. The chief neurologists of HMOs could also be targeted for outreach.

Dr. Amelie Gubitz said that the meeting reports are helpful, and ATSDR is transparent about them. It would be helpful to share highlights from the meetings, as opposed to a 30-page report. The highlights could focus on data, milestones, accomplishments, next steps, action items, and benefits from the National ALS Registry.

Dr. Bradley said that the highest enrollment in the Registry appears to be in the states with the largest number of ALS specialized centers. He suggested stimulating states to develop more of these centers within their structures. ALSA, MDA, and the community can advocate for that growth.

Dr. Mehta agreed that some clinics and chapters are not accessible to some areas, such as the mountain states. It is also likely that the percentage of ALS cases is lower there than in the more metropolitan states. Enrollment is driven by neurologists: some promote the Registry and encourage enrollment, and others are indifferent and may not have the information.

Mr. Harada said that the question of clinics and ALSA chapters may be a question of "which came first, the chicken or the egg?" Places with large clinics are also likely to have a large footprint of MDA and ALSA offices. Some clinics may have better enrollment because they are near MDA or ALSA locations.

Dr. Mehta said that the non-referral project will shed light on the percentage of neurologists who do not know about the National ALS Registry and how to address the problem. He agreed that enrollment in the Registry is driven at the clinic and neurologist level.

Mr. Goldstein stressed that key stakeholders have to commit to spreading the word about the Registry to their databases. Published literature regarding compliance may be instructive as well. There are probably best practices and benchmarks associated with keeping patients involved in programs. The literature could provide guidance for setting benchmarks. As researchers start accessing the biorepository, interest from neurologists is likely to increase.

Mr. Kingon thanked the participants for their input. He noted that the live-streaming of the meeting would end, as the next presentations included preliminary research findings. Though divided into two segments, the ATSDR-funded research updates have been combined in one location in this document for ease of reading.

End of Day 1 Questions

Robert Kingon, MPA, Facilitator
Carter Consulting, Inc.

Mr. Kingon noted that the live-streaming of the meeting would resume for the last session. Time at the end of the first day of the meeting is traditionally reserved to reflect on the day and to share comments or reflections. He opened the floor for general discussion.

Discussion Points

Mr. Goldstein wondered how the previous research projects might utilize data from the National ALS Registry. He also wondered how to provide direction to the projects funded through the Registry and how the Registry questionnaire might be modified or advanced scientifically based on the research project findings.

Dr. Mehta answered that the Michigan study utilized the National ALS Registry Research Notification Mechanism for recruitment.

Dr. Goutman confirmed that the participants are directly recruited from the Registry, and many of them come through the ALS clinic at the University of Michigan. The project uses some standardized questions from the Registry surveys but does not directly utilize data from the Registry.

Mr. Goldstein suggested that there might be double work and double money spent on determining how to ask the same questions. If the questions about exposure to pesticides or smoking are standardized, there may be lessons learned regarding how to use the survey information and to guide additional future research.

Dr. Kaye said that the way in which a question is asked depends on whether a researcher is asking the question, or whether the participant is filling in a survey on his own.

Mr. Goldstein said that it would be helpful from a patient perspective, especially for patients who cannot speak or type, to provide that information one time in the National ALS Registry.

Dr. Kaye replied that some participants in the Michigan study are enrolled in the Registry, but others are not. Data cannot be combined from different questionnaires.

Dr. Mehta added that ATSDR cannot release information from specific participants in the Registry directly to researchers. Sharing that information would violate terms of security and privacy. If a GUID system were implemented in the future, then a central database could allow researchers to access participants' survey responses.

Mr. Harada said that the surveys provide researchers with information about commonalities and root causes associated with ALS. The National ALS Registry provides data, but it is also a tool for providing researchers with a population base from which to recruit regionally or across the US.

Dr. Horton said that ATSDR heavily suggests that researchers in every funded study utilize the National ALS Registry as a recruitment source. Risk factors for sporadic ALS are poorly

understood, so the more studies that are conducted, the more clearly defined the risk factors will become. ATSDR is an environmental public health agency and is very interested in the environmental etiology of ALS. The Michigan study is appropriate for their focus.

Mr. Harada asked whether Mr. Goldstein was suggesting that the scientific studies are not using enough National ALS Registry data in their research.

Mr. Goldstein answered that perhaps in a perfect world in five years, data from the Registry could be released, the biorepository would be well-established, and a GUID would be available. It is important to think about how to get to that point and how to prepare for success.

Dr. Horton said that ATSDR does not want to be prescriptive and tell researchers what to study. Rather, ATSDR funds researcher-initiated studies.

Dr. Mehta added that the surveys in Dr. Goutman's study are likely to be much more specific to his region than the surveys in the National ALS Registry. The national Registry has questions similar to that one, but the questions are broader.

Noting that initial data collection for the Registry began 5 years ago, Dr. Brooks asked about the future of the Registry in terms of the vision for the next 5 years and for the next 10 years.

Dr. Horton answered that in the spirit of collaboration, ATSDR looks to the collective ALS community to help shape the future of the National ALS Registry. ATSDR can propose initiatives such as the biorepository or new surveys, but looks to stakeholders for collective feedback.

Dr. Mehta added that ATSDR is the caretaker of the Registry. The Registry belongs to the US. Feedback is vital regarding its' future direction.

Dr. Brooks observed that scientific questions are one level, and implementation is another level. Researchers would like a way to change the questionnaires on the National ALS Registry. There may be easier ways to accomplish this. Another important issue is associated with genotyping. The Registry leads the field by providing a national Registry for ALS at the largest level. The next step is to reach the 22% of patients who are not in the Registry, and this effort is an important advance. A challenging task for the next five years may be encouraging ALS patients to embrace the Registry. Patients should be offered something in return, such as free genotyping.

Dr. Mitsumoto agreed with Dr. Brooks. Genotyping and environment-gene interactions are potential important future directions for the Registry. Studying environment-gene interactions will require large numbers of patients. The National ALS Registry is a vehicle for identifying these critical issues. He recalled when Dr. Horton first introduced the idea of the National ALS Registry to a group of researchers. There were many negative comments, criticisms, and skepticism about it. The Registry has come a long way in a few years to now consider marketing, branding, funding research, and increasing enrollment of ALS cases. He agreed that there should be intangible benefits for people involved in the Registry.

Dr. Horton said that ATSDR stayed the course after that initial meeting. Many of the people at that meeting are now among the Registry's biggest allies. A Registry or a surveillance system is a long-term investment. It takes time to build, then analyses and other initiatives can grow. If he had to do it over again, he would set the expectations better. Patients may have felt that the

Registry would lead to finding a cure for ALS. That result does not happen immediately. All population-based registries, whether they are for ALS, cancer, etc. are long-term projects that take time to mature and develop. And this is definitely true for the National ALS Registry since it covers the entire United States.

Dr. Kasarskis concurred that communication with the patient community has to set the expectations that the National ALS Registry is, at the most, hypothesis-generating. Patients have an obvious urgency to get answers. The diagnosis of ALS forces a life review. One of the first questions he hears from newly-diagnosed patients is, "What have I done in my life that caused my disease?" The patients then construct a narrative about what caused the disease. The individual patient hypotheses may be supported or may not be supported by detailed studies. The first Gulf War Study came to be because a nurse in the internal medicine clinic at the VA observed that "We have too many ALS patients in our boys." These hypotheses are not incompatible. The Michigan study represents a level of detail that ATSDR could never reach with the National ALS Registry. One feeds the other. This kind of message should be communicated with patients who are helping to build a research platform for the future. Surveillance is very challenging without a biomarker for the disease, and the Registry is an evolution of methodology and concepts. It is understandable that patients want a cure next week, but the Registry should not be oversold to a population that is not aware of the scientific process. There are many challenges, but the National ALS Registry should celebrate all of its milestones, not just the reports. The achievements and concepts of the Registry will relate to a lay audience.

Mr. Wildman commented that the National ALS Registry has evolved considerably over time, with the addition of new risk factor surveys and the biorepository. It has evolved based on feedback from patients and the research community, and that feedback is likely to continue. ALS patients do want to know, "Why me?" and initial harsh feedback is probably due to that question not being asked by the Registry. ATSDR added the unusual step of an open-ended question so that participants could share their theory about why they have ALS. It is important to point out that the Registry is not static. There are many benefits to the Registry beyond incidence and prevalence. The Research Notification Tool allows ALS patients to participate in and learn about studies that they may never have heard about before. The risk factor data can lead to further studies. The connection of samples in the biorepository to epidemiological data holds great promise. People should be made aware of the various benefits and elements of the Registry. The patient community is the most important, but the research community and industry are also important partners in fully utilizing the Registry and its potential to advance the cause. He asked about the process for getting more information from surveys, or changing surveys.

Dr. Horton said that surveys can be added to the Registry. There is a process that involves IRB/OMB approval, but anything is possible.

Dr. Bowser said that in the future, it will be important to link data from the National ALS Registry to other data that is being generated, such as through genetic studies. This direction should be emphasized in the Registry's 5-year plan or 10-year plan.

Dr. Horton said that a GUID could link the datasets. ATSDR is pursuing this possibility aggressively so that the systems can communicate with each other. ATSDR created a new survey module based on feedback from PALS. The open-ended questions address PALS concerns that the Registry collects the right data. Analysis of these questions is ongoing. He

agreed that the National ALS Registry is constantly changing, adapting proactively so that it is a tool for everyone to use.

Dr. Reznick asked whether environmental health is automatically the central theme when ATSDR asks PALS what their priorities are, based on where ATSDR is housed, or whether PALS are really being asked what is most important to them.

Dr. Horton answered that ATSDR is an environmental public health agency, but it is not known if ALS is caused by environmental factors or factors beyond the environment. The purpose of the Registry is to "put everything on the table" and then set priorities.

Dr. Reznick clarified that there is room on the agenda if there are suggestions beyond the environment.

Dr. Horton said that until there is a clear picture of the cause of ALS, nothing is "off of the table."

ATSDR-Funded Research Update

A Prospective Study of Biomarkers and Risk Factors for ALS Incidence and Progression

Kathryn Fitzgerald
Doctoral Candidate
Harvard Medical School

Ms. Kathryn Fitzgerald described a project led by Alberto Ascerio on pre-diagnostic biomarkers and ALS. It is likely that genetics may be insufficient to clarify all of the steps needed for ALS pathogenesis. This project focuses on these processes by considering a multi-stage model of ALS. It focuses on metabolomics as an untargeted aim and targeted aims associated with tocopherols and carotenoids and urate levels. The study includes five different prospective cohort studies:

- Nurses Health Study (NHS)
- Health Professionals Follow-up Study (HPFS)
- Cancer Prevention Study II-Nutrition Cohort (CPS-II)
- Multiethnic Cohort Study (MEC)
- Women's Health Initiative (WHI)

The NHS began in 1976 and initially included 121,700 female nurses aged 35 to 55 at baseline. They completed mailed questionnaires assessing risk factors and lifestyle characteristics. Follow-up continued through biennial questionnaires, with diet assessed every four years. Blood was collected in a subset of 32,826 women in collections during 1989 and 2000. The HPFS, initiated in 1986, is a similar cohort in which 51,529 male health professionals aged 40 to 65 years were enrolled. Blood was collected in a subset of approximately 20,000 participants in 1993-1995. The Nutrition Cohort of CPS-II includes a subset of 86,404 men and 97,786 women from the full CPS-II study cohort. They were aged 50 to 79 years in 1992. Blood was collected in a subset of 39,371 in 1998-2000.

ALS deaths were identified from the National Death Index (NDI). A validation study was conducted on the death certificate data. The MCS consists of 96,937 men and 118,843 women aged 45 to 75 years with self-reported racial and ethnic backgrounds of African American, Japanese American, Latino, Native Hawaiian, and Caucasian. They completed a mailed questionnaire assessing lifestyle and risk factors at study baseline. ALS deaths were identified from the NDI. The WHI includes 161,808 women, aged 50 to 79 at baseline, who participated in the original trial or the observational study component. The original interventions included a low-fat eating pattern, hormone replacement therapy, and calcium and vitamin D supplementation. Blood was collected at baseline for all women in 1992 at their screening visit, prior to any interventions. ALS deaths were identified from the NDI.

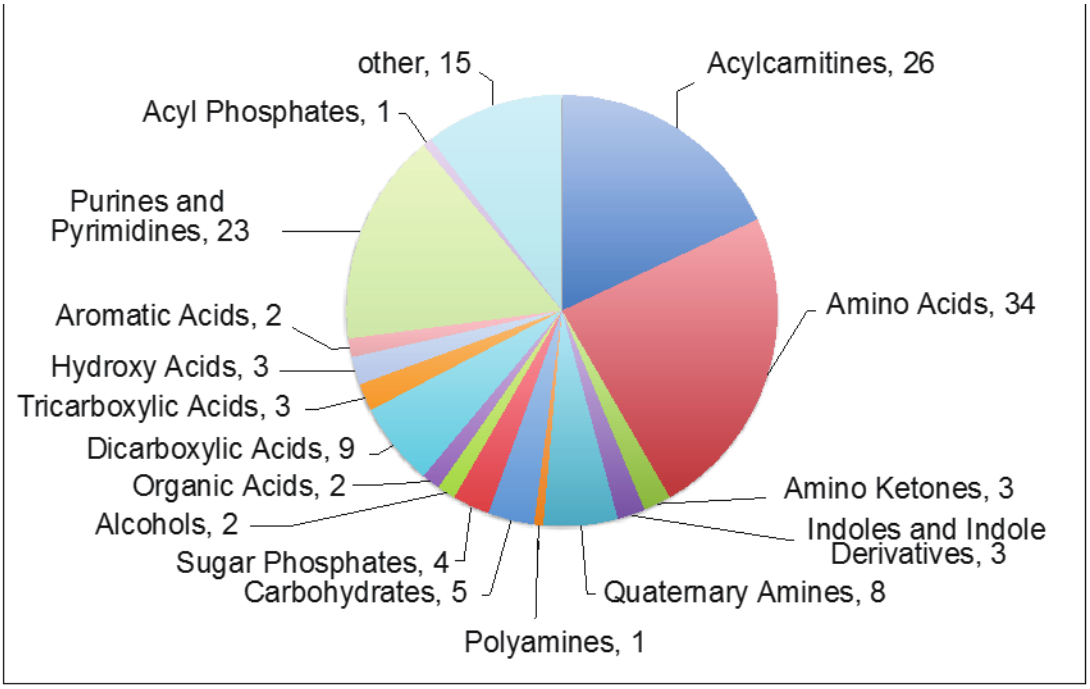
As broken down in the following table, 335 ALS cases were identified with blood prior to disease onset:

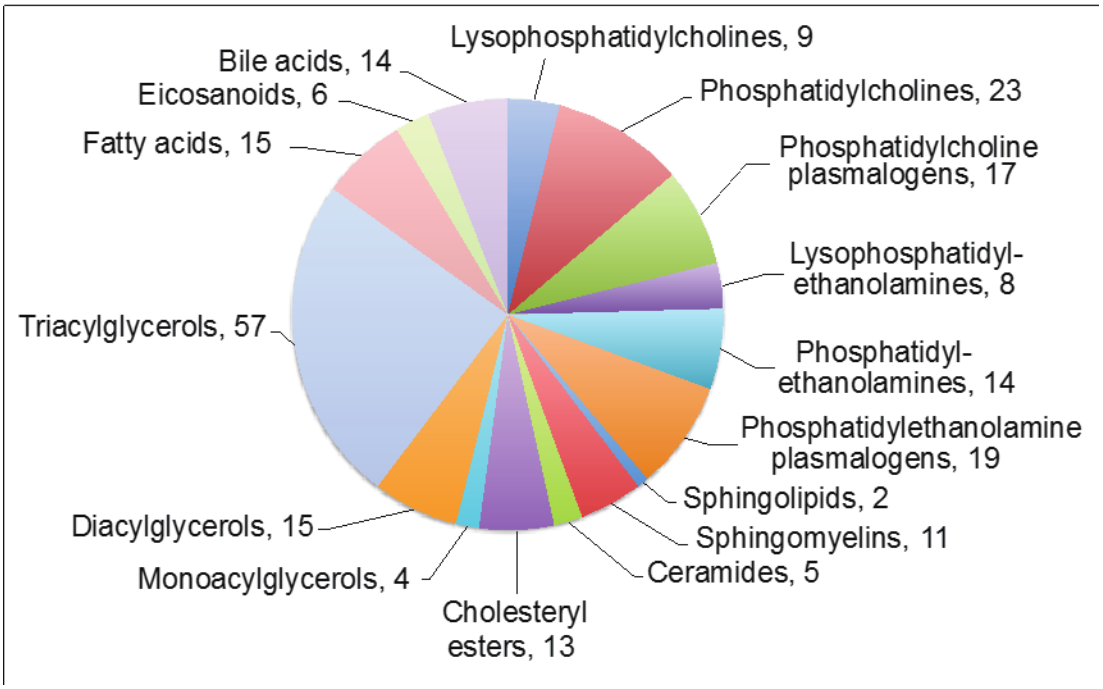
Cohort (inception date)	Age range at (baseline)	No. of participants	Year of blood collection	No. of ALS cases
NHS (1976)	30-55y	32,826	1989-2000	61
HPFS (1986)	40-75y	18018	1993-1995	34
CPS II N (1992)	50-79y	39371	1998-2001	83
MEC (1993-96)	45-75y	67594	2001-2006	37
WHI (1992)	50-79y	161808	1992	121
TOTAL		**319,617**	**1989-2006**	**335**

A case-control study was conducted, with two controls collected per ALS case matched by cohort, gender, and exact year of birth. The controls were randomly selected among cohort participants who were at risk of developing ALS at the time of diagnosis. The study focused on three potential biomarker aims: Metabolomics, Tocopherols and Carotenoids, and Urate.

Regarding metabolomics, in the superoxide dismutase-1 (SOD-1) model, hypermetabolism precedes disease onset. The conditional deletion of Transactivation Response (TAR) DNA binding protein-43 (TDP-43) causes a dramatic loss of body fat, possibly due to loss of *Tbc1d1* mediated leanness. In addition, in analysis using these cohorts, higher body mass index (BMI) was associated with a dramatically lower risk of ALS. This finding was confirmed in seven-year lag analysis, which found a similar relationship, in addition to possible prediagnostic weight loss or lack of weight gain. The metabolomic biomarker builds upon initial studies of ALS patients versus controls. Initial case-control studies have suggested that lower levels of leucine or higher levels of circulating glutamate are associated with higher risk of ALS among early ALS patients. Another metabolomic study distinguished ALS from ALS mimics and controls, with an area under the curve (AUC) of 0.81. Enriched metabolites included in that study were phosphate, cortisone, delta-tocopherol, and palmitoyl sphingomyelin.

144 polar metabolites





232 lipids

Metabolomic profiling is ongoing. More than 300 known metabolites are expected to be identified. The results are expected in the coming weeks. Approximately 144 polar metabolites can be identified from one of the platforms, and another platform identifies approximately 232

lipid metabolites. The initial pilot study suggested that approximately 330 metabolites will pass quality control (QC).

A targeted analysis plan is being developed to determine the best means for analyzing the metabolites. A three-pronged approach is proposed to: 1) Consider each individual metabolite; 2) Group the metabolites by classification, such as amino acids, aminoketones, and bile acids; and 3) Utilize a Weighted Gene Correlation Network Analysis (WGCNA), originally developed for gene expression studies. It is possible to test whether a specific module is associated with ALS versus control and to test for enrichment within the molecules for novel pathways that may be informative. A metabolite-metabolite interaction network has been developed using binary reactions to reach subnetworks of important modules or relevant pathways.

The tocopherols and carotenoids approach builds upon initial dietary results from these populations for dietary vitamin E and dietary carotenoids. It has been suggested that higher dietary vitamin E intake and long-term vitamin E supplementation is associated with lower risk of ALS. The studies have not found an association for overall vitamin E intake, but it was not possible to distinguish between the different types of tocopherols. Supplemental vitamin E is primarily α-tocopherol, but it has different isomeric forms, and Ɣ-tocopherol is the most abundant form of vitamin E in food. Additionally, significant inverse associations between intake of dietary carotenoids and lower risk of ALS have been observed, particularly for lutein and β-carotene. The results suggest that higher intakes of β-carotene are associated with a lower risk of ALS. Analysis are ongoing, and the data include measurements of carotenoids and Ɣ-tocopherol, δ-tocopherol, and α-tocopherol. Initial QC values indicate that the data are of good quality.

In terms of urate, oxidative stress is implicated in the pathogenesis of ALS. Urate is a potent antioxidant and can prevent the oxidative damage caused by reactive nitrogen and oxygen species. Studies of urate and Parkinson's Disease suggest it to be potentially neuroprotective, as it is associated with lower risk and lower rate of progression of Parkinson's Disease. Preliminary case-control studies have also suggested that lower urate in ALS cases relative to matched controls predicted a faster progression. Adjustment for BMI attenuated the associations, as individuals with higher BMI typically have higher urate levels. The associations in the original analysis are similar to those observed for Parkinson's Disease. A comprehensive database of prediagnosis biomarkers is expected in 335 ALS cases and 670 controls. This includes the agnostic approach regarding metabolomics and the more targeted, specific metabolites. Results are expected in the next year.

Discussion Points

Dr. Bradley clarified that the metabolomics study is returning to the blood draws from the large population databases to conduct analyses. He asked about evidence regarding the shelf-life of the specimens and biomarkers over time from the initial draw.

Ms. Fitzgerald answered that prior to this analysis, there has been a great deal of interest in using the proposed platforms with these cohorts. Extensive pilot studies using delayed processes resulted in over 300 metabolites passing the QC values. Better evidence is the use of the same panel and approach to identify markers associated with pancreatic cancer. The results were positive.

Dr. Bowser said that even if the metabolites pass QC, they are not necessarily stable. It does not mean that what was originally in the tube two decades ago is still there. He asked about the

standard operating procedures (SOPs) used across the different studies. For instance, were the same types of tube used to collect blood, given that different tubes can change metabolomic signatures? If different tubes are used and there are different effects on the metabolomics, then the results may not match up and the informatics will be challenging.

Ms. Fitzgerald answered that one of the pilots considered two-year stability between the molecules. The study suggested initially that the two-year stability is fairly good. However, the data are not yet available to provide a more detailed answer. Regarding blood collection, she acknowledged that the different means of collection represent a challenge. The approaches are split. NHS used heparin tubes, and the others used ethylenediaminetetraacetic acid (EDTA). The analyses will likely be conducted separately.

Dr. Brooks clarified that this amazing study is the first to examine samples of chemicals in the blood of participants who did not have ALS when the sample was collected. He agreed with concerns regarding the shelf life of the metabolites. The National Health and Nutrition Examination Survey (NHANES) also grapples with specimen and metabolite shelf life.

Ms. Fitzgerald noted that this study is based on a platform that has been applied to other diseases and was able to detect associations. For instance, the pancreatic cancer study found an association for branch-chain amino acids. The underlying literature supports that this association is biologically plausible and relevant. That context provides a good argument for the ALS study's ability to detect associations.

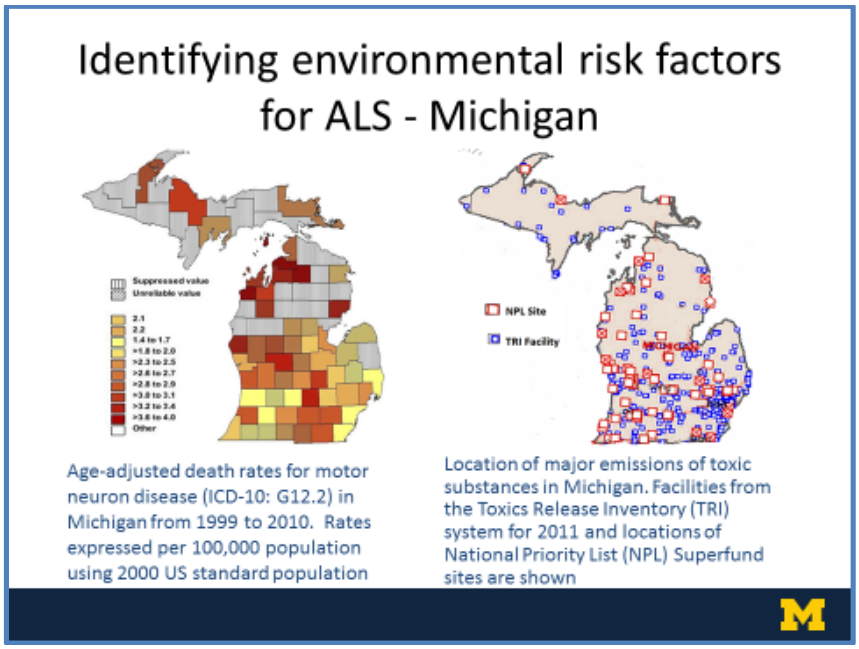
Dr. Mitsumoto agreed that the study is incredible. He asked about the average period from baseline to ALS disease onset.

Ms. Fitzgerald answered that for the 335 ALS patients in the cohorts, the average time to disease onset is approximately 10 years.

Identification and Validation of ALS Environmental Risk Factors

Stephen Goutman, MD
Director, ALS Clinic / Assistant Professor, Neurology
University of Michigan Health System

Dr. Goutman reported that this study grew from the recognition that the number of US ALS deaths from 1999 – 2009 was higher in the Midwest than in the rest of the country, particularly in Michigan. A visual comparison of age-adjusted death rates from MNDs to the locations of major releases of toxic substances in the state of Michigan seems to indicate a correlation:



Areas with higher toxic releases appear to correspond to higher MND death rates. This point is important because of the growing notion that ALS is not just a disease of genetic burden, but caused by a combination of environmental factors that cause cellular damage. When a threshold is crossed, the disease presents.

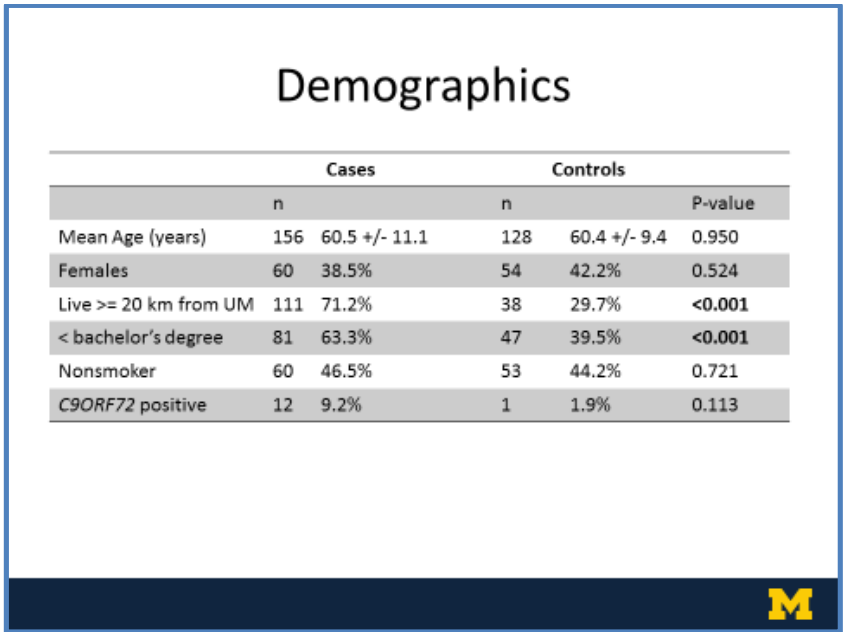
The University of Michigan ALS Patient Repository was created with the goal of establishing a national bank of familial and sporadic ALS patients to facilitate the study, understanding, and potential treatment of ALS. The repository includes a comprehensive assessment of environmental exposures; clinical data; and blood/DNA/RNA, fibroblasts, lymphocytes, iPS cells (future), brain, spinal cord, and teeth.

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

The project has a case-control design and includes a comprehensive environmental risk factor survey with telephone follow-up. The project measures exposures to persistent environmental pollutants that have long half-lives and examines the concordance of reported and measured exposures. Pilot data were published in 2014. The importance of the concordance issue addresses the mismatch between the number of patients in the Registry who had completed occupational surveys and not necessarily residential surveys. Occupational and residential exposures both affect the bloodstream. Exposure is measured to determine the cumulative exposures of both.

Complete data for age, gender, educational level, smoking status, and occupational risk factors are available for 126 of the 156 ALS patient participants. These participants have completed all of the 98 variables in the occupational history questionnaire or via telephone follow-up. Complete information is available on 118 of the 128 controls. Blood samples are available for 129 patients and 119 controls. Of the 156 ALS patients and 128 controls, complete data are

available for 101 and 110 of them, respectively. The demographics are detailed in the following table:



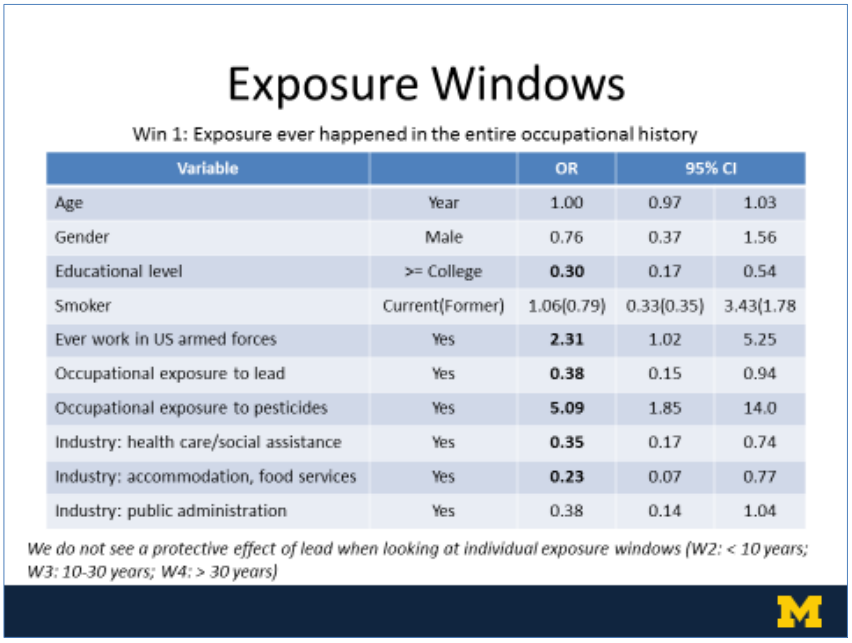
There are some concerns associated with the differences in where people live. Cases are drawn primarily from greater than 20 kilometers from the University Michigan, while many controls live closer to the university. The cases are less likely to have an educational attainment of less than a Bachelor's degree, and controls are more likely to have higher educational attainment. These differences are likely due to the way that controls are recruited.

To address the first study aim, a survey assesses residential history, occupational history, physical exercise, hobbies, military service, smoking status, and demographics. It was developed from ATSDR and is self-administered, with telephone follow-up. The occupational survey assesses exposures to dusts, fibers, chemicals, fumes, or radiation; uses of personal protective equipment (PPE); symptoms experienced at work such as fatigue, weakness, or difficulty swallowing; skin contact with any materials; and poor ventilation at the workplace. These elements are assessed for up to four occupations, with 22 questions resulting in 98 variables each.

Data are examined in four exposure windows:

- ❑ Exposure over the entire occupational history
- ❑ Exposure within the last 10 years
- ❑ Exposure within 10 – 30 years
- ❑ Exposure greater than 30 years

Preliminary data indicate that educational level appears to be protective. There is a higher association of ALS among individuals who report working in the armed forces. Occupational exposure to lead appears protective in these data, but this result is not seen in the other exposure windows or in the pilot data and is likely not accurate. Occupational exposure to pesticides, which has been demonstrated in other studies and in the pilot study, has an odds ratio of five. This ratio is seen in the other exposure windows as well.



Exposure Windows

Win 1: Exposure ever happened in the entire occupational history

Variable		OR	95% CI	
Age	Year	1.00	0.97	1.03
Gender	Male	0.76	0.37	1.56
Educational level	>= College	**0.30**	0.17	0.54
Smoker	Current(Former)	1.06(0.79)	0.33(0.35)	3.43(1.78
Ever work in US armed forces	Yes	**2.31**	1.02	5.25
Occupational exposure to lead	Yes	**0.38**	0.15	0.94
Occupational exposure to pesticides	Yes	**5.09**	1.85	14.0
Industry: health care/social assistance	Yes	**0.35**	0.17	0.74
Industry: accommodation, food services	Yes	**0.23**	0.07	0.77
Industry: public administration	Yes	0.38	0.14	1.04

We do not see a protective effect of lead when looking at individual exposure windows (W2: < 10 years; W3: 10-30 years; W4: > 30 years)

The project is measuring three categories of environmental pollutants that have no neurotoxic effects and a detection frequency of greater than 30%:

- ❑ Chlorinated pesticides, which have been banned since the 1980s but which persist in the environment and in human blood for years to decades.
- ❑ Brominated Flame Retardants (BFRs), which were added to plastics and foam products. They persist in the environment for years and in humans for months to years.
- ❑ Polychlorinated Biphenyls (PCBs), which were used in coolants and lubricants in electrical equipment until they were banned in 1979. They persist in the environment for years to decades.

These measurements are all correlated. This correlation creates a challenge, as considering them with only a univariate analysis will lead to significant odds ratios just by chance. It is important to control for this result with statistical models. The project is utilizing a multivariable exposure model. There is some possibility for false positives, so it is not possible to say that a particular compound is protective, but the results indicate that some pesticides and PCBs are more associated with ALS.

The odds ratios are adjusted for age, gender, and educational level, but there are differences in educational attainment between the cases and controls. These differences could be due to referral patterns and the collection of controls. ALS patients in the most recent ALS mortality report tended to have higher educational levels. This area needs further exploration.

The preliminary results of the project indicate that reported occupational exposures to pesticides are associated with ALS, military service is associated with ALS, and pesticides and PCBs are associated with ALS. The suggested protective effects of some toxins are likely false positives due to the correlated exposure measurements. The concordance appears to be modest and is likely to have an impact on the future directions of the environmental exposure and risk factor assessments in the National ALS Registry. Individuals may think that they have been exposed and were not, or they could have been exposed and are unaware. Some of the newer

pesticides and toxins have shorter half-lives and are not necessarily measurable in a time frame that the study can capture.

The neurotoxic effects of the compounds that the study can capture are taken into account. Pesticides can cause sustained depolarization, leading to the release of neurotransmitters, including glutamate, and hyperexcitability. PCBs can impair neurotransmitter reuptake, including glutamate, calcium homeostasis, and signal transduction. These factors can accelerate cell death. Persistent environmental pollutants alter global DNA methylation.

Future directions for the study are to evaluate residential exposures; develop improved methods to assess multicollinearity of the environmental exposure measurements; evaluate the epigenetic changes and their association with the pollutants that are being measured; and evaluate specific pathophysiologic mechanisms based on the exposures.

The University of Michigan is embarking on statewide engagement. The Michigan ALS Research Consortium of Hospitals (MARCH) has been developed. It includes all ALS clinics in the state and is supported by ALSA. The goals of MARCH are to: 1) Offer patient and family educational opportunities. The first patient symposium on ALS, sponsored by ALSA, was attended by over 100 persons; 2) Encourage ALS National Registry participation; and 3) Improve research participation for PALS in the state so that a person who gets care at an ALS clinic that is not involved in research will not lose the opportunity to participate in research. The collaboration will also improve the regional assessment of environmental risk factors and collect cases and controls from the entire state. Another next step is national engagement, using the National ALS Registry to determine whether the exposures in the Michigan cohort are region-specific and whether they can account for the variations in the national ALS disease burden.

Discussion Points

Dr. Nelson commented on the inverse association with educational attainment and the five-fold increase in risk associated with pesticides. She asked how the controls were defined.

Dr. Goutman answered that the controls are over the age of 18, with no family history of ALS or neurodegenerative diseases within two generations. They are recruited through the University of Michigan's mechanism for finding persons who are interested in participating in research. They are essentially volunteers, although they receive a small fee for volunteering their time and samples.

Dr. Nelson clarified that since the cases come from referral centers, they represent the surrounding geographic regions. She suggested that the five-fold increase in pesticide could be due in large part to those differences. The same results were observed in early Parkinson's Disease case control studies, although it does turn out that pesticides are associated with Parkinson's Disease. The cases are drawn from a larger, likely more rural, region; controls are exactly the opposite. The reverse can happen with education, as individuals in rural areas may have lower educational attainment as opposed to volunteers that live closer to the university. This volunteer bias can lead to an inverse association. It is challenging to get controls, especially when the referral center is the source of cases.

Dr. Goutman shared the concern, which is contributing to the effort to recruit controls more broadly within the state. The controls live close to the university now, but the researchers have geocoded their residential history, which is not as tightly knit.

Dr. Nelson said that control recruitment is especially challenging within a referral center, as it is not population-based.

Dr. Goutman said that the group is struggling with the best recruitment approaches. Through broad engagement within the state, especially with other clinics, there will be more geographically distributed controls.

Dr. Nelson noted that volunteers tend to be the "worried well" and may have lower prevalence of smoking. Differences may be observed, but it is not clear what they are due to.

Dr. Reznick asked whether the analyses are based on "ALS, yes or no," or whether there will be opportunities to consider different symptoms, progressions, and differentiation within the broad category of ALS.

Dr. Goutman said that those analyses have not yet been conducted, but phenotype has been collected on all of the patients.

Dr. Brooks said that the analyses will be important pertaining to lead, as the SOD-1 model indicates that lead slows the rate of progression. If data are available on rate of progression, then the lead dichotomy can be re-examined in term of fast progressive, slow progressive, and issues of phenotypes.

Dr. Goutman said that lead does not appear to be statistically significant in the other time windows, but the point is important.

Dr. Bradley agreed with concerns regarding the controls. He raised problems associated with recall bias. Patients who have ALS or any other major disease often ask, "Why did I get this?" where population controls may not have thought about these issues. One approach is to examine a variety of different diseases that may lead a person to reflect on his history and select those patients as a clinical bias control group.

Dr. Goutman agreed that recall bias is a challenge in any disease state. This work may help inform other ongoing efforts because it can measure pollutants in the blood. Some people are reporting exposures, but no pollutants are measurable in their blood. The reverse is also true. Information about participants' employment history is also instructive. Pesticides are common in the few prior studies on ALS risk factors. They also figure into the National ALS Registry. He hoped to start with the correlations between what is measured and what is reported, and whether these factors play into a specific pathophysiologic mechanism. If the correlations are real, then they could inform efforts to ameliorate the environment and serve as a preventive mechanism.

Dr. Oleg Muravov suggested extending the evaluation of exposure history to hobbies. Some exposures may not come from occupation.

Dr. Goutman said that information is being collected about hobbies. They have not yet examined the hobbies in the residential information, but it will be conducted for concordance. These exposures do not occur "in a bubble." Other factors, such as how close a person lives to a golf course or whether they use pesticides and fertilizers on their lawns will be considered.

Dr. Muravov said that the question would be specific for different kinds of exposures, such as pesticides or lead. The National ALS Registry added surveys on lifetime hobbies, which may include substantial exposures, such as for individuals who blow glass.

Dr. Goutman said that the Michigan surveys ask about woodwork and metalwork, and how long the participant participated in the activity.

Cognition, Behavior, and Caregiver Burden in Amyotrophic Lateral Sclerosis

Christopher Brady, PhD
Director, Scientific Operations
Boston VA Research Institute, Inc.

Dr. Brady noted that when he attended last year's meeting, he had just received word that they were being funded. At the time, he shared some preliminary plans for their research and received some good feedback that was implemented in the project to the degree possible. As a reminder, the original ATSDR RFA called for projects to assess risk factors for ALS and caregiver burden. Boston University (BU) thought it would be interesting to evaluate risk factors for cognitive dysfunction in ALS and how that may impact caregiver strain and ALS. BU's background is in aging and dementia research, in addition to the Brain Bank. The Cognition, Behavior, and Caregiver Burden in the Amyotrophic Lateral Sclerosis study represents additional BU work and is not related to the biorepository.

There has been continuing and renewed interest in the changes in cognitive function in ALS. In addition to the motor and speech impairments associated with the disease, there is also a fair amount of interest in studying changes in cognitive function in ALS. Recent reports have estimated rates of cognitive dysfunction in ALS to range from 10% to 75%, depending upon the study. Dementia estimates range from 5% to 41%, with ALS-FTD being about 15%. The pattern of deficits have been primarily described as being frontotemporal disorder or deficits in executive function, but some other studies have also noted that perhaps there is some memory impairment as well. Again, it depends upon the samples used in the studies (e.g., incidence or prevalence), the age of the sample, site of onset, and potential predisposition.

A review paper by Raaphorst et al in 2009 showed that different cognitive domains demonstrate greater or lesser degrees of impairment, as reflected in the following graphic:

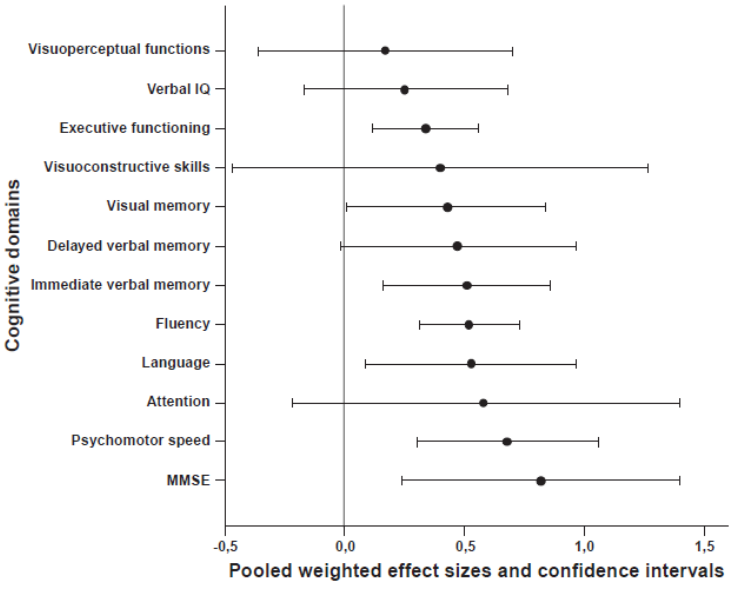
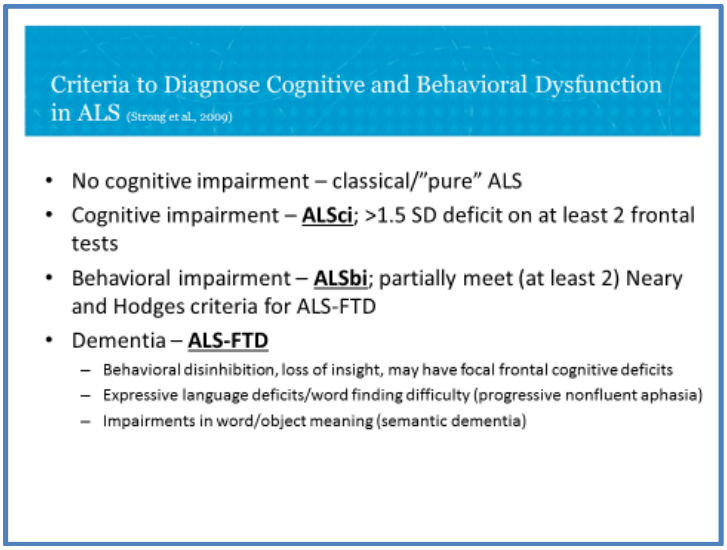


Figure 1. Pooled weighted effect sizes (●) and 95% confidence intervals of the cognitive domains calculated from available studies. A positive effect size indicates a worse cognitive performance of ALS patients compared to controls for that domain. If the horizontal line does not bracket the vertical bar (0), the effect is significant at the 0.05 level.

Across studies, there are a variety of degrees of the severity of impairment. Most cognitive domain studies have shown that there is some degree of cognitive impairment in executive function and memory function, and to a lesser degree in verbal IQ or visuoperceptual functions.

Along with the interest in cognitive dysfunction in ALS, there is also an interest in behavioral changes that occur as a function of the disease. There is some discussion pertaining to whether this is related to the disease or if it is a psychological reaction to the diagnosis and the effects of the disease. Among studies that have assessed this, there have been frontally-mediated behavior changes such as apathy, disinhibition, and mental rigidity. There has been some documentation of that in the literature as well.

In the mid-2000s, the following strong consensus criteria were utilized for assessing particular diagnostic subtypes within ALS:



Thinking about cognitive dysfunction and ALS, in addition to the importance of multidisciplinary clinics, PALS caregivers are critically important. Whether that is a family member or a professional caregiver, caring for someone with ALS creates a fair amount of burden. There is a developing literature in caregiver stress in ALS that has found that caregiver burden/stress related to the severity of ALS motor dysfunction, apathy, disinhibition, congruence of caregivers mood with PALS mood, and executive cognitive ability dysfunction. Also important to note is that caregiver burden/stress increases over time. Similar to the Alzheimer's caregivers literature, perceived social support by the caregiver also is very important with respect to mitigating the effects of caregiver stress in ALS.

In terms of the RFA, the BU investigators considered that cognitive impairment in ALS is prevalent and heterogeneous with a predominant pattern of frontal system dysfunction, so perhaps behavioral dysfunction is also prevalent. Cognitive and behavioral dysfunction appears to be related to caregiver burden/stress. It is important to determine if cognitive/behavioral symptoms/subtypes in ALS are associated with caregiver burden/stress, and to examine the time-course of disease progression/caregiver burden associations.

With that in mind, the following specific aims were developed for the Cognition, Behavior, and Caregiver Burden in Amyotrophic Lateral Sclerosis study:

- ❑ Specific Aim 1- Characterize cognitive/behavioral subtypes in a large national cohort of persons with ALS (PALS) and identify risk factors for these subtypes

    - Relative prevalence of cognitive/behavioral subtypes
    - Rate of conversion over observation interval
    - Risk factors for conversion

- ❑ Specific Aim 2- Study cross-sectional and longitudinal relationships among cognitive/behavioral subtypes in PALS and caregiver burden, and whether these relationships affect ALS disease progression over a 3-year interval

    - Cross-sectional analyses
        - PALS cognitive/behavioral symptoms and disease severity
        - PALS cognitive/behavioral symptoms and caregiver burden
        - Caregiver burden and disease severity

    - Longitudinal analyses
        - PALS cognitive/behavioral/mood symptoms at enrollment predict
            - Subsequent caregiver burden trajectory
            - Subsequent disease progression
        - Caregiver burden/mood at enrollment predict
            - Subsequent disease progression

- ❑ Specific Aim 3- Validate brief cognitive/behavioral/caregiver burden measures that can be administered to patients/caregivers over the telephone

Specific Aims 1-2 includes a national cohort (n=600) of PALS/caregiver dyads recruited from two ongoing national cohorts of PALS: The National ALS Registry maintained by the ATSDR and the VA Biorepository Brain Bank. Specific Aim 3 is comprised of a local cohort (n=60) of PALS/caregiver dyads recruited from a veteran ALS clinic sample in New England. The following is the layout for Specific Aims 1 and 2 in the national assessment:

Table 1. Assessments given to PALS and/or caregivers in the national cohort

	PALS		CG	
Measures	Enrollment	Follow-up	Enrollment	Follow-up
ALS severity	X	X		
Cognition	X	X		
CG burden			X	X
Mood/behavior	X	X	X	X

The plan is to conduct initial enrollment assessments and annual follow-ups for up to three years. The behavioral and cognitive assessments in PALS will be conducted annually, the caregiver assessments will occur annually, and a semi-assessment will be conducted of caregiver burden in order to have a better resolution with respect to changes in caregiver burden that occur over the course of the disease.

The longitudinal component will be interesting, given that individuals can be assessed from enrollment to determine what changes occur in cognition and behavior over time, and how that is related to changes in caregiver burden. If particular types of deficits are observed in patients in the clinics that are known to be risk factors for higher degrees of caregiver burden, it will be interesting to know so that additional support can be provided to caregivers going forward.

Given that the study is being conducted primarily by telephone and through the mail, the investigators decided to run a concurrent validation study to ensure that the tests are working well (Aim 3). That study will be conducted at Boston VA Research Institute as part of the multidisciplinary ALS clinic. The battery given to the national sample will be administered to those who present to the clinic, in addition to an in-person neuropsychological and caregiver assessment to determine how well the telephone and mail assessments link to the gold standard of an in-person neuropsychological assessment.

With respect to the battery, last year's meeting was very beneficial. Though initially there were no plans to give the ALS CBS, it was included when they learned that others were giving it. They also had not considered financial burden until that was suggested during last year's meeting. The following battery is planned:

Telephone cognitive assessment of PALS given to PALS or caregivers (if PALS cannot complete due to speech/motor impairment):

- ALS CBS
- Telephone Interview for Cognitive Status – modified + additional tests
- Cambridge Behavioural Inventory Revised (CBI-R)

Questionnaire assessments of mood and behavior given to PALS and caregivers:

- Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD PHQ)
- Beck Depression Inventory-II (BDI-II)
- Beck Hopelessness Scale (BHS)
- Dysexecutive Questionnaire (DEX)

Questionnaire Assessments of caregivers:

- The Zarit Burden Interview
- Social Support Questionnaire-Short Form

The telephone/questionnaire assessments in the national cohort will include an in-person assessment of PALS using neuropsychological tests for attention, frontal systems, working/ episodic memory, language, cognitive processing speed, and general cognitive ability/IQ. In-person interviews will also be conducted with caregivers.

Since last year, the contract was set up. There were consultations with Drs. Mitsumoto and Feldman, who graciously sent BU investigators their batteries and adjustments were made of the planned batteries to maximize the impact of the results across the respective studies. Staff have been hired and trained. Approvals have been received from Boston VA ALS clinic and the IRB. There are some aspects of the study that are not believed to fall within the purview of the OMB review, so negotiations are underway regarding how to mitigate the impact of the OMB review with respect to completing the study. Some study results should be available for the 2016 ALS annual meeting.

Discussion Points

As a caretaker, Mrs. Reznick said she understood intuitively that taking care of people who are challenged mentally and physically is hard on caregivers so she appreciated that focus. However, she was trying to understand what new knowledge would be gained from this study.

Dr. Brady responded that in Alzheimer's disease, caregivers have an opportunity to settle into their role. People receive the dementia diagnosis and over time there are some cognitive changes, but impacts on functional abilities, ADLs, et cetera come later in the disease and there is time for people to settle into that. In ALS, this is flipped and there is little time to settle into the caregiver role. Depending upon the diagnosis and disease progression, functional impairments occur very early and then cognitive impairment. That would suggest that there may be different indicators that could be good markers for those who at higher or lesser degrees of risk of burden depending upon the type or subtype. For example, it is known that someone with a pure ALS subtype is going to have functional limitations like everyone else. However, that person may have a different trajectory than someone who has a behavior or cognitive issue in addition to the functional issue. Over time, trajectories vary as a function of subtypes or they may not change at all. It may be similar to the Alzheimer's literature, but no one has examined this so they thought it would be very interesting to assess whether people can be categorized so that interventions could be more targeted and implemented earlier in the process. This could allow caregivers to do their jobs much better and with less chance of stress and burden.

Mrs. Reznick emphasized that one aspect of caregiving that is important is that those people who have the financial means to have help in their homes are likely to be very different from those who do not and are providing full care themselves.

Dr. Brady recalled that Mr. Tessaro said the same thing during last year's meeting and they incorporated this into the study protocol. Monitoring social isolation, social support, and other aspects of caregiver burden that are traditionally assessed but ignoring the substantial financial impact of ALS on families would be a major study limitation.

Since it is known that sleep and ventilation impact cognition, Ms. Armstrong wondered whether consideration had been given to including factors in the study to measure CO_2 levels and progressive hyperventilation, and the technology of respiration equipment and the caregiver burden of the mounting medical equipment that comes into the home and how people deal with that.

Dr. Brady replied that they will be asking people about their respiratory status, whether they are using a Bilevel Positive Airway Pressure (BiPAP) machine, et cetera. However, they will not be able to collect CO_2 levels as a function of the study because this is being done by mail and telephone. Numerous questions will be asked with respect to environmental exposures (e.g., occupational, military service, hobbies, et cetera), which will provide data about risk factors for particular subtypes. The other reason to include the components that Drs. Mitsumoto and Feldman are using is that when their respective studies are completed, they will have a base of comparison because the three studies will have administered similar measures.

Ecologic Study to Evaluate Spatial Relationships between ALS & Potential Environmental Risk Factors

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

Dr. Bradley indicated that the first year of the planned two-year study of the "Ecologic Study to Evaluate Spatial Relationships between ALS & Potential Environmental Risk Factors" was just concluding. The study is being conducted in Florida and New England. Dr. Elijah W. Stommel is the PI in New England. Dr. Bradley shared some preliminary results from the first year of the study.

ALS is recognized to be a syndrome with many causes, particularly in terms of sporadic ALS which must be caused by a broad number of environmental factors impacting genetic predispositions. It may well be that there is an individual predisposition for each of the individual environmental factors. The prevalence of each specific genetically-determined susceptibility may be low, which will be an issue in the effort to determine a gene-environment correlation.

A large number of environmental factors have been incriminated over the years in the literature, including the following:

- ❑ Environmental toxicants
  - Lead*, mercury
  - Pesticides
- ❑ Certain occupations*
  - Construction, metal workers, electricians
- ❑ Smoking*
  - Electrocution
- ❑ Military deployment*
- ❑ Sports/Head injuries*
- ❑ Chemicals
  - Solvents
  - Agricultural exposure

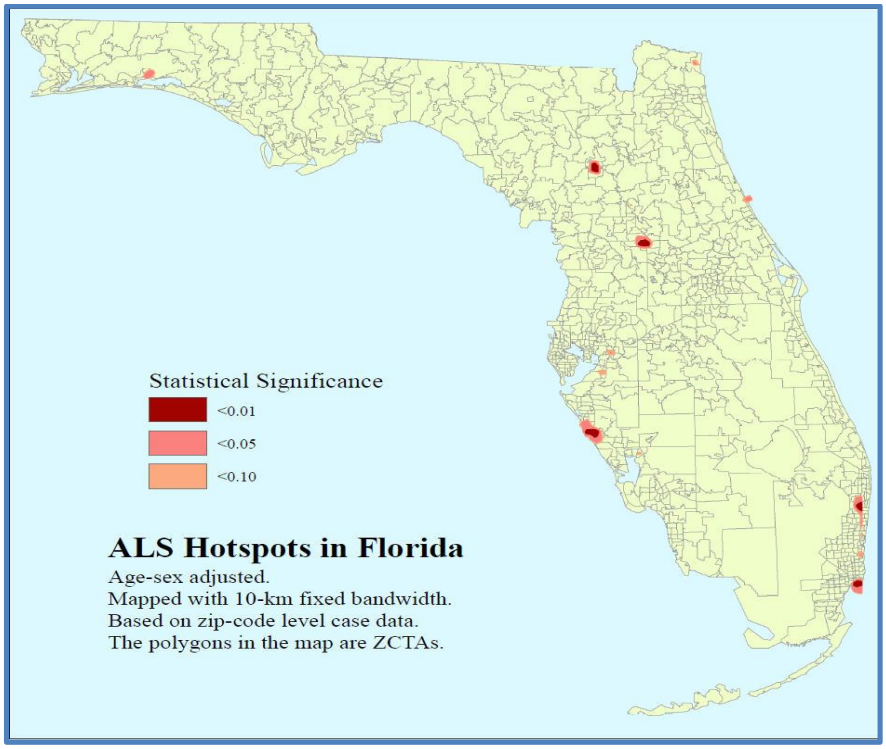
- Cyanobacteria and beta-N-methylamino-l-alanine (BMAA)

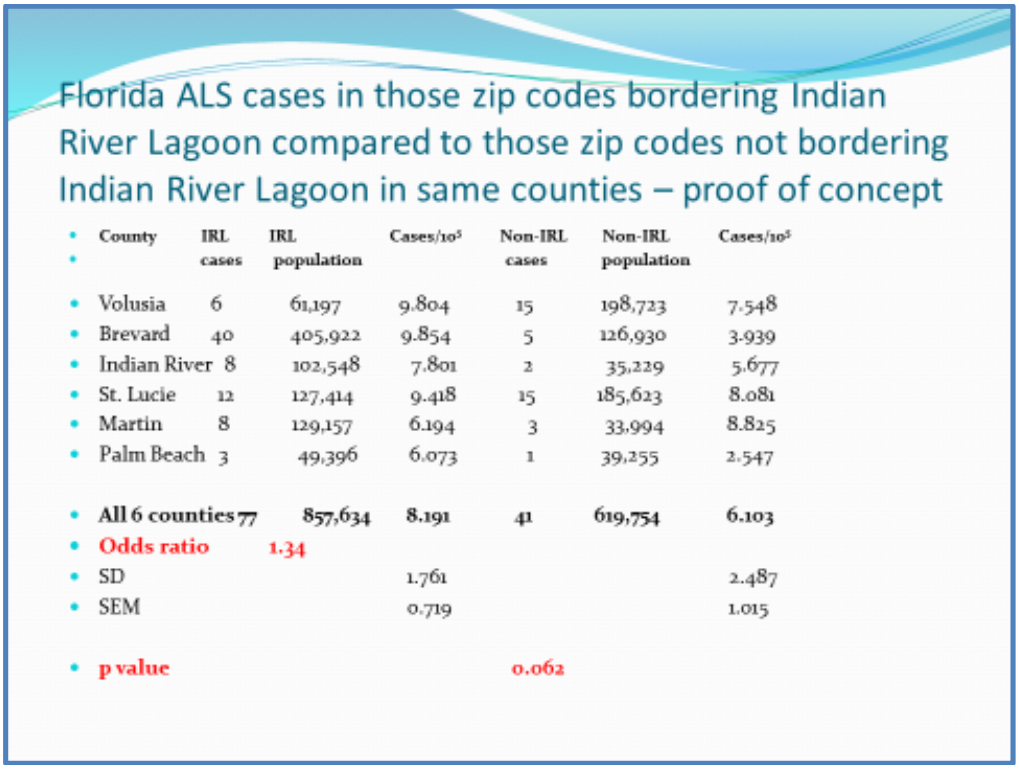
  * demonstrated in several studies and widely accepted

In terms of the current research, the hypothesis is that "Greater exposure to yet-to-be proven environmental neurotoxins and neurotoxicants increases the risk of developing ALS." This does not take into account anything about predisposition. Instead, it is a dose-effect case-control study of estimated lifetime environmental exposure to environmental toxicants from a variety of sources (e.g., Superfund and brownfield sites, landfills, municipal incinerators, and agricultural use of pesticides; and proximity to lakes with the cyanobacterial toxin, BMAA). There is a questionnaire-based component and a lifetime history of addresses, as much as possible, where patients and controls have lived over their lifetimes.

The Florida component includes 1451 patients collected in the National ALS Surveillance Program in Florida. It includes addresses and other demographic and clinical data on file at the Florida Department of Health (FL DOH). The investigators currently have the zip codes of residences at enrollment, and a request for de-identified patient addresses is under review by the FL DOH for 11 months. Dr. Bradley believes they eventually will receive these addresses.

There are some hotspots based on zip code distribution of patients. These are hotspots of a statistically increased frequency of ALS patients compared with a random distribution of patients. One preliminary analysis has been performed of the distribution of ALS patients around the Indian River Lagoon, which has a 30-year history of massive cyanobacteria algae blooms. The area runs along the East Coast of Florida from Cape Canaveral to Palm Beach. The zip codes bordering the Indian River Lagoon were compared to the zip codes further away from the Indian River Lagoon to assess the prevalence of ALS. The hotspots and findings are shown in the following map and table:





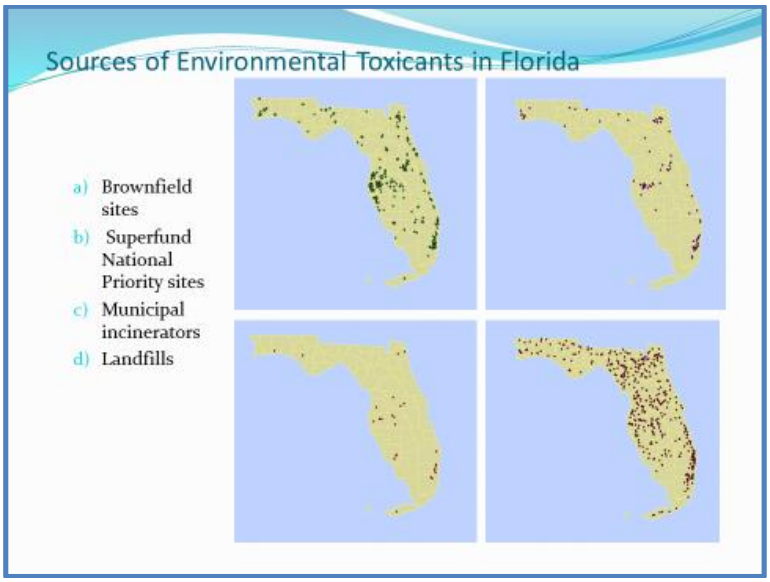
Florida ALS cases in those zip codes bordering Indian River Lagoon compared to those zip codes not bordering Indian River Lagoon in same counties – proof of concept

County	IRL cases	IRL population	Cases/10^5	Non-IRL cases	Non-IRL population	Cases/10^5
Volusia	6	61,197	9.804	15	198,723	7.548
Brevard	40	405,922	9.854	5	126,930	3.939
Indian River	8	102,548	7.801	2	35,229	5.677
St. Lucie	12	127,414	9.418	15	185,623	8.081
Martin	8	129,157	6.194	3	33,994	8.825
Palm Beach	3	49,396	6.073	1	39,255	2.547
All 6 counties	**77**	**857,634**	**8.191**	**41**	**619,754**	**6.103**
Odds ratio	1.34					
SD			1.761			2.487
SEM			0.719			1.015
p value				0.062		

The odds ratio for having ALS was 1.34 for the zip codes bordering the Indian River Lagoon compared with those zip codes not bordering the lagoon, however it did not reach statistical significance. The investigators plan to conduct similar analyses for the entire state with water bodies, cyanobacteria content, and actual patient addresses. Hopefully, that will demonstrate whether there is an association between living fairly close to cyanobacteria blooms in water.

There is an extensive database of water quality in Florida, which is comprised of data from the 5 water management districts covering the whole of Florida. This includes 5735 sampling sites, and is a tremendously good resource for the analyses. Collection of water quality data for the last 25 years is completed. Data include date of collection, GPS coordinates of collection point on water-body, genus and species of cyanobacteria, biomass of each sample (um^3/ml), and total cells/ml. There are less complete data for microcystins, phycocyanins, chlorophyll-A, total nitrogen, total phosphorus, and pH. There are no BMAA measures.

Databases of environmental toxicants in Florida are completed and are comprised of landfills, municipal incinerators, Brownfield and Superfund sites, Geomap sites that identify chemicals and their mode of distribution (wind, water supply, et cetera), and agricultural pesticides/land-use. Sources of environmental toxicants in Florida are depicted in the following maps:



With all of those geocodings and the geocodings of the addresses of the ALS patients, the investigators can examine the question of risk at various distances from those sources to determine whether there is an association between the location where people live and the sources of environmental toxicants nearby.

The geographical information system (GIS) analysis is constructed by:

- ❑ Generating a GIS layer of address of each patient
- ❑ Generating a GIS layer of estimated exposure to each environmental toxin/toxicant
- ❑ Generating a GIS layer of *expected* age- and gender-adjusted number of patients in each pixel within the state ("artificial controls")
- ❑ Comparing exposure value for patients v. artificial controls = odds ratio
- ❑ Conducting a Monte Carlo simulation study to determine statistical significance

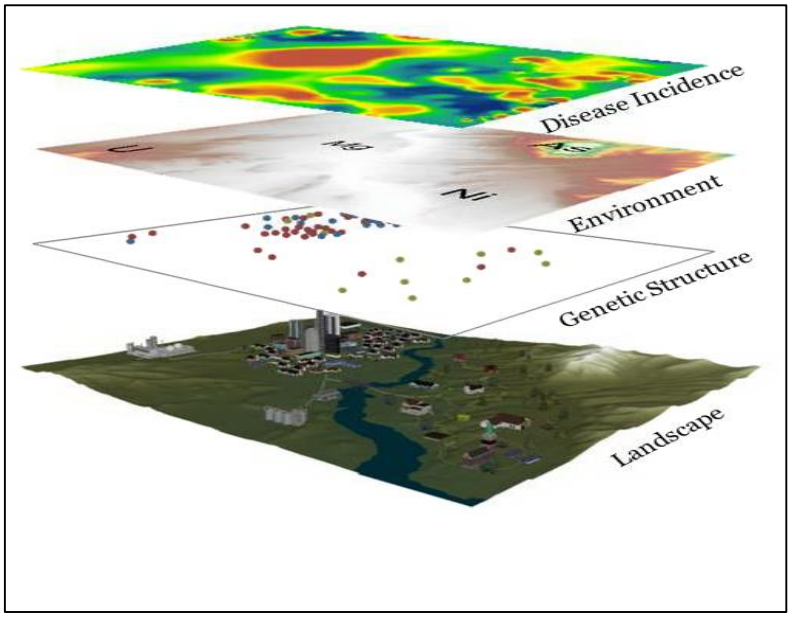


Illustration: GIS Analysis

Some of the specific cyanobacteria studies already started with the Florida databases include the following:

- ❑ Generate the GIS data layer of cyanobacterial content of sampled water bodies

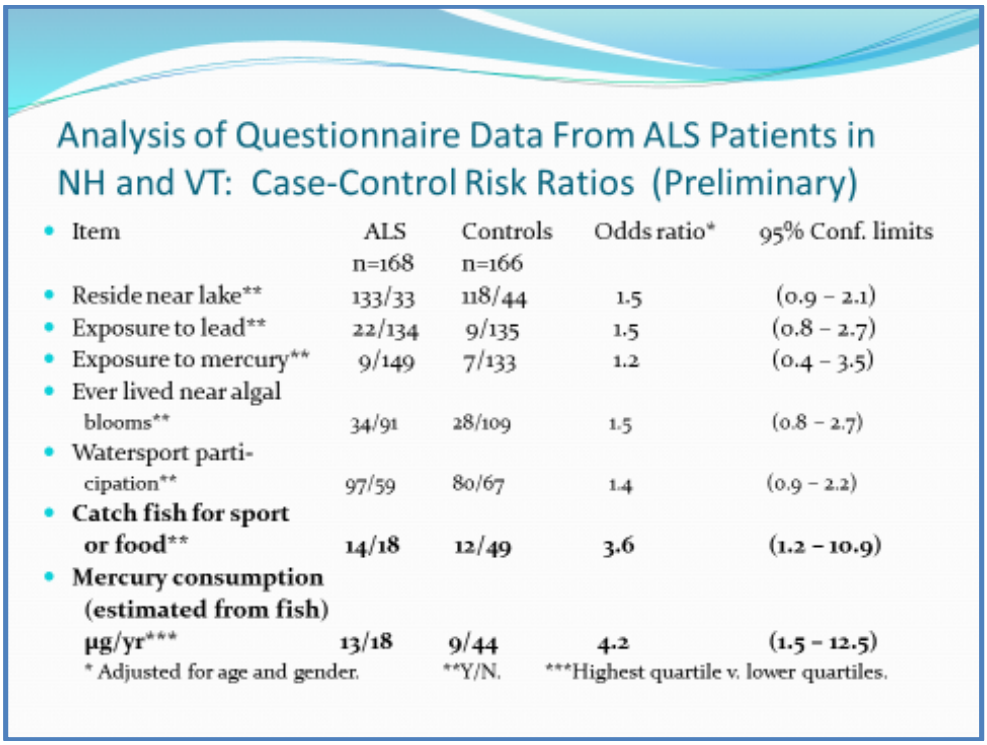
- ❑ Generate the GIS data layers for individual sources of environmental toxicants (Superfund and brownfield sites, landfills, municipal incinerators, agricultural land use)

- ❑ To be initiated once de-identified ALS patient addresses released by FL DOH
  - ➢ Generate the GIS data layer of ALS patient addresses
  - ➢ Analyze risk of developing ALS from living near each source of environmental toxin/toxicant and distance over which that risk extends

Regarding New Hampshire and Vermont, Dr. Stommel has collected almost 500 (n-442) patients to date. There are 238 population controls from a recent cancer study.* Approximately 280 questionnaires have been collected from clinic "recall-bias" controls. Recall bias controls are patients with various neurological diseases that are "idiopathic" wherein patients search their memory for life events that might have caused the unknown disease (MS, brain and spinal cord tumors, adult-onset epilepsy, autoimmune non-familial neuromuscular diseases). They are approximately age- and sex-matched [* Heck JE, Andrew AS, Onega T et al. Lung cancer in a US population with low to moderate arsenic exposure. Environ Health Perspect 2009;117:1718-23]. The New Hampshire/Vermont questionnaire collects the following information from ALS patients:

- ❑ Lifetime history of residence addresses (Google Earth Lat-Long coordinates), water supply, proximity to industrial dumps, landfills, municipal incinerators, water bodies with algal blooms (currently correlating only the place they lived at the time of diagnosis, though the database of previous residences is being built)
- ❑ ALS clinical data
- ❑ Family history of neurodegenerative and other diseases
- ❑ Past history of head injuries, electrical injuries, medications, military service, vaccinations, smoking
- ❑ Lifetime history of occupations and exposures
- ❑ Fish consumption (relevant for mercury and BMAA)
- ❑ Recreational activities (water sports, athletics)

The following are the results from a preliminary analysis of about half of the questionnaires comparing the association between controls and ALS patients for the factors shown:



Analysis of Questionnaire Data From ALS Patients in NH and VT: Case-Control Risk Ratios (Preliminary)

Item	ALS n=168	Controls n=166	Odds ratio*	95% Conf. limits
Reside near lake**	133/33	118/44	1.5	(0.9 – 2.1)
Exposure to lead**	22/134	9/135	1.5	(0.8 – 2.7)
Exposure to mercury**	9/149	7/133	1.2	(0.4 – 3.5)
Ever lived near algal blooms**	34/91	28/109	1.5	(0.8 – 2.7)
Watersport participation**	97/59	80/67	1.4	(0.9 – 2.2)
Catch fish for sport or food**	**14/18**	**12/49**	**3.6**	**(1.2 – 10.9)**
Mercury consumption (estimated from fish) µg/yr***	**13/18**	**9/44**	**4.2**	**(1.5 – 12.5)**

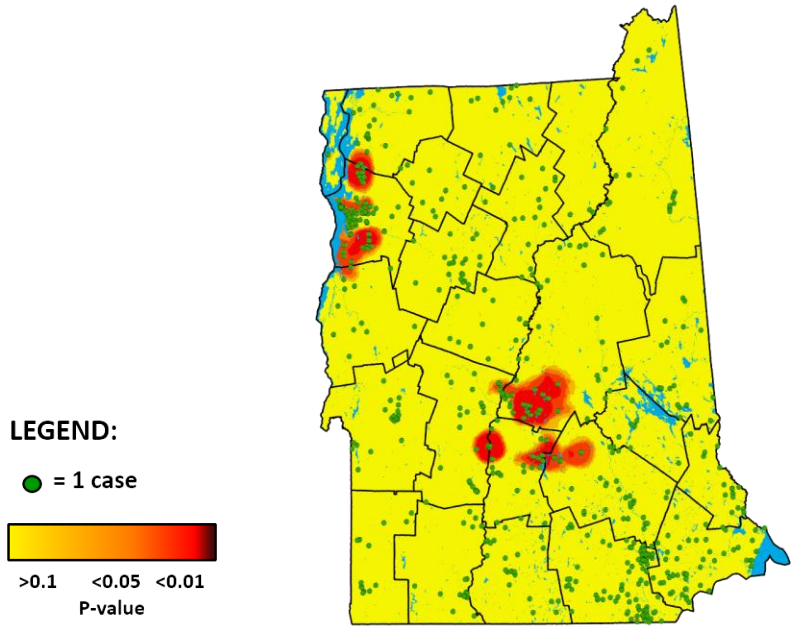
* Adjusted for age and gender. **Y/N. ***Highest quartile v. lower quartiles.

While positive odds ratios were achieved for most of the factors, statistical significance was reached only for mercury consumption. The major source of mercury for humans in the US is fish consumption. In fact, a very good correlation can be made of how much fish, what type of fish, where the fish came from, and mercury intake. There is a 4.2-fold increase in ALS patients' consumption of mercury compared with controls.

A fairly extensive database is already constructed for New Hampshire and Vermont of the water quality in lakes. Water quality databases are comprised of 2868 direct sampling sites and cyanobacterial content and cyanotoxins (microcystins). Industrial databases include toxicants in landfills, municipal incinerators, Superfund and brownfield sites, and agricultural databases include pesticides and agricultural land-use.

Dr. Bradley and colleagues are collaborating with Applied GeoSolutions LLC, a company of research workers who use remote satellite sensing platforms to quantify the content of cyanobacteria in water bodies. The actual samples directly collected will be correlated with the satellite spectra, and they will be able to look at every water body that is more than 8 hectares in area with regard to cyanobacteria content.

There are statistically significant clusters of ALS patients in New Hampshire and Vermont, as depicted in the following map:



The red area in the center is the area around Lake Mascoma where Dr. Stommel originally observed a cluster of ALS patients in a small village with approximately 20 times as much ALS as should be present in a random distribution. At the top left-hand side of the map, there are two other hotspots around Lake Champlain where there are quite significant algal blooms. It has been shown that BMAA occurs in the organs of fish and that microcystins, toxins produced by cyanobacteria, similarly occurs in fish. The process is underway of generating the geocoding of the lakes, ALS patients, and sources of environmental toxicants.

Additional studies are planned, which are not a part of the original ATSDR-funded research, including the following:

- ❑ Control cases
  - ➢ Recall-bias disease controls
  - ➢ Population-based controls

- ❑ Bio-specimens
  - ➢ CSF, blood
    - Lead, mercury, BMAA
  - ➢ Nails, hair
    - Lead, mercury
  - ➢ DNA from ALS patients and controls with completed environmental questionnaires
  - ➢ Autopsy
    - Brain BMAA, mercury
    - Bone lead
    - Cyanobacteria in lung tissues

- ❑ Micropore filters of air samples collected at lakes in NH and VT
  - ➢ Cyanobacteria, BMAA, microcystins

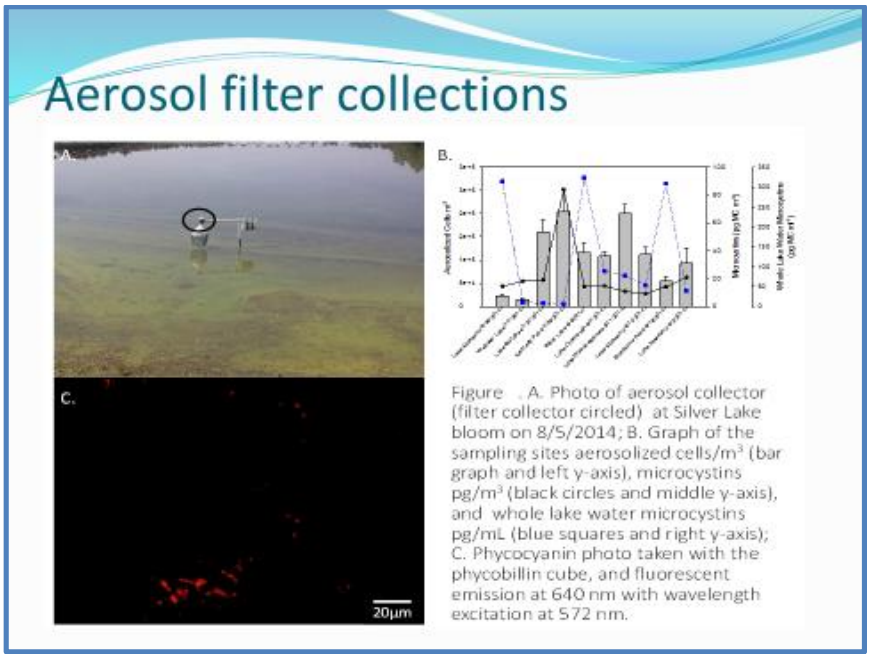
- ❑ Expansion of study to northern Ohio in collaboration with Dr. Erik Pioro, Cleveland Clinic ALS Center

- ❑ Therapeutic trials of L-serine in ALS patients

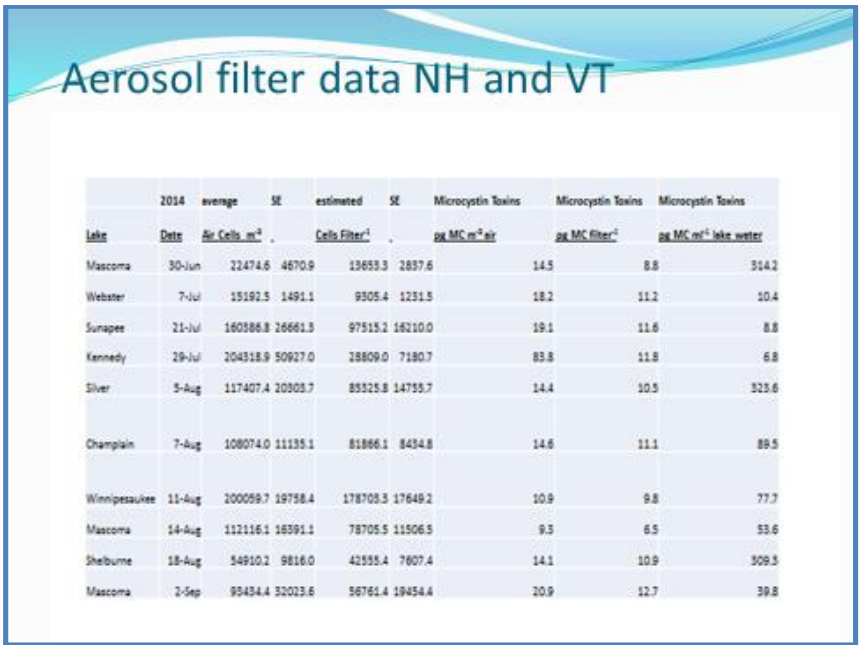
Collaborative efforts have been expanded to join with Dr. Erik Pioro in Cleveland Clinic ALS Center to assess his database of patients. They will be resubmitting a grant application during the next funding cycle to study the same types of issues in Northern Ohio.

It is an amazing fact that a very large amount of material from water bodies is distributed by wave action into the air, and is blown by the prevailing winds for distances of hundreds of miles. The data to date show that living within a half a mile of a lake is a risk factor for ALS, so more in-depth analyses will be done to gain greater insight into this.

The following figure shows the aerosol filter apparatus, with the bottom left panel (C) showing cyanobacteria:



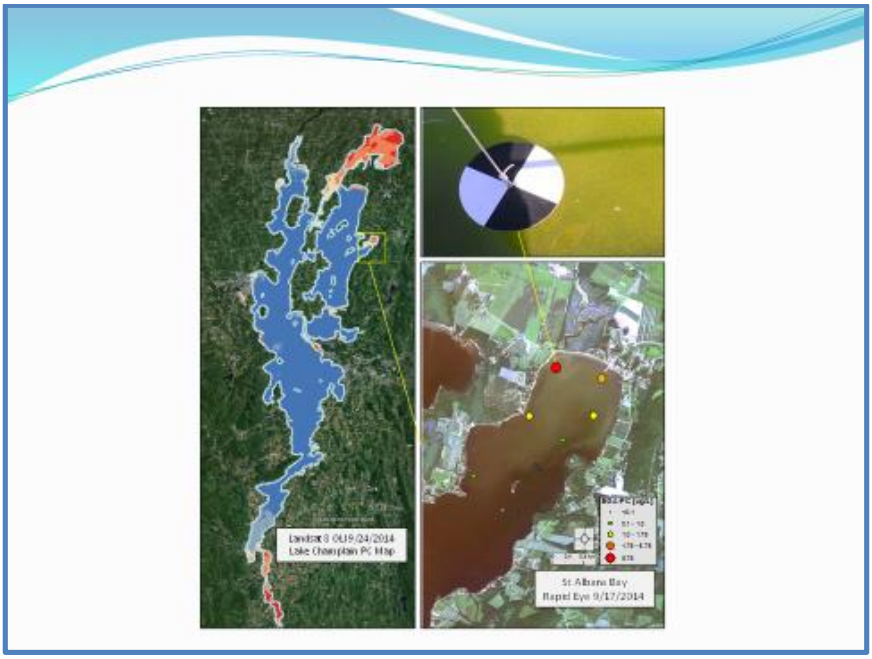
The following table illustrates some of the measures obtained through the cyanobacteria cells and content of microcystin for New Hampshire and Vermont:



Lake	2014 Date	average Air Cells m^3	SE	estimated Cells Filter^1	SE	Microcystin Toxins pg MC m^3 air	Microcystin Toxins pg MC filter^1	Microcystin Toxins pg MC ml^1 lake water
Mascoma	30-Jun	22474.6	4670.9	13653.3	2837.6	14.5	8.8	314.2
Webster	7-Jul	15192.5	1491.1	9305.4	1231.5	18.2	11.2	10.4
Sunapee	21-Jul	160386.8	26661.3	97515.2	16210.0	19.1	11.6	8.8
Kennedy	29-Jul	204318.9	50927.0	28809.0	7180.7	83.8	11.8	6.8
Silver	5-Aug	117407.4	20303.7	85525.8	14755.7	14.4	10.5	323.6
Champlain	7-Aug	108074.0	11135.1	81866.1	8434.8	14.6	11.1	89.5
Winnipesaukee	11-Aug	200059.7	19758.4	178708.3	17649.2	10.9	9.8	77.7
Mascoma	14-Aug	112116.1	16391.1	78705.5	11506.5	9.3	6.5	53.6
Shelburne	18-Aug	54910.2	9816.0	42555.4	7607.4	14.1	10.9	309.3
Mascoma	2-Sep	95434.4	32023.6	56761.4	19454.4	20.9	12.7	39.8

This demonstrates at least the beginnings of the proof of concept that aerosol substances from cyanobacteria do get into the environment. Nasal swabs will be done on people who are putting these filters in to determine whether cyanobacteria is getting into patients' noses.

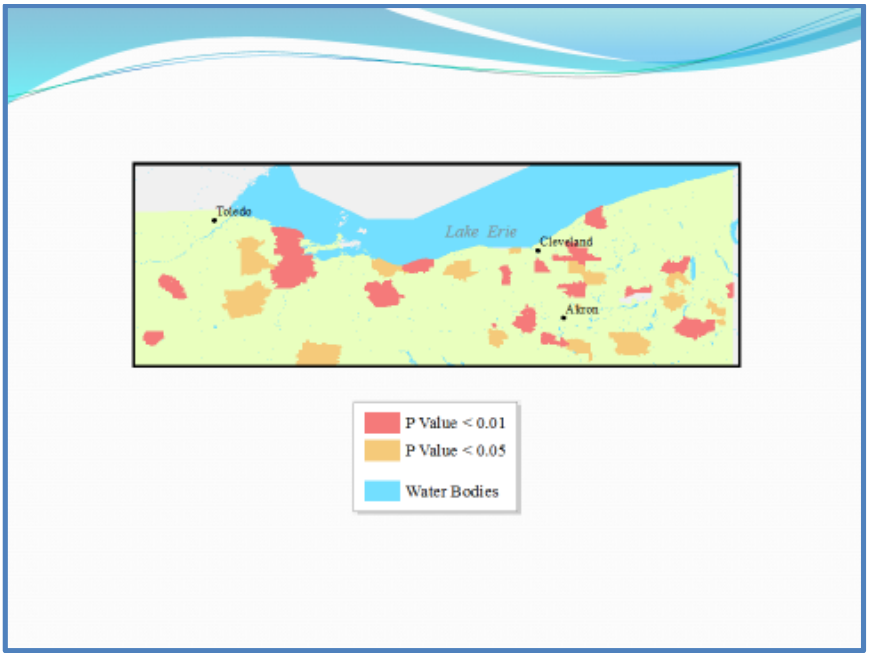
Here is an illustration of the satellite remote sensing process used to determine the cyanobacterial content of Lake Champlain:



The left-hand panel shows Lake Champlain. To the top right of that same panel is a red area, which is St. Albans Bay. In the bottom right panel are the direct water assays of cyanobacteria,

which shows high levels of cyanobacteria that correlate with the satellite representations and detections of cyanobacteria pigments.

Though very preliminary, this is the distribution of 1000 ALS patients in Dr. Erik Pioro's Cleveland Clinical Database:



There are statistically significant clusters of ALS patients, based on zip codes. The pink areas are statistically significant for increase of ALS patients. The Western end of Lake Erie has massive annual cyanobacteria blooms that in the previous two years resulted in the shutdown of various water supplies because of high microcystin levels in the water. Microcystin gets through the filtering process of municipal water. This seems to be a very fertile area for extending these studies in an effort to take a second run at demonstrating whether there is an association between water quality and ALS.

Discussion Points

Dr. Traynor complimented Dr. Bradley and colleagues on a marvelous job of approaching this in a robust manner. He wondered how the statistical analyses were being approached for the clusters. He wondered whether machine learning might be of benefit; that is, the idea of letting the computer find the statistical model that fits best.

Dr. Bradley replied that they have essentially been looking at the total population of ALS patients in the whole state and comparing that with small areas. That is essentially the statistical analysis.

Dr. Traynor emphasized that there might be an opportunity to be more sophisticated about this. One problem might be that it is amazing how much families do not move apart from one another. It is possible to imagine a scenario in which a family has a genetically increased risk of developing ALS, they all live around the lake, and they never move away from each other. Knowing the genetics would be great in that instance, but there might be another way. For example, patients could be subdivided by those who moved into the area and those who were

born, raised, and lived their entire lives in an area to look for an increased risk in those who moved in. That might be a way to divorce themselves from the genetic component of this.

Dr. Bradley replied that one of the other criticisms of the approach pertains to the fact that there are many "snowbirds." While they have the data to analyze this, they have not yet done anything with past history of residences. But the suggestion is a very interesting stratum in terms of the analysis of lifetime history.

Dr. Kasarskis requested clarification regarding the Vermont controls and Florida.

Dr. Bradley clarified that there are two groups of controls for New Hampshire/Vermont. One is the controls from a population study related to examining cancer risks. None of those individuals had cancer themselves. They do not have any controls in Florida, which is inevitable in the way that Florida was collected. The analyses there will involve assessment of the uniform distribution of patients compared to the observed distribution of patients.

Dr. Brooks asked whether any of the population-based NHANES studies collect DNA data, and whether there should be a systematic genetic profiling of the controls through these types of studies being conducted ultimately to provide the type of control data necessary for studies going forward.

Dr. Horton replied that the NHANES is a national survey that is conducted annually. The survey collects information about the population's health. Certain biological specimens are collected, and one of the suggestions that has been made is that this could serve as a potential source for controls. ATSDR has been asked previously about why the registry is not collecting its own controls. Registries are not really set up to do that. Registries track those with disease. Typically, it is up to researchers to identify their own controls. NHANES may be a good place to start, and ATSDR has suggested this to researchers who have asked about controls.

Dr. Kaye added that a number of specific genetic studies have been conducted through NHANES, but they have not done genotyping on all of the specimens.

Dr. Brooks emphasized that he was thinking about where they need to be in 5, 10, 15, and 25 years. That discussion must begin now, and it goes beyond the National ALS Registry. It is a discussion about providing the kind of matrix that must be in place for many diseases. It would be an incredible source of commitment by ATSDR or whomever takes it over, but it is obviously necessary.

Dr. Bradley indicated that one of the specific aims for the grant to the National Institute of Environmental Health Sciences (NIEHS) is to be able to collect blood for genetic testing from controls and ALS patients.

Dr. Brooks said that while that is a great start, Dr. Traynor believes 40,000 cases are needed to look for genes and Dr. Bradley has 200 cases. In terms of the modeling, he wondered what Dr. Bradley would be able to find with this dataset.

Dr. Bradley indicated that with the Florida database of approximately 1400 patients and about 500 patients to date in New Hampshire and Vermont, they believe they have a statistical power that is quite sufficient to demonstrate the regional distribution in relation to the sources of environmental toxicants. Until they can provide Dr. Traynor with enough samples from controls and cases, they will never be able to do the power calculation that is needed for this.

Mr. Tessaro noted that he lives on a lake with a significant Large Mouth Bass population. His neighbors regularly eat fish of 4 to 6 pounds. He wondered whether that type of bacteria was something he could request that their water management facility test for, or if it was so specific to a unique set of data they would not know what to do with it.

Dr. Bradley responded that standard testing is done for harmful algal blooms that occur in eutrophied lakes; that is, lakes that are polluted by agricultural runoff and human sewage runoff that produce green, mucky ponds by which people live.

Mr. Tessaro was surprised by this, and said he would add it to the data and would like to know more about it.

Dr. Bradley indicated that the environmental department representatives will collect these data in areas where there are algal blooms.

Dr. Traynor asked whether zip codes are being collected by the Registry, and if those data could be accessed for cluster analyses across the entire country instead of confining them to two states.

Dr. Kaye responded that they are not collecting zip codes in the Registry.

A Prospective Comprehensive Epidemiologic Study in a Large Cohort in the National ALS Registry: Identifying ALS Risk Factors

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 described the ATSDR Risk Factors Epidemiologic Studies in ALS (ARREST ALS) study. The ARREST ALS study is based on the ALS Multicenter Cohort Study of Oxidative Stress (ALS COSMOS), which is nearly completed. The 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. The specific aims of the ALS COSMOS study 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

At this point, the 24-month follow-up has been completed and the 30-month follow-up is nearing completion. A number of papers have been or are in the process of being published on the ALS COSMOS study regarding the baseline. Functional progression and survival data are currently being analyzed to correlate with OS.

The investigators' experience with ALS COSMOS (n=355) was the basis for the expansion. They thought the National ALS Registry would be a fantastic way to assess the entire nation. Now that they have conducted the cohort study at the center level, they can examine 50 states. Building upon the ALS COSMOS study, the objectives of the ARREST ALS study are 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

Patients participate voluntarily in the ARREST ALS study by enrolling themselves into the National ALS Registry and initiating their participation. In terms of the approach for the ARREST ALS study, the key is to increase awareness of this national project for potential patients. Patients who are diagnosed with ALS will register under the National ALS Registry and will then initiate a call to Columbia's ALS Center at 1-855-STOP ALS. Everything will be done over the phone (obtaining informed consent, medical records, all interviews, et cetera). Cognitive testing will be done over the phone. A pilot study has just been completed that shows equivalency for most cognitive screening tests. DNA and urine samples will be obtained. Patients' follow-up schedules are similar to ALS COSMOS. The goal is to enroll 420 patients from 50 states.

The following table describes the case enrollment and ascertainment data collection.

Description of Case Enrollment and Ascertainment Data Collection

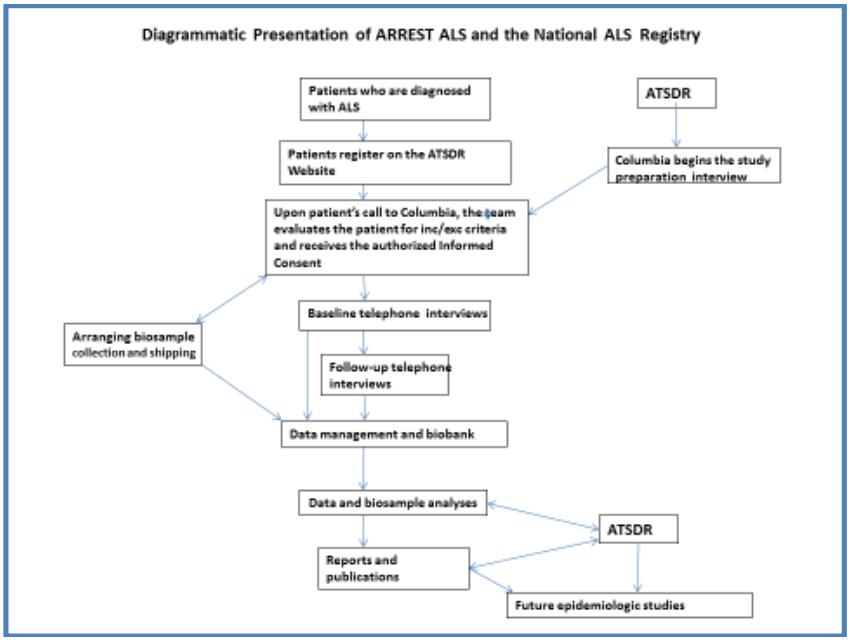
Items	Number of Items Administered	Items	Number of Items Administered
Subject initials	1	Duration between symptom onset and enrollment	1
Capacity Assessment Record	13	Anatomical region of onset	1
Case Eligibility Form	12	LMN and UMN Signs	54
Enrollment Form	4	Diagnostic Testing	5
ALS Center physician	1	Familial ALS	6
Date of birth	1	Atypical Features	4
Date of enrollment	1	Disease Progression	2
Date of diagnosis	1	Diagnostic Certainty	1
Date of symptom onset	1	PLS or PMA	1
Total Items (exam or question):	**110**		

This table describes the questionnaire data that will be collected related to oxidative stress.,

Description of Questionnaire Data Collected: Items Related to Oxidative Stress

	Section Totals: Num.ber of Items	
	Minimum	Maximum
Demographics	9	17
Residential	15	90
Occupational	8	510
Military	2	210
Physical Activity	1	72
Hobbies	1	54
Tobacco and Alcohol	4	29
Psychological Measures	88	97
Baseline Interview Total	128	1079
Self-Administered Diet Questionnaire		115

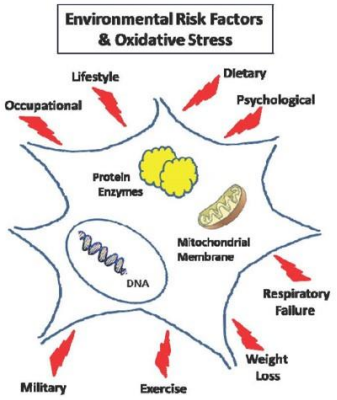
The following is a diagrammatic presentation of ARREST ALS and the National ALS Registry:

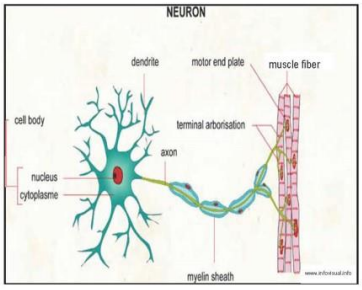


An attractive brochure/flyer with a catchy title was developed to give to patients to provide them with information about ARREST ALS:

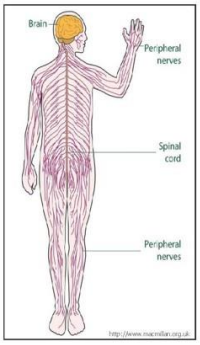
Background Information

- ALS (amyotrophic lateral sclerosis or Lou Gehrig's disease) is a neurodegenerative disease that leads to skeletal muscle paralysis, difficulty speaking, swallowing, and eventually breathing. The cause of this disease is still unknown.
- In sporadic ALS (patients with no immediate family member that has ALS), the cause and mechanisms of the disease are still unknown.
- We have a medication to treat ALS called riluzole, but it only modestly slows disease progression.
- An increasing number of new gene mutations have been discovered as the cause of familial ALS. In fact, several percent of sporadic ALS patients are found to have the same gene mutations.





- In sporadic ALS, environmental factors, such as occupational, lifestyle, dietary, and psychological factors, may influence disease risk and progression in ALS.
- Studying factors which influence the rate of ALS progression may help identify the causes.
- We must investigate the relationship between environmental risk factors and ALS progression. To accomplish this task, we need a large number of patients with ALS to participate in the research study.

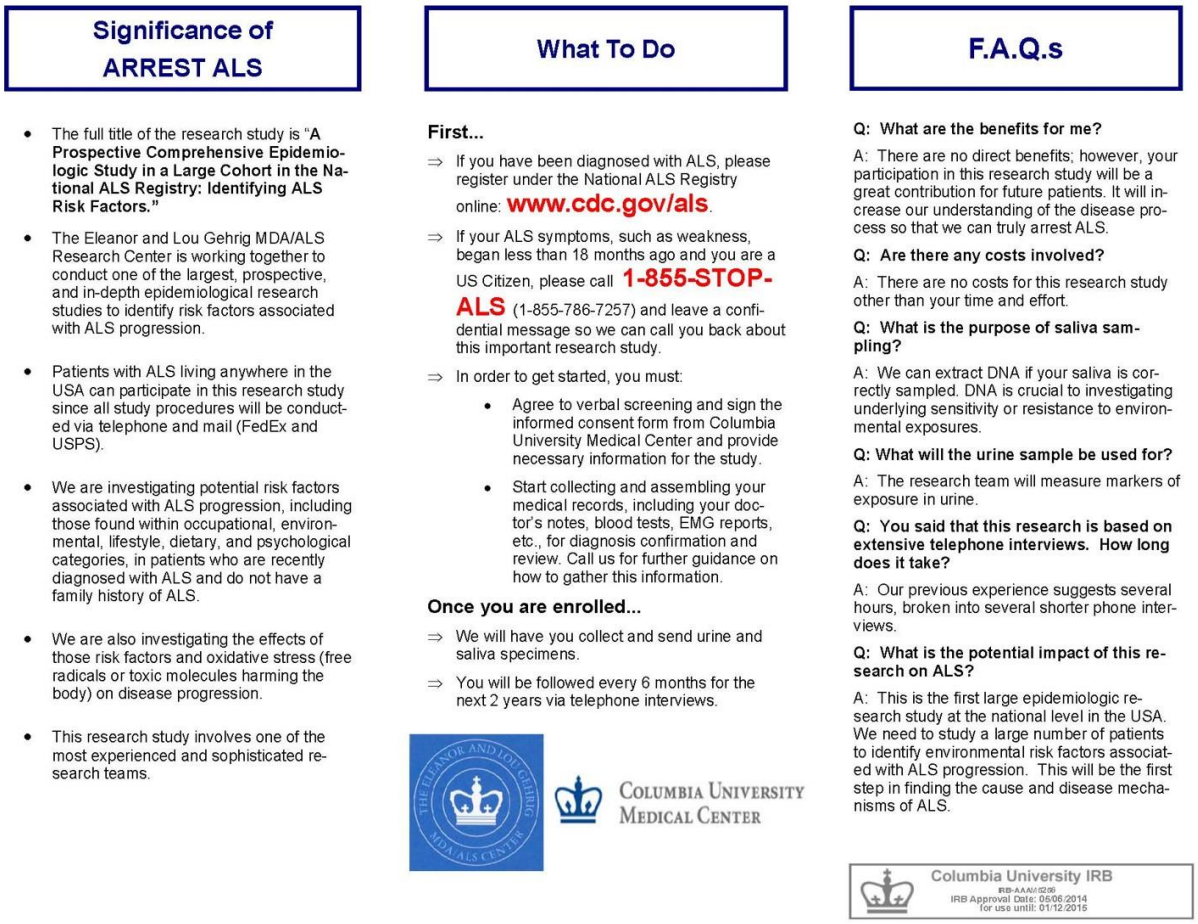


- Several years ago, voluntary disease organizations, such as the ALS Association (ALSA) and the Muscular Dystrophy Association (MDA), worked together to develop the National ALS Registry.

ARREST ALS
RESEARCH STUDY

Identifying ALS Risk Factors…
Please call:
1-855-STOP-ALS

Columbia University IRB
IRB-AAAM0266
IRB Approval Date: 05/06/2014
for use until: 01/12/2015



Significance of ARREST ALS

- The full title of the research study is "**A Prospective Comprehensive Epidemiologic Study in a Large Cohort in the National ALS Registry: Identifying ALS Risk Factors.**"
- The Eleanor and Lou Gehrig MDA/ALS Research Center is working together to conduct one of the largest, prospective, and in-depth epidemiological research studies to identify risk factors associated with ALS progression.
- Patients with ALS living anywhere in the USA can participate in this research study since all study procedures will be conducted via telephone and mail (FedEx and USPS).
- We are investigating potential risk factors associated with ALS progression, including those found within occupational, environmental, lifestyle, dietary, and psychological categories, in patients who are recently diagnosed with ALS and do not have a family history of ALS.
- We are also investigating the effects of those risk factors and oxidative stress (free radicals or toxic molecules harming the body) on disease progression.
- This research study involves one of the most experienced and sophisticated research teams.

What To Do

First...

⇒ If you have been diagnosed with ALS, please register under the National ALS Registry online: **www.cdc.gov/als**.

⇒ If your ALS symptoms, such as weakness, began less than 18 months ago and you are a US Citizen, please call **1-855-STOP-ALS** (1-855-786-7257) and leave a confidential message so we can call you back about this important research study.

⇒ In order to get started, you must:

- Agree to verbal screening and sign the informed consent form from Columbia University Medical Center and provide necessary information for the study.
- Start collecting and assembling your medical records, including your doctor's notes, blood tests, EMG reports, etc., for diagnosis confirmation and review. Call us for further guidance on how to gather this information.

Once you are enrolled...

⇒ We will have you collect and send urine and saliva specimens.

⇒ You will be followed every 6 months for the next 2 years via telephone interviews.

COLUMBIA UNIVERSITY MEDICAL CENTER

F.A.Q.s

Q: What are the benefits for me?

A: There are no direct benefits; however, your participation in this research study will be a great contribution for future patients. It will increase our understanding of the disease process so that we can truly arrest ALS.

Q: Are there any costs involved?

A: There are no costs for this research study other than your time and effort.

Q: What is the purpose of saliva sampling?

A: We can extract DNA if your saliva is correctly sampled. DNA is crucial to investigating underlying sensitivity or resistance to environmental exposures.

Q: What will the urine sample be used for?

A: The research team will measure markers of exposure in urine.

Q: You said that this research is based on extensive telephone interviews. How long does it take?

A: Our previous experience suggests several hours, broken into several shorter phone interviews.

Q: What is the potential impact of this research on ALS?

A: This is the first large epidemiologic research study at the national level in the USA. We need to study a large number of patients to identify environmental risk factors associated with ALS progression. This will be the first step in finding the cause and disease mechanisms of ALS.

Columbia University IRB
IRB-AAAM0206
IRB Approval Date: 05/06/2014
for use until: 01/12/2015

The current goals are to:

- ❑ Generate enough publicity to encourage newly diagnosed ALS patients to register and call Columbia University
- ❑ Determine if the telephone interview is sufficient in collecting all the needed information:
  - ➢ Develop telephone-based cognitive testing (n=30)
  - ➢ Diagnostic certainty through medical record information
  - ➢ Basic physical data: weight, FVC, etc.
- ❑ Obtain needed biosamples

Cognitive testing batteries to be used include the following:

- ❑ ALS Cognitive Behavioral Screen (ALS-CBS)
- ❑ ALS Cognitive Behavioral Subscale (ALS-CBS Caregiver Portion)
- ❑ Written Verbal Fluency Test (WVFT)
- ❑ Controlled Oral Word Association Test (COWAT)
- ❑ Frontal Behavioral Inventory (FBI-ALS)
- ❑ The Center for Neurologic Study-Lability Scale (CNS-LS)

- ❑ Telephone Interview for Cognitive Status (TICS)
- ❑ Mini-Mental State Examination (MMSE)

Regarding the pilot study to determine if telephone cognitive testing is equivalent to in-person testing, some tests were modified so they could be used over the phone. Patients with ALS (n=30) were randomly assigned to either in-person first or telephone first cognitive testing. 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 Food and Drug Administration (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 a secondary analyses. Sequence effects were also analyzed. The following table shows the results from equivalence testing across visit types:

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 enrollment to date, 73 individuals have been screened. Of those, 35 were enrolled and 9 are completing the consent process. The average age is 62, with a range of 50 through 78. In terms of gender, 71.4% are male and 28.6% are female. Regarding race, 91.4% of enrollees are White; 0% are African American, Asian, or Other; and race is not yet known for the 8.6% who have not yet completed their interviews. For ethnicity, 2.9% of enrollees are of Hispanic / Latino origin and is unknown for the 8.6% who have not yet completed interviews. Regarding enrollment source, 68.6% of enrollees are from the National ALS Registry, 11.4% are from the recruitment pamphlet, and 20% are CUMC patients. Average disease duration at the time of screening was 13.1 months with a range of 4 to 8 months for Subjects 1-3, 5, and 7-35. Subjects 4 and 6 were mistakenly enrolled into ARREST ALS despite their disease duration being greater than 18 months at the time of screening. Arrest enrollment by state is as follows:

ARREST ALS: Enrollment

Enrollment by State (#)

AL	0	GA	0	MD	1	NJ	7	SC	0
AK	1	HI	0	MA	3	NM	0	SD	0
AZ	1	ID	0	MI	0	NY	2	TN	0
AR	0	IL	1	MN	2	NC	1	TX	4
CA	2	IN	0	MS	0	ND	0	UT	0
CO	0	IA	0	MO	0	OH	1	VT	0
CT	2	KY	0	MT	0	OK	0	VA	1
DE	0	KS	1	NE	2	OR	1	WA	1
DC	0	LA	0	NV	0	PA	0	WV	0
FL	1	ME	0	NH	0	RI	0	WI	0
								WY	0

Discussion Points

In order to increase the number of minority participants, Dr. Kaye asked whether consideration had been given to trying to partner with Dr. Dan Newman at Henry Ford. They have a high percentage of African Americans at their clinic. Dr. Stacy Rudnicki in Arkansas also has a large number of African American participants.

Dr. Gubitz inquired as to why the enrollment criterion for progression after disease onset is limited to 18 months.

Dr. Mitsumoto replied that initially it was believed that environmental factors might impact an earlier stage more. The ALS COSMOS study used 18 months or less, so ARREST ALS cannot expand because the patient population has to be similar.

PALS Perspective on the Registry

Steven Reznick, PhD

PALS
Professor of Psychology, UNC Chapel Hill
Durham, North Carolina

Dr. Reznick expressed his appreciation for having been invited, and emphasized what a great experience it had been. He shared a thought that kept arising across much of the discussion. There has been a lot of focus on enrollment, but he has not heard as much about participation once someone is enrolled. He wondered about the slide showing that some people do not remember whether they are in the Registry. Also, as Dr. Brady mentioned, many people with ALS begin experiencing difficulties with cognitive processing and other problems. From Dr. Reznick's perspective, he has experienced some blockages in his participation in the registry. For example, in June he received two email messages telling him his password was about to expire and that he had not been on the website in a long time. That was weird because he goes on the site every time he is asked to do so. Nevertheless, he wanted to take care of that. He realized that this may be related to constraints pertaining to monitoring. One problem is that the email messages inviting him to take care of those problems did not have a link to the website. A person who was enrolled with the assistance of someone else may not have a direct link, or

have kept the information. Typing is very difficult for some people with ALS. In trying to update his password, he was blocked for 24 hours because he made two mistakes. The next morning, he went on too early and was blocked for another 24 hours. It would be beneficial to facilitate contact with the website and be less rigorous on some items. Another thing that surprised him was that when he signed up to be a patient, he was not asked to give a couple of contacts or caregivers with whom he could also give permission for someone to speak. It occurred to him that as his progression continues, he will reach a point where he may or may not be checking email in the same way or have the same functionality. It would seem appropriate at that point for an email to go to his wife, Donna, and his daughter, Leah regarding surveys, the details of his "end game," et cetera. He also thought there should be further discussion regarding incentives for participation, recognizing that there are IRB issues involved. It does not have to be monetary. The website is currently confusing with a lot of information that needs to be better-organized. But also, he would visit the website more if it had something that really attracted him to go see it such as a weekly report on recent findings about ALS. Patients should feel more invested in the studies and would likely be happy to play more of a role in selection of future studies. There are many topics he would like to help with, so building in efforts that help patients feel good about what they are doing would be beneficial. There has been a lot of discussion about biomarkers, and he would be glad to donate his blood to the Registry. He would also appreciate getting some information about his genes. If they get his blood, they should share something back with him. He was pleased that he and his fellow patients were invited to attend this meeting and share this type of perspective. He wondered as this moves forward if there is a way to involve patients in study selection, reviewing and offering input on surveys before they are submitted, and advising on the marketing changes. Patients want this registry to work really well and would be glad to help.

Discussion Points

Dr. Mehta indicated that someone is available Monday through Friday from 8:30 to 5:30, but thought perhaps the phone number needs to be made more prominently available for the password reset.

Dr. Reznick indicated that there was a phone number and email address, but there is no link to click and go to the site. It would also be beneficial not to have to reset the password so often.

Dr. Mehta indicated that they would review the information sent out to PALS to make sure that information is included. Unfortunately, the password reset requirement is a security issue.

While Dr. Reznick agreed that for one's bank account that might matter, it seemed the standards could be adjusted for the website.

Dr. Horton said this had already been done. He emphasized that the Registry was not setting the constraints. It falls under the umbrella of CDC security and internet technology, and they must abide by the rules. This concern was presented to the CDC IT representatives shortly after the Registry was launched. At that time, the reset requirement was every 60 days. Since then, the time has been extended to 180 days. As far as he knows, no other program has achieved this agreement to extend it this far. They clearly understand the constraints and do their best to address these issues where possible.

Ted Harada

Patient Advocate / National Trustee
ALS Association, Georgia Chapter
Atlanta, Georgia

Mr. Harada indicated that this was his third year attending the Annual ALS Meeting, and that every year the information becomes more robust. He stressed that when he suggested opportunities for improvement, he was not being negative. In some ways, he thought they were victims of their own self-promotion but lacked a story of success. Every year, Drs. Mehta and Horton go to DC to encourage people to go tell their Congressman what is needed. He does not think that the results have been made relevant to PALS at this point. Obviously, this is relevant to researchers. But to patients who are constantly asking for money, it does not seem relevant to them. They do not understand what is in it for them. Part of that will be the storytelling, which has been discussed for the last few years.

Best practices were glossed over to some extent the previous day. A best practice is not a person who enrolled everyone in one state or another. It is a great story, and certainly a compelling story, but if it is not replicable, it is certainly not a best practice. Some good information has been disseminated in Georgia about what works and what does not work, and that outlined what is good and what must be done. There need to be deliverables on best practices and follow-ups in order to assemble concrete best practices that will roll down to chapter and regional levels. The chapters have an obligation not only to their patients, but also as business partners with CDC. ALS and MDA are paid as associations to promote the Registry, so he would think they want to understand the results of that investment. Perhaps the funds should be given to a marketing firm. If nothing comes from a best practice, and a measurement, and a follow-up then they have done nothing. When all is said and done, more got said than done.

Grassroots level meetings are also important as well. Local chapter and regional representatives must get together, and must be tracked. Some of the tools created seem to be used only once. All of the videos that were created took two years to get approved and released. Someone is diagnosed with ALS every 90 minutes, so there is a whole new audience non-stop so these tools need to be created. If they believe radio is a good investment, why do they make it a one-shot deal? He heard Drs. Mitsumoto and Brady talk about telephonic interviews and mailing surveys. Everyone has acknowledged for several years that there is a problem in rural areas with internet access for numerous reasons, but the problem just seems to have been accepted. It is likely that many people who do not have internet access are also not going to a clinic. While he does not know the cost or IRB or OMB rules, and can callously say that he does not really care, perhaps telephonic opportunities should be scheduled twice a month. Perhaps there is a form that can be mailed out. If they want this to be robust and be a tool for researchers, there must be outreach to ALS patients where they are. Sign-up day events in particular areas would be beneficial. It is not clear to him what they are measuring. PALS will give nonstop information and time on Capitol Hill, but something must be given back to them from the Registry as well.

Rebecca "Becky" Kidd

PALS / Emory ALS Clinic
Avondale, Georgia

Ms. Kidd expressed appreciation for being invited again this year. Last year, she was inspired by and reached a new level of understanding about the Registry and its potential and power. She spent a great deal of time this year working with Mr. Tessaro, and in trying to find ways to increase the Registry's capabilities and functions. That progress is increasingly visible. She thanked everyone for the amazing efforts they have put in this year on behalf of herself, all of her PALS, and their families. Last year, she felt things were pretty open-ended. This year, it felt less that way. Many of the suggestions made last year have, in fact, been acted on. She loves the new marketing and communications firm. They are amazing. She saw in almost every presentation a start at measures and score cards to try to show baseline and progress. She expressed gratitude for that as well.

She has been thinking about her call to arms or takeaway for this year, so she said she was somewhat emotional. This is her fourth year living with ALS, and not much has changed. Last year, she told everyone at the meeting that those living with ALS, except for an extremely, extremely small percentage who are benefitting from a clinical trial, have absolutely nothing to go on day-by-day except hope. Living with hope versus false hope, aside from the physical battle of living with ALS every day, there is an enormous emotional battle, particularly for someone who is a mom or dad with ALS because they also have to watch this experience through their child's eyes and that is tough. But, this meeting refilled her little bottle of hope that is sitting right next to her bottle of RILUTEK® in her medicine cabinet, for which she expressed gratitude. Her call to arms this year would be taking everything that was discussed and moving with a real sense of urgency. She knows it is there, but it would be so amazing if this organization within this big federal bureaucracy could be known as the organization that is just not going to put up with any "bullshit," that cares about the people living with ALS, and is just going to push and push and push. She is in year four. She does not know how much longer she has. God has been very good to her. She is able to nag her son when he is annoying her and hug him when he is not annoying her. She has been lucky on a lot of levels, but every year that she comes to this meeting, she has had to say good-bye to some very special people, one she just learned of that morning, and she wants to stop doing that. She is pragmatic enough to know that that is probably not going to happen in her experience, in her journey with this disease, but they have to make that go away for the people behind them. She knows that they can, and she was getting a sense that that would start happening.

She reiterated that her call to arms this year was that sense of urgency, which she knew they all had, but also a call for empathy. She called for those who did not participate in the Ice Bucket Challenge to do it in August, and encouraged them to look at the work by Sarah Cogninese called "What Would You Give?" She is an amazing PAL in San Francisco. She is asking people who do not have ALS to give up something for one day, such as feeding themselves or walking, to get a sense of empathy of what it is like to live with this disease. Stephen King could not write a better horror novel than what it is like to live with ALS, and to still have no cure and no treatment. She stressed that she did not want to end this on a negative note, because she was extremely encouraged by what she had seen and heard during this meeting. A pragmatic plan of action that builds upon the great work of this past year must be developed immediately with measurable short-, medium-, and long-term goals and progress reports in order to offer enthusiasm and real hope. That plan needs to be messaged so that PALS will have incentive to come in, to learn, to know, and to participate.

Edward Tessaro

Retired/Philanthropy
MDA for ALS / St. Jude's Hospital / CF
Alpharetta, Georgia

Mr. Tessaro said that his number one takeaway was that when he went home to have dinner with his wife, who likely would not be able to remember what he said to her the previous day. He brought up Dr. Brady, who remembered something he said 12 months ago and gave him new armaments in his domestic life. He said he had three things on his mind having to do with the Registry: selling it, sharing it, and thanking ATSDR for it. Everyone feels ALS in a different way. In his case, in his 7th year, he and his wife have decided that the best work he can do is raise money for science to support it. So, they have raised about $5 million over six years. He does not sell to friends and family. He is a corporate guy who goes after businesses under the premise of being a great corporate citizen. When he is talking about ALS to Coca-Cola or Choate Construction in Atlanta, his message is, "Here's what the population is like. Here's how random it is. Here's how horrific it is. But, look at what is happening with 22 clinical trials. This unbelievable Registry is what you're supporting." He has a hard time talking about the Registry like that, because he cannot really give it flesh and bones. He needs something that will help ALS indirectly by allowing him to raise more money. He needs something usable. Even with the new public relations company, no one could pick two flatter words than "surveillance" or "Registry" in the American vocabulary. How do you sell surveillance, particularly today? The name is "Registry," but the marketing campaign has to make more sense than that. Sixty years ago, there was the slogan "Uncle Sam Wants You." They really have to market this idea about the Registry to get people out of their seats to want to self-register. They must sell self-registration from a citizen standpoint, and the benefit of the Registry from the corporate standpoint. He wants people to know where the money is going. He is a clinical trial patient, so he has a lot to talk about. But, this is about the Registry. He wants to garner funding that will indirectly help what they are all doing.

In terms of the sharing point, there have been some local successes assembling ALSA and MDA for fundraising activities. He welcomes that because he is a big believer that silos exist everywhere, even when it is said that they do not. Everybody wants the research recognition for what they are doing even though they say, "We'll share. This is available." He encouraged everyone to do as much as possible to bring everyone together. There are many good organizations, but he does not believe they share very well. Lastly, he thanked everyone. Gratitude is a big part of how his life has changed in seven years. This has nothing to do with the Registry. He put it on the back of his boat the year after he was diagnosed. He has come, as an individual, to love and feel and receive love more as a result of the fact that he has so much less life than others. He challenged them that his life would perhaps be fuller than theirs will. That may sound pretentious, but it is an old cliché. He is grateful for this much deeper perspective that he has gained on life as a result of having less of it. Interacting with everyone at this meeting and understanding that they are devoting their lives to something that affects only 30,000 people, he thanked them all from the bottom of his heart. Who else is going to do this unsung hero type of work? They just need to name it something different and get a little sexy on the marketing side, and they will get more people thanking them for a wildly successful Registry.

Recommendations and Strategies for Strengthening the Registry

Wendy E. Kaye, PhD
Senior Epidemiologist
McKing Consulting Corporation

Robert Kingon, MPA, Facilitator
Carter Consulting, Inc.

Dr. Kaye reported that last year, Tom Hicks spent a lot of time reading the meeting transcripts to sort out everyone's recommendations. This took a lot of time and interpretation. This year, they made a list of categorized recommendations and a determined a subset of those about which they would like to have discussion and perhaps develop action items, set timeframes, and identify volunteers to work on those items. Mr. Kingon first presented the list of categories and recommendations, and the following action steps were articulated and discussed during this session:

- ❑ Provide enrollment data at a smaller geographic level than the states; try to replicate the pilot effort in Georgia to provide data by health districts in other states
- ❑ Could standard procedures be developed for local chapters and clinic staff (conducting follow-up phone calls, reaching out directly to ALS patients, et cetera)?
- ❑ Develop better metrics to measure progress in increasing enrollment and maybe participation
- ❑ Provide one-on-one support to help PALS enroll:
  - ➢ Increase access for people without internet
  - ➢ Help people with less internet familiarity
  - ➢ Help people with physical limitations
- ❑ Provide more information in the form of infographics, such as research funded by the Registry
- ❑ Produce short and easy to read meeting summaries
- ❑ Develop a 5-year plan for moving the Registry forward, including enrollment and participation goals

Discussion Points

Ms. Kidd: Replicating the pilot effort in Georgia would be a good idea if it produces more data.

Mr. Wildman: We talked about it yesterday. That is critical to get more data. It allows us to measure what we are doing and if we are having an effect and allows us to target. That would be huge if we could do that in other states in addition to Georgia. That would be huge.

Ms. Embro: I think specifically if it is targeted to the under-enrolled states, but where else could we start?

Dr. Kasarskis: I have an obvious question: Is there a standard definition from state-to-state of what a "health district" is? I suspect no.

Dr. Kaye: Every state has defined health districts.

Dr. Kasarskis: There is? Okay, defined health districts, but how did they define it? How do they break them up? Are the definitions the same from one to another, or is it a matter of political convenience?

Mr. Wildman: Wendy and I had a discussion about this yesterday, and I don't think it matters from state-to-state for marketing, a targeted enrollment strategy, or a promotion strategy. I don't think it matters if how it is defined from state-to-state is different or the same. It doesn't matter. It just allows you, in that particular state, to focus your outreach whether the health district was defined as X, Y, Z in this state, it doesn't really matter. As long as you can in some way quantify or identify where the cases are, whether it's in the health district or the Congressional district. If you can somehow identify that, it will help us target our outreach, and help us measure the effect of our outreach as well.

Dr. Horton: I would totally agree with that. Right now, the way we're giving data back is at the state level, letting ALSA and MDA know which states are good recruiters and which states are lacking. But, if we drill down below the state level, we can see, like what Ted did, you can see what pockets of the state we have gaps in. You know, you can set a course and target those specific areas. So, I think this is also very critical.

Mr. Harada: I think that as well, and maybe I need to clarify what I meant yesterday, again, the goal is to make that clear as well so that when you're giving the information, you need to be able to measure it. Again that 80% number I talked about yesterday, maybe I wasn't as clear with it. So, they have an expectation. They are telling us we're under-enrolled or improperly enrolled based on their expectation of what they've seen from CMS, et cetera. So, we know they're missing 22%. But nonetheless, I know we can't give them the number they need to get to, but we need to give them a percentage to get to. So, you know, you have enrolled 80%, and I'm just throwing 80 out there. You guys figure that number out. You're a lot smarter than me. But, 80% of the expected patients, whatever that is, because otherwise, it's just fluff. It's just pie in the sky. We've really got to put something substantial to it.

Mr. Wildman: I completely agree, and I think if you have this level of data, you will be able to measure that. Right now, we can't measure that. We have no idea whether we're getting 50%, 40%, or 80%. We have no idea whether we're doing that. This type of data will allow us to try to measure that so we not only target what we're doing and where we're doing it, but measuring the effect of that and also setting goals, as you said. I mean, that's critical.

Mr. Harada: It leads to accountability.

Dr. Kaye: I think we're saying that we should move forward with getting data at a lower level than states to being able to do better marketing and recruitment, and if something should happen that would make it so that OMB was no longer an issue, we could modify it at that time.

Mr. Harada: But, in the meantime, we don't need a law passed to get health district information.

Mr. Kingon: Who could take the lead now on developing sub-state data?

Dr. Kaye: Only ATSDR.

Dr. Mehta: So the premise is, I mean, I think what you're asking is so we have the data right now, and so the next step is talking to ALSA or MDA and figuring out what state to target next. At that point, we can go ahead and use our resources to look at the data much more closely and go from there. So, I think that's what you're question is. So, it's ourselves as well as the associations.

Dr. Horton: But I think before we can get there, we need some kind of standardized approach so that not every state is going rogue and doing their own thing. If we have some kind of standardized approach, that will be much better.

Dr. Kasarskis: So, I'm interested in getting back to the first bullet point, because I think this is kind of where we started. I mean, in the meantime we can schedule a cruise for Barack Obama, the Pope, Boehner, and McCain, who solved global warming. It will probably maybe happen before we change OMB. But the first bullet point, I think there's a question that we could put to ATSDR, "Do you folks have the capability of analyzing the existing data on the basis of a health district, and putting out those results to the community?" Because the second step will be then to take that data . . .

Dr. Kaye: We're not allowed.

Dr. Kasarskis: I mean, you could put out a report, can you not, that says, "We have a certain prevalence?"

Dr. Kaye: No. That's one of the things that OMB has said we can't do. We can't go below the state level.

Dr. Mehta: The way we got around that is because in the pilot project, we didn't give specific numbers. We simply said, "Look at these target areas." The premise with a new pilot project is we would simply say, if it's California, "We need efforts in San Joaquin Valley." So, we can simply do it that way by not giving out hard numbers, but simply saying target your work in this particular area. So, that's how we got around that right there.

Ms. Embro: Right, so just to expand on that a little bit, what we did once we got the health districts, we overlaid that on our existing map of patients that were registered with our chapter. So, we didn't actually capture new patients or unreached patients, but we looked at the patients we already had registered with our association and identified those that were not currently registered with the CDC ALS Registry and targeted those.

Dr. Kasarskis: So, what you're saying is we have at least the first attempt at a process of how to do this. That's right. So, you're saying that basically, that process could be applied nationwide.

Ms. Embro: It could be replicated with MDA databases, with ALS databases . . .

Dr. Kasarskis: With all of the existing constraints, it can be done in that fashion.

Dr. Horton: But, it would have to be a sustained thing, not a "one and done." People are diagnosed every day, so is there commitment at the chapter level to do something like this? Obviously, ATSDR couldn't do it alone. But, I mean, we could essentially provide data. We would provide data, but it would be up to the chapters . . .

Dr. Kasarskis: So, I think one of the action items coming out of this meeting can be a detailed recipe of how Step 1 is to do X, Step 2 is to do X, Step 3 is to do X, then it's a matter of finding out who is going to do it at each state level.

Mr. Kingon: So, it could be a process and procedure that's laid, and then select states.

Dr. Kasarskis: I had a colleague that was in the Chemistry Department and, of course, he always had monkey sheets, meaning the process was debugged to the level that a monkey could do it, which was your average graduate student. So, that's what I think we are asking for. If we have one example of Georgia that is broken down on this one unit rather than everyone imagining what might have happened, this is a statement of fact. So, I mean, you should be able to put out the recipe.

Unknown: I can't help but think that there are four different types of subjects that we're talking about: 1) those that are internet users and those that are not? internet users, and not necessarily those that don't have internet access, but just don't use the internet for whatever reason (they don't have it, they can't use it, they're not interested in using it; 2) those that go to an ALS clinic or don't go to an ALS clinic; and then we can subdivide it further 3) those that are interested in research and those not interested in research; and then maybe 4) a group of people who are and are not trusting of the government. And so, as we talk about looking at different geographic regions, that's one way to think about: How do we increase engagement in the Registry? Or maybe we rename the ALS Treatment and Cures Initiative. I don't know. But, maybe we also need to think about what types of patients there are that we are and are not capturing and can we create engagement initiatives for them. And I don't know if you have the ability, I mean, obviously you guys capture Social Security Numbers (SSNs) and have contact information for people that you think have ALS through the algorithms. Is there any ability to contact people who, maybe OMB would be needing to approve this, but to contact people and say, "Are you aware of this initiative?" and just do some sort of root cause analysis and talk to them and figure out, "If you know about it, why have you registered? Why haven't you registered?" That may give some insight into what can be done to engage people in the future.

Dr. Horton: So, just a couple of things, and I'm sure Wendy is probably chomping at the bit on this. We only have contact information for the people who register through the portal. So, the people that we identify through the national dataset, we don't have their phone number, email address, or anything like that. Having to go back and contact people for whatever specific reason, it wouldn't necessarily require OMB approval I don't think, but it would require IRB approval. Before we can do anything along those lines, we have to go to IRB with a clear objective and say, "This is what we want to do and why." So, it's not saying that we couldn't do that, but you know.

Dr. Kaye: No, you can't do it. Your CMS and VHA agreement do not allow contact.

Mr. Harada: I'm thinking of your flipchart yesterday with "keeping your eye on the ball." So, I agree, I'd like to finish up point one and replicate the effort. So, I think we're all in agreement that we can do a state-by-state layout by health districts. Is that correct, Wendy?

Dr. Kaye: Or something similar.

Mr. Harada: Two, I think we heard from Sarah and I'm pretty sure that I would agree, that we can, at a chapter level, at both the MDA and ALSA, we can take that information and use it to drill down and identify—taking the process that we did already in Georgia plus some other best

practices out there, combine it into a replicable process that can be done over and over and over again—taking, you know, a process flowchart. You know, you have turnover, here's a new person, here's the flowchart, make it happen. So, that can be done as well. Three, my suggestion is now, you know, Kevin made the point that you guys are going to buy into it and keep going because you have brand new patients over and over again. Okay, well, that comes back into that goal, that expectation. Again, let's throw out a number of 80%. If they know the expectation, it's as you grow, you're going to fall behind 80% if you're not continuing to do the process. So, the minute you get below 80% of expectations, you know that in your process there's a breakdown someplace. So, I think that answers Kevin's question about continuing to do it, because you're going to be held accountable to that 80%. I'm not sure what's left, but it seems to me that changing the laws and other things are important down the road, but in the meantime, we can do something substantial that can have an immediate impact.

Mr. Kingon: So you're saying it would be the two associations getting together to identify which states . . .

Mr. Gibson: I'm still confused. What are you providing? I thought it was just the chapter putting this together. So, what are you providing?

Dr. Kaye: What I gave Ted was data that I recoded for all of the enrollment data from 2010 through 2013 to the health district level. Then I could see in Georgia how the districts did because I had the population data, so I could see where the under-reporting areas were. That's what I told Ted, you know, Metro Atlanta looks pretty good, and actually, the sort of spread around Metro Atlanta looks pretty good. But when you get in these areas, and one of them was in Augusta, around Augusta, one of them is really close to Macon, why is that?

Dr. Kasarskis: So, Wendy, how did you do this? Because you just told me that was illegal, that you couldn't get down below the state level.

Dr. Kaye: No, what I said was that I can't give you numbers. I didn't give them numbers. I gave them qualitative data saying, "You're below in this area." I didn't say, "You have 10 people."

Dr. Kasarskis: That's good output.

Ms. Embro: Right. This district or that district. My biggest frustration in two years has been why am I under-enrolled? You just tell me my state is under-enrolled. Where's the data to prove it. What am I measured against, you know? I'm measured against prevalence or incidence rate, but that doesn't necessarily match up with who I have on my chapter registry, so how can I identify where I need to target my efforts in, you know, making stronger pushes with the patient base that is known to register with CDC? That information was very helpful, and quite surprising. Two districts where two of our three clinics are located are under-enrolled, so now we know we've got to do some more education with clinic staff and have a better relationship with that information.

Mr. Kingon: Wendy, can you provide that data to six other states?

Dr. Kaye: Oh, six, yes. I mean, 50 would be ideal . . .

Mr. Kingon: But, it seems to me that's where we need to start is with some subset.

Mr. Gibson: We could do six. We couldn't do 50. The challenge is, well, I call it a best practice. We couldn't take it to every state because the chapters don't have the bandwidth to do that, and we also can't force the chapters to do things. We're a federated model.

Mr. Goldstein: If I could just add, there are a lot of other ALS organizations that aren't in this room, like we haven't talked about Les Turner, which does an amazing job in Chicago. You know, as Kit said, NGOs can help. Reach out to this great organization that Steve helped set up called "Collaboration for a Cure." Why not make participating in and promoting this . . .

Mr. Gibson: That could be one of those things that our task force could look at. Absolutely.

Mr. Goldstein: Right, and extend that, but I think we just have to keep in the back of our minds that there are dozens of other organizations.

Mr. Kingon: Who will take the lead in kind of pulling this collaboration together to do a pilot?

Mr. Gibson: Kris and I will take the lead, and Rob who was the first person on our task force (simultaneous conversation).

Mr. Goldstein: I want to make sure that this gets spoken about on the 12th. It should be an agenda item for our meeting on the 12th.

Mr. Kingon: Okay, so we know who is going to take the lead, we know it is going to be a pilot of six, and we are going to develop some standard, replicable procedures and policies. Wendy will provide what they need.

Dr. Mitsumoto: Also, qualitative data for trouble spots or whatever. But also, it would be helpful to show the reverse, the very good spots. In Alabama, there is very good enrollment. I think that information is also very encouraging and of intangible benefit, so those people are more encouraged and more are doing the things. So, I think both types of information is equally important.

Mr. Wildman: Wendy, one other question about what you'll provide (microphone squealing, not sure this is everything he said). Clearly, enrollment and completion of risk factor surveys are important. Can we get information along the same lines in the same fashion about whether people in a particular state have completed the risk factor surveys?

Dr. Kaye: With a little bit of manipulation, we could probably figure out what percentage of people who registered in a particular state also took surveys if that would be helpful. If you did want to know, of the people in my state, did they take—in reality, people in my opinion fall into two categories: takers and non-takers. The takers take everything. The non-takers don't take anything. We don't have very many where somebody took one and then didn't do anything else. You know, they took six, they took seven, they took all 17. It's whatever was available when they started doing it. So, just knowing that somebody took surveys, at least one, might be helpful.

Dr. Horton: But it seems like before we get to that point, we need to figure out where the gaps are in the particular states.

Mr. Kingon: Alright, let's move on to the second bullet—the second recommendation. Could standard procedures be developed for local chapter and clinic staff, such as conducting follow-up phone calls, reaching out directly to ALS patients?

Mr. Wildman: We actually have checklists for chapters of what they can do both to promote the Registry and to help enroll in the Registry, and that is something that's part of the task force so that we can work with other ALS organizations to make sure that that type of information is shared across the community.

Dr. Kaye: It's just not one. It's the number of times you're allowed to call somebody from an IRB perspective—how many times can you call before it is considered to be harassment. I mean, you can't get to the harassment stage. I think we can agree that you can't call them 20 times.

Mr. Harada: But, the chapters call for other reasons and while they're on the phone, "Oh, by the way . . ."

Dr. Kaye: That's different.

Mr. Harada: We already have touchpoints. Within that, we should be making and sharing the Patient Services Committee. You know, I know there are touchpoints that exist that we've said, "Okay, the process is that we want to make sure we have a contact with the patient every 90 days, et cetera, et cetera." That could be in the conversation. Again, you have your little process. When I get on the phone, these are the questions I need to ask. One of those questions is, "Have you enrolled? Have you been on the Registry recently?" It gets incorporated into the behavior. Make it muscle memory so that it's just one of the things that you do over and over again. You're not calling specifically about the Registry. You're calling because you're an ALS patient being serviced by an ALS organization and you have a touchpoint.

Mr. Kingon: I see people shaking their heads in agreement to that.

Mr. Goldstein: I would just add, Ted, to your point earlier about selling, if we inform that army of people making those phone calls of selling points to start the conversation with, you know, you're offering before you make an ask. So, I think that's important that that gets built into the best practices module that you're talking about putting together.

Mr. Kingon: Patrick and Steve, this falls right into your responsibilities, correct?

Mr. Gibson: Number one? Yeah, we already have it, so it's, I mean . . .

Mr. Wildman: It's just a matter of working with the task force that Kris and Steve will lead and incorporating something into that.

Mr. Kingon: Third bullet: Develop better metrics to measure progress in increasing enrollment and maybe, picking up on Steve this morning, participation.

Mr. Gibson: I'm all for metrics. I don't want them to be just on enrollment primarily based on what Ted said, on what Dr. Bowser said. We will never get 100% enrollment. More importantly, this Registry has always been about two things: being a strong research engine and finding out about risk factors. So, you've got to have something there that is part of that besides

enrollment. You know, how many companies are using the research tool? There's got to be something else. It can't just be focused on enrollment.

Dr. Traynor: It's also dangerous a little bit from the scientific perspective, because if you see a region where enrollment is low and then you sort of come in and you say, "Okay, we're going to increase enrollment until we hit this level," you know, now you're entering into this sort of group think where every region is going to have the same level of enrollment, and the same incidence, and the same prevalence. That kind of can lead to problems down the road when you're trying to interpret the data. You know, you have to be very careful not to set metrics whereby you say, "We're going to increase enrollment here until we hit such and such an incidence rate."

Mr. Harada: That's never been discussed. What's been discussed is the CDC understands what, based on the numbers they already have, what the expectation is. Are you X percent of that expectation? The expectation isn't going to be the same in every health district. So, you're trying to capture a percentage at the minimum of whatever. It's not going to be like 20 people every place you go. If they think based on the data they already have that the State of Georgia should have 500 people across the board, they're not going to tell us it's 500. But, the way we could go from red to green is where across the board we've got at least 80% of the expectation. In Alabama, it might be 300 people they should get, so for them to get to 80%, they could get 240 people across the state. So, it's about the expectation. It's not going to be we've got 20 people in every health district. You're not trying to prove that the incident rate is 2 per 100,000. That's not necessarily what you're trying to do.

Mr. Wildman: I agree with you. It definitely has to be more than just enrollment. But, I think Bryan what you're saying, is prevalence is going to be different across states, from state-to-state.

Mr. Goldstein: Wendy, you said there are survey takers and those that don't take them. There is an entire body of research outside of the ALS world on getting people to actually take surveys online. You know, so I think from just a metric standpoint, trying to improve in trying to get more people to take those surveys—I don't know the level. Maybe you can tell us the stats on it. But, going from 40% to 60% or whatever it is, is another metric that we can go to, to finish the thought from a selling perspective that collectively, these US taxpayer dollars have been spent to increase this amount of data—not just getting people signed up, but getting them to provide that rich data that the scientists need.

Dr. Kaye: I will say that the percentage of people who are taking surveys has increased. It's over 50% who take at least one. When we first started, it was into the 30% range. So, I will say people have done a really good job of getting the word out that the Registry is more than just signing up. Obviously, for those people who came into the Registry in 2010, they may no longer be available to go back and do surveys even if they would have been interested if they didn't do it then. I think it's important to see how we do moving forward.

Mr. Goldstein: I think it helps to set those metrics in a realistic kind of consumer way. There are really great companies. One of them is PatientsLikeMe® that does this for a living. You know, they may be able to provide CDC some guidance on what would be an industry best standard to have people compete these types of things in ALS. They have a huge database of ALS patients, and they have great experience in incentivizing people to provide this information.

Dr. Kaye: The scientific standard is 80% or better. Would you agree, Bryan? You want 80% or more people to do your survey.

Dr. Traynor: Yes.

Dr. Kaye: The new standard is lower, especially with random digit dialing (RDD), if you get in the 30% range, you're doing well. So, you're actually not so bad.

Dr. Reznick: Having people with ALS participate, was that idea that I mentioned about having a potential proxy, is that feasible?

Dr. Kaye: The IRB protocol allows for people to have a caregiver or somebody with them help them do it. At events, if ATSDR has staff at events, we also have permission to help people do them at events. We don't have the capacity right now to do that over the phone, and it's a little bit more difficult because of the consenting issues because we're not physically there with them.

Dr. Reznick: But the next point on helping enroll, if there is a way to add a potential proxy, it does feel like that could increase participation and enrollment. I'm saying someone to contact if the patient is no longer able to do it yourself, including receiving an invitation yourself, that there's a potential proxy who could make you aware of it. Is that possible?

Dr. Horton: As long as whoever's helping is sitting next to the patient and walking them through the consent form. We don't want a proxy to sit there and try to answer it on behalf of that person who is not sitting there with them, because these are very detailed surveys and that proxy may not know every piece of information that the patient would know. If the patient has manual dexterity issues and they can't do it, then yes, we want a proxy there to help them out.

Dr. Reznick: Okay, but I'm saying in the long-run, when they register, if there is the name of someone else who could be contacted if we're not able to reach them.

Dr. Horton: Yes, we'd have to go to IRB and get IRB approval to contact that proxy person who would help the patient. That's not to say we can't do it.

Dr. Kaye: I have this question for Steve. What if I allowed you to have more than one email address so that the email went to you and someone else?

Dr. Reznick: Yes, that would help, too.

Dr. Kaye: Well, no, but I mean, it wouldn't be a personalized letter because I wouldn't say, "Hey, we haven't been able to get ahold of Steve." But, it would be you giving us permission to provide the same email to someone else by providing two email addresses.

Dr. Reznick: Yes, that would work and Dawn would say to me, "Did you see the survey?" But also someday when I'm not checking emails, she would say, "There's a survey. Do you want to fill it out?" Again, as I mentioned before, someday you might want information about how my "end-game" took place.

Mr. Harada: Great idea.

Mr. Kingon: You can do that.

Dr. Kaye: That actually is a much easier thing to do, because we are already getting email addresses and so it's sort of a minor modification.

Dr. Gubitz: In terms of the deliverables, the surveys are a key component of the registry and that's going to be the research tool. So, on your earlier slide yesterday, you had a number of how many surveys you had already completed by patients. I think that's a really positive and strong message. So, is this front and center in your messages as a highlight? It's not only that you have captured so many patients, but now you have X number of risk factor surveys available that will serve as research tools, and by the way, they are already being utilized by X number of scientists. I'm actually not sure if the data from the surveys is already available upon requests from scientists. But, then we should also message when the data release is planned, because that's also a milestone that you can highlight and that's a deliverable.

Dr. Horton: That's one of the big things on our plate right now—developing that platform so that we can allow researchers to request the data for analyses. Hopefully in 2016 we can do that.

Dr. Gubitz: That's the true value.

Dr. Kaye: I have a question for the PALS in the room. So, one idea that we had was that on your individual page where you can take surveys, you could have a little thermometer so that you could see, like charities getting money, as you did surveys, it would get colored in so you know your progress in completing all 17. Does that sound like something that would be helpful or would be useful or would encourage people?

Dr. Reznick: We're the kind of people that are here. We did all of the surveys as soon as we got them. But, I do think that something like that—in fact, that was why I was contacted about one of the surveys that I was not allowed to participate in because I'm not a woman was showing as an uncompleted survey, so I requested that it be changed.

Mr. Goldstein: Wendy, are there rules that limit the amount of outreach the Registry can do to those people that haven't completed the surveys?

Dr. Kaye: Yes. It is regulated by the IRB.

Mr. Goldstein: So, could you tell me those rules? Are you allowed to email them once, twice? What's the limit?

Dr. Kaye: Once every 6 months for 2 years.

Mr. Goldstein: Is there a way to modify those rules to maybe once every 3 months for over 2 years?

Dr. Kaye: Yes, they can be modified. But, whether the IRB would consider that harassment or not, that's something else. This is voluntary. Everybody has the right to do it or not do it.

Mr. Goldstein: Just an idea. In the marketing world, the more times you get your message across the better. If you hit somebody every 6 months with ALS, it's a rapidly progressing disease. You could have caught them on a really bad day and they deleted everything, so they're not going to hear about it for another 6 months. So, I'm just offering a suggestion.

Dr. Kaye: I think you might be able to make an argument that when somebody first enrolls, you do it every three months for, you know, the first 6 months or 9 months and then you go to every 6 months or something like that.

Mr. Goldstein: To help get this past IRB, you could do some testing perhaps, you know, taking a group of 50 people that don't fill them out in the first 6 months and hit them up every 2 months, another group where you only hit them up every 6 months, and make the case that maybe some additional outreach will increase the number of people completing the surveys, which just increases the scientific value of the surveys to the scientists down the road.

Dr. Mehta: Another thing is if we collect addresses in the future, we could send them a postcard. I mean, emails are only as effective as your spam folder or if you read it. If we collect addresses in the future, a nice little postcard, "Hey. How are you? We have this and that." I mean the premise is like what Rob is saying, you know, constant contact is so important. These days, websites measure not the hits or page views, but how long you are on the website itself. That's what's important. So, if you just go to the Registry, "one and done, read something and you're gone, that's 5 to 10 seconds, maybe a minute, but these big companies, they measure the time you spent on their website reading the content.

Dr. Kaye: You could have other names of contacts with an email address, but you can't send postcards. That violates confidentiality.

Mr. Gibson: So, to follow up on Rob's comment about what OMB can and can't do, and after reading last night the 139 Tweets from when I left my hotel room until I got back to my hotel room from one disgruntled advocate, it would be very helpful to have expanded FAQs that say what we can and can't do. Because the same sort of things that were Tweeted last night about giving money to incentivize people to enroll, I mean, that needs to be posted somewhere so when the next disgruntled advocate has a bad day, we can shoot a link that shows this is the rule. Because what's starting to happen is it looks like none of us who are working hard on this Registry have brains. I will just share with communication folks, I really wish we could give them the package of information for out toolkit that we gave IRB and how much was edited on what we couldn't say about the Registry, why it's important, some of the metrics you want to use, et cetera. That stuff, you know, we're kind of like in this little hamster wheel of trying to respond to these same things over and over again. If this information was on the website, "unfortunately this is not allowed," that would settle that. A list of limitations.

Mr. Wildman: I just wanted to pick up on something that Amelie said in terms of the messaging, and what we've been putting a huge focus on when talking to members of Congress and others, and that's the value of the registry in terms of research whether it's papers projects, projects funded, whether it's risk factor surveys, whether it's the biorepository. That's the big selling point. That was one of the concerns quite frankly up front from Congress when we were first pursuing it was that Congress was saying, "We don't want something that just sits out there and doesn't do anything." The fact that the Registry is now producing things and producing results and moving forward on the research side of things, that's huge and that's a huge selling point regardless of who our constituency is, whether we're talking to people with ALS, the Hill, or the research community. Those are key points.

Diane: This is way too much. I'm a person who wouldn't fill out 17 surveys. If you're trying to reach people like me who give up after a survey and say this is way too much, I think it would be helpful to explain that there are 17 surveys, and this is what they do, and this is why they're important. Many people like me would just bail out. So, something that would help people understand what the value of those surveys is.

Dr. Reznick: Seeing the whole stack of all those surveys might not be a great incentive for new enrollees to get rolling.

Mr. Harada: Wendy, you said you can communicate every 6 months for the first 2 years. What happens after 2 years? I mean, I understand that a greater portion of the population may be deceased, but there's also others that aren't.

Dr. Kaye: You have to put a limit on these things. I mean, if you felt that we should ask for up to 3 years, we could ask for that modification. But, just given the number of emails we have that come back as being bad when ATSDR sends a notification, you know, no longer in use or whatever, I'm not sure that using email addresses after a certain period of time would be very good.

Mr. Harada: I guess my point is, and you know, you heard Becky say 4 years, isn't that what you said? You know, 4 years, I mean, is there something to be learned from patients who are around longer?

Dr. Kaye: Definitely.

Mr. Kingon: Okay, so we started off by measuring progress and increasing enrollment, and we've pretty much said that enrollment is not the only thing we need to measure. We talked about participation. I think we've captured a number of good ideas about increasing participating, so I think let's move on. So, the last point "Provide one-on-one support to help PALS enroll. Increase access for people without internet. Help people with less internet familiarity. Help people with physical limitations."

Mr. Harada: I heard Wendy say you couldn't do it telephonically right now because there are too many challenges. So, what about—I think a couple of you mentioned mailings that you did do some mailings to the house. So, you know, is that a possibility to send the whole questionnaires?

Dr. Kaye: No. At this time the questionnaire is not designed as a paper form and we do not have permission to distribute it in that way.

Mr. Wildman: I think some of this falls under number one, because if you can target more, then you'll know whether a chapter conducts home visits, and whether there is a support group in the area. I mean, we provide tablets to all of our chapters to go out and bring the Registry to the people who don't either have—they have hotspots, so we can bring the Registry to people who either don't have internet access or don't have a computer whether that's during a home visit, whether that's during a support group meeting, or at a Registry symposium. Things that we have across the country. So, that's number one. If you can target areas where you know you need it . . .

Mr. Harada: Once again, that points to the prioritization of the collaboration. The bandwidth and the footprint for each organization is a little bit different. So, that grassroots level collaboration with all of the different organizations, and as Rob said, not just the major ones, all of them, is going to be imperative. It's just not feasible for one organization to go out to 100% of the states and highly rural states.

Mr. Wildman: Every state has different capabilities and resources, and that's where it's critical to continue partnerships with other organizations. It's a community-wide driven thing. It's not just specific to an organization.

Mr. Goldstein: Can I ask a question on Bullet 3, helping people with physical limitations? I mean, obviously, this disease is all about limitations. In a lot of ways it is. You know, you mentioned earlier that the website for the Registry is not the best, and you want it be better, and you're looking to improve it. Do you have an idea of a timeline on that, or are there some best practices that our organizations can help with? I will just offer that our organization just went fully mobile, fully socially integrated, and we've seen some differences in how people participate. We would be happy to share that with the Registry.

Dr. Mehta: I believe the deadline is currently March 2016 for this new responsive design through CDC. There are some things that we have to look at, because we have an application built in with the survey-taking and signing up and to make sure that it is integrated in the mobile application.

Mr. Goldstein: Will you be able to overcome that issue?

Dr. Mehta: We've actually provided this information to our IT department to look at to make sure it can go in and hopefully they can provide some sort workaround or a fix for it, because you've got the app and when it's static, it's not a problem. The issue arises when it becomes not static when you're entering in information, doing passwords, and then you go in the back and you take surveys to make sure they are all properly formatted and you can read them correctly, et cetera.

Mr. Goldstein: Have they been instructed with the common communication devices that people in later stages of ALS may be using, other tablet forms, to ensure that the responsive technology actually frames correctly?

Dr. Mehta: That's a very good question. I know there are, I mean, Wendy correct me if I'm wrong, I know there's like, for example, hard of hearing. But, I'm not sure if there's any sort of like . . .

Mr. Goldstein: Devices work differently when typing, and some platforms work on a different size tablet. I would suggest that the IT department get people to look at some of those in real time, or enlist some PALS to do some troubleshooting.

Dr. Mehta: That's real interesting. That's not something we've thought about before in actually adapting.

Dr. Kaye: We did field-test the surveys with some people with the ALS chapter, and they did do the surveys online and worked with the navigation and all. So, we did do that. The font size got increased. There were some issues about being able to blow it up really big. As I get older, I really appreciate that.

Mr. Goldstein: If you did it 4 years ago, I think that's great. I'm just suggesting doing it again with such a major customer change.

Dr. Kaye: Unfortunately, as Kevin mentioned, part of it is limited by the HHS and CDC requirements of what you have to do, which may not necessarily go with what we all think we should do.

Dr. Mehta: So, for example, we have a design we have to stick with. We can't have flash. We can't have, you know, something really fancy like you see on other websites. It's got to be a

format which is approved by CDC. We can't be as fancy as other things out there, unfortunately.

Dr. Kaye: Government websites have to be 508-compliant. We can't have pop-ups. It's got to have mouse-overs so that somebody who can't read, it can be read to them. It's got to have all those things.

Mr. Goldstein: You want these people engaged. These people are going to be engaged with this over years, so I just think planning ahead, you know, as that person is using a Tobii device or other technology, you know, if they can no longer access their data because it doesn't work on that device, that would just be a shame.

Mr. Kingon: All right. Let's move on: "Provide more information in the form of infographics, such as research funded by the Registry."

Dr. Mehta: We can certainly provide an infographic. We can work on one for research funded by the Registry. We are in the process of funding a R01, investigator-initiated, over the next few months. So, we can certainly go in and create some sort of, infographic for that. We already have infographics for enrollment, the first report, et cetera. But, certainly, we can have something like that.

Mr. Wildman: Paul, this gets at what we were talking about earlier with the value. I mean, if we could more easily demonstrate value through graphics and communicate not just funding, but published papers, the biorepository, all that stuff, it would just make it a lot easier to promote to people.

Dr. Mehta: We're going to be working on an infographic brochure on the biorepository in the near future. That's on our "to do list" as well, so that we have something to give out to PALS.

Dr. Kaye: Can anybody tell me if infographic are better than brochures?

Dr. Mehta: For people who have to read it, it's a lot easier.

Dr. Kaye: Okay. So, all of the things—many of the things we have up here, except for the shorter meeting summaries, would make good infographics, right? I know that the MDA has a really long brochure, but we could take part of it—a nice brochure that explains the difference between what MDA is doing and what ATSDR is doing. If we could make that into an infographic, it would be good.

Mr. Goldstein: If I could add a potential infographic suggestion, much of the conversation yesterday and today has been about planning ahead and planning for success. I wonder if possible if there could be an infographic outlining that 5-year plan, or as Becky said, that 1-year plan for the Registry in some way, maybe showing the progress over the last 4 years, "Hey, it launched on this date. This is how many people enrolled." I think showing progress and movement excites people. I think that may be a potential infographic that could be a useful advertising tool for the Registry.

Dr. Mehta: So kind of like previous accomplishments and future accomplishments, or future things to do? Something like that?

Mr. Goldstein: Yeah, like a mountain or a timeline or something that just shows some progress.

Dr. Mehta: Date of launch, first report, first survey taken, et cetera?

Mr. Goldstein: In general, that's what I'm thinking.

Ms. Kidd: Maybe testimonials. I mean, what about a PAL who got into a research study because they were invited through the Registry.

Mr. Goldstein: There are so many NGOs. I mean, our organizations can do that without government essentially so it doesn't have to be done through the registry. If it has to be done through the Registry, I imagine that there will be 18 roadblocks. So, those testimonials, through collaboration, is something that we could ask all of our collaborators to do. I'm sure that I can. I'm sure that many of our other partners in Collaboration for a Cure could put those out in a branded way to help advertise.

Mr. Wildman: We've done some of that. The limitation on that is it just can't be scripted. It has to be in the person's own words. We've done some of that. Ted is right. Some of its repackaging. Some of it's getting more organizations to do it and more involvement.

Dr. Boylan: For some of the accelerated outreach efforts, is it feasible to put links to some of these sites on the government website so you're saying, "Go look at this" and it's actually the message you want to convey but can't get past OMB?

Dr. Mehta: We do have partner links on the website. They're all there.

Dr. Boylan: That might be one way to get this message out faster.

Dr. Mehta: Well, I mean, they are links to their home pages.

Dr. Boylan: Well, the message could be built into something like that.

Mr. Wildman: We put a link to studies in the biorepository and things like that. We do have that.

Dr. Kasarskis: So, I think the one thing that's missing in the last slide and this slide, the last slide was detailing the physical interface of patients responding to the questions and trying to get people to register. But, this slide should be a little bit about where the Registry fits in with the scientific process that you're trying to accomplish, because you've heard that from some of our patients here today. They're the ones who know about ALS. They are sort of the hypothesis-generators of a little bit about what might be in their environment, or what their life story has been that may or may not be relevant to the process of how ALS begins, or how it unfolds, or how fast, or what makes it slow. You know, what the Registry is trying to map into is an epidemiologic scientific process. If you're telling the patients, "Here is your contribution. This is where you fit into this whole thing," I think that's the overarching message. You know, we've had a lot of discussion about the barriers that are there in the process of the Registry's function. But, you know, you're asking a research partner to put in his or her time to contribute the information that only they hold in their brains and their experience. I think that's part of the business of making the Registry sexy and attractive. I think that's really an important piece that needs to be conveyed in some way to maybe a general audience that is not scientifically sophisticated, or hasn't thought about science, or has run away actively from science. I think that's what we're asking our patients to do. That's their contribution, and trying to heighten the excitement and importance of their contribution, you know, they're the only ones who can do this piece of the science. How do you encourage them to do that? Then the rest of the stuff is

interface. How do you make a motivated patient able to contribute their information? I mean, that's mechanism. That's details. But, I think the motivation of how people come to the point where they say, "Yes, I will sign up for this." I mean, guilt works great for some things, but I think it only goes so far.

Mr. Wildman: We're hoping to get the answer to the question, "Why me?" I would like to ask Steve, and Ted, and Becky your thoughts on why they enrolled.

Dr. Kasarskis: Maybe that's the tag line that gets the whole thing going.

Mr. Harada: I can't remember. In the video that we produced a couple of years ago, it may have been in there why I enrolled. When I got diagnosed in August 31 2010, the Registry opened in October. I did happen to read about the ALS Registry and I thought, "I guess I should register." It just made sense to me to do it, you know because I was like, "This is a rare disease, and they don't know anything about it." It just made sense to me. Everybody's got different motivations. I think you're asking the wrong people, Bob, because we're here. You're "preaching to the choir" here.

Dr. Reznick: For me the "Why me?" the way I made sense of my diagnosis was, "All right, as a scientist with ALS, I'm now going to be in a position to hopefully help advance our understanding of this disorder, and possibly someday there will be a cure." For me also, the question of why I got it is less interesting to me than the question of, "What's going to be happening next?" I can't do anything about why I got it. But, moving forward, that is still a topic that I'm interested in more than the other one.

Ms. Kidd: I think, you know, it's different for all of us. I kind of stumbled on the ALS Registry at a public policy meeting a couple of years ago. For me, why I keep going in and sticking with it, is I'm a mom with ALS. Quite frankly, what I tell people is that how I do this journey is the last and most important lesson I'm going to be teaching my son, and I want him to see courage, and fight, and helpfulness. That's why I do it.

Mr. Kingon: Okay, I'm going to move on. We have just 10 minutes left: "Produce short and easy to read meeting summaries. I don't know why that is in blue. Here's the last one I want to deal with, and maybe the most important one: "Develop a 5-year plan for moving the Registry forward, including enrollment and participation goals." What should be included in this 5-year plan?

Ms. Kidd: There was a slide on the first day, I think Kevin's slide, that talks about why it even exists, right? What were the three things? I mean, I think the plan needs to talk about, "This is our measurable goal associated with why we exist" whether it's to find a cure, finding a cause—whatever.

Mr. Kingon: Like an overarching mission goal.

Ms. Kidd: Right. Exactly. Then underneath that, have the breakdown steps to get there. Shorter-term steps, low-hanging fruit, et cetera. I can't find the slide, but there were three things, I think.

Dr. Horton: At this point, we've hit a lot of these. Well, we've hit two out of three. You know, we want to know the incidence and prevalence of this disease in the US. Who does it affect? We've got those two things. The third thing is risk factors. We have collected 46,000 completed

risk factor surveys, and we're going through that right now. So, we've followed the letter of the law. We've done a lot of what Congress has wanted us to do. Now we're talking about enhancing the Registry and making it better. So, we've introduced the biorepository and we're doing all of these other things linking patients to studies. So, we're well on our way.

Mr. Gibson: So, I think that has to say more than just "enrollment goals." It's got to say research, et cetera so it's broader. But, a question regarding risk factors. How many surveys do you need to fill out and analyze for you to come back and say, "Smoking is a risk factor. X is a risk factor." That is an important number, because many people actually fill out these surveys because they want to find out what risk factors are, or they think they know what their factor was. So, I think we've got to have some plan to have a process to identify risk factors.

Dr. Bruijn: I think there are two phases to what we can get out of the Registry. I got a sense that from the modules, you get an indication of something being a risk factor but not proven. Then it's really through study recruitment that you're going to get the answer. I think that's a very important two-level message to give, because it talks to the expectations thing. So, if people are expecting that from 5 years of the Registry, 50% of the surveys are completed and now we're going to know the answer if smoking is a problem, my concern is that there is an expectation that we will have a clear answer of what environmental factors are important through the Registry. Yes we will, but it's through studies that are going into the Registry. So, I think we need to be a bit pedantic and spell that out.

Mr. Kingon: After 5 years, now we should be able to . . .

Dr. Bruijn: Actually, maybe I didn't make it clear then. There are two things a Registry can do. One is give an indication of something being of interest from the risk factors surveys. The other part of this, which is why you have this research thing and why you're funding research is that people then, specialists like Lorene and Mark and others, who can really set up the surveys and go back in and get the data that they need and the people that they need, and then do a more rigorous study. I don't think you can get a conclusive indication in 5 years or 10 years from just surveys. You can get that in combination with other efforts, and I think that has to be well-described.

Mr. Kingon: My question would be then how do you 0measure how you progress to those endpoints?

Dr. Bruijn: They're two different endpoints, and you measure each one individually. One endpoint is that it is our goal to get as much information into the Registry so we can get a good assessment of what might be interesting risk factors. The other is how many studies can you fund? How effective are those studies? How well do they recruit people into well-designed studies? Those are the ones you publish. So, there are two outcomes for this 5-year plan.

Dr. Kaye: What about linking the studies, or requesting studies be done on the risk factors that the Registry identifies as interesting. So, after you go through the data and you say, "Oh, it looks like pesticide exposure seems to be of interest." Then maybe the next announcement could be more data hypothesis-generating.

Dr. Bruijn: I think people involved in this who are maybe less knowledgeable who are convinced that the Registry is going to tell them what environmental factor is causing their disease. So, I think, to be honest, it might give a better presence among the scientific community who know that that can't be achieved, so there would be a view of the value of the Registry at two levels.

Mr. Gibson: That's actually a 5-year plan. Forget about numbers of enrollment. If we could identify some risk factors and you have a plan that says, "Here are probable areas. Here is the roadmap we're going to take. Here's how much money we are going to put in that area," that helps us on the Hill with budgets, and it helps us with PALS to understand what's important to them. Forget about other metrics.

Dr. Mehta: Yes, but we can't get to the risk factor completion without enrollment, so that's certainly important.

Dr. Bruijn: They go hand-in-hand.

Dr. Bradley: I want to follow-up on what Lucie said. The Registry, unfortunately, does not have controls. You can't make any scientific analysis of the risk factors unless you have controls. We've given a good deal of thought to how to try to use the Registry risk factor surveys by collecting controls in the same region with studies that are more limited geographically than the total national studies. I would like to have received the data from the risk factor modules, then we could compare them with case-control analyses. It is possible for these studies to be funded from the mechanism by which you already are funding grants, and then provide that data back to the Registry to make comparisons in-house. So that, I think, is the only paradigm that you're going to be able to use in risk factor analysis over the next 5 years.

Dr. Brooks: I think there are some low-lying fruits here. I mean, you could look across the entire Registry from the point of view of risk factor data, versus site of onset risk factor data, versus site of onset location geographically. There are ways of parsing this out. Your report did this a little bit in the initial part of it. I think the ultimate—well, you have to keep people wanting to come back because you are doing something.

Mr. Mitsumoto: Also, you combine with the biorepository and the environmental data you're collecting. You cannot get onset, but in the future, you can get correlation with biomarkers and also epidemiological data. Furthermore, adding then to the comment if you have more survival data in this patient population, exposure data and survival, you can correlate how certain exposures are associated to more of those things that clearly you can demonstrate in the future, not now, but a certain concern is that like Dr. Bradley, you need a control. But, you can again look at the list of those frequent exposures. You can list those in the future.

Dr. Traynor: I just want to read out some Senate resolutions that passed during the 114th Congress, which is this Congress: A concurrent resolution recognizing the daisy as the flower for military caregivers, and a resolution to rename one of the streets in DC as Oswaldo Payá Way. So, I think there should be some way in which we can actually get this moved forward and really make the registry more nimble from a regulatory perspective.

Dr. Mehta: If I could just quickly add to that right there, there's two words that I think the government fears, "public pressure." Case in point, a few months ago, scientists published in the *American Journal of Public Health*—CDC's clearance process. If I write a report, it goes to Kevin, my Team Lead, it goes to our Division Director, it goes to our Center Director, it goes above that, and it goes through cross-clearance. So, the premise was, these scientists got together and wrote an editorial in the *AJPH* simply saying, "This is so cumbersome, CDC. Fix it." It went to the Director of CDC, Tom Frieden, and they read it and, you know, lo and behold, there are certain processes in place now to make clearance of documents much more streamlined. So, public pressure is very, very important. Our government is of, by, and for the

people. You know, we can only do so much. But, the premise is, if public pressure is there to go out and make changes happen.

Bob Kingon: Okay. I have to ask one more question. Who would like to be involved in putting together the details of this 5-year plan? Do you want to put together a virtual task force that is email-driven? A show of hands. Who would like to be involved? Wendy, can you take down the names? Mr. Goldstein. Dr. Bruijn.

Closing Remarks

Paul Mehta, MD
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Environmental Health Surveillance Branch, DTHHS
Agency for Toxic Substances and Disease Registry

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

Dr. Mehta presented certificates of appreciation to the following PALS and neurologists in attendance as a small token of appreciation for all of their support for the past few years:

PALS
Mr. Ted Harada
Ms. Rebecca Kidd
Dr. Steven Reznick
Mr. Edward Tessaro

Neurologists
Dr. Robert Bowser
Dr. Christopher "Kit" Brady
Dr. James Berry
Dr. Kevin Boylan
Dr. Walter Bradley
Dr. Benjamin Brooks
Dr. Feldman
Dr. Kasarskis
Dr. Mitsumoto
Dr. Sorenson

Dr. Horton said he wanted to mention something that he should have mentioned at the beginning of the meeting. Earlier this year in January, their Statistician, Marchelle Sanchez, passed away unexpectedly. When she passed away, it left a huge void in the program. She was not only a colleague, but also was a friend. She attended the annual meeting year in and year out. They miss her and wanted to let everyone know. May she rest in peace.

Congress came to CDC to conduct a task that has never been done before—create a registry that tracks a disease that is a non-notifiable and non-communicable. This has not been done

before on a national level. It has been done at the state level sporadically, but this was a major undertaking. If ALS was a notifiable disease, they would have been "off to the races" years ago. It is important to keep in mind that a small group within ATSDR and contractors had to develop a novel approach to track new and existing cases of ALS. This was not an easy feat. Nevertheless, they developed the Registry. The Registry tracks incidence, prevalence, and mortality. However, as mentioned during the discussion, it is important to focus on what else the Registry can do. ATSDR is very excited about linking patients with researchers to participate in clinical trials or epidemiological studies. As PALS have emphasized, clinicaltrials.gov is not user friendly. Navigating clinicaltrials.gov is very cumbersome and very clunky. Is the Registry system the best? That's debatable. However, it offers another avenue for patients to take part in research. This is delivered via email to PALS' emails.

While only one year of data has been published, this is a brand new system. Year 2 and 3 data are anticipated to be published in 2016. In the meantime, ATSDR has published numerous journal articles thus far on the incidence and prevalence of ALS. He recognized that they could probably do a better job of selling that, but the ATSDR website includes all of these journal articles. The biorepository is a major undertaking. Samples are being collected from people in places like rural Idaho who are not anywhere near a referral center. That has not been done before. ATSDR is trying to be bold in terms of engaging in new efforts. Of course, they are going to have their share of critics. No system is ever perfect, and ATSDR will be the first to acknowledge that the Registry is not a perfect system either. However, it is the best and only system of its kind. With the addition of the biorepository, this will become a world-class ALS registry. The existing ALS registries in Europe have existed for decades. In just the past couple of years, with the data collected and the number of people in the ATSDR ALS Registry, there will be more people in the first year than in all of those registries have combined for the dozens of years that they have existed.

ATSDR knows that there is a lot of work to do, but it is important to remember how much work has already been done in just the 4 years that the Registry has been up and running. However, it is important to remember that this is a collective effort. CDC/ATSDR cannot do this alone. They do not have the capacity. They cannot do this without groups like ALSA, MDA, Les Turner, TDI, etc. It is imperative for people to get in front of patients and neurologists to educate them about the Registry in order to achieve maximum impact. People are diagnosed every day, and this must be a sustained effort—not only by ATSDR, but also by the collective group.

Dr. Horton expressed his gratitude to everyone, especially to the PALS, for taking time to attend the meeting. For some PALS, it is not easy to get out and make the trip to Atlanta, so he said he greatly appreciated them taking time out of their schedules to attend the meetings and offer candid and frank feedback. He said he has developed thick skin over the last couple of years, as the Registry has had a few critics. But ATSDR does take what people say, evaluate it, prioritize it, and implement what they can. There are just some things that the agency cannot do from a logistical standpoint. He also offered gratitude to all of the scientists, physicians, and researchers who take time out of their schedules to attend the meetings and offer their input.

ATSDR does sense the urgency. That is not lost on them. ALS is known to be a quick, fatal disease. That makes them work all the more diligently, but they do face challenges. It is important to understand that many of these challenges are not because of the Registry, but are due to outside entities they have to deal with. That does not mean that they should not be challenged, or that other arrangements should not be made. ATSDR constantly tries to push the boundaries to see what they can do to speed things up. For example, they took the

password issue to the CDC IT staff and told them that it was ridiculous. That had never been done before. The point is, it never hurts to ask. It will not hurt to ask OMB to provide a waiver. If they say no, ATSDR will try again next year.

In conclusion, Dr. Horton thanked everyone for their attendance and sharing their expertise. He indicated that they would receive a draft summary of the meeting in order to ensure that their comments were captured accurately. He stressed that much of the reason that this is the program about which he is most passionate is because patients are passionate about it. If there is something ATSDR can help fill a scientific gap, find a cure, or discover a risk factor, that is why they are in public health. He encouraged anyone with suggestions after the meeting to send an email or give them a call. He wished everyone safe travels and concluded by saying, "From the bottom of my heart, thank you very much for coming."

Dr. Kasarskis extended a group hug and said he hoped to be able to speak on behalf of everyone. He has been with this Registry and in attendance at the annual meeting since its birth. He thought the community and the world probably owed a lot to Dr. Horton's leadership on this effort. He quipped that perhaps Dr. Horton had Kevlar underneath his understated jacket. He pointed out that though Dr. Horton mentioned that he had developed thick skin, he thought that was part of his quiet leadership and persistence with this program. He imagined that other leaders could have brought this Registry to this point; however, he thought a lot would have just blown up and it would have gone no further. He thought everyone had Dr. Horton personally to thank for this effort.

Dr. Horton thanked Dr. Kasarskis and said that while he did not have a gavel, he thereby declared the meeting adjourned.

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