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

August 13 – 14, 2014
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.

Executive Summary

Because much remains unknown about the causes(s) of Amyotrophic Lateral Sclerosis (ALS), the National ALS Registry was established in 2010 by the Agency for Toxic Substances and Disease Registry (ATSDR) to describe the incidence and prevalence of ALS, to describe the demographics of ALS patients, and to examine the risk factors for the disease. The first report from the Registry was published in CDC's *Morbidity and Mortality Weekly Report* (*MMWR*) on July 25, 2014. The report includes the first-ever prevalence estimates of ALS for the United States (US).

Each year ATSDR convenes the Annual ALS Surveillance Meeting to bring together leading ALS experts to help shape the Registry. The meeting is designed to update stakeholders on the progress of the Registry, to present the Registry data and its implications, and to discuss strategies to further enhance the Registry for all stakeholders.

Overview of the National ALS Registry

The ALS Registry Act, enacted as Public Law 110-373 in October 2008, directs CDC/ATSDR to establish and maintain the National ALS Registry. It is the only congressionally mandated population-based registry for the U.S. ATSDR described the methodology used by the Registry. The Registry combines ALS data from existing national databases (i.e., Medicare, Medicaid, VA Health Administration, and the VA Benefits Administration) with information directly entered into a secure web portal by persons with ALS. In addition to registering, 15 risk factor surveys are also available to ALS patients on the Registry web site. 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 is also implementing several initiatives to strengthen the Registry including:

- The Research Notification System
- Additional risk factor surveys
- The Biorepository Pilot Study
- The State and Metropolitan-Based Surveillance Project, and
- ATSDR supported ALS research

An important aspect of the meeting is the discussion following each presentation. This discussion is critical as it generates recommendations concerning Registry issues and suggestions for enhancing the Registry.

First Report on Registry Results

The results from the first surveillance report from the National ALS Registry, Prevalence of Amyotrophic Lateral Sclerosis – United States, 2010-2011, were presented. The report was published on July 25, 2014 in the *Morbidity and Mortality Weekly Report* (MMWR) and includes data from the date the Registry was launched, October 19, 2010, through December 31, 2011.

A total of 12,187 persons were identified as having definite ALS via the Registry, which includes those in the national databases and the persons registering on the web portal. The

number and percentage of identified ALS cases were described by source, age group, and sex. Prevalence rates for ALS were presented by age group, sex, and race.

Information about potential risk factors is gathered for descriptive purposes only. Information was provided for persons responding to risk factor surveys, which included smoking history, alcohol history, education history, military history, and employment status.

Research Notification Mechanism Update

ATSDR described the Research Notification Mechanism, which was introduced in the National ALS Registry with the objectives of linking researchers with persons with ALS (PALS), facilitating their interaction, and expediting the process of recruitment. PALS may give their consent to receive notifications when they enroll in the Registry. Researchers submit proposals to ATSDR, including a research protocol that has been approved by their institution's IRB and other documents, which are reviewed by an approval committee. If the research is approved, eligible PALS are notified about the research and if they are interested, then they contact the researchers. Since November 2012, ATSDR has used this system to link PALS with nine research studies.

Risk Factor Data Analysis

Results were presented from the risk factor surveys completed by persons with ALS who self-enrolled in the online Registry web portal in the time period October 2010–December 2011. The results were from surveys on demographics, smoking and alcohol use history, military history, occupational history, and family history of ALS, Alzheimer's disease, or Parkinson's disease. The results of the demographic survey were presented by age, race, ethnicity, sex, and educational attainment. The results of the other surveys were presented by percent of respondents engaging in the activity, the degree to which they engaged in the activity, or by other indices.

Outreach Challenges

ATSDR solicited information and input from the meeting participants to ensure that the National ALS Registry is having maximal impact and reaches as many PALS as possible. This request resulted in a lengthy discussion regarding challenges and potential approaches to address reaching as many PALS as possible.

Registry Promotion and Outreach

ATSDR

ATSDR described its marketing strategy for generating awareness of the National ALS Registry, which focuses on working with partners and targeting different audiences. The audiences include PALS, family members and caregivers, health care providers, researchers, and ALS support organizations and entities. The metrics associated with visits to the Registry and new projects and features were also described. Some of the new products include: new web buttons that focus on particular audiences, such as caregivers and rural populations, the "Get the Facts" infographic, videos and Webinars. Although the Registry continues to be promoted through traditional printed materials and the print media, this effort continues to be expanded to include social media messaging and online ads.

The ALS Association

The ALS Association stressed the goal shared by members of Congress, ALS researchers, and PALS, which is for the National ALS Registry to be a powerful research engine. The ALS Association conducts a Listening Tour of each of its 38 chapters to learn about things that are important to PALS. Through these tours the chapters identified challenges such as internet access and limited knowledge about the Registry. Based on the feedback from the Listening Tour, The Association created a National ALS Registry Toolkit to help chapters address these challenges. This toolkit has been distributed to ALS Association chapters and affiliated clinics and centers across the country.

The ALS Association also described how their outreach to health professionals, researchers, veterans, elected state officials, and the general public is impacting enrollment in the Registry. Another strategy being used by The ALS Association is their partnering with minor league baseball to promote the Registry through events at baseball parks across the country, many in rural areas that are under-enrolled in the Registry. The Association is also heavily engaged in promoting the Registry online through social media and online advertisements.

Les Turner ALS Foundation

The Les Turner ALS Foundation described how Les Turner, a businessman in Chicago who was diagnosed with ALS in 1976, and his family formed the foundation in 1977. An idea based on used books sales spawned the creation of the Mammoth Music Mart in 1978. This event continued for 25 years, providing funding to the foundation. Also described was how the foundation has grown over the years. The Les Turner Foundation now supports two ALS research laboratories at Northwestern University and the Les Turner/Lois Insolia ALS Center to provide services to PALS. The foundation also provides a wide variety of patient and family support programs throughout the Chicago area.

The Les Turner Foundation also described how it promotes the National ALS Registry through their team of communications professionals who work with social media and send regular e-mail blasts, through information on the Registry provided on the Les Turner webpage, through the Home and Community Advocate Team which also helps promote the Registry, and through the distribution of materials to new patients in clinics, home visits, and in support groups.

The Muscular Dystrophy Association

The Muscular Dystrophy Association (MDA) described how MDA is the world's leading nonprofit health agency dedicated to finding treatments and cures for muscular dystrophy (MD), ALS, and other related neuromuscular diseases. MDA has dedicated almost $325 million to ALS research and healthcare services. 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.

Also described was the tremendous research commitment MDA has dedicated to ALS and MDA's many efforts in information dissemination about the Registry. MDA described their three publications, which include promotions about the Registry and their strong social media presence.

CME Training Modules Update

ATSDR presented a review of data from users completing the ALS Continuing Education Module for the period October 1, 2010–June 30, 2014. Users of the module pursued different credit types, including Continuing Education (CE), Continuing Medical Education for Physicians (CME-P), Continuing Medical Education for Non-Physicians (CME-NP), Certification for Nurse Educators (CNE), Continuing Education Units (CEUs), and Certified Health Education Specialist (CHES). The user data was presented by type of user, educational level, work setting, credit type, number registered and number and percent completing the module.

State and Metropolitan Area Surveillance Findings Update

The goal of the State and Metropolitan Area Surveillance Project was to evaluate the completeness of the National ALS Registry. Neurologists who had diagnosed and/or provided care to an ALS patient in specified state or metropolitan areas from January 1, 2009, through December 31, 2011 were identified and requested to report their ALS cases to the project. Surveillance data was provided in three states and eight metropolitan areas including: Texas, Florida, and New Jersey, and San Francisco, California; Los Angeles, California; Las Vegas, Nevada; Chicago, Illinois; Detroit, Michigan; Atlanta, Georgia; Philadelphia, Pennsylvania; and Baltimore, Maryland.

The methods were described for identifying and recruitment of providers, case ascertainment, quality assurance, and for selection of reported cases for case verification. Results were described for the number of cases reported, age, race, ethnicity, sex, time from onset of symptoms to diagnosis, metropolitan area and by practice type. The limitations, recommendations for use of this type of active surveillance for ALS, and methods for distribution of the findings were also described.

Mobile Service Locator Apps

ATSDR's Geospatial Research, Analysis, and Service Program (GRASP) provided an overview of the ALS Service Locator Apps. GRASP provides a Service Locator Tool to help PALS find the closest clinics, ALS Association chapters, and MDA offices by using a Zip code. The web application service locator was has been transformed onto mobile platforms. The mobile application is available in iOs and Android marketplaces. Metrics data for the mobile applications were also described.

End of the Day Questions

During this session, the floor was opened for meeting attendees to ask questions or make comments regarding any ALS issues or concerns.

ATSDR Funded Studies

Research is critical to learn more about the etiology of ALS. 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. The following ATSDR-funded studies are listed on the National ALS Registry website and were presented by their principle investigators.

A Prospective Comprehensive Epidemiologic Study in a Large Cohort in the National ALS Registry: Identifying ALS Risk Factors, presented by Hiroshi Mitsumoto, MD, DSc, Columbia University Medical Center

Identification and Validation of ALS Environmental Risk Factors, presented by Eva Feldman, MD, PhD, University of Michigan

Ecologic Study to Evaluate Spatial Relationships between ALS and Potential Environmental Risk Factors, presented by Walter Bradley, MD, DM, FRCP, University of Miami

Cognition, Behavior, and Caregiver Burden in Amyotrophic Lateral Sclerosis, presented by Christopher Brady, PhD, Boston VA Research Institute, Inc.

NeuroX Genome-Wide Association Study, presented by Bryan Traynor, MD, PhD, MMSc, MRCPI, National Institute on Aging, NIH

PALS Perspective on the Registry

Four persons with ALS attended the meeting. Each of the PALS shared his/her perspective regarding issues and concerns about living with ALS, about the work that is being done in laboratories, clinics, and offices in order to learn more about the causes of ALS and potential treatments, and about the National ALS Registry.

There was discussion about creating better incentives for PALS to enroll in the Registry and to complete the risk factor surveys and the desire for more access to data from studies that PALS participate in. Questions were raised regarding why opportunities to encourage and assist PALS with enrolling in the Registry are not being taken advantage of and how should the problem of reaching PALS who do not have access to a computer be addressed. Frustrations were voiced regarding how privacy laws appear to be slowing information sharing in the medical field.

It was also pointed out that the Registry needs to do a better job of explaining to PALS and other stakeholders what will happen each year, what data will be available, what the data will be useful for, and what is anticipated for the future. It is not clear whether efforts to build enrollment in the Registry is having an impact.

Recommendations were presented to address these issues and concerns and PALS offered their assistance as well. They also recognized the accomplishments of the Registry and acknowledged the challenges it faces. And they thanked everyone attending for their hard work on the front lines and behind the scenes.

Next Steps

This session was an open-ended discussion of any remaining questions or concerns, which were primarily focused on how the Registry can be improved to make it more meaningful for all ALS stakeholders.

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Acronyms Used in this Document

Acronym	Expansion
AAN	American Academy of Neurology
ADL	Activities of Daily Living
ALS	Amyotrophic Lateral Sclerosis
ALS COSMOS	ALS Multicenter Cohort Study of Oxidative Stress
ALSA	Amyotrophic Lateral Sclerosis Association
ALSFRS	Amyotrophic Lateral Sclerosis Functional Rating Scale
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised
AMA	American Medical Association
ANA	American Nurses Association
AP	Associated Press
APHA	American Public Health Association
ARREST-ALS	ATSDR Risk factors Epidemiologic Studies in ALS
ATSDR	Agency for Toxic Substances and Disease Registry
BFR	Brominated Flame Retardant
BMAA	Beta-Methylamino-L-alanine
BMD	Becker Muscular Dystrophy
CBI-R	Cambridge Behavioural Inventory Revised
CDC	Centers for Disease Control and Prevention
CE	Continuing Education
CHES	Certified Health Education Specialist
CME-NP	Continuing Medical Education for Non-Physicians
CME-P	Continuing Medical Education for Physicians
CMS	Centers for Medicare and Medicaid Services
CNE	Certification for Nurse Educators
CSF	Cerebrospinal Fluid
DMD	Duchenne Muscular Dystrophy
DME	Durable Medical Equipment
EEC	El Escorial Criteria
EMB	Environmental Medicine Branch
EMG	Electromyography
FAQs	Frequently Asked Questions
FDA	Food and Drug Administration
FSH	Facioscapulohumeral Muscular Dystrophy
FTD	Frontotemporal Dementia
FVC	Forced Vital Capacity
GIS	Geographic Information Systems
GPS	Global Positioning System
GRASP	Geospatial Research, Analysis, and Services Program
GWAS	Genome-Wide Association Study
HIPAA	Health Insurance Portability and Accountability Act
HMO	Health Maintenance Organization
ICD	International Classification of Diseases
IRB	Institutional Review Board
JAMA	Journal of the American Medical Association

Acronym	Expansion
MD	Muscular Dystrophy
MDA	Muscular Dystrophy Association
MMD	Myotonic Muscular Dystrophy
MMWR	Morbidity and Mortality Weekly Report
MND	Motor Neuron Disease
MS	Multiple Sclerosis
MTA	Material Transfer Agreement
NAPS	North American Precis Syndicate
NCEH	National Center for Environmental Health
NCHS	National Center for Health Statistics
NDI	National Death Index
NEALS	Northeast Amyotrophic Lateral Sclerosis Consortium
NGO	Non-Governmental Organization
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
OMB	Office of Management and Budget
OS	Oxidative Stress
PALS	Persons with Amyotrophic Lateral Sclerosis
PCB	Polychlorinated Biphenyl
PLS	Primary Lateral Sclerosis
PSA	Public Service Announcement
RDC	Research Data Center
RFA	Request for Application
RFP	Request for Proposals
SMA	Spinal Muscular Atrophy
SNP	Single-Nucleotide Polymorphism
SOP	Standard Operating Procedure
SSDI	Social Security Disability Insurance
TBI	Traumatic Brain Injury
VA	(United States Department of) Veterans Affairs
VBA	Veterans Benefits Administration
VHA	Veterans Health Administration

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
August 13 – 14, 2014

Theme / Purpose

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

Purpose: Update stakeholders on the progress of the National ALS 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, welcomed the group at 8:30 am. He reviewed ground rules for the meeting, noting that portions of the day would be streamed live on the Internet. The meeting participants introduced themselves. An attendance roster is provided at the end of this document.

Opening Remarks

CAPT William Cibulas, PhD, MS
Senior Advisor for Public Health, Office of the Director
Associate Director for Science
Agency for Toxic Substances and Disease Registry/
National Center for Environmental Health

Dr. William Cibulas greeted the group and welcomed them on behalf of the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Center for Environmental Health (NCEH) Director and Deputy Director. He acknowledged the importance of convening leading Amyotrophic Lateral Sclerosis (ALS) experts to shape the National ALS Registry. He shared his personal experience with ALS and emphasized the disease's impact on families, friends, and loved ones. There is no known cause for ALS at this time.

The Registry is a groundbreaking effort to assist scientists as they work toward a cure for ALS. The Registry is making real progress. The first report from the Registry was published in CDC's *Morbidity and Mortality Weekly Report* (*MMWR*) on July 25, 2014. The report includes the first-ever prevalence estimates of ALS in the United States (US). Since going live in October 2010, the Registry's web portal has collected demographic and risk factor information on thousands of Persons with ALS (PALS) across all 50 states. More PALS are registering every day. Further, thousands of PALS have been detected in the large administrative databases held by the Centers for Medicare and Medicaid Services (CMS) and the US Department of Veterans Affairs (VA). ATSDR uses these data to help populate its registry. ATSDR continues to publish registry findings in peer-reviewed journals and in the *MMWR*.

Other initiatives are underway for the Registry to improve its usefulness, including a biorepository feasibility study. A mechanism is available to link PALS directly with researchers. Active state and metropolitan area surveillance activities are also underway.

NCEH/ATSDR is in a transition state, but support for the activities and goals of the Registry remain strong. The search for a new NCEH/ATSDR director has included two national recruiting efforts in the past year. The second effort is ongoing and has yielded a number of good applicants. Telephone interviews have been conducted, and face-to-face interviews will be conducted soon.

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

Dr. Ed Murray said that the success of the National ALS Registry depends on collaborations among ALS stakeholders, including PALS, researchers, physicians, and support groups. To achieve success, ATSDR continues to foster new relationships and maintain existing relationships.

A number of internal partners keep the Registry program moving. The Office of Communication has been very effective in promoting the Registry. The funding for the program comes from NCEH. The Environmental Medicine Branch (EMB) is responsible for continuing education modules, and the Geospatial Research, Analysis, and Services Program (GRASP) has developed an app for mobile devices. A number of neurologists throughout CDC also assist the program.

External support comes from groups such as the Muscular Dystrophy Association (MDA), the Les Turner ALS Foundation, and the Amyotrophic Lateral Sclerosis Association (ALSA). Those groups have helped to promote the Registry and were represented at the meeting. Researchers and professional organizations such as the American Academy of Neurology (AAN), the American Nurses Association (ANA), and PALS are also important partners who were present at the meeting. Four PALS were in attendance.

The Registry is committed to promoting ALS research initiatives that can help identify risk factors. ATDSR provides funding to help ALS patients and to build understanding of risk factors for the disease. New awardees include:

- Columbia University Medical Center
- University of Michigan
- Dartmouth College
- Boston VA Research Institute

Overview of the National ALS Registry

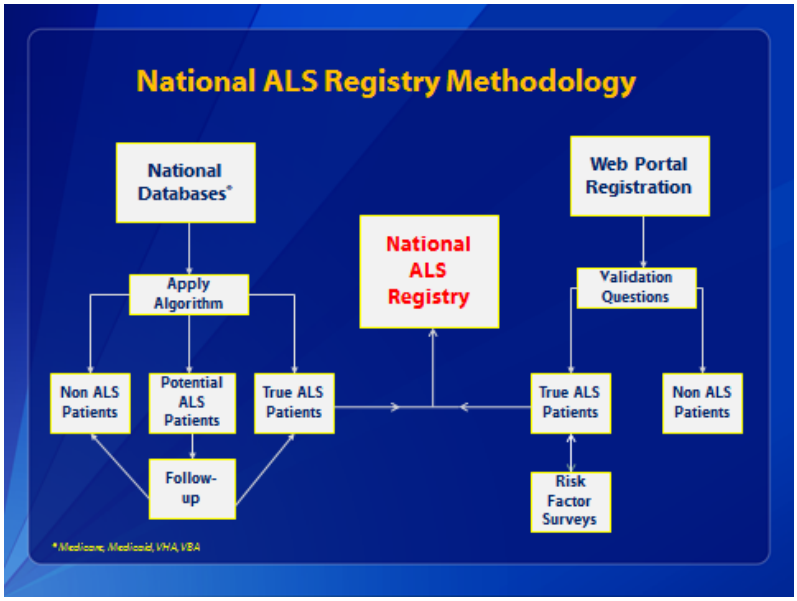
D. Kevin Horton, DrPH, MSPH
Chief, Environmental Health Surveillance Branch
Division of Toxicology and Human Health Sciences
Agency for Toxic Substances and Disease Registry

Dr. Horton welcomed those attending in person and via Internet streaming. He encouraged participants to ask questions, challenge ATSDR, and offer constructive criticism to make the Registry the best it can be. ATSDR is excited about the Registry's progress and findings and looks forward to more growth.

ATSDR is a federal agency co-located in Atlanta, Georgia, with its sister agency, the Centers for Disease Control and Prevention (CDC). The National ALS Registry exists because of the ALS Registry Act, which was passed in October 2008. The act allows CDC/ATSDR to create and maintain the Registry. There are other ALS registries in the US, but the National ALS Registry is the only Congressionally-mandated, population-based Registry for the entire US. The language of the act specifies that the purpose of the Registry is to describe incidence and prevalence of ALS; describe the demographics of ALS patients; and examine risk factors for the disease.

Past estimates of the incidence and prevalence of ALS were based on small-scale estimates extrapolated to the US. The Registry collects key information about the demographics of the disease. The online portion of the Registry was launched in October 2010, and the first report from the Registry was published in July 2014.

The methodology for capturing ALS cases in the US with the Registry employs a two-pronged approach. The first prong utilizes large national databases, including CMS, the Veterans Health Administration (VHA), and the Veterans Benefits Administration (VBA). An algorithm created via a pilot process is applied to the databases. The algorithm looks for the specific International Classification of Diseases (ICD) code for ALS, but the ICD coding alone is not reliable for identifying cases. Other elements are also considered, such as a prescription for Rilutek®



(riluzole), the only drug approved by the Food and Drug Administration (FDA) to treat ALS. The frequency of neurological visits is also examined. The algorithm separates people into multiple categories according to whether a person does not have ALS, has ALS, or is a potential case. If insufficient information is available to determine whether a person has ALS, then the case is put aside until more information can be gathered.

The other approach of the Registry is the Web portal. Through the Web portal, PALS can enroll directly in the Registry. The registration includes a series of validation questions. Patients who enroll through the Web and are also captured in the large databases are de-duplicated by matching of Social Security numbers. Fifteen risk factor surveys are available to ALS patients on the Web portal, which include information on such things as demographics, where people lived or worked, family history of ALS, hobbies and other activities in which they take part, and how they are coping with their disease.

The disease progression survey, assessed via the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS), can be taken multiple times to assess how the disease is affecting a patient's quality of life. As of August 12, 2014, almost 33,000 surveys have been completed. This number is good, but additional support is needed to encourage PALS to take the surveys. The surveys are designed to be brief and intuitive. ATSDR is in the process of analyzing the risk factor data that has been collected so far.

A number of initiatives are strengthening the Registry, including the following:

- ❑ The research notification system
- ❑ Additional risk factor surveys
- ❑ The biorepository feasibility study
- ❑ The state/metropolitan-based surveillance projects, which are yielding strong incidence data
- ❑ Funding opportunities for Registry support

PALS want to take part in research, specifically in clinical trials. Government websites for clinical trials are not always easy to navigate, so the Registry has a mechanism to link PALS

with researchers who are conducting clinical trials and epidemiologic studies. A high percentage of PALS enrolled in the Registry have opted to participate in the Research Notification Mechanism. All of the studies that incorporate PALS from the Registry will be shared with the PALS so they can see how the Registry is being used. Two more risk factor surveys will be deployed this fall. One focuses on trauma and traumatic brain injury (TBI), which is associated with ALS. Another addresses healthcare insurance.

The Registry collects data on the "who, what, when, where" of the disease, but collecting biological samples is also an important part of learning about ALS. To that end, ATSDR is in the third year of a four-year study to determine whether it is feasible to roll a biorepository into the Registry. The biorepository is a potentially rich source of data, as the biological samples can be linked to details about the patient's history.

The State and Metropolitan Surveillance projects are helping to test the completeness of the Registry. These projects take an active surveillance approach. Information from these efforts will be compared with the data that is already in the Registry for the three states and eight metropolitan areas in which the projects are taking place. The comparison will show whether more cases are detected via the active surveillance approach versus the cases that are already in the Registry. If so, then the case finding approach of the Registry will be modified to ensure that all expected cases are captured. The surveillance activities have concluded, and the analyses have begun. Data from this work will result in a number of papers.

Research is critical to learn more about the etiology of ALS. Information from research studies may not only help the ALS community learn more about the disease, but may also help prioritize new risk factor modules for the Registry. The studies that ATSDR funds are shared on the website and via social media:

Study Name (n=7)	Institution	Investigator
Epidemiology of ALS	Harvard University	Marc Weisskopf, PhD, ScD
Large-scale genome-wide association study of ALS	National Institutes of Health	Bryan Traynor, MD, PhD
Gene-environment interactions in ALS	Northwestern University	Teepu Siddique, MD
A Prospective Comprehensive Epidemiologic Study in a Large Cohort in The National ALS Registry: A Step to Identify ALS Risk Factors	Columbia University Medical Center	Hiroshi Mitsumoto, MD, DSc
Identification and Validation of ALS Environmental Risk Factors	University of Michigan	Eva Feldman, MD, PhD
Ecologic Study to Evaluate Spatial Relationships between ALS and Potential Environmental Risk Factors	Dartmouth College	Elijah W. Stommel, MD, PhD
Cognition, Behavior, and Caregiver Burden in ALS	Boston VA Research Institute, Inc.	Kit Brady, PhD

2014 is a critical year for the Registry. The first report has been published, but the report is not the "be-all, end-all." The Registry is just starting. It is a surveillance system that is building

evidence which will span multiple years and multiple reports. The ongoing initiatives will strengthen the Registry and build evidence to describe the ALS experience in the US. This work involves many partners, each with a part to play.

Discussion Points

Dr. Walter Bradley asked about the proportion of patients enrolled through the web portal compared with the national administrative databases.

Dr. Horton said that those details would be addressed in a presentation at the meeting.

Ms. Wendy Abrams asked how many unique patients are represented in the number of risk factor surveys that have been completed.

Dr. Horton said that the first report from the Registry only addresses the first seven risk factor surveys that launched in October 2010. Approximately 53% of patients enrolled in the Web portal took the first demographic survey.

Dr. Wendy Kaye added that the percentage of participants who take the surveys varies from about 45% to 53% of those registered. As time goes on, more people take the surveys. It is important to spread the word about the surveys.

Dr. Horton said that the general response rate has been good. Other federal surveys see response rates of approximately 20%. However, in order for the Registry to provide high-quality data, all participants need to take the surveys. The surveys do not have to be taken all at once.

Ms. Rebecca Kidd asked whether ATSDR has a set of goals for how frequently data will be published. She said that a measurable schedule of outputs to give an idea of the Registry's progress and usability would be an incentive for PALS to take the surveys. In her experience, the surveys are easy to take.

Dr. Horton said that while they do not have a specific publication schedule, they intend to publish frequently, especially in the first years as the data come to fruition. He added that researchers can request data from the Registry to conduct their own analyses. ATSDR and CDC should not be the only sources for publishing the data. The Registry will be maximally used if others utilize the data as well.

Dr. Kevin Boylan asked how many more risk factor surveys can be added to the Registry.

Dr. Horton indicated that the Office of Management and Budget (OMB) evaluates the number of questions that the federal government can ask citizens so that respondents are not overburdened. The Registry is approaching what might be considered the time limit, but they can create new modules and replace old ones. It is important to continue asking questions without causing undue burden.

Dr. Kaye added that the OMB rules are not hard and fast, as the rules are concerned with overall burden, which is set at approximately one and one-half hours to complete all of the surveys at once. At present, it is estimated that completing the registration process and all 15 current surveys would take approximately 83 minutes. Because of the unique structure of the surveys included in the Registry, they may have some flexibility and the ability to make a compelling argument to exceed the 90-minute limit.

Dr. Horton said that ATSDR would love to ask 100 different surveys, and PALS would likely provide that information gladly. The community of PALS is dedicated to helping contribute to knowledge about the disease.

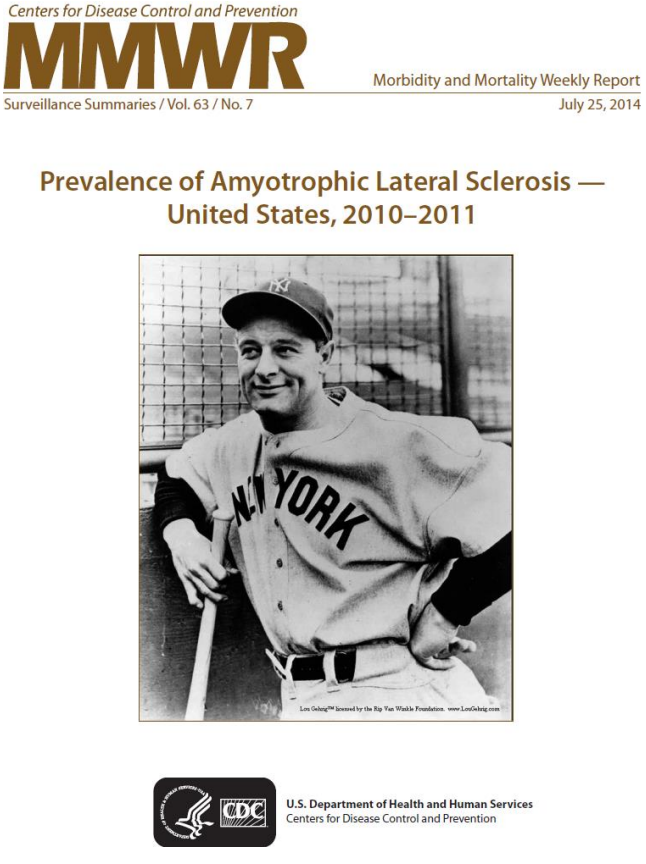
Mr. Ted Harada said that the Research Notification Mechanism of the National ALS Registry is a great tool that represents a win-win for researchers and patients. He recalled participating in a Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS) Webinar. The presenters indicated that they were struggling to enroll patients in a trial, and he asked whether they were utilizing the National ALS Registry. The doctors were not aware that the tool exists.

Dr. Horton said that ATSDR is trying to message to a variety of groups, including AAN, NEALS, and clinic directors for different groups, but they still need help sharing messages about the Registry. They could consider a joint webinar with other groups for clinical directors to educate them about the Registry and its tools.

First Report on Registry Results

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

Dr. Paul Mehta presented the results from the first surveillance summary report from the National ALS Registry. The report was published on July 25, 2014 in *MMWR*, which is CDC's primary public health journal.


Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Surveillance Summaries / Vol. 63 / No. 7
July 25, 2014

Prevalence of Amyotrophic Lateral Sclerosis — United States, 2010–2011

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

MMWR often focuses on surveillance summaries as well as on trends and patterns. Working with *MMWR* editorial staff allows for a timeline for publication. Through *MMWR*, there is no cost to the public to review the report. Further, publishing in *MMWR* allows for tandem publication with other journals, such as the *Journal of the American Medical Association* (*JAMA*), *Annals of Internal Medicine*, and *The American Journal of Public Health*.

The first report from the Registry includes data from October 19, 2010 through December 31, 2011. The next report will include data from 2012. In the time period covered by the first report, 12,187 persons were identified as having definite ALS via the Registry, which includes the national databases and the web portal. The prevalence rate of ALS was 3.9 cases per 100,000 persons, using 2011 Census data for the denominator. ALS was more common in whites, males, non-Hispanics, and persons 60 through 69 years of age. Males had a higher

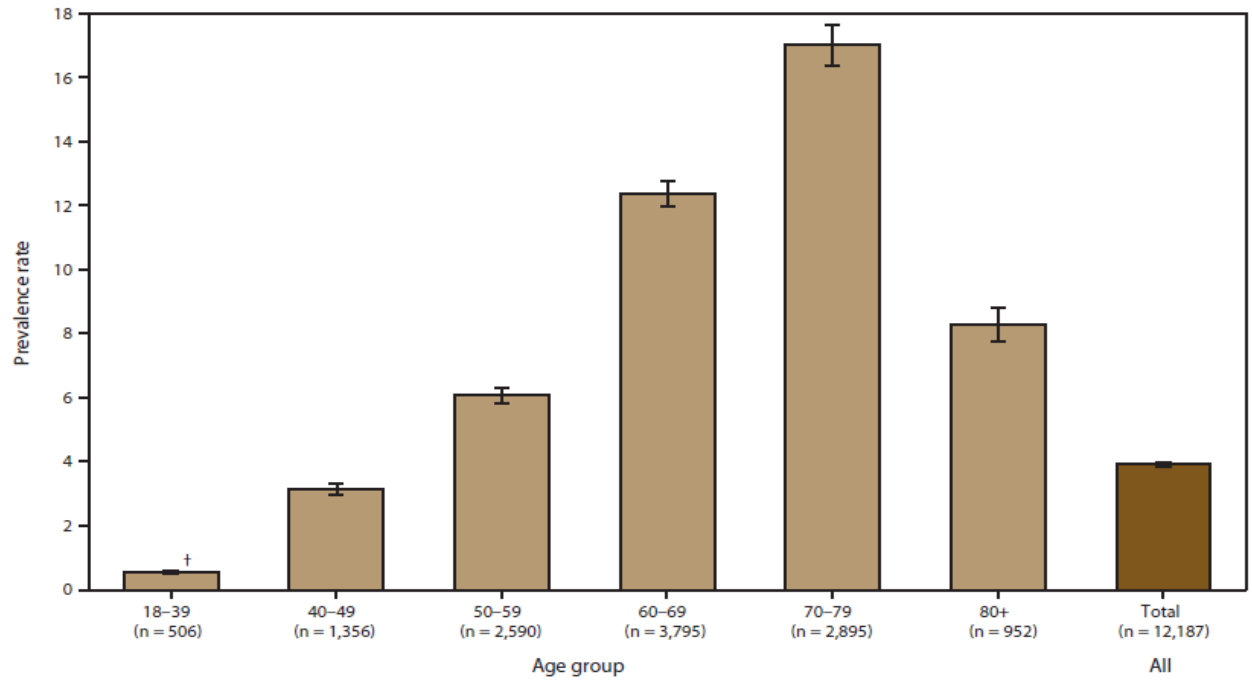
Number and percentage of identified cases of amyotrophic lateral sclerosis (ALS), by source, age group, and sex – National ALS Registry, United States, October 2010-December 2011

	Web portal only		National databases only		National databases and portal		Total*	
Characteristic	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Age group (yrs)								
18–39	186	(9.7)	252	(3.0)	68	(3.8)	**506**	**(4.2)**
40–49	396	(20.6)	749	(8.8)	211	(11.8)	**1,356**	**(11.1)**
50–59	616	(32.0)	1,476	(17.4)	498	(27.8)	**2,590**	**(21.3)**
60–69	457	(23.7)	2,703	(31.9)	635	(35.5)	**3,795**	**(31.1)**
70–79	152	(7.9)	2,411	(28.5)	332	(18.6)	**2,895**	**(23.8)**
≥80	27	(1.4)	880	(10.4)	45	(2.5)	**952**	**(7.8)**
Unknown†	92	(4.8)	1	(0)	—	(0)	**93**	**(0.8)**
Total	**1,926**		**8,472**		**1,789**		**12,187**	
Sex§								
Male	1,141	(59.2)	5,158	(60.9)	1,110	(62.0)	**7,409**	**(60.8)**
Female	785	(40.8)	3,280	(38.7)	675	(37.7)	**4,740**	**(38.9)**
Unknown†	—	(0)	34	(0.4)	4	(0.2)	**38**	**(0.3)**
	1,926		**8,472**		**1,789**		**12,187**	

* The number of registrants in the web portal only was 1,926 (15.8%), the number of registrants in the web portal and national databases combined was 1,789 (14.7%), and the number of cases identified through national databases only was 8,472 (69.5%).
† Missing age or sex.
§ Sex does not match consistently across databases.

prevalence than females. Prevalence increased with age, with the highest prevalence among persons 70 through 79 years of age. The lowest number of ALS cases was among persons aged 18 through 39 and over 80 years. In the portal data alone, the highest prevalence was among persons aged 50 through 59. The ALS patients in the national administrative databases tend to be older than those in the web portal. Most of the cases in the Registry came from the databases. These findings are consistent with other registries and with small-scale epidemiological studies. A National Institutes of Health (NIH) study found a prevalence rate of 4 per 100,000. A smaller study in Missouri found a prevalence rate of 3.9 per 100,000.

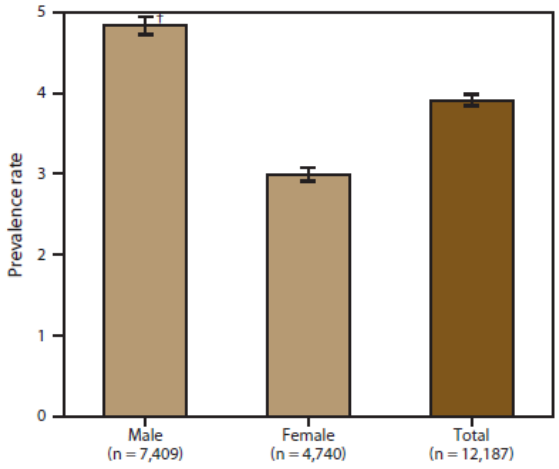
Prevalence rates* for cases of amyotrophic lateral sclerosis (ALS), by age group — National ALS Registry, United States, October 19, 2010–December 31, 2011



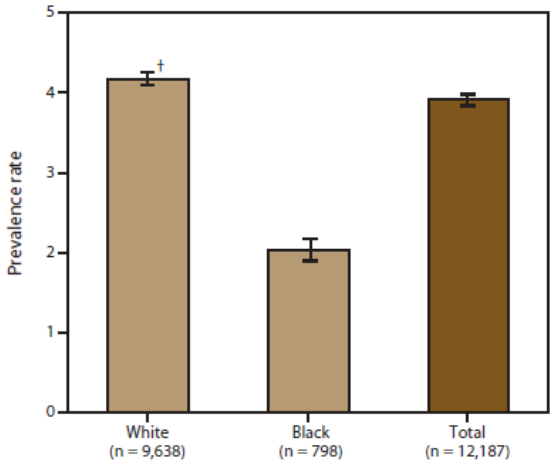
* Per 100,000 population.
† 95% confidence interval.

Males had a higher prevalence rate overall of 4.8 per 100,000 persons and a higher prevalence rate across each data source. The prevalence rate among females was 3.0 per 100,000 persons. The ratio of males to females was 1.56. Race was known in 10,971 cases. Of the cases, 79.1% were white and 6.5% were black. Prevalence among whites was twice that of blacks, with a 4.2 per 100,000 persons rate among whites and a 2.0 per 100,000 rate among

Prevalence rates* for cases of amyotrophic lateral sclerosis (ALS), by sex, and race - October 19, 2010 - December 31, 2011



* Per 100,000 population.
† 95% confidence interval.



* Per 100,000 population.
† 95% confidence interval.

blacks. The web portal alone is not representative of all PALS due to differences in age of those registering and because a higher proportion of whites registered in the web portal.

Smoking history was provided by 1647 respondents, and half of respondents were either former or current smokers. Half were nonsmokers. Alcohol history was provided by 1640 respondents. Approximately 40% of respondents identified themselves as current drinkers, 40% as former drinkers, and fewer identified themselves as nondrinkers. Education history information was provided by 1828 respondents. Of these, 71% reported education levels of high school or beyond. Military history was provided by 1651 respondents, with 23% having served in the military. Of the 1711 respondents to questions regarding employment status, 45% were disabled; 31% were retired; and 15% were currently employed full-time. The job titles held for the longest period of time were educators and healthcare professionals, and the industries worked the longest period of time were professional, scientific, and technical services, followed by healthcare and social assistance and education services. Information about potential risk factors is gathered for descriptive purposes only. No inferences are made regarding ALS. As the Registry matures, conclusions may be possible. Many published findings have addressed a potential link between ALS and military service. The national average of military service is 9.1%, and the data from the Registry indicate that 23.5% of respondents served in the military. Serving in the military is a possible risk factor, but more research is needed and no definitive etiologies have been identified.

There are limitations associated with the report. ALS is not a notifiable disease; therefore, under-ascertainment is possible. No surveillance system can capture all cases of a disease. Pilot studies leading to the launch of the Registry showed a sensitivity and specificity of 87% and 85%, respectively. Additionally, the merging of datasets represents a potential limitation, as there can be errors in misspelling of names, duplicate records, and data entry errors. Even if these errors are present, the conclusions are not likely to be affected.

Incidence cannot be determined, as the date of diagnosis is not available in the national administrative databases. The Web portal asks participants to self-report their date of diagnosis, but there is the potential for errors. ATSDR is undertaking other initiatives to examine incidence, such as the state-metropolitan projects. These projects can assess incidence at a smaller, geographical level. Incidence is currently available for the state of New Jersey. Further, the Registry is still maturing. It may not be representative of all ALS patients, but as more participants join the Registry, it may lead to a better understanding of ALS risk factors. The prevalence rate may also change.

An in-depth analysis of risk factors is planned. The data are being analyzed, and a paper is planned for external publication in Fall 2014 through Winter 2015. The paper will delve into risk factors, and associative factors, using additional survey information. The Future Report is planned for release in May 2015 to coincide with National ALS Awareness Month. It will include data from calendar year 2012 and make comparisons to the 2010-2011 report and share information from additional risk factor surveys and enhancements to the Registry.

Discussion Points

Mr. Ed Tessaro noted the reluctance to make inferences based on the Registry data, but he commented on the information regarding veterans and ALS. The VA drew a strong distinction between ALS and military service in 2008, and he wondered about the hesitance to draw conclusions from the Registry.

Dr. Mehta agreed that published reports establish that persons who served in the military have a higher potential for ALS, and 23% of respondents in the Registry indicated a military history. The report cited those published reports, but there is no definite etiology between ALS and military service, so they are careful. For instance, it is not clear what exposures veterans experience that make them more likely to get ALS. They hope to discover those relationships in the future.

Dr. Brooks said he assumed that all persons included in the prevalence estimate were alive at the time, but noted that the report did not specify that detail. This report represents the first analysis of live patients. Most previous analyses have been conducted on mortality data. The ALS population needs to understand how rich and important this step forward is.

Dr. Mehta agreed that the report should have specified that the patients were alive at the time of reporting. Dr. Kaye concurred that not making that clear was an oversight.

Dr. Ed Kasarskis commented on the limitations of using a computer-based web portal. Many patients in his clinic, which is in a poor state, are not connected to the web. Their information on risk factors and other issues is important, and the web portal does not reach them. It is important to exercise caution in interpreting the findings regarding risk factors gathered from the web portal.

Dr. Mehta agreed and noted that the penetration of web access varies according to several factors, including socioeconomic status. A paper-based questionnaire survey could be a useful addition to their approach.

Dr. Horton indicated that ATSDR funded MDA and The ALS Association, groups that work with PALS on a daily basis and often in rural areas, to purchase tablet computers as they go to areas where people may not have Internet access to help them enroll in the Registry. Some clinics also have computers set up so that PALS can enroll in the Registry there. ATSDR welcomes input regarding strategies for reaching hard-to-reach populations.

Dr. Bradley congratulated Dr. Mehta and the staff on the publication of the first report. He thinks of the national administrative databases as the complete gold standard that collects all ALS cases; however, the Registry includes 1926 cases that enrolled via the Web portal who were not included in the national databases.

Dr. Kaye indicated that four groups participated in the pilot project leading up to the launch of the Registry: the Mayo Clinic, the state of South Carolina, Emory University, and a consortium of nine Health Maintenance Organizations (HMOs) across the country. Based on their individual reviews, the groups felt that 80% of ALS cases would be identified via the national databases. The portal was designed to find the other 20% of cases, not to capture all ALS cases. The national databases do not capture all cases. Persons with ALS are eligible for Medicare immediately after they receive their Social Security Disability Insurance (SSDI), but not all persons apply for benefits. Some people will not be eligible for Medicare because they did not work enough quarters. In years past, only 20% of veterans qualified for VA medical care, so there is the potential to miss cases. The portal appears to be successfully discovering patients who are younger and who have either not qualified for benefits or who have not chosen to take them. The Registry only includes patients who are alive, so it does not incorporate data from the National Death Index (NDI). The 2012 report will utilize the NDI to adjust the prevalence estimates. The NDI cannot identify cases, but it can provide status based on a list of names.

Dr. Jodi Wolff asked about the cases that the Registry is missing and whether the prevalence rate has been adjusted to accommodate the specificity and sensitivity of 85% and 87%.

Dr. Kaye clarified that sensitivity and specificity are not related to the number people that the Registry will capture; rather, they are related to the accuracy of the cases that are captured. About 87% of the time, a case identified as having ALS really has it and 85% of the time, the cases that were omitted from the Registry should have been omitted. The 20% estimate was based on the individual pilot projects which compared data from individual clinics with national database data. The prevalence rate has not been adjusted, but capture-recapture analyses will address that question. Another project will compare the actively-collected cases from the state-metropolitan projects to the national databases to learn about the cases that are missing.

Dr. Mehta said that the prevalence rate in the first report will likely increase in future reports that will include more data and because PALS are living longer with better care.

Ms. Abrams commented that different groups report different statistics about prevalence. Organizations should use the same standard of numbers. Different government agencies report in different ways as well. Dr. Mehta agreed and noted that the NIH recently updated their statistics.

Mr. Harada asked about the incidence rate for the state of New Jersey. Dr. Mehta said that the New Jersey Department of Health published that information, which was determined as part of the state-metropolitan projects. Dr. Kaye added that the department of health did a great deal of work, and the paper will be published in the *Journal of Neuroepidemiology*.

Mr. Patrick Wildman said that there is more to the Registry than the prevalence rate. The ALS Association has worked to inform people that the first report only represents one year of data, and as more data are gathered and analyzed, they will have a better sense of its accuracy. Further, as information is received from the state-metropolitan projects and compared to the National ALS Registry, the prevalence rate will be more certain.

Dr. Mehta noted that the Registry is mandated to collect information on risk factors: "causes … can someday lead to cures." The Registry is also actively funding research to reach potential causes and cures.

Mr. Tessaro said that the number is very important for raising funds, if not for science related to the disease. He raised funds for cystic fibrosis before his diagnosis with ALS. Approximately the same number of people have cystic fibrosis as ALS (30,000). If the number is 60,000, then more attention and funding can be brought to the problem. Fundraisers are competing with major diseases that touch the lives of families everywhere. Having a concrete number makes an impact with foundations and funders which support research and care.

Dr. Mehta noted that MDA and Les Turner are on the front lines. Their collaboration is critical to share messages with PALS.

Dr. Bradley said that from a public relations and fundraising point of view, the incidence rates are not as relevant as the number of deaths that occur. For instance, in the 50 through 75 age group, one in 150 to 250 deaths is due to ALS. That message is powerful and shows that ALS is not a rare disease, but one that is deserving of attention.

Dr. Brooks encouraged ATSDR to publish all of its papers in open-access journals like the *MMWR* and others. He suggested that funds be set aside to make the state-based work open-access as well.

Dr. Mehta agreed and said that the work does no good if PALS, caregivers, and other stakeholders cannot access it.

Dr. Horton said that many of the journals have copyright considerations, but while the journals own the formatting, they do not own the content. The content was generated by government employees and is owned by the government.

Ms. Kidd said that the private sector sets goals and works across organizations to achieve them. There are opportunities in marketing and communications for the Registry so that a layperson can respond to the information as well as a scientist or statistician. She uses the statistic that ALS is 100% fatal. Breast cancer, in contrast, is 98% curable. She offered her assistance in coordinating efforts across organizations and stakeholders. Marketing and communications can be done inexpensively.

Mr. Harada recalled that many of these conversations regarding marketing have been taking place for some time. He hoped that their "takeaways" from this meeting would include action items in this area. He agreed that the story is important, but there is also great interest in the prevalence rate. When the number was released, there was no context to help people understand what they meant. Individuals and organizations need help framing the story and the numbers.

Mr. Wildman agreed and said that The ALS Association and MDA have monthly calls to talk about these issues. With the release of the report, it is critical that they have consistent messaging to raise awareness about the disease and the Registry.

Dr. Kaye said that personnel from New Jersey who were watching the stream of the meeting forwarded her the incidence rates from their state: the crude average incidence rate in New Jersey for the three-year time period was 1.87. The average age-adjusted incidence rate, which takes into account the age distribution of New Jersey, was 1.67. Point prevalence on December 31, 2011 was 4.40. She explained that the first cancer registries were created in 1982-1984, and they were not allowed to publish data until they had been active for three years. The first two years of data were not published because of the feeling that it takes that long for a registry to mature. They are confident about their data from the first year of the Registry, but as time goes on, the results will be more accurate and more stable. Because of the nature of ALS, they did not want to delay publication, but the results will be even better in the future.

Mr. Steve Derks asked about follow-up efforts to drill down on risk factors and how that information will be interpreted and shared. He understood the challenges associated with making connections between risk factors and ALS, but staff on the ground will be asked about these issues if the numbers are released without guidance.

Dr. Mehta said that ATSDR is actively working on risk factor analysis and on making associations. A paper is slated for publication in Fall 2014 – Winter 2015. That paper will present some assumptions and associations regarding military service and ALS, as well as smoking and alcohol.

Dr. Horton encouraged researchers to utilize and analyze data from the Registry. ATSDR is conducting "30,000-foot views" looking at risk factors, and other researchers can create other, more specific studies about military service or certain occupations. ATSDR is a small group that cannot do all of the work, but they are eager to share the data. The Registry can also serve as a recruitment tool to learn more about a given topic.

Ms. Alicia Charleston asked whether the algorithm allows for a breakdown of where the respondents came from and whether the data could be shared by state.

Dr. Kaye replied that some respondents are included in the Registry based on only one criterion, while others qualify under multiple criteria, and across multiple data sets.

Dr. Horton added that state-by-state breakdowns are a goal of the Registry, but they hope to build the numbers further before conducting those analyses. In the meantime, they are interested in comparing the national data with state data. These comparisons will be interesting, particularly with states such as Massachusetts where ALS is a mandatory-reportable disease.

Mr. Josh Von Schaumburg asked about plans to integrate state-based surveillance programs into the Registry.

Dr. Mehta said that information from the state-metro projects will be qualitatively and quantitatively compared to the Registry.

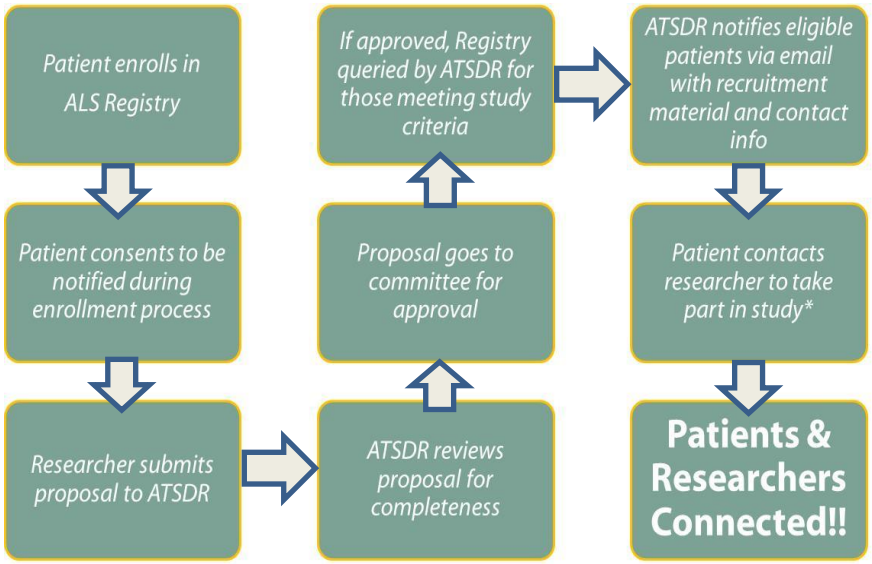
Dr. Kaye said that the data from state systems will not be integrated into the Registry, per their agreements and approvals with Institutional Review Boards (IRBs). The data collection for the Registry was conducted under a waiver of informed consent. The time periods of collection are different among the systems as well.

Research Notification Mechanism Update

Vinicius C. Antao, MD, MSc, PhD
Lead, Registries Team
Environmental Health Surveillance Branch, DTHHS
Agency for Toxic Substances and Disease Registry

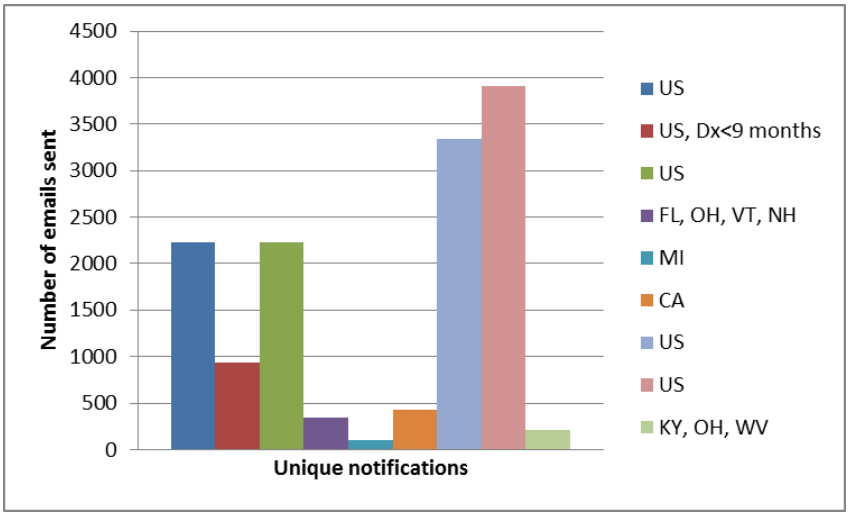
Dr. Antao explained that the Research Notification Mechanism was introduced in the National ALS Registry with the objectives of linking researchers with PALS, facilitating their interaction, and expediting the process of recruitment. The process begins when PALS enroll in the Registry and give consent to receive notifications about research projects. Researchers can submit proposals to ATSDR via an online form, including a research protocol that has been approved by their institution's IRB and other documents. The proposal is reviewed by an approval committee. If the proposal is approved, then ATSDR queries its database according to the criteria of the study and forwards recruiting materials from the researchers to PALS. If the PALS are interested in participating in the study, then they contact the researchers.

Research Notification Mechanism



The Research Notification Committee includes internal and external specialists and is comprised of eight neurologists, two statisticians, four epidemiologists, two ethicists, two ALS family members, and four laboratorians. Since the research proposals have already been approved by the institution's IRB, CDC IRB approval is not required, which expedites the process considerably. Several notifications have been released since February 2013, when the mechanism became available. The response from PALS to the notifications has been strong and positive.

Number of Notifications since 02/2013



The number of days between ATSDR receiving the application from the researcher and sending emails to PALS has been decreasing. At present, it takes approximately 30 days from receipt of a successful application to the date emails are sent to PALS. The applications received since November 2012 represent different kinds of studies:

Applications since 11/2012

Study Name (n=9)	Institution	Investigator
Risk Factor Analysis in ALS	Medical University of South Carolina	David Stickler, MD
Phase II/III, Randomized, Placebo-Controlled Trial of Arimoclomol in SOD1+ Familial ALS	University of Miami	Michael Benatar, MD, PhD
Mindfulness, Psychological Well-being, and Physical Degeneration in People with ALS	Harvard University	Ellen Langer, PhD
A Spatial Analysis of ALS in Florida, Ohio, New Hampshire, and Vermont	Dartmouth-Hitchcock Medical Center	Elijah Stommel, MD, PhD
Mexiletine for the Treatment of Muscle Cramps in ALS	University of California, Davis	Björn Oskarsson, MD
Epidemiologic Risk Factors and the Genetics of ALS	University of Michigan	Eva Feldman, MD, PhD
The Experimental Treatment of Bulbar Dysfunction in ALS	Center for Neurologic Study	Richard Smith, MD
The Natural History and Biomarkers of C9ORF72 ALS and Frontotemporal Dementia (FTD)	National Institute of Neurological Disorders and Stroke/National Institutes of Health	Mary Kay Floeter, MD, PhD
Developing a Satellite ALS Center at a Remote Site Incorporating Regional Resources and Telemedicine	University of Kentucky	Edward Kasarskis, MD, PhD

Dr. Antao presented a brief summary of each study that used the Research Notification Mechanism.

A paper recently accepted by *Muscle and Nerve* describes the first research notification conducted with the Medical University of South Carolina. The investigators in that project were impressed by the speed of the notification process and co-authored the paper with ATSDR.

Future enhancements include the development of a computer interface for the research notifications. The process is now somewhat cumbersome, as it requires a manual search of the database, data dump, and manual application of the research criteria. ATSDR staff also double- and triple-check the patient list before the emails are sent to ensure that the patients fulfill the research criteria, have agreed to be notified, and are still alive. A future interface will apply research criteria to the patient pool so that the time between receipt of research applications and the patient notification will be even shorter.

Discussion Points

Dr. Bradley asked how ATSDR ensures that patients are alive. He asked about the proportion of emails sent as compared to the number of patient responses received by the investigators.

Dr. Antao answered that the Registry can only determine whether patients are alive to a certain extent, as they may receive notifications from family members of ALS patients who have died. They will also check the Registry data against the NDI to update the status of Registry enrollees. Regarding feedback, some research studies do not build that question into their protocol. There may be no formal way to determine how the study participants learned about the research studies. ATSDR receives communications from researchers and asks for an estimate of how many participants contacted them because of the Registry mechanism. All of the patients in the South Carolina study were involved because of the mechanism. The Harvard study had good representation from the Registry as well. Other studies had fewer participants from the Registry, but all of the information is anecdotal.

Dr. Bradley asked whether researchers can contact the next-of-kin of patients who have died.

Dr. Antao replied that there is no mechanism for that contact. The Registry only includes one email address per participant, and that address could belong to the patient or to a family member.

Dr. Eva Feldman said that the response to her study in Michigan was not as robust as the response to the South Carolina study. She wondered whether the *Muscle and Nerve* paper includes best practices.

Dr. Antao said that the response depends on the number of patients who enroll in the Registry from certain areas. There is considerable variety in state enrollment. Michigan does not have a very high rate of enrollment in the Registry.

Dr. Feldman hoped that they could discuss these issues further, because it is important for individuals who direct ALS centers to understand the best practices of states with good enrollment.

Dr. Antao said that ATSDR sends lists of states and their enrollment statistics to its partners with The ALS Association and MDA on a monthly basis. This communication helps make partners aware of the regions that need additional outreach and awareness-building regarding the Registry.

Dr. Horton added that the South Carolina study included the entire country, so its response was larger. The Michigan study focused only on Michigan, which could explain some of the differences in response rates.

Dr. Robert Bowser suggested developing a metric to determine how many emails from the mechanism result in contact with researchers and enrollment in studies. He said that many studies include controls that are spouses or family members of patients. He wondered whether there are limitations on those persons becoming enrolled in a study based on the email from the Registry.

Dr. Antao did not believe that there would be a limitation on that enrollment. It would be up to the patient and the next-of-kin. The emails facilitate the process of recruitment.

Mr. Josh Von Schaumburg said that when his brother Eric was diagnosed 14 months ago, each clinic they visited encouraged that he enroll in the Registry. No one mentioned, though, that registration could lead to contact for experimental drugs. After the diagnosis, they were eager to find clinical trials. They would have been more incentivized to register if they had known about that feature of the Registry.

Dr. Antao said that their social media posts and marketing could be framed to ensure that patients are aware of that benefit of the Registry, and he thanked Mr. Von Schaumburg for sharing his insight.

Risk Factor Data Analysis

Leah Bryan
Statistician
Carter Consulting, Inc.

Ms. Bryan reminded the group that the National ALS Registry has two components: the national administrative databases and the secure web portal. The purpose of the portal is to ascertain cases not included in the administrative databases and to collect individual-level demographic and risk factor data. The results she presented were only from the risk factor surveys in the portal and did not include information from the national databases in the time period October 2010 – December 2011. The results were from surveys on:

- Demographics (49.2% participation rate)
- Smoking and alcohol use history (44.4% participation rate)
- Military history (44.6% participation rate)
- Occupational history (46.2% participation rate)
- Family history of ALS, Alzheimer's disease, or Parkinson's disease (43.6% participation rate)

The results of the demographic survey are reflected in the following table:

	n	%
Current Age		
18-39	87	4.8
40-49	296	16.2
50-59	595	32.5
60-69	566	31.0
70-79	247	13.5
80+	35	1.9
Race[1]		
White	1735	94.9
Black	34	1.9
Other	50	2.7
Unknown	9	0.5
Ethnicity[2]		
Hispanic or Latino	44	2.4
non-Hispanic or non-Latino	1775	97.0
Sex		
Male	1121	61.3
Female	707	38.7
Educational Attainment		
Less than HS	38	2.1
HS graduate or GED	341	18.6
Technical or trade school diploma	105	5.7
Some college	372	20.3
College graduate	601	32.9
Graduate degree	334	18.3
Other	37	2.0

Regarding the cigarette smoking and alcohol consumption survey, the respondents were approximately half nonsmokers and half current or former smokers, or "ever smokers." More than half of the "ever smokers" had greater than or equal to 15-pack years, which is defined by the number of packs smoked per day by the number of years. Regarding alcohol consumption, most respondents were light drinkers.

The national estimate for veterans in the US population is approximately 9%. The respondents in the Registry Web portal were more often veterans, with a rate of 23.5%. The survey also asked about the branch of military, and Army, Navy, and Air Force had the highest frequency of respondents. Of the veteran respondents, 34% had been deployed to the war arena. Afghanistan was the most frequent location of deployment, followed by Vietnam. It is surmised that Afghanistan has a high rate because the respondents to the Web portal tend to be younger, and that conflict is more recent than others.

Regarding occupational history, 75% of respondents are retired or disabled, which is expected given the disabling nature of ALS. The years of longest-held employment are evenly distributed. Family history was calculated by determining how many respondents had at least one first-degree relative with ALS, Alzheimer's disease, or Parkinson's disease. Approximately

Occupational History

	n	%
Employment Status		
Full-time employed	248	14.5
Part-time employed	72	4.2
Retired	532	31.0
Disabled	770	44.9
Full-time student	3	0.2
Homemaker	34	2.0
Unemployed	27	1.6
Other	26	1.5
Years of Employment at Longest Held Occupation		
<= 10 years	260	15.2
10 < time <= 20 years	488	28.5
20 < time <=30 years	497	29.0
> 30 years	415	24.2

5% of the survey respondents had a first-degree relative with ALS: 13% with Alzheimer's disease and 5% with Parkinson's disease.

Discussion Points

A meeting attendee asked whether the survey asked about the age of diagnosis of first-degree relatives with Alzheimer's disease. Ms. Bryan answered that the survey did ask about the age of diagnosis, but the analysis only considered whether the relative had the disease.

Dr. Bradley said that the dramatic bias of the web portal toward white non-Hispanics may prove problematic for the Registry's breath of analysis of the entire US population. He was interested in the high proportion of veteran respondents who had been involved in more recent wars. The literature has suggested, based on the "incubation period" derived from the Persian Gulf experience that the signal disappears after approximately 10 years of military service. The

Registry results support the idea that ALS is an acute phenomenon in terms of exposure, rather than a long history of exposure.

Dr. Brooks asked about differences in the demographics between those who did and did not respond across the different surveys.

Ms. Bryan replied that the analysis has not been conducted, but it is "on the radar."

Dr. Kaye said that in the process of applying for OMB approval for three more years of data collection, they shared information on takers and non-takers of surveys. The demographics are fairly similar, with no strong differences in age and sex. The distribution by state was almost identical.

Dr. Eric Sorenson said that the age distribution may not account for the higher proportion of veterans reporting deployment in Afghanistan, as the second Persian Gulf conflict was essentially concurrent, and the demographics of the veterans are likely to be similar. There is much less representation from the second Persian Gulf conflict in the Registry than from Afghanistan.

Mr. Gibson asked if the results could be shared electronically.

Dr. Kasarskis recalled the first Gulf War study, in which the denominator was nearly 800,000 people who went to the Persian Gulf for one year. That number is larger than reported numbers of personnel in Afghanistan and Iraq at any single point in time. He agreed with Dr. Bradley's comments regarding the incubation period. Within the boundaries of the first Gulf War study, the period was within approximately five years after the period of deployment. Veterans from other conflicts represent an aging population, so the demographic is shifting to a more at-risk denominator for developing ALS. He commented on the issue of who is included in the VA database. The Paralyzed Veterans of America has been very active in the effort to register veterans who may not have received care through the VA system. The VA files are likely to be accurate regarding case ascertainment. People found through the VBA database may or may not take the risk factor surveys, but they are likely to be included in the Registry.

Dr. Brooks felt that it would be important to analyze the clinical surveys, particularly regarding the clinical site of onset of those enrolling in the Registry; the type of disease relative to the age distribution of the Registry; and other aspects that will bring richness to the database. The El Escorial Criteria (EEC) are also important, and studies on the EEC are available from the state registries. Other research is ongoing regarding ALS-Plus, which is ALS with other neurological disease entities. This subset may have different therapeutic treatment implications. There are many ways to enrich the Registry in the future.

Mr. Tessaro commented that one of the principal ALS researchers in the country, Dr. Richard Bedlack of the Duke University ALS Center, has been elected to the VA National ALS Committee. His participation with the VA will be highly beneficial.

Outreach Challenges

D. Kevin Horton, DrPH, MSPH
Chief, Environmental Health Surveillance Branch, DTHHS
Agency for Toxic Substances and Disease Registry

Dr. Horton solicited information and input to ensure that the National ALS Registry has maximal impact and reaches as many PALS as possible. He asked the group to consider the question: How do we reach people who are not covered by Les Turner, MDA, and The ALS Association?

A high percentage of PALS are reached by one or more of those organizations, but some are not. Messages shared via social media are not received by people with limited or no access to a computer, for instance.

Discussion Points

Mr. Harada is the Public Policy Chair and Patient Services Chair for the ALS Association of Georgia. Noting that Georgia is below the curve in respondents to the Registry, he asked whether information is available on a more specific, regional basis within the state so that he can concentrate his recruitment efforts.

Dr. Horton replied that until the first report was published, ATSDR was not able to release those numbers. They are now more able to drill down and provide that information to organizations and support groups, realizing that the numbers will not be 100% complete. He agreed that a more honed-in approach would be helpful.

Dr. Kaye said that the Registry does not have county-level data. They could analyze state numbers based on regions or areas, such as the western part of a state. They have learned from the state-metro projects that if a person with ALS does not live in a metropolitan area, there is only approximately a 50-50 chance that he or she will go to a referral center. She guessed that the further from a metropolitan area, the more likely that people have not enrolled in the Registry because they are not aware of it.

Mr. Harada agreed and said that he would appreciate information on where to focus in a large state. He observed that best practices information from states that are excelling at enrollment would be helpful as well.

Dr. Horton concurred that some ALS Association and MDA chapters are finding more success than others. Engagement is critical. Now that the first report is complete, they can work to provide data below the state level to be helpful without jeopardizing confidentiality.

Ms. Kidd said that in human behavior, "you tend to get what you inspect, not what you expect." Making enrollment as simple as possible for clinics and the organizations and providing incentives could be beneficial. Clinics may be motivated by a volunteer program to help collect data so that their personnel are not overburdened. The approaches could be published in a manner that values the contribution and appeals to people's competitive spirit.

Dr. Horton agreed and noted that the organizations can learn from each other's creative approaches to pool resources to saturate the population.

Dr. Brooks suggested that outreach should be targeted. ALS patients are surviving longer, and subgroups of long-surviving ALS patients could have specific outreach to encourage them to enroll and to enrich the datasets. Clinics could be encouraged to reach out to patients that are not in the Registry.

Dr. Sorenson commented on the demographic differences in the Registry and pointed to the under-representation of minorities in the database. Outreach could be targeted not just geographically, but also to those who have challenges associated with access to care. Clinics and researchers struggle to achieve adequate representation of the population.

Mr. Wildman said that The ALS Association has been considering how to reach minority populations and people who are not going to clinics, and how to learn where they are going. One of their strategies has been to work with religious and other community groups, as these patients may receive support through their communities and not through an ALS Association clinic or chapter, or an MDA chapter. He agreed that information below the statewide level to show differences among urban and rural areas will help inform their outreach strategies.

Dr. Horton said that some PALS are supported by The ALS Association, MDA, and Les Turner, but are not comfortable enrolling in the National ALS Registry. ATSDR must not cross a line and appear coercive in its outreach efforts. They can provide information about the Registry so that patients can decide to enroll. Physicians and neurologists can be helpful in this regard and include literature about the Registry in information that they provide to new patients.

Mr. Josh Von Schaumburg suggested that organizations could incentivize participation in various ways, perhaps via referral codes. The approach would have to be acceptable to the IRB.

Dr. Horton said that some people do not want to participate in the Registry, for whatever reason. The best that we can do is share the collective message about the Registry and what it provides.

Dr. Kasarskis asked whether data were available from the portal on how long patients have had ALS.

Dr. Horton said that the date of diagnosis is collected by the portal, but not necessarily in the national administrative databases.

Dr. Kasarskis commented on problems associated with patients having the stamina and/or the time to register. A rapidly progressive ALS patient is dealing with major issues that will have precedent above enrolling in the Registry. Those patients may be extremely informative regarding environmental exposure and lifestyle factors. That data will not be collected unless the patients are highly motivated and have strong family and financial support. By and large, patients who are newly diagnosed with ALS have already gone through nine to twelve months of progressive weakness before they receive a confirmatory diagnosis. It is important to understand this context when reaching out to them regarding the Registry. Over the long-term, future populations with ALS may understand the importance of the Registry, but there are still realities and challenges associated with the disease that must be understood. ATSDR and PALS should be commended for what the Registry has accomplished so far.

Dr. Horton agreed with the importance of sensitivity. It is not expected that newly-diagnosed patients will be immediately encouraged to enroll in the Registry. They need time to process

their diagnosis and their challenges. Clinic visits may be a more appropriate venue for education about the Registry.

Dr. Kasarskis said that the length of time that a patient spends at a visit to the multidisciplinary clinic is likely three to four hours. Clinicians and personnel are exhausted by the end of the day and may not be the right persons to assist with Registry enrollment.

Mr. Gibson said that more metrics are needed. Two sets of metrics are available now: a list of states in which nobody has enrolled within the past two months, and a list of states that are under-enrolled. Clarity regarding those definitions would be helpful.

Dr. Kaye answered that the metrics are based on the estimated average percentage of cases that are enrolled in the US as a whole. For instance, if the national enrollment is 50% of cases and a given state registered 45% of its cases, then that state is under-enrolled. The number is not based on other states' enrollment, but on the national percentage.

Dr. Brooks asked whether mortality data reported by states could be utilized retrospectively.

Registry Promotion and Outreach

National ALS Registry: Marketing Update

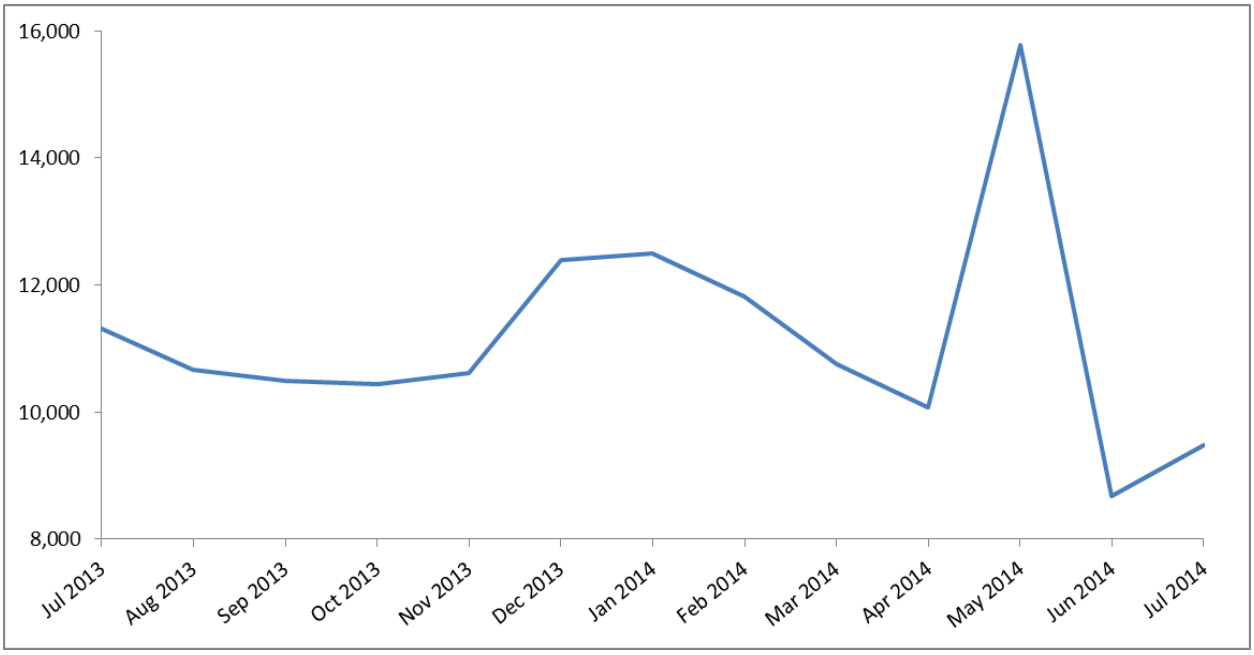
Marchelle Sanchez, MS
Health Scientist
Environmental Health Surveillance Branch, DTHHS
Agency for Toxic Substances and Disease Registry

Ms. Marchelle Sanchez provided an update on the last year of marketing for the National ALS Registry. The marketing strategy is to work with partners to generate awareness of the Registry. It is important to work with the right partners, and they have focused their strategy based on meetings and working with different individuals and groups. The strategy focuses on different audiences:

- ❑ PALS, the most important group
- ❑ Family members and caregivers
- ❑ Specialized health care providers such as neurologists and physical therapists
- ❑ ALS researchers who work with patients
- ❑ ALS support organizations and entities

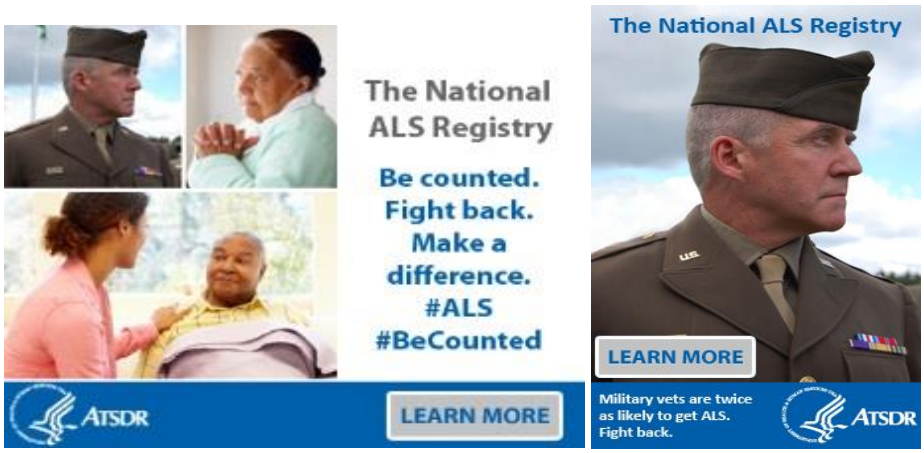
The total views of the National ALS Registry website are 249,353 from November 2010 through July 2014. There have been 136,034 views since 2013, which represents an increase of over 7,500 views from 2012-2013. There has been more marketing and outreach over the past year, which has driven the spike in traffic. May 2014 had 15,784 views, where May 2013 had 8,279. The spike in May 2014 corresponds to ALS Awareness Month. There was another, smaller spike in June – July 2014, which corresponds with the release of the *MMWR* report. As awareness of the *MMWR* report grows and more papers are released, it is likely that the website will continue to see increased traffic.

Monthly Visits to the National ALS Registry Web Site
July 2013 – July 2014



An ALS Service Locator App is available on the main ALS web page. The app is available on Apple platforms as well as Android platforms. The app has been downloaded on Apple platforms 349 times.

New Web buttons have been created for the Registry that focus on minority, athlete, veteran and rural populations. The new buttons also reach out to caregivers and incorporate Twitter



hashtags. The CDC Facebook page has approximately 319,000 followers, and the NCEH/ATSDR Twitter page, @CDCEnvironment, reaches approximately 10,000 people. The Registry does not have its own Facebook account because we can achieve bigger outreach using the CDC Facebook page and its established following.

The new Infographic was released in early 2014 and has received positive feedback:

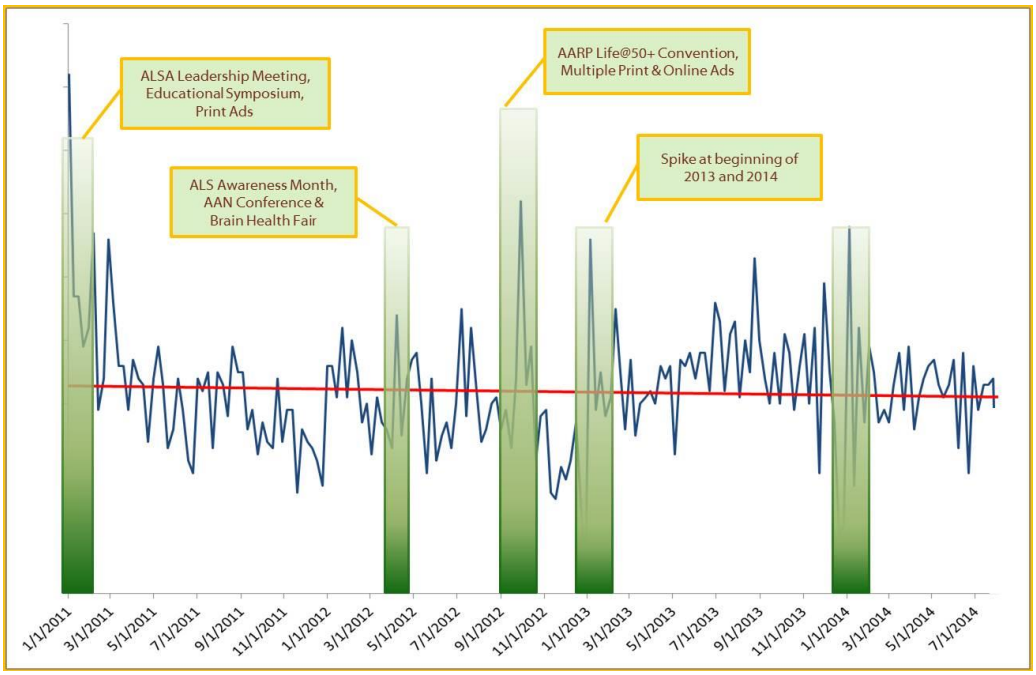
Registry marketing products include:

- ❑ Registry Infographic
- ❑ Patient Guides
- ❑ Provider Guides
- ❑ Fact Sheets
- ❑ Quick Start Guides
- ❑ Continuing Education Guides
- ❑ Doctor Office Posters

Overall, 46,000 of these products have been distributed by ATSDR via different organizations. The organizations themselves also have their own guides and products. The Provider Guide has been recently updated with information about the Research Notification Mechanism. Other products, including the Patient Guides, are in the process of being updated.

The graph on the following page depicts the number of new registrants in the Web portal and highlights spikes in enrollment during the time period since its beginning in January 2011 through July 2014. The first spikes correspond to The ALS Association Leadership Meeting and the opening of the portal. Another spike occurred in May of 2012 to coincide with ALS Awareness Month. November 2012 saw the AARP Convention and multiple print and online advertisements. Increases at the beginning of 2013 and 2014 may be due to the New Year. A spike in September 2013 correlates with increased outreach with MDA and The ALS Association.

New Registrants in National ALS Registry Web Portal
Jan, 2011 – Jul, 2014



ATSDR has been working on videos and Webinars, which are in the final stages of clearance and approval. One video to be posted on the website is "Veterans: Fight Back Against ALS," which includes an interview with a veteran with ALS. A second video is "Be Counted: Your Role in the Data Gathering Process." That video is an animated version of the Infographic, with a quick guide to the Registry and enrollment process. Three prerecorded Webinars include an overview of the Registry, the risk factor surveys and their questions, and the Research Notification Tool.

Traditional media outreach efforts include an article and advertisement in *Caregivers* magazine. The article was placed in the April 2014 issue. Another article was published via the North American Precis Syndicate (NAPS), which pushed it to 10,000 different publications and websites. So far, the article has been placed in approximately 2300 publications or outlets in all 50 states, Washington DC, and US territories, with an estimated readership of 1.8 million. Many of these outlets are small, weekly outlets in rural areas. There have been approximately 24.6 million unique visitors to the websites on which the NAPS article was published. A Spanish-language version of the article has been created and pushed to appropriate areas. ATSDR has identified ten priority publications for outreach regarding the Registry.

When the first report from the Registry was released in *MMWR*, ATSDR reached out to the medical correspondents of all of the major news networks. The Associated Press (AP) published a short article on the report, which drove coverage in approximately 80 news outlets, including MedScape, the Huffington Post, and others. There was an increase in overall website traffic when the report was released. There were 9475 hits to the Registry page in July 2014, an 800-visit increase from June 2014.

Amyotrophic Lateral Sclerosis Association

Steve Gibson
Chief Public Policy Officer
Patrick Wildman
Director, Public Policy

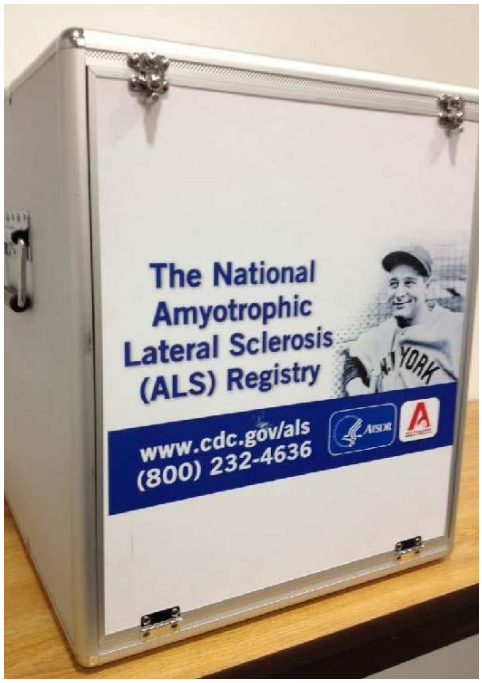
Mr. Gibson recalled that before the ALS Registry Act was introduced, its goals were established. A spreadsheet of people with ALS was not enough. The National ALS Registry should be a powerful research engine. This goal is still the goal of members of Congress, ALS researchers, and PALS. When The ALS Association works with decision-makers on Capitol Hill and in other contexts, they frequently hear that the Registry should not be just a database that is never used.

The ALS Association conducts a Listening Tour of each of its 38 chapters to learn about things that are important to PALS. The Association's chapters serve thousands of patients and provide input from the individuals and families in their service areas. Regarding the Registry, chapters indicated that some of the materials were not easy to read and to navigate. They also identified some challenges, including:

- Internet access
- Computer literacy, even in areas where there is Internet access, and concerns about information being lost
- Lack of resources and materials
- Limited knowledge of what a Registry is and does, including confusion about enrolling in the Registry versus enrolling with an ALS Association chapter or Medicare
- The nature of the disease

Based on the feedback from the Listening Tour, The Association created a National ALS Registry Toolkit, which includes promotional tools, information on the history and goals of the Registry, Frequently Asked Questions (FAQs), and computer tablets and hot spots.

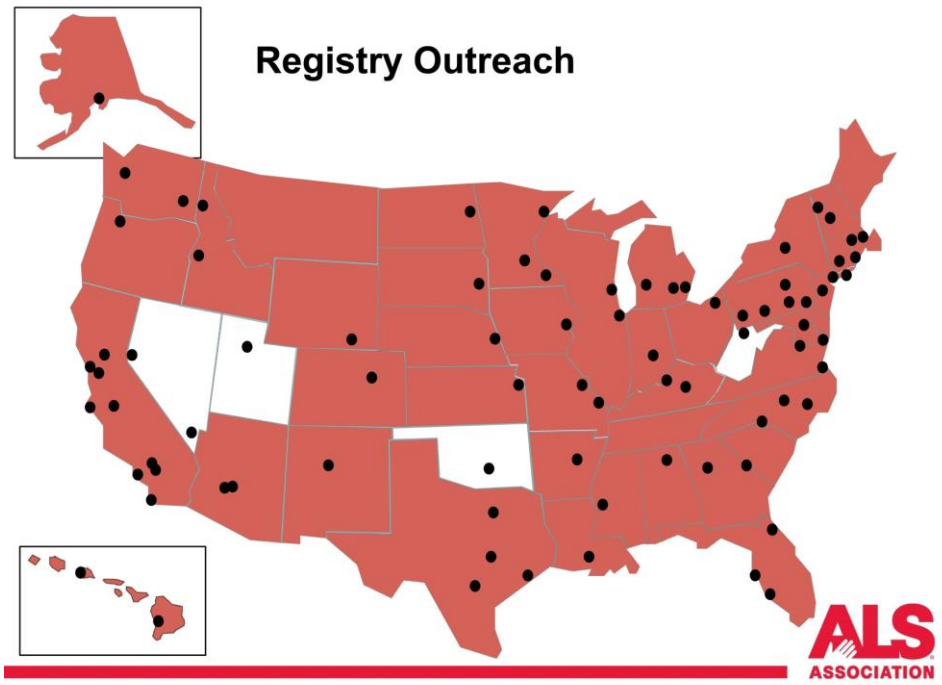
National ALS Registry Toolkit



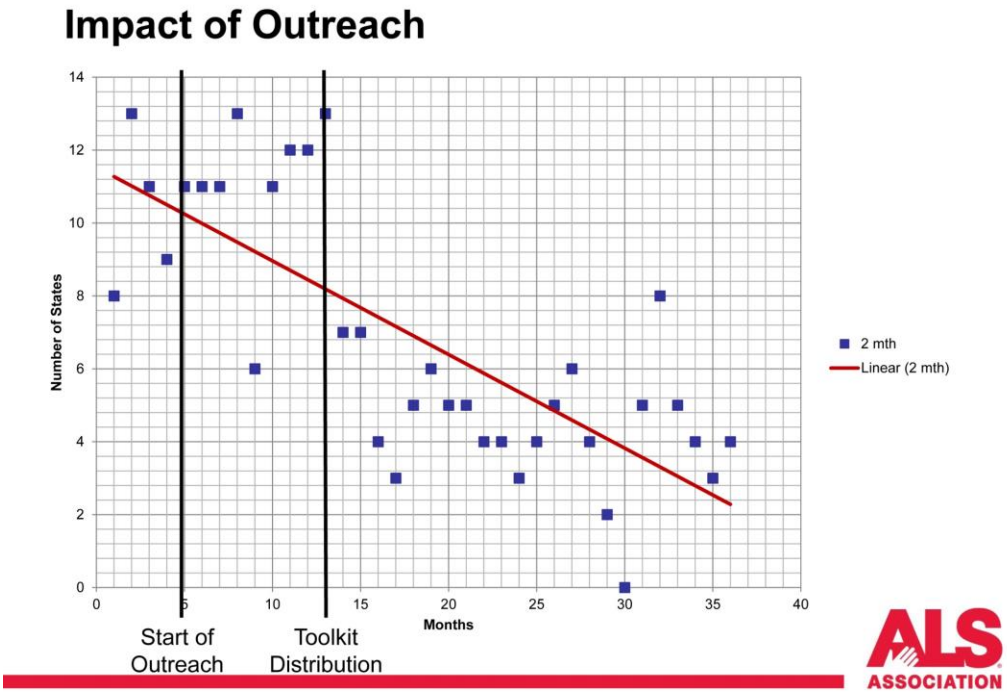
A binder in the toolkit includes information and materials that can be taken into the field so that advocates can explain the current modules, the interaction of the national databases and the web portal, and future plans. The toolkit also includes checklists to help chapters promote the Registry.

The Listening Tour also yielded best practices that chapters were using to promote the Registry to their patients. In one of the states that has never been under-enrolled in the Registry, one person diagnosed with ALS took it upon himself to visit every patient with ALS and get them enrolled in the Registry. Association chapters use the toolkit and checklists to enroll patients in the field. One chapter enrolled patients at a support group. Others devoted a room at its symposium to the Registry. The ALS Association has found that clinics are not the most opportune times to enroll people in the Registry, but clinics represent a good time to have contact with patients and answer their questions.

The ALS Association serves all of the US except four states, but ardent supporters in those four states have helped to spread the word about the Registry. Advocates have partnered with many minor league baseball teams to create a forum to share information about ALS.



All ALS Association chapters receive a monthly list of states that have not enrolled any PALS in the Registry for the last 2 months. The graph on the next page presents the impact of outreach efforts. As outreach efforts increased, fewer states saw no enrollments. In January 2014, every state had enrolled PALS in the last two months.



In addition to ALS organizations in different states, The ALS Association partners with health practitioners, neurologists, drug companies, professional organizations, and biotech companies among others.

Mr. Wildman said that The Association explored how to use its existing partnership with minor league baseball to promote the Registry. Minor league baseball has 160 teams throughout the US, and their attendance level was nearly 42 million during the past year. The teams are not necessarily in large cities, but in rural areas.

The ALS Association has worked with individual teams and the minor league baseball organization to develop a program that allows teams to hold ALS Registry events at parks during games. The program is turnkey, easy to use, and customizable to meet the needs of different teams and chapters. It includes on-field events, a booth to provide Registry materials, giveaways for fans, and opportunities for chapter volunteers and PALS to participate in game-day broadcasts.

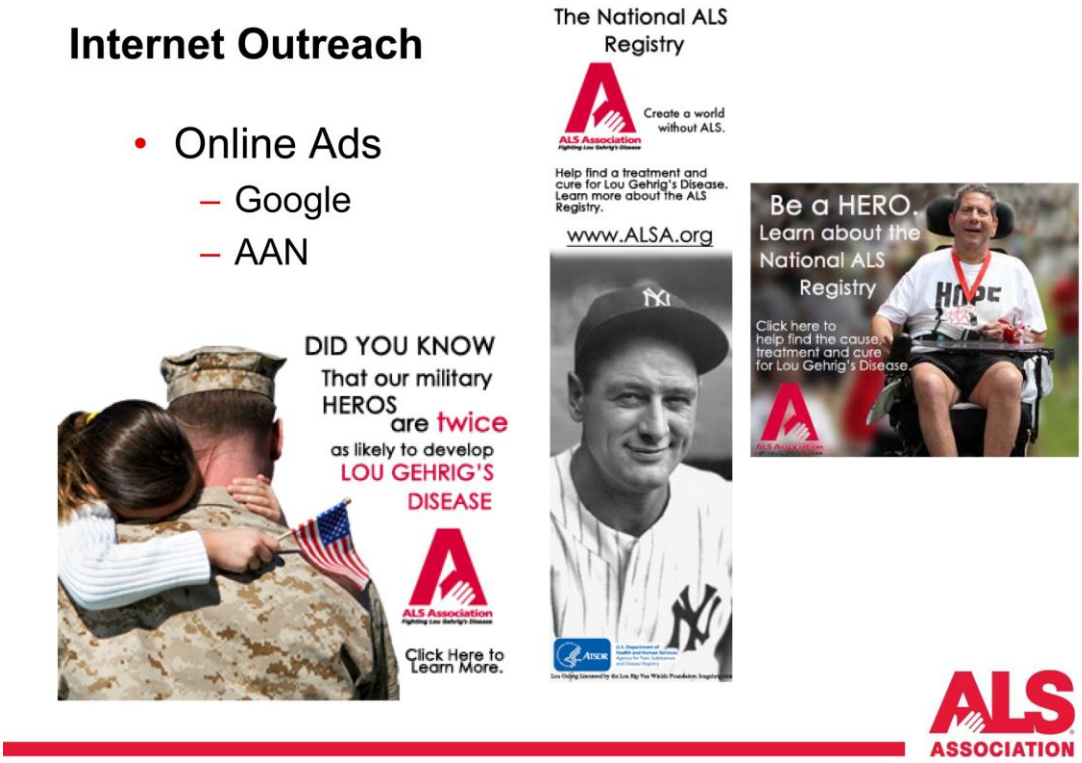
The partnership has been very successful. Nearly 100 events have taken place at baseball parks across the country, many in areas that are under-enrolled in the National ALS Registry. Much of the outreach has been targeted to states that have enrollment that is lower than expected.

The outreach with baseball has included the development of a Public Service Announcement (PSA) featuring Tommy John, a visible personality in baseball. He filmed three versions of the PSA to promote the Registry. It has been aired at ballparks throughout the US and also in the broader television market. The PSA has aired approximately 3300 times, with nearly 54 million impressions. The donated air time has a value of approximately $310,000. The states in which

the PSA has aired most frequently tend to be target states that are under-enrolled in the Registry.

The Association has also engaged online via social media, including Facebook and Twitter. They have developed a section of its website devoted to the Registry which was launched in 2013. It includes much of the information included in the toolkit and is designed to appeal to PALS, providing a forum to share why the Registry is important to them. The peer-to-peer communication will help drive enrollment and continue to raise awareness. The theme of the communication is that PALS are heroes.

The Association has published online advertisements through Google and AAN. These communications have different looks and approaches to appeal to different audiences, but they focus on the heroism of PALS who fight the disease and participate in the Registry. The online advertisements ran for a two-week period, and they resulted in 10,478 clicks and 2,277,688 impressions. There were 12,886 new visitors to the Registry section of The Association website, which represents an increase of 451%. The states with the largest number of visits were California, Texas, New York, Florida, and Illinois. They are the largest states in the country, but some of them are target states because of low enrollment. The Association will move forward with these initiatives, working with ATSDR, MDA, Les Turner, and others to



determine how to take advantage of continued outreach to further drive enrollment and traffic to the Registry website.

Much of The ALS Association's focus has been, and will be, to promote all of the goals of the Registry. Statistics regarding incidence and prevalence are important, and they add to

knowledge about the disease; however, those statistics are not the only purpose of the Registry. The other goals of the Registry need to be communicated and further incentives need to be provided for PALS to enroll. Those incentives include the research that is taking place and that will take place. The risk factor surveys are "the meat of the Registry." It is not enough just to sign up for the Registry. Participants must be encouraged to complete the surveys. The Association works through its chapters to follow up with PALS to help them complete all of the surveys.

The Registry was envisioned from its beginning as a potential source of ALS research funding. The project is now an important source of funding and is funding important research that might not otherwise occur. This idea must be communicated to the field. The Research Notification Tool is a significant incentive for PALS to enroll and complete the surveys.

The biorepository has the potential to be a powerful source of information, especially when it is tied to the epidemiological data from the Registry. The ALS Association looks forward to the results of the feasibility study and will communicate the idea that the Registry is important because of its other projects and potential to drive ALS research. All of the work that has been conducted, and will be conducted, must be communicated so that the breadth of the program is clear.

Some challenges remain. One of the chief challenges concerns the IRB. It is difficult to respond quickly when IRB clearance can take a year, particularly in the social media arena. CDC has instituted a clearance process that takes days rather than months, which is an improvement, but the timeline is still not friendly to social media. When the first report was released, The Association did not have sufficient lead time to evaluate the report, generate material, and have the material cleared to communicate to the field. One strategy to address this challenge is to anticipate issues and develop and clear materials well in advance.

Another challenge is conveying all of the Registry's goals beyond incidence and prevalence statistics. There is a perceived lack of benefit to PALS, which can be addressed by providing information and incentives. There is also confusion among PALS regarding whether they are enrolled in the Registry, as they are frequently included in a number of databases from organizations or national entities.

Mr. Wildman described Karen Carlson, who was named ALS Advocate of the Year in May 2014. Ms. Carlson is from Oklahoma and travels across that large state to visit PALS, promote the Registry, and to help PALS enroll in the Registry. She has undertaken this work on her own and done a remarkable job. People like Ms. Carlson are key to the success of the Registry.

Discussion Points

Dr. Feldman asked whether The ALS Association asks for metrics from each of its chapters concerning the Registry, and if so, what has been successful.

Mr. Wildman replied that the Listening Tour included a survey of chapters to learn what they are doing and to learn what is working. Chapters can be very creative, and if chapters discover approaches that are successful, then The Association will seek to replicate those approaches not only within The ALS Association, but with MDA and Les Turner. Data had not been available from ATSDR to demonstrate effectiveness; the information was primarily word-of-mouth. More "hard data" are needed to inform their outreach. The ALS Association has specific expectations of its chapters concerning the Registry as well.

Ms. Kidd thanked The ALS Association for their work on behalf of PALS. She asked whether data are available by Association chapter regarding the percentage of PALS that are enrolled in the Registry.

Mr. Wildman answered that the data are not broken down by state, but chapters have metrics associated with promoting the Registry to every person associated with the chapter. Technically, IRB prohibits tracking enrollment by specific ALS Association chapter.

Ms. Kidd observed that those statistics would be a key metric that could drive strong communications.

Mr. Wildman said that they have a good sense of chapter success, and chapters know who is enrolled and who is not enrolled. They face challenges regarding resources and identifying volunteers within chapters who will follow up with PALS.

Les Turner ALS Foundation ALS Registry Promotion and Outreach

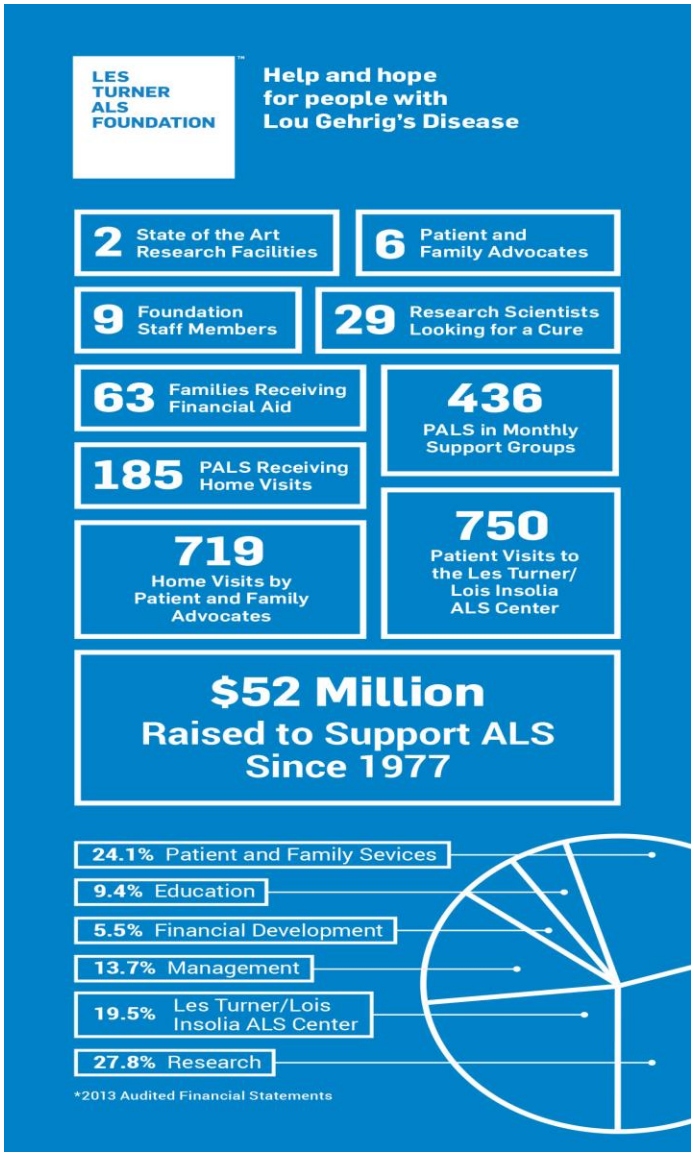
Shari Diamond
Director of Patient Services
Les Turner ALS Foundation

Ms. Shari Diamond explained that Les Turner was a businessman in Chicago, Illinois who was diagnosed with ALS in 1976 when he was in his late 30s. At the time, there were no resources available for patients with ALS. Mr. Turner and his family raised funds to build needed support. The first Les Turner Foundation fundraising event was the Mammoth Music Mart, an 11-day sale of vinyl records. The event was extremely successful for 25 years and raised not only funds, but also awareness, for ALS. The event was discontinued because of changes in technology, but it is remembered fondly.

The Mammoth Music Mart provided the foundation of funds needed to create the first ALS Research Laboratory, which opened its doors at Northwestern University in 1979. The laboratory was led by Dr. Burk Jubelt, who served as its first medical director. There are now two ALS research laboratories at the Les Turner Foundation, one led by Dr. Teepu Siddique, who focuses on familial ALS, and the other led by Dr. Hande P. Ozdinler, who focuses on the brain, the motor cortex, and motor neurons. After 1979, the laboratory was operational and fundraising efforts were strong. There was an additional need to provide services to PALS. The foundation opened the Les Turner/Lois Insolia ALS Foundation Clinic in 1986.

In addition to the laboratories and the multidisciplinary clinic, the foundation provides a variety of different patient and family support mechanisms throughout the Chicago area. The Home and Community Team serves a wide range of patients and consists of six patient/family advocates, four registered nurses, and two social workers. They provide a variety of services to the community in their homes, receiving referrals from the clinic as well as from community sources. Their goal is to enhance the continuity of care and to help problem-solve day-to-day issues that arise between the three-month clinic visits.

The Les Turner ALS Foundation Overview



In addition to support groups, the foundation provides equipment to patients, including some durable medical equipment (DME). They have a loaner pool and a communications equipment bank that helps patients receive speech-generating devices that they would not otherwise be able to get. The foundation provides grants to patients in the Chicagoland area who demonstrate financial need, assisting with issues such as caregiving help in the home, equipment, and home modifications. The foundation also provides transportation to and from the Patient Care Center at Northwestern University and provides a variety of materials and programs.

The most challenging aspect of working at the foundation is securing enough funding to provide the needed services. The foundation hosts a number of events and activities, including walks and activities, and parties. The Walk For Life is a major event that is held in September. Local spokespeople also support the foundation and share its message. The bulk of funds that are raised are devoted to patient and family services, as well as to research.

The Les Turner ALS Foundation promotes the National ALS Registry in several ways. The Foundation Communications Team includes professionals who work with social media and send regular e-mail blasts. A link on the Les Turner webpage provides information on the Registry, including assistance with registration. The foundation helps patients understand why the Registry is beneficial to them as well.

The Home and Community Advocate Team also helps promote the Registry. The home visits are self-scheduled, so patients are in the comfort of their own home and not in the tiring atmosphere of the clinic. The advocates provide information about the Registry and can assist PALS with enrollment.

The foundation recently began tracking how often, and how many, patients were given Registry information. The Registry is revisited as much as necessary. The foundation distributes materials to new patients in clinics, in home visits, or in support groups. The information includes information about the CDC and the Registry.

The greatest advocates are PALS who promote the importance of the Registry to patients and families in the ALS community.

Muscular Dystrophy Association

Carolyn Minnerly
Director of Support Services
Muscular Dystrophy Association

Ms. Minnerly said that MDA is the world's leading nonprofit health agency dedicated to finding treatments and cures for muscular dystrophy (MD), ALS, and other related neuromuscular diseases. MDA pursues its goals by funding worldwide research and providing comprehensive healthcare services and support to MDA families in the US. MDA supports communities to fight back through advocacy, fundraising, and local engagement.

MDA's involvement with ALS began in the early 1950s, when Eleanor Gehrig, widow of Lou Gehrig, was searching for a way to fight ALS. Mrs. Gehrig served for more than a decade as MDA's national campaign chair. Since its inception, MDA has dedicated almost $325 million to ALS research and healthcare services. MDA promotes the National ALS Registry in a number of ways, including through essential services:

- ❑ MDA Clinics and dedicated MDA ALS Centers
- ❑ Legislation and healthcare policy
- ❑ Support groups and educational seminars
- ❑ Home visits
- ❑ Fundraising events
- ❑ Outreach and emotional support

MDA operates a nationwide equipment loan program and a DME repair assistance program. They also offer flu shots. All of MDA's websites include a link to the ATSDR website. The MyMuscle Team is a care coordination site for patients registered with MDA. There are currently approximately 10,000 members of the team, and the Registry will be promoted on their website. MDA also generates numerous publications that include promotion of the National ALS Registry.

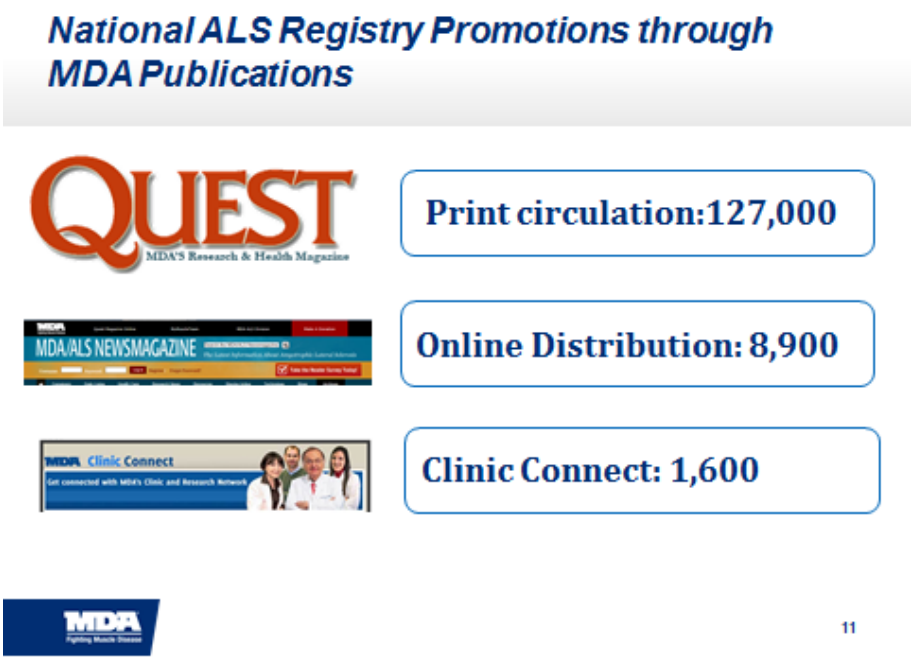
The core mission of MDA is to save and improve lives. They have a network of nearly 200 specialized clinics through the US and Puerto Rico. People with muscle disease make more

than 62,000 annual visits to MDA clinics where they receive skilled diagnosis and medical diagnosis from top health professionals. Persons with ALS comprise approximately 12% of the population seen in MDA clinics.

Of the 200 MDA clinics nationwide, 44 are dedicated ALS Centers. There are 66 clinics that see adults and those with ALS, and five are networked ALS clinical research centers. The MDA clinics meet with every patient and provide disease information, offer services, and provide information on the Registry. MDA's Health Service Coordinators attend each clinic session and have laptops available to demonstrate the Registry website. MDA is working on additional promotional materials to provide at the clinic visits.

MDA offers approximately 90 support groups across the country appropriate for PALS and their caregivers and family members. MDA is working with ATSDR to have materials about the Registry available for distribution at those groups and also via specialized talks. In 2013, approximately 100 MDA seminars were offered that promoted the Registry. Some of the seminars were specific to ALS, while others were general and included topics of importance to the wider neuromuscular community.

In addition to the information materials, MDA offers three main publications, each of which includes promotions about the Registry: *Quest* magazine, MDA/ALS Newsmagazine, and *Clinic Connect,* which is directed to clinic physicians and team members.



MDA's annual conference series consists of the MDA Scientific Conference and the MDA Clinical Conference, occurring in alternating years. The Scientific Conference was held in Washington, DC, in 2013, with approximately 500 in attendance. The Clinical Conference was held in 2014, with approximately 700 in attendance. ATSDR was represented at the Clinical Conference and will be represented at next year's Scientific Conference.

MDA has a strong social media presence, with weekly postings on Facebook and Twitter about the Registry. There are approximately 136,000 fans on Facebook and approximately 33,000

Twitter followers. MDA is also visible on YouTube, Google, and Instagram. MDA supports 50 ALS research projects worldwide, with a total commitment of $15 million.

The MDA US Neuromuscular Disease Registry was launched in 2013. It is the first comprehensive registry that collects information from health professionals through MDA's network of clinics throughout the US. The clinics provide high-quality medical care at major centers for PALS. Many types of treatments for ALS care are offered at MDA clinics. More information is needed to find out how effective those treatments are: when to start them, and how long to use them. The MDA registry focuses on information that will answer those questions. The MDA registry will record information about medical care provided to patients and the MDA clinics who take part in it. Currently, approximately nine sites are entering information for ALS. In 2015 MDA will begin the expansion of the MDA Registry to additional MDA clinics with the goal of it being implemented in all clinics over the course of the next three years.

The goals of the National ALS Registry and the MDA Registry are somewhat different. The information from the combined registries will provide a complete picture of the story of ALS. MDA is excited to partner with ATSDR. There may be confusion about the two registries, but MDA has created a brochure to explain the importance of the registries and why they are both important.

Discussion Points

Mr. Tessaro asked how many persons were enrolled in the MDA Registry and what their future goals might be.

Ms. Minnerly said that nine sites are entering information for ALS, with 540 patients enrolled and consented. Of those, 213 are female and 325 are male. The registry will be launched in all MDA clinics in 2015.

Dr. Wolff said that large sites are going through the IRB process now. The goal is to include a few thousand patients with ALS and to track their clinical care within the next eight to twelve months.

Mr. Harada asked how many ALS patients MDA serves.

Ms. Minnerly answered that approximately 13,000 ALS patients are currently in the MDA database. It is an ongoing process to ensure that the number is accurate.

Dr. Oleg Muravov asked which conditions are included in the registry.

Dr. Wolff answered that the registry includes ALS, Duchenne Muscular Dystrophy (DMD), Becker Muscular Dystrophy (BMD), and Spinal Muscular Atrophy (SMA). Facioscapulohumeral Muscular Dystrophy (FSH) and Myotonic Muscular Dystrophy (MMD) will be added in the next year. MDA serves nearly 13,000 people with ALS annually.

Dr. Antao asked for clarification regarding whether physicians, rather than patients, enter information into it. Dr. Wolff confirmed that physicians provide information to the MDA Registry.

CME Training Modules Update

Amanda Cadore, MPH
Behavioral Health Scientist
Environmental Medicine Branch, DTHHS
Agency for Toxic Substances and Disease Registry

Ms. Amanda Cadore presented a review of data from users completing the ALS Continuing Education Module. The Environmental Medicine Branch develops e-learning and educational tools primarily for health professionals and primary care professionals, but also for the general public. A few years ago, there was a presentation regarding developing an online tutorial for ALS patients to enroll in the National ALS Registry. This presentation addressed the module for medical professionals.

The data review from users included different methodologies, including focus groups and formative evaluations. The review includes continuing education from October 1, 2010, through June 30, 2014. Data can be broken up by quarters from each year. The e-learning modules underwent an Instructional Design review, formative and post-education evaluation on a quarterly basis, structured writing, and risk communication via message mapping. Data were gathered from the Office of Continuing Education, considering web hits and page views as well as information about users of the module.
Users of the module pursued different credit types, including Continuing Education (CE), Continuing Medical Education for Physicians (CME-P), Continuing Medical Education for Non-Physicians (CME-NP), Certification for Nurse Educators (CNE), Continuing Education Units (CEUs), and Certified Health Education Specialist (CHES). From October 1, 2010, to June 30, 2014, there were 1140 registrations in the ALS Online Registry Learning Module, with 831 completions for an overall completion rate of 72.89%. The breakdown is as follows:

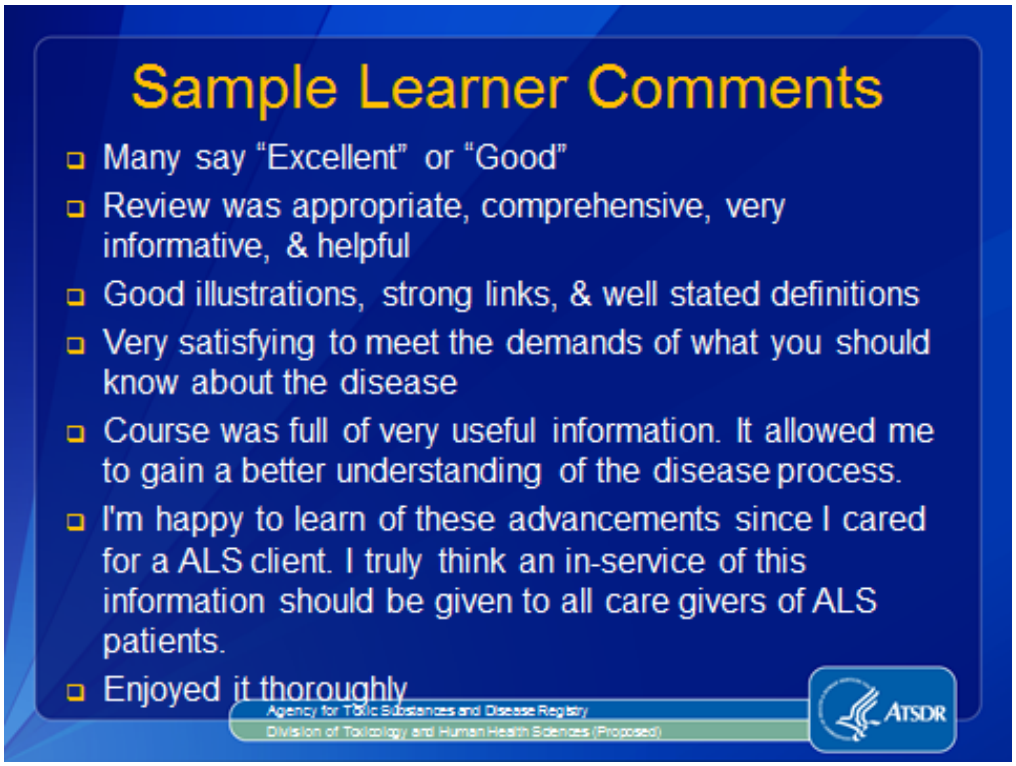
Credit Type	Registered	Completed	Completion Percentage
CME (for physicians)	115	89	77.39%
CME (attendance for non-physicians)	126	82	65.08%
CNE (for nurses)	629	472	75.04%
CEU (for other professionals)	160	119	74.38%
CHES (for certified health education specialists)	89	61	68.54%
Audit	21	8	27.78%
Totals	1140	831	72.89%

During the same period, the majority of takers had an educational level of some college or college graduate/health professionals. Regarding work settings, the work setting with the highest cumulative summary was "healthcare," and the second-most popular setting was "public health agency." There were 2344 unique visitors to the site from August 1, 2013 to July 31, 2014. About 3173 page views and 2540 visits were recorded. A page view is a single click on a page, where a visit is a visit of at least 30 minutes, whether on one page or multiple pages.

A number of evaluation questions were presented to takers of the module. The responses were:

- The Content and Learning Materials Addressed a Need or a Gap in my Knowledge or Skills: 44% responded "strongly agree," and 54% responded "agree."
- The Difficulty Level Was Appropriate: 38% responded "strongly agree," and 58% responded "agree."
- The Length and Pace of the Activity Was Appropriate: 34% responded "strongly agree," and 60% responded "agree."
- I Can Apply the Knowledge Gained as a Result of This Activity: 38% responded "strongly agree," and 60% responded "agree."
- The Availability of CE Credit Influenced My Decision to Participate in This Activity: 50% responded "strongly agree," and 46% responded "agree."

Direct comments tended to be positive regarding the usefulness of the information and comprehensiveness of the course.



The CE module is being renewed and updated and should be available soon. Users can access the module via the ATSDR website and gain access to additional information about ALS.

Discussion Points

Dr. Horton commented that the target audience of the National ALS Registry is PALS who will enroll in it. Healthcare professionals are another critical audience, which is why the CE module was created. He wondered about reasons why users start the module and do not complete it.

Ms. Cadore answered that the training is designed to take 60-90 minutes and will result in a maximum of 1.75 credits for CME, 1.5 credits for CNE and CECH, and 0.2 credits for CEU. It is not clear why some people start but do not finish the modules, which is the case with many education modules. The modules have an 80% completion rate, which is among the highest completion rates for CE modules.

Dr. Brooks said that it will be important to learn how people will use the modules. At his center, the modules are used to train physicians, residents, and other professionals who come through the clinic. His center also recommends that home care nurses undergo the training. A potential target audience for the module is home care personnel, particularly given questions regarding patients who are not followed by an ALS clinic. A module that is specific to the needs of those healthcare workers would be helpful. Another potential audience is neuromuscular respiratory therapists. The patient care organizations can also publicize the learning module for those who care for ALS patients.

Ms. Cadore said that ATSDR can work to develop additional educational materials for other populations. Her branch typically focuses on educational information for healthcare professionals, and their main marketing goal is CE credits. They also consider information for the general public and can develop tools for people who take care of ALS patients, including family members and home care personnel.

State and Metropolitan Area Surveillance Findings Update

Laurie Wagner, MPH
Study Coordinator
McKing Consulting Corporation

Ms. Wagner presented the overall results from the State and Metropolitan Area Surveillance projects. The objective of the project was to identify neurologists who had diagnosed and/or provided care to an ALS patient in specified state or metropolitan areas from January 1, 2009, through December 31, 2011 and request that they report their ALS cases to the project. The ultimate goal of the surveillance was for ATSDR to use the data to evaluate the completeness of the National ALS Registry. Three states participated in the project: Texas, Florida, and New Jersey. Eight metropolitan areas provided surveillance data: San Francisco, California; Los Angeles, California; Las Vegas, Nevada; Chicago, Illinois; Detroit, Michigan; Atlanta, Georgia; Philadelphia, Pennsylvania; and Baltimore, Maryland.

The project reviewed comprehensive lists from the American Medical Association (AMA), conducted Internet searches, and called various practices to identify all ALS specialists in the state and metropolitan areas. The project removed sub-specialties that were not likely to see ALS patients, such as pediatric neurologists. Health care providers were contacted via a variety of means to ensure that the list was accurate. For recruitment, providers were called using the developed list and project information packets were mailed and faxed to the providers. Project

staff continued to contact the offices and conducted office visits, when necessary, until case reports were received or it was determined that there were no more cases in each office.

Physician Recruitment

	Overall	States	Metro Areas
	# (%)	# (%)	# (%)
All Neurologists	4,844	2367	2477
Diagnosed/treated ALS Patient	910 (18.8)	628 (26.5)	282 (11.4)
Reported Cases	554 (11.5)	408 (17.2)	146 (5.9)
Did not report cases	356 (7.3)	220 (9.3)	136 (5.5)
Did not diagnose/treat ALS Patient, but would	644 (13.3)	368 (15.5)	276 (11.1)
Does not diagnose/treat ALS Patients	3200 (66.1)	1307 (55.2)	1893 (76.4)
Unknown	85 (1.7)	61 (2.6)	24 (1.0)
Other Physicians Reporting Cases	5 (0.1)	3 (0.1)	2 (0.1)

For case ascertainment, case reports were collected for ALS patients who were cared for or diagnosed between January 1, 2009 and December 31, 2011. This work was somewhat challenging for the metropolitan areas. Zip code lists and county lists were created, as some participants lived within the county but outside the Zip code area. Additional ICD codes were provided to help find participants with electronic systems. Case reporting forms were collected identifying information as well as demographic and other diagnosis information. Each physician that reported cases filled out and submitted a case reporting form for each ALS case. The form was available electronically, which helped the larger practices report to the project. Many practices filled out the forms by hand and submitted them securely via fax.

For quality assurance, approximately 10% to 20% of the case reports were verified. A completed Medical Record Verification form was submitted by the reporting neurologist and reviewed by the consulting neurologist, Dr. Sorensen. The Medical Records Verification form included disease signs and symptoms and, when available, a copy of the electromyography (EMG) report was provided. Death data was also requested from each area, which resulted in identification of additional cases that had not been reported. Project staff attempted to contact physicians and asked them to report those cases.

The approach to selecting cases for verification depended on the size of the practices. In smaller practices, 100% of cases were verified. These practices tended not to see many ALS cases. In practices with 5-20 cases, 10-20% of the cases were verified. In large practices with 21-50 or more cases, 3-10% of the cases were verified. Cases were also selected for verification if they were very young, had the disease for a long time, and if they were deemed "unclassifiable" by the reporting physician.

The data are still being evaluated and analyzed, and there are still some duplicates in the dataset at this time. It is not likely that the duplications will affect the results, but the numbers will be checked before any data are published. The project expected 6677 cases, and 7602 case reports were received. The de-duplicated case total is 5914. Based on these numbers, the incidence was 1.53 per 100,000 population. The age and sex of reported cases in the

project is consistent with other findings in the literature: 56% of the cases were male, and 43% were female.

Reported El Escorial Criteria classification of all reported prevalent ALS cases by race and ethnicity

El Escorial Criteria classification	Overalla (n=5914)		Race						Ethnicity			
			White (n=4421)		African-American/Black (n=547)		Asian (n=216)		Hispanic (n=638)		non-Hispanic (n=4578)	
	#	%	#	%	#	%	#	%	#	%	#	%
Definite	3085	52.2	2382	53.9	274	50.1	87	40.3	404	63.3	2379	52.0
Probable	1303	22.0	993	22.4	115	21.0	48	22.2	125	19.6	1018	22.2
Probable-Lab Supported	483	8.2	319	7.2	54	9.9	29	13.4	41	6.4	378	8.3
Possible	758	12.8	536	12.1	74	13.5	39	18.1	49	7.7	600	13.1
Not Classifiable	285	4.8	191	4.3	30	5.5	13	6.0	19	3.0	203	4.4

a Includes cases with a reported race of White, African-American/Black, Asian, Other or Unknown and a reported ethnicity of Hispanic, Non-Hispanic or Unknown.

Regarding race and ethnicity, the metropolitan areas selected had higher minority populations, so the rates among minorities in the metropolitan areas are slightly higher than the rate in the states. Overall, the rates are consistent with the general US population. A paper is about to be published that delves into the disparities and differences between the cases by race and ethnicity.

The findings regarding the time from onset of symptoms to diagnosis of the cases were as follows:

Time from Onset of Symptoms to Diagnosis of Reported Cases

	Overall	States	Metropolitan Areas
	# (%)	# (%)	# (%)
Under 12 months*	2600 (44.0)	1631 (44.8)	969 (42.6)
12-17 months	1065 (18.0)	646 (17.8)	419 (18.4)
18+ months	1603 (27.1)	904 (24.8)	699 (30.7)
Unknown	646 (10.9)	459 (12.6)	187 (8.3)
Total	5914	3640	2274

The project calculated the concordance between the reporting provider and the consulting neurologist. There was general concordance between the two. Of the non-classifiable cases, only two were determined after verification not to be ALS. The non-classifiable cases may have been seen by a provider who did not have enough information to give an ALS diagnosis but were later classified as ALS by the consulting neurologist who may have been provided additional information.

The project concluded that most neurologists do not diagnose or care for individuals with ALS. Overall, most cases were reported by ALS referral centers. This finding is more specific to the metropolitan areas. The number of unique case reports received was close to the expected number. The age and sex distributions of reported cases in the project were similar to those reported in the literature. The percent of cases with familial ALS and dementia was lower than expected. Less than 2% of verified cases were determined to be "Not ALS." There was no significant difference in the percentage of "Not ALS" determinations between referral centers and all other neurologists. Approximately 72% of "Non Classifiable" cases received from the reporting neurologist was determined to be ALS by the consulting neurologist.

There are limitations associated with the project approach. Active surveillance is extremely time-consuming. It is difficult to rely on neurology office staff to determine whether the practice cared for ALS patients. Physicians are not always responsive to requests. Most VA medical centers could not participate because of decisions by their individual privacy officers. Death certificate data are difficult to obtain and to use. Hospital discharge data are not available for most areas. This type of surveillance is good for evaluation, but not for ongoing surveillance. The retrospective case reporting worked best, but there were still problems because doctors forgot about older cases, did not have access to old records, and had retired and/or passed away. The case verification is an important process.

The findings from the project are being disseminated in a variety of ways, including poster presentations at a number of professional organization and society meetings. A fact sheet has been created for each metropolitan area and each state that participated in the project. The factsheets summarize all of the information obtained for each project area and can be easily shared via websites and hard copy. Each site that reported to the project will receive the fact sheet for the area in which it is located, as will state neurological societies. Local and national ALS Association chapters will receive the factsheets, and ATSDR will share them on the web page. Twelve manuscripts are in progress.

Discussion Points

Dr. Bradley said that one of the main goals of the Registry is to determine the number of ALS cases over a certain time period. Case information will also come from the NDI and from capture-recapture approaches. It would be interesting to learn how the numbers from the state-metropolitan project compare to the Registry.

Dr. Horton answered that the analysis would be started in Fall 2014, as the state-metropolitan project is complete and the first dataset from the Registry is available. The analyses will consider whether cases are being missed and how surveillance activities can be adapted to capture the expected cases. The state-metropolitan project helps "paint a picture" of the ALS experience in the US. The Registry is unable to calculate incidence because date of diagnosis is not available on persons identified from the national datasets, however the state and metropolitan projects will provide strong incidence data on a large segment of the US. The publications will be made available when they are published, as will the fact sheets.

Dr. Mitsumoto congratulated ATSDR on the study. It can be challenging for epidemiologists to conduct studies in the US because of the size of the country, but projects such as the state-metropolitan project present opportunities to look at regions and yield important results. He asked how the "expected numbers" were derived.

Ms. Wagner answered that the expected numbers were based on national ALS rates for each area's population.

Mr. Mitsumoto asked whether the project resulted in any surprising results.

Dr. Kaye answered that the paper is still under review, but the paper on ethnic and racial minorities will be interesting. The eight metropolitan areas were selected to have higher representation of African Americans, and there are differences in incidence rates between the whites and non-whites and whites and Hispanics. These rates have been reported in the literature, but with smaller population sizes. This project confirms those numbers.

Dr. Brooks was interested in the El Escorial Criteria, which will be important for future clinical trials. It will be important to know the degree to which there is belief that a person has definite ALS at a certain time in his or her disease progress. He suggested that a secondary paper examine the additional information or the time from the original assessment by the doctor in the clinic and the additional information from the consulting neurologist. Some studies have considered training people to do this work.

Ms. Wagner agreed and noted that the project was not entirely certain whether the doctor who assigned the El Escorial Criteria was specifically trained and specialized in diagnosing ALS.

Dr. Sorenson said that physicians were supposed to submit the most recent information, but there was a shift in the assessment from less-probable ALS to more-probable ALS to definite ALS over time.

Dr. Brooks said that putting a timeline on those elements will be helpful for clinical trial assessments. Several papers have shown this migration, and it is important regarding the burden of disease.

Dr. Wolff asked how the 910 neurologists provided information and whether individual cases had to consent before identifying information was submitted.

Dr. Kaye answered that the VA has strict privacy rules above and beyond the Health Insurance Portability and Accountability Act (HIPAA). Each hospital has a privacy officer that determines whether data can be shared. The project has waivers of informed consent from the IRB, and most state health departments do not require consent for surveillance.

Ms. Wagner said that the project was cleared through the IRB and OMB. All sites in the state-metropolitan project had ALS surveillance specialists and staff members who were responsible for their own surveillance and outreach. They gathered the data from neurologists and sent it to McKing Consulting and ATSDR.

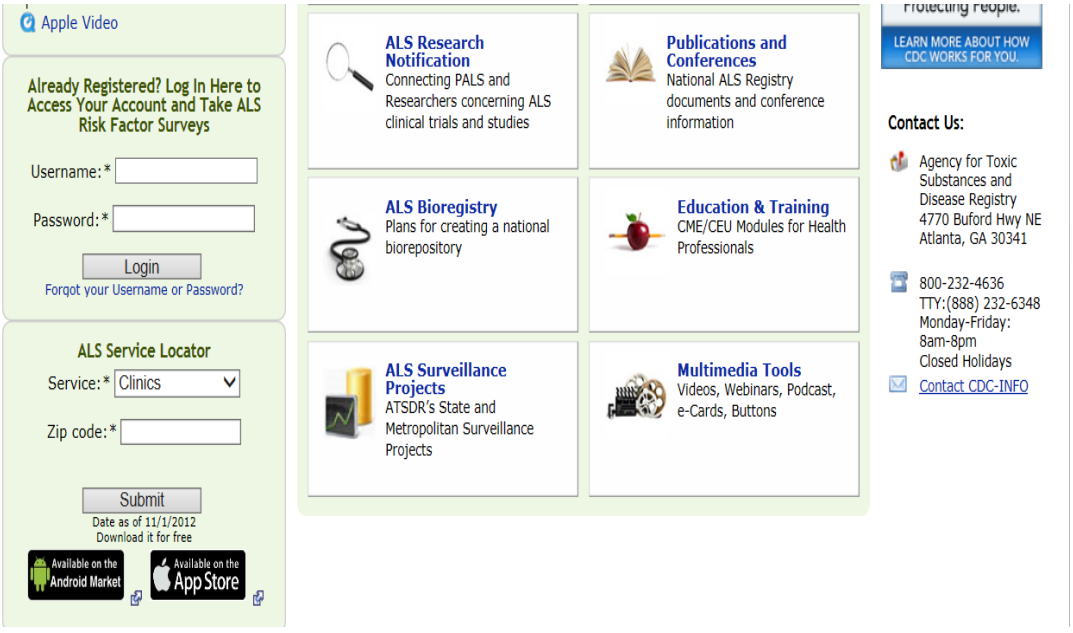
Mobile Service Locator Apps

Matthew Smith
Systems Analyst, Booz, Allen, Hamilton
Geospatial Research, Analysis, and Services Program (GRASP), DTHHS
Agency for Toxic Substances and Disease Registry

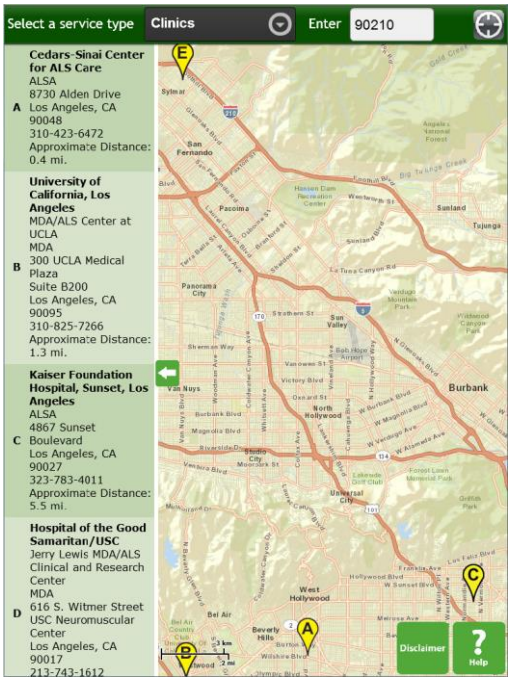
Mr. Matthew Smith provided an overview of the ALS Service Locator Apps. GRASP is located within ATSDR and is comprised of 25 diverse team members, including epidemiologists, Geographic Information Systems (GIS) analysts, developers, statisticians, and demographers. The mission of GRASP is to help apply geography and geospatial services across the agency as it relates to public health. For the National ALS Registry, GRASP provides a Service Locator Tool to help PALS find the closest clinics, ALS Association chapters, and MDA offices by using a Zip code. A web application service locator was developed and has been transformed onto mobile platforms.

The Registry main web page provides the entry point to the ALS Service Locator web application. Users submit a Zip code, and the application returns the five closest clinics and facilities. The application calculates a straight line to the facilities that are housed in the database. One of the main goals in providing the locator tool was to combine different facilities' data and to provide one resource for searching across The ALS Association, MDA, and clinic facilities. The web application utilizes Adobe Flash Player, which could be transported to the mobile environment.

National ALS Registry Main Web Page



The mobile application is available in iOs and Android marketplaces. It provides the same workflow for users to select service types, enter a zip code, and receive a list and map of the five closest facilities. The mobile application can also utilize the device's Global Positioning



System (GPS) for the search. Because of the way the initial web application was developed, it was not a tremendous effort to convert it to the mobile environment. GRASP reused much of the original code, and the iOs and Android versions use the same service and query the same data using the same methods.

GRASP worked with the Office of Communication to deploy the mobile applications through the appropriate marketplaces. The ALS Service Locator is included in the marketplaces with other official CDC applications. CDC has many applications that utilize public health data. Metrics data are received on a weekly basis and compiled on a monthly basis. The locator has been downloaded a total of 470 times since it was released in September 2012. The metrics data include the country of origin when the application is downloaded. The majority of users, 305, are in the US. The application has also been downloaded in India, Japan, France, the United Kingdom, Germany, Italy, and other countries. Less detail is received from the Google marketplace. That version of the application was released in May 2014. To date, there have been six downloads from that marketplace.

Discussion Points

Dr. Brooks agreed that it is important to distribute the applications throughout multiple platforms. Groups in England are considering a similar locator tool, but tying the information to emergency rooms with expertise in ALS care. It is important for the stakeholders to think about how the locator might be enhanced and how the Registry might eventually be accessed from a handheld device.

Mr. Eric Von Schaumburg asked about challenges associated with getting downloads and advertising the application's availability.

Dr. Horton answered that ATSDR has not done a great deal of marketing regarding the application, which explains the relatively small number of downloads. The application is promoted at conferences and via social media, but help in promoting the application would be appreciated. The application is likely to be helpful for newly-diagnosed patients who may not know where support groups or the nearest clinics are. He noted that Les Turner facilities are also included in the application.

End of the Day Questions

Robert Kingon
Facilitator

During this session, Mr. Kingon opened the floor for meeting attendees to ask questions or make comments.

Discussion Points

Dr. Brooks recalled a discussion regarding the National ALS Registry as the first "living Registry" for ALS patients. It is important to convey the urgency needed to keep the Registry going. The successive reports will have more data as the Registry "ripens," and patients must understand that it is important to be counted.

Dr. Horton commented that the state-metropolitan project was time-consuming, labor-intensive, and expensive, which illustrates why a national approach is the best approach. The state-metropolitan surveillance approach is cost-prohibitive to conduct in every state. A national approach is more efficient and a more economical way to track ALS cases in the US.

Dr. Boylan asked about the timeline for releasing data from the Registry for researchers to use it.

Dr. Horton answered that they are considering how to make a de-identified public use data set available to researchers, as other surveillance systems have done. Their initial focus was on finalizing the first data set.

Dr. Wolff asked about the possibility of issuing Requests for Applications (RFAs) to help promote the availability of the data set and to explore questions that may not be within the scope of the Registry.

Dr. Horton answered that ATSDR has issued RFAs regarding research questions or hypotheses of interest. The job of promoting the Registry is a collaborative effort with different strategies. The best people to do this work are partners at Les Turner, MDA, and The ALS Association, who are on the front line supporting clinics that see ALS patients every day. ATSDR is still in the early stages of considering use of data from the Registry. CDC has different ways for making data available, such as the Research Data Center (RDC) through the National Center for Health Statistics (NCHS). Researchers request data from that system, and the data are provided with tools to help guide its use.

Dr. Mitsumoto agreed that a national approach is preferable to the state-metropolitan surveillance approach for capturing ALS cases. He pointed out that ALS is still not a reportable

disease, so the Registry remains voluntary for patients. The state-metropolitan surveillance is extremely important for comparison to the Registry, as well as for reaching rural areas. Both approaches are mutually supportive.

Dr. Horton concurred and noted that the bulk of ALS cases in the Registry come from the national administrative data sets. There is enough data from the state-metropolitan projects to cross-reference with the Registry data to determine whether the Registry data are complete. There are no current plans to conduct surveillance in other states.

Ms. Diamond asked about partnering with the National Hospice Organization or tapped into the larger hospices in communities and states. Eventually, most ALS patients receive hospice support.

Dr. Horton said that ATSDR reached out to the hospice group in the past and were not able to get traction. They may revisit that approach.

Mr. Tessaro observed a surplus of obstacles associated with sharing data. He wondered if the obstacles were due to human nature and a reluctance to share beyond silos. There is a history of not sharing information at the government level, and he wondered whether there is a similar phenomenon among researchers. He asked whether enough information is being shared among the major available databases.

Dr. Horton answered that the Registry was created for ALS patients and researchers. Some groups in different sectors do operate in silos, but it is important that everyone can use the Registry. ATSDR does not have the resources in its small group to conduct all the different analyses that they would like to do, so they take an "all hands on deck" approach. The different groups want to help each other. For instance, the Massachusetts ALS Registry has offered to share data for cross-reference. There are many limitations to sharing data, however. For instance, it is challenging to gather data from CMS and the VA.

Mr. Tessaro said that data are probably available in the major centers and have not been shared. The Registry would be enriched if it was populated with all of that information, but the heads of the centers will have to agree.

Dr. Horton agreed that it is important to leverage resources. It would be beneficial, for instance, to compare the MDA Registry information to the National ALS Registry. It is a matter of execution and "red tape."

Dr. Kaye clarified that Medicare and Medicaid data would not be available when the data from the Registry became available for analysis, and that only the self-reported data through the web portal would be available.

Dr. Horton said that the Registry is a combination of the portal data and the national administrative databases. ATSDR has to pay for the data from CMS.

Dr. Kaye added that under the agreement, the CMS data and VA data cannot be re-released. The exception to that rule under CMS is the End-Stage Renal Disease Registry, which is a special subset within CMS. There is a price structure to get data from CMS.

Ms. Charleston said that since CMS data will never be released, the Registry may need to be compared to Massachusetts data and MDA data.

Dr. Horton hoped that the data may be able to be shared in the future.

Dr. Muravov noted that some persons who enroll through the web portal may also be in the other administrative data sets.

Mr. Gibson said that the persons in their database are self-reported, and The Association does not know whether they are living or whether they have other conditions, such as Kennedy's Disease or Primary Lateral Sclerosis (PLS).

Ms. Minnerly said that MDA's database of registered patients could include persons with PLS in addition to ALS. Their status is self-reported, often from families and clinics, and is often not received in a timely manner.

Mr. Gibson added that accurate, real-time data are not available on whether persons are deceased. The data would have to be verified. The ALS Association certifies its centers, but they are run by their host institutions.

Mr. Tessaro asked about the possibility to verify patients' status.

Ms. Minnerly replied that they strive to ensure that their data are correct. Regarding sharing, MDA is partnering with ATSDR and wants to provide information. HIPAA regulates a great deal of what they do.

Mr. Tessaro hoped to learn ways to build the Registry and whether the MDA and The ALS Association databases can help them.

Mr. Wildman said that The Association wants to populate the Registry as quickly as possible so that all ALS patients are counted. The IRB prevents them from enrolling patients from their database. Patients must enroll themselves. Chapters therefore encourage patients to enroll.

Dr. Brooks observed the difficulty associated with populating a Registry with the different available data sets. It would be helpful for the non-governmental organizations (NGOs) to convene an educational forum with researchers and epidemiologists to address this problem. Advocacy can bring the issue into the open.

Dr. Bowser clarified that patients enrolled in the Registry through the Web portal can be invited by researchers to participate in studies. If a researcher wishes to utilize the Registry data for an epidemiological study, the only information available is from the enrollees in the Web portal, after the data are released.

Dr. Kaye said that the CMS and VA data include very little epidemiological information. That rich information comes from the risk factor surveys in the web portal. The information from the administrative database is important for context and for calculating prevalence, and potentially for incidence in the future. The administrative data are also important to determine whether the persons completing the surveys are representative of the population with ALS.

Dr. Bowser said that there is potential for sharing information across data sources. He co-chairs the NEALS Biorepository, which has approximately 20,000 samples of biofluids and clinical information from patients, but no epidemiological data. He wondered about ways to link patient information from the NEALS Biorepository to the risk factor data in the Registry. That linkage

would permit a range of studies to answer critical questions about ALS. The NEALS Biorepository has a universal de-identifier number that could be incorporated.

Dr. Kaye said that studies would have to be reviewed and approved individually.

Dr. Bowser said that patients' true identifier, such as the Social Security Number (SSN), is linked to a global de-identifier so that information is linked. There are technological challenges associated with linking CDC information outside the federal system.

Dr. Kaye said that the Registry data does not exist on the Internet for security reasons. It is "swept" at midnight every night.

Dr. Horton said that ideas can be discussed and debated, and if a project cannot be done today, perhaps it could be done in the future. Cross-collaboration and creative thinking is necessary. ATSDR has spoken to representatives from PatientsLikeMe, and that group has offered data for cross-referencing.

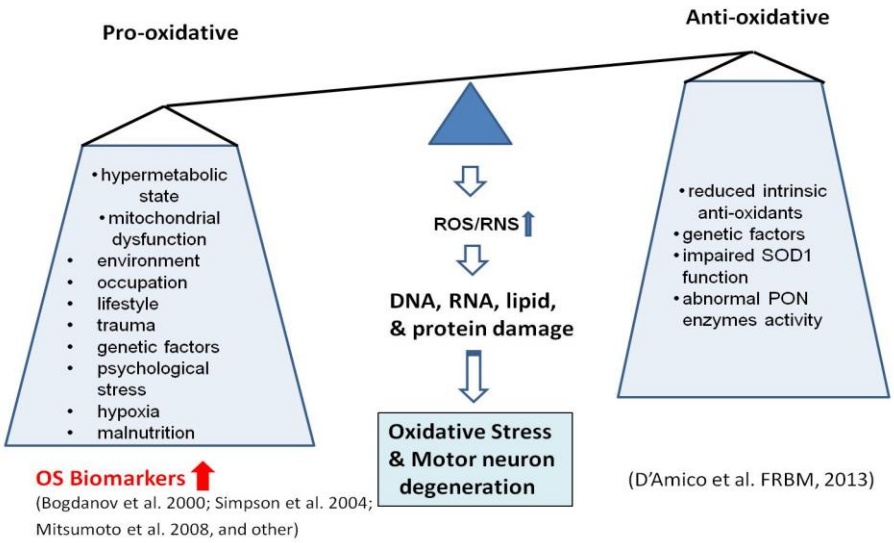
ATSDR Funded Studies

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 project ATSDR Risk factors Epidemiologic Studies in ALS (ARREST ALS). The study is based on the ALS Multicenter Cohort Study of Oxidative Stress (ALS COSMOS) studies, which examine the relationship between oxidative stress (OS) and disease progression.

Exposures are expressed in the body as OS. ALS patients have increased OS biomarkers. The body has anti-oxidative mechanisms, but if an imbalance occurs, there is DNA, RNA, lipid, and protein damage as well as increased OS and motor neuron degeneration. The principal hypothesis of the COSMOS study is that OS is associated with the progression of "sporadic" ALS, ALS without a family history. In cases with more OS, the disease will move faster and shorten survival. The study is a cohort study with no control populations.



The study's specific aims are to:

- ❑ Determine whether markers of increased exposure to OS, measured via questionnaire or biomarkers, are associated with the progression of ALS
- ❑ Examine the associations between OS biomarkers, the OS index, and survival of patients with ALS
- ❑ Determine whether a variety of environmental, psychological and lifestyle factors are associated with increased levels of OS biomarkers at baseline
- ❑ Evaluate associations between lipid profiles and ALS progression, measured by the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) and survival
- ❑ Examine associations between baseline markers of OS and distinct subtypes of ALS via exploratory analyses

The study is conducted at multiple sites, with samples taken, examinations performed, and tests administered at three, six, twelve, eighteen, and twenty-four months. The Columbia Center also

Study Schedule

Months	0	3	6	12	18	24	36
Eligibility	X						
Informed Consent	X						
Medical Evaluation & Assessment	X	X	X	X	X	X	
Physical Exam	X					X	
Neurological Exam	X					X	
Cognitive Screening	X			X			
Forced Vital Capacity	X	X	X	X	X	X	
ALSFRS-R	X	X	X	X	X	X	
Blood , urine, and DNA & SKIN	X X	X	X	X	X	X	
Drug list	X	X	X	X	X	X	
Final Survival							X
Web-based data entry	X	X	X	X	X	X	X
Done by the CUCC							
Baseline interview	X						
Follow up interview		X	X	X	X	X	
Brief FFQ	X		X	X		X	
Psychological interview	X	X	X	X	X	X	

conducts interviews and questionnaires over the phone. The case ascertainment and enrollment process includes a 110-item questionnaire and examination at the study site to define patient populations. One of the key enrollment criteria is disease duration, which should be 18 months or less from symptom onset.

Items on the enrollment questionnaire pertaining to OS are related to demographics, residential history, occupational history, military service history, physical activity, hobbies, tobacco and alcohol, and psychological measures. There is a minimum of 128 questions and a maximum of 1079 questions. The process takes an average of one and one-half hours, and repeat phone calls may be utilized to complete the questionnaire if patients grow tired. The diet questionnaire has 115 questions.

A total of 355 patients were enrolled in the study. Their ALSFRS-R scores and region of onset were similar, but differences in their El Escorial Criteria (EEC) were due to biased opinions from Columbia's ALS neurologist, Dr. Mistumoto. The COSMOS study was center-based, and the investigators sought to reach out to patients in all 50 states, who can participate via telephone, via the National ALS Registry as a recruitment vehicle. Other objectives of the ARREST ALS study were to:

- ❑ 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 the ALS COSMOS study

- Patients participate voluntarily by enrolling themselves into the Registry and initiating their participation

ALS COSMOS data collection comes from patients and caregivers. For case ascertainment, it is critical, but time-consuming, to confirm the neurologist's diagnosis. Other data collected include:

- Demographic, clinical, ALSFRS-R, forced vital capacity (FVC) if possible, ALS management status such as the use of assistive devices, medication list

- Cognitive screening test

- Occupational, military, and hobby information

- Residential, lifestyle, smoking, alcohol drinking, and exercise information, and also the newly-added elements of trauma, fatigue, and sleep status

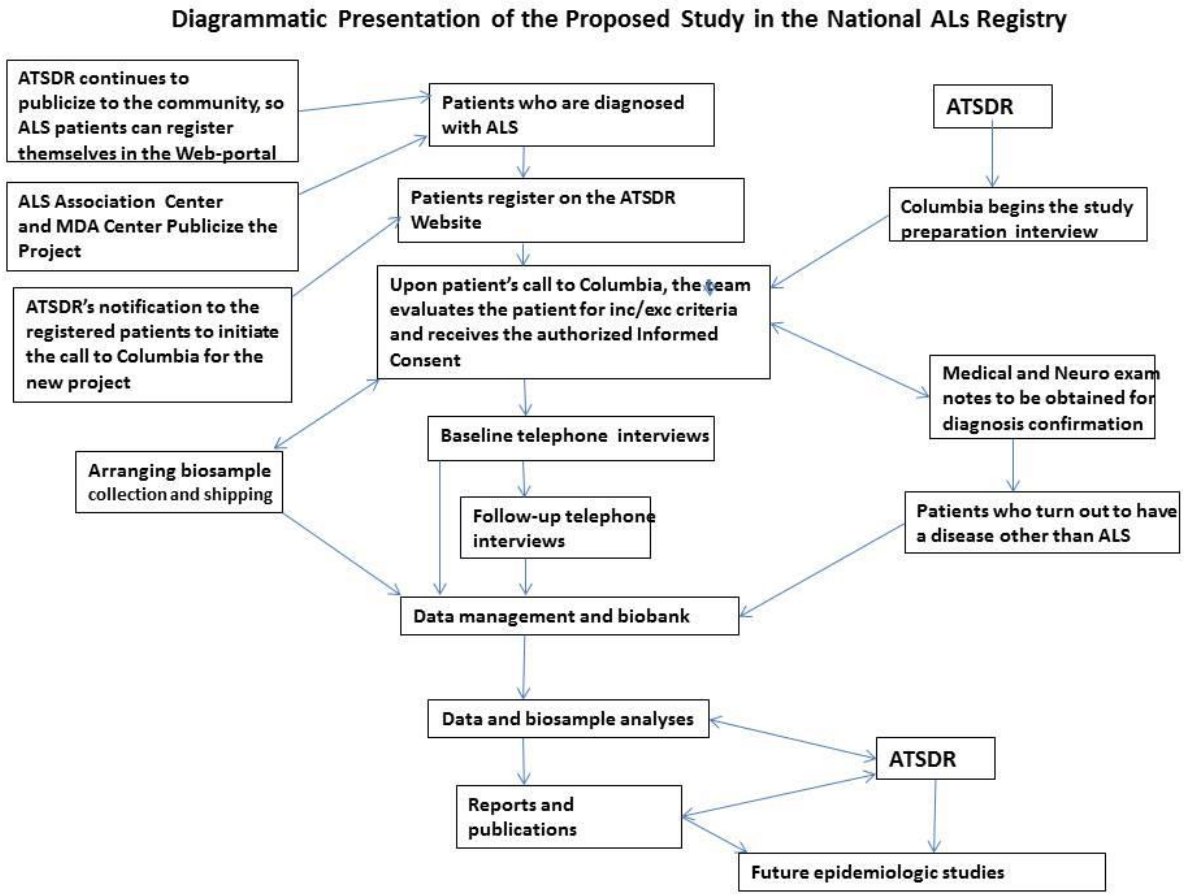
- Dietary information via the self-administered Diet Frequency Questionnaire

- Psychological analysis

- Disease progression based on ALFRS-R and perhaps FVC, and survival

- Biobank with two saliva swabs and urine: the study hoped to collect blood, but it was cost-prohibitive

In order for ARREST ALS to be successful, it will be critical to increase awareness of this project for potential patients. The Registry is a great tool for introducing the study, and the NGOs are helping to share information as well. Patients can contact the study by calling 1-855-STOP ALS. The study is conducted entirely over the phone. A pilot study concluded that cognitive testing over the phone and in person were equivalent for most cognitive screening tests. DNA and urine samples will be obtained. Patients' follow-up schedules are similar to the ALS COSMOS study. ARREST ALS has the goal of obtaining 420 patients from 50 states. When patients call the study phone number, the inclusion/exclusion criteria are applied. Baseline interviews are conducted, and the process of collecting biosamples and conducting additional interviews begins. A pamphlet about the study has been prepared for distribution to ALS patients to invite them to participate.



The study does not have controls and is not researching the causes of ALS; rather, the study considers the relationship of OS, risk factors, and disease progression. Their challenges include generating enough publicity to encourage newly-diagnosed ALS patients to call the phone number and participate. Further, the telephone interviews may be a challenge, but the investigators are confident that they will be sufficient to collect the needed information. Obtaining biosamples is another potential challenge, but the study has a careful approach.

The grant was funded in late 2013, and they are ready to initiate beta testing with patients from ALS COSMOS sites before opening the study to the entire country.

Discussion Points

Dr. Feldman asked about the kind of DNA analysis that will be conducted on the saliva samples. She assumed that urine would be evaluated for OS measures, and she wondered about getting accurate measures from urine, given technical requirements for preserving and shipping urine to be tested for OS.

Dr. Mitsumoto answered that DNA would be analyzed with exome sequencing, which is expensive and will require additional funding. In the future, they will conduct genome sequencing. Urine does not have to be frozen; an ice pack is sufficient to keep it chilled. They measure 8-oxo-deguanosine and isoprostein, which are fairly stable with regular shipping. In

355 patients, they have shown that increased OS is associated with increased levels of oxidative markers and associated with lower ALSFRS.

Dr. Brooks observed that the ARREST ALS study illustrates the importance of the Registry. The controls are internal, and ALS patients will be very interested in learning about the risk factors. He asked what risk factors in the ARREST ALS are new compared to the risk factors in the literature, and what factors will be confirmatory to other studies.

Dr. Mitsumoto agreed that there are a number of strong epidemiological studies in this area. The ARREST ALS hypothesis is as inclusive as possible, looking at the natural environment that has a number of risk factors, such as residence, occupation, lifestyle, psychological factors, and diet. Humans may only be susceptible to a few of the factors, and some might be more sensitive to different factors than others. Combining the factors into the natural environment may provide final evidence regarding OS. Combining the factors will also result in an OS Index. The study is considering occupational and environmental exposures as far back as 60 years. The study is a work in progress, but eventually they will be able to combine factors and make associations with ALS disease progression.

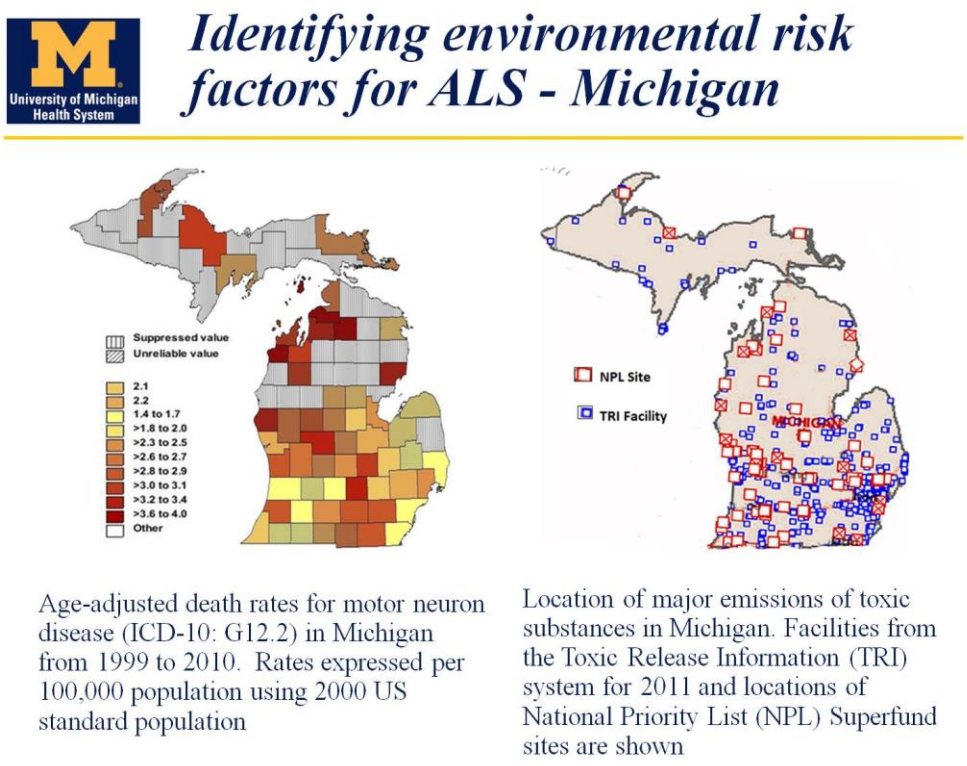
Identification and Validation of ALS Environmental Risk Factors

Eva Feldman, MD, PhD
Director, Program for Neurology Research and Discovery
University of Michigan Health System

Dr. Feldman has practiced at the University of Michigan for 25 years and has been involved with the ALS Clinic during that time. There appears to be a substantial incidence of ALS in Michigan. A 2013 report showed that the Midwest region has the highest rates of ALS/Motor Neuron Disease (MND)-associated deaths in the country. In one area of Michigan, Dr. Feldman worked with four husband-wife teams that all had ALS. They had grown up in the same area, and most of them had known each other since kindergarten.

The idea that Michigan experiences associations between environmental exposures and ALS is not unique. A well-known study implicated environmental factors as a cause of ALS in the Western Pacific, and multiple studies support the idea as well. While the idea is not new, there are new ways to approach the question scientifically.

This work began at the University of Michigan approximately five years ago with a grant from an interested philanthropist. The study first examined age-adjusted deaths from MND in Michigan from 1999 – 2010. The investigators also worked with the state of Michigan to map major emissions of toxic substances in the state and Superfund sites. The two maps were superimposed on each other to find potential associations, and associations were found.



Age-adjusted death rates for motor neuron disease (ICD-10: G12.2) in Michigan from 1999 to 2010. Rates expressed per 100,000 population using 2000 US standard population

Location of major emissions of toxic substances in Michigan. Facilities from the Toxic Release Information (TRI) system for 2011 and locations of National Priority List (NPL) Superfund sites are shown

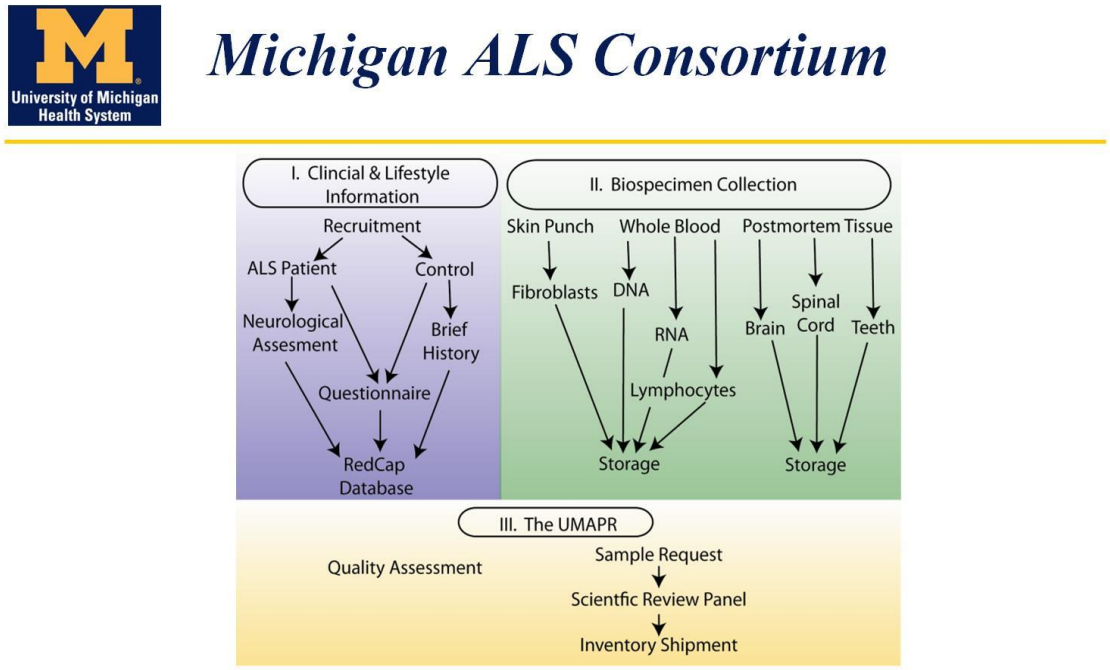
The next step was a small case-controlled study of the toxic environment in Michigan. The study provided preliminary data for a CDC grant. It is estimated that approximately 1000 individuals in Michigan have ALS, and Michigan is one of the top generators of hazardous materials in the US, with 69 unclean Superfund sites, 750 facilities that report toxic releases on an annual basis, and 1800 sites including Superfund sites that are targeted for cleanup. The researchers developed a 44-page questionnaire with the School of Public Health and administered it to 66 individuals with ALS and 66 controls. There was a consistent and robust association with ALS and pesticide exposure and use of lawn fertilizers. These data were published in July 2014.

The University of Michigan utilizes a multifaceted approach to ALS. They are interested in understanding the biology and pathogenesis of the disease. They are also interested in therapy, with stem cell trials. Because of the large ALS patient population in the state, the University of Michigan intends to make that clinically-rich population available to other investigators to answer the question of whether there is a toxic and environmental component to the pathogenesis, onset, and progression of ALS.

The CDC/ATSDR grant was awarded in September 2013 and has two aims, which are to: 1) evaluate environmental exposures using: a detailed questionnaire; occupational and environmental exposure measures based on national and state-level databases; and biomarker assessments in collected biospecimens; and 2) identify environmental risk factors by comparing biomarker and exposure data collected in Aim One and explore potential disease risk models. The goal is to provide insight into ALS pathogenesis and potential disease biomarkers, and to set the stage for national ALS risk factor analyses.

The Michigan ALS Consortium enrolls approximately 90% of ALS patients at the UM ALS clinic into the study. Patients receive a complete neurologic assessment using standard neurological

tools. The data are quantitative and consistent. In addition to the epidemiological assessment, including a detailed questionnaire, a complete battery of cognitive assessments is administered. These data are entered into a database that can be queried. In parallel, biospecimen collection is conducted. Patients have a skin punch biopsy and fibroblast cultures are taken and stored. Whole blood is taken for DNA and RNA. There is a robust autopsy program in place. Additionally, blood is taken for environmental assessments of exposures. The Consortium encourages sample requests. All requests that have been received and reviewed have been honored. Clinical information is shipped with the inventory.



University of Michigan ALS Patient Repository (UMAPR)
http://www.pnrdfeldman.org/research/michigan-als-consortium/

Goal: To establish a national bank of familial and sporadic ALS patients to facilitate the study, understanding, and potential treatment of ALS.

In the last 11 months, 104 ALS and 82 control patients have been enrolled into the CDC study. The cases are placed into four exposure windows based on numerous covariates derived from the questionnaire.

- Window 1: Entire occupational history
- Window 2: Latest 10 years
- Window 3: 10-30 years
- Window 4: more than 30 years ago

The preliminary occupational risk factors for ALS are education level, occupational exposure to pesticides, occupational exposure to toluene, and workplaces in healthcare or social assistance. These factors have increased hazard ratios of ALS. Exposure to pesticides has an increased hazard ratio of nearly eight, which is remarkable. Participants with occupational exposure to pesticides were approximately 8 to 12 times more likely to have ALS. Educational level and

occupational exposure to pesticides were significant in all exposure time windows. Participants with education levels higher than high school were 83% to 87% less likely to have ALS.

Occupational risk factors for ALS

	Variable		β	SE	HR	95% CI		p-value
Win 1: Exposure ever happened in the entire occupational history								
* +	**Education level**	**> high school graduate**	**-1.88**	**0.51**	**0.15**	**0.06**	**0.41**	**0.000**
	Smoking year x cigarette packs	year-pack day^{-1}	0.00	0.01	1.00	0.99	1.02	0.767
	Ever work in the US armed forces	Yes	0.51	0.52	1.67	0.60	4.61	0.326
	Poor ventilation	Yes	0.65	0.43	1.91	0.82	4.45	0.133
	Occupational exposure to lead	Yes	-0.89	0.59	0.41	0.13	1.31	0.131
*	**Occupational exposure to pesticides**	**Yes**	**2.06**	**0.62**	**7.83**	**2.34**	**26.19**	**0.001**
*+	**Occupational exposure to toluene**	**Yes**	**-1.68**	**0.76**	**0.19**	**0.04**	**0.82**	**0.026**
†	Workplace: durable goods manufacturing	Yes	0.80	0.47	2.22	0.88	5.56	0.090
*	**Workplace: health care/social assistance**	**Yes**	**-0.99**	**0.50**	**0.37**	**0.14**	**0.99**	**0.048**

+ Variable also significant in Exposure windows: 10 years, 10-30 years, and more than 30 years ago
* Variable significant in all Exposures windows *except* more than 30 years ago.
† Variable *only* significant in Exposure window 10-30 years

Blood samples were collected from 90 ALS subjects and a similar number of controls. The study is measuring 122 compounds, including brominated flame retardants (BFRs),

Biomarkers – BFRs

Compound		β	SE	p-value	HR	95%CI	
BFRs (n = 83)	TBBPa	-0.11	0.08	0.168	0.89	0.76	1.05
	BDE-028	0.10	0.03	0.003	1.10	1.04	1.18
	BDE-047	0.12	0.03	0.001	1.12	1.05	1.20
	BDE-066	0.12	0.05	0.014	1.13	1.02	1.24
	BDE-100	0.29	0.07	<.0001	1.34	1.17	1.54
	BDE-099	0.18	0.05	0.000	1.20	1.09	1.33
	BDE-085	0.01	0.02	0.617	1.01	0.97	1.05
	BDE-154	0.04	0.04	0.306	1.04	0.97	1.11

Models were matched with age and gender, and adjusted with education

polychlorinated biphenyl (PCB), and pesticides. These compounds were chosen based on the epidemiological survey. There are four BFRs in which there is a clear increased hazard ratio of exposure in the ALS patients' sera. There is also an increased hazard ratio with PCBs which are measurable in ALS patients' blood compared to controls. The hazard ratios are not as great for pesticides, and the confidence intervals are good.

The data are new and emerging, but the research has found 34 compounds that are significantly associated with ALS. The compounds will be vetted biologically in a separate proposal funded by a philanthropist. Most of the BFRs and pesticides and part of the PCBs (penta-, hexa-, hepta-) were all associated significantly with ALS. Positive associations indicate that higher concentrations lead to higher ALS risk. For example, a one-unit increase in exposure to a particular and common BFR increased the odds of ALS by 12%.

Future plans include superimposing the data from the 90 patients on the geomaps to integrate and analyze the data. Subject recruitment, survey assessment, and chemical exposure assessments are continuing. The collection will be expanded by the addition of teeth from autopsy material. The researchers seek to engage members of the National ALS Registry in the study in a more robust manner. Michigan may need a stronger infrastructure and support system to assist this goal. The researchers also encourage use of the biorepository.

Discussion Points

Dr. Sorenson asked how the controls were recruited.

Dr. Feldman answered that at the suggestion of the School of Public Health, the UM Clinical Studies agency was hired to recruit controls that are matched in age, gender, and geographic location. They did not want to use spousal or relative controls for this study.

Dr. Brooks observed that it is clear that research presented in the 1990s regarding environmental risk factors for ALS in the US is true. These findings connect to the need for an environmental Registry. The other MND associated with pesticide exposure is paralytic polio. He asked whether the state of Michigan has examined paralytic polio sites relative to Superfund sites.

Dr. Feldman said that the question is interesting, and they have not conducted that analysis. The data clearly indicate that the surveys should ask questions about these families of compounds. The preliminary study is relatively small, but the associations are robust.

Dr. Bowser said that similar data have been published from Pennsylvania, looking at Superfund sites. Pesticide exposures and occupational risk factors also appeared in these studies. He asked whether the pesticide levels measured in the sera are due to chronic or acute exposure to the pesticide.

Dr. Feldman said that sera measures more acute pesticide exposure. The study is collecting DNA from patients in parallel in hopes of studying the epigenetic modifications in this group of patients. Preliminary analysis has been conducted on approximately 50 patients, and it is possible to divide the epigenetic modifications into high-exposure and low-exposure individuals based on the questionnaire. More robust epigenetic modifications correlate with environmental exposures. The next step after identifying environmental exposure in the Registry will be to understand the mechanism behind the exposures.

Mr. Tessaro commented that data "come so much more alive when there is a hard example." He asked whether the BFR flame retardants were the chemicals that are used in infant sleepwear and similar products. He wondered if the industry is ready to hear the data about exposure, which will affect millions of units of product.

Dr. Feldman replied that the data are based on 90 patients. Her goal is to recruit 100 more patients, and 100-150 patients per year. When the data are more robust and based on more individuals, then they can call that question. Scientific validation will be needed to establish relationships and associations in the laboratory.

Mr. Tessaro said that it took decades for lead-based paint to be understood, and some of those issues are still in litigation.

Dr. Antao asked how the study addresses migration in and out of Michigan and whether it is only interested in Michigan-specific exposures.

Dr. Feldman said that the study considers exposure windows for exposures and occupations. Michigan is an interesting state, in that there is typically little migration out of the state when a patient has been diagnosed with ALS. They have noticed migration into the state of patients with ALS. She did not feel that there would be major problems with the data, and she was encouraged with what they were finding.

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

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

Dr. Bradley said that ALS is not a single disease. It is clearly a syndrome with multiple causes that produce the same clinical phenotype. For instance, many different genes have been identified to cause Familial ALS, and many different environmental factors are responsible for Sporadic ALS, presumably on the background of genetic predisposition in specific individuals who develop it. Many environmental factors have been linked to Sporadic ALS, and some are more accepted than others.

The CDC/ATSDR-funded a study focused on cyanobacteria and beta-Methylamino-L-alanine (BMAA). It is an ecologic study to evaluate the spatial associations between the place of residence of ALS patients and potential environmental risk factors. The hypothesis is that greater exposure to environmental neurotoxins and neurotoxicants increases the risk of developing ALS. The study concentrates on mercury in addition to cyanobacteria and BMAA because mercury and BMAA in vitro are adjuvants and mercury has been suggested as a risk factor for ALS. The research also includes a questionnaire-based case-control study of other environmental and lifestyle risk factors that have been suggested to be associated with ALS, such as head injuries and military service history.

The questionnaire includes:

- Lifetime history of the individuals' residence addresses from birth

- ❑ Lifetime residential history of water supply, including proximity to industrial dumps, landfills, incinerators, and water bodies with algal blooms
- ❑ ALS clinical data
- ❑ Family history of neurodegenerative and other diseases
- ❑ Details of head injuries, electrical injuries, medications, military service, vaccinations, and smoking
- ❑ Lifetime occupational history and exposures
- ❑ Fish consumption, which is relevant for BMAA and mercury
- ❑ Recreational activities such as water sports and athletics

Questionnaires have been completed by 141 ALS patients and 125 clinic control patients. The controls are individuals in the neurology clinics who do not have age-related neurodegenerations. They have been approximately age- and sex-matched. The study is supported by the National ALS Registry and began six weeks ago. Another grant from The ALS Association began two weeks ago and facilitates recruitment of patients in the northern New England area.

A study in Florida comes from the National ALS Surveillance Program, which is a high-intensity, hands-on effort to record all ALS patients in the state of Florida within a three-year period. A total of 1451 confirmed cases were found, and their addresses and demographic and clinical data are on record at the Florida Department of Health. To protect confidentiality, only Zip Code locations of the patients have been released.

The study will analyze geographic proximity to potential environmental hazards using Geographical Information System (GIS) analysis to superimpose geocoding of residences on geocoding of exposure parameters for environmental toxins and toxicants. The questionnaire allows for examination of non-geographic environmental and lifestyle exposure data from questionnaires. The study analyzes ALS cases versus controls.

The databases include water quality databases that have information about cyanobacterial content throughout the three states in the study area. There is direct sampling and indirect satellite sensing. Databases also include landfills, municipal incinerators, Brownfield and Superfund sites, and more. Databases are available regarding agricultural chemicals and agricultural land use.

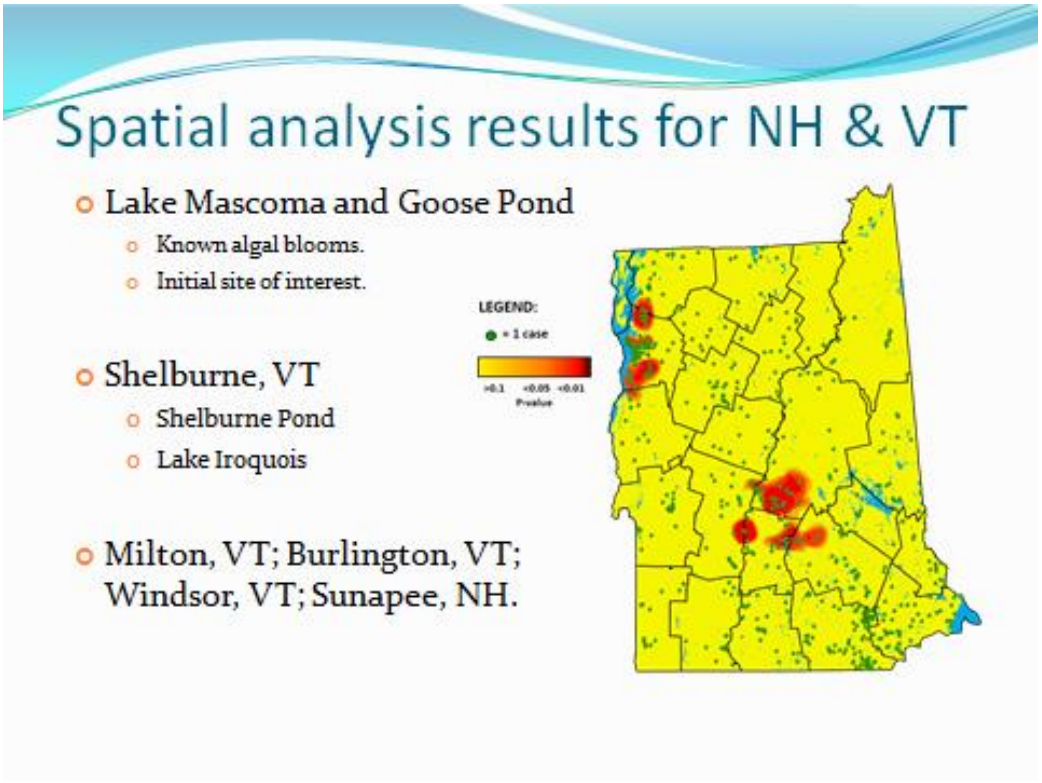
Water quality data have been collected throughout the state of Florida for both marine and fresh water for the last 25 years. The data come from five water management districts, the Department of Health, the Department of the Environment, and other sources. The data include latitude and longitude parameters for each of the water bodies, the total amount of algae, the total amount of cyanobacteria, their individual species, the biomass, total number of cells, and some information on the cyanobacterial toxin microcystin and other parameters that measure other elements. No analyses are available on BMAAs. Microcystins and BMAAs are both produced by cyanobacteria, but they are produced in variable amounts and variable times. The control of that production is not well-understood. The more algal bloom, the more likely that cyanotoxins are present; however, the relationship is not one-to-one and there is no way to measure BMAA exposure. Cyanobacterial content serves as a surrogate.

The background of this study begins in the discovery of significantly higher ALS frequency in Guam than in the rest of the world in 1945. The origin of the BMAA found in the brains of Guam natives who had ALS was found to be cyanobacteria in the roots of the cycad trees. ALS patients in Florida also had BMAA in their brains. BMAA was also found in the brains of

patients with Parkinson's disease and Alzheimer's disease, but not in control patients. It was confirmed that BMAA enters proteins of the brain and remains for long periods of time, producing a mis-incorporation into proteins and leading to mis-folding of the protein, protein aggregates, and cell death. That process was competitively inhibited by co-exposure in tissue culture with L-serine. Cyanobacteria are ubiquitous and are even found in the desert.

Clusters, or non-random distribution or regions of increased incidence, of ALS cases have been reported for decades. Associations must be attributable to factors other than chance. The clusters have been described by epidemiologists as errors of small samples and/or of persons with similar genetic background; however, many researchers believe that the regional areas of increased incidence present pointers toward factors that are environmentally responsible for Sporadic ALS.

A study in New Hampshire focused on a cluster of six ALS patients from a small town of 3500 in New Hampshire. They all lived near a lake with recurrent signs of algal blooms. The frequency of the ALS patients was many times more than would be expected based on standard rates of ALS. The full paper from this study was published in 2013 and identified 11 clusters of statistically significantly higher incidence of ALS cases in northern New England. The hypothesis was that aerosolization of cyanobacteria and cyanotoxins from bubble effect and wave effect builds up in the air close to lakes. It is well-known that microcystins can be absorbed by people who water ski on lakes with cyanobacterial blooms. The same mechanism is hypothesized to be the reason that people living adjacent to lakes with cyanobacteria could be at risk of developing ALS.



There are areas of "hot spots" of ALS patients in the northern New England area. The study is examining the distribution of ALS patients and their proximity to water bodies that have cyanobacterial blooms as well as the frequency of ALS around water bodies that do not have cyanobacterial blooms. Preliminary data show that fish in Lake Mascoma have microcystins

and BMAA in their proteins. The passage of BMAA from the cyanobacteria in the bottom of Florida Bay into fish and crustaceans, and to the brains of ALS patients, has already been demonstrated. There is an increased risk for developing ALS in the area of northern New England where individuals live within half a mile of Lake Mascoma.

Satellite remote sensing is not part of this project, but the research consortium has applied this technique to "sweep" the globe on a continuing basis. If the appropriate spectrum and size filters are applied, it is possible to see the content of chlorophyll, the specific pigment phycocyanins, and to quantitate the amount of cyanobacteria in surface waters in lakes and water bodies.

In Florida, researchers have analyzed ALS data from Zip Codes along the border of the Indian River lagoon on the southeast coast of Florida. The lagoon has had a long history of algal blooms because of the human passage of nitrogen from sewage-treated water into the lagoon. The frequency of ALS patients in Zip codes that bordered the lagoon was compared to the frequency of ALS patients in Zip codes in the same counties that do not border the lagoon. The results of the brief analysis did not achieve significance; Zip codes are not particularly precise in terms of geographical location of residents. The results do show a trend that supports the overall hypotheses.

Florida ALS cases in those zip codes bordering Indian River Lagoon compared to those zip codes not bordering Indian River Lagoon – 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**
SD			1.761			2.487
SEM			0.719			1.015
p value				**0.62**		

Additional studies are planned. A control study will consider recall bias, and other studies will examine various biospecimens for BMAA for mercury. These specimens as well as DNA and RNA are being collected from patients and controls. Autopsy biospecimens are being studied for brain BMAA, methyl-mercury, and cyanobacteria in lung tissues. Micropore filters of air samples will be collected adjacent to water bodies in another study. Since L-serine will block

the effect of BMAA in tissue culture, the researchers have launched a clinical trial of L-serine in ALS patients.

Discussion Points

Dr. Feldman noted that the state of Michigan is exposed to all but one of the Great Lakes. Many of her ALS patients come from Toledo, Ohio, where a recent algal bloom forced the shutdown of the city's water supply. Those patients are not included in their studies. She asked which one or two serum measurements in patients could be added to the study to move it forward. She further asked about the difficulty of gathering data from bodies of water.

Dr. Bradley said that blood levels of toxins only indicate a relatively acute window of time. They are interested in lifetime exposure or exposure in the last five to ten years. BMAA can be measured in the blood and cerebrospinal fluid (CSF), but is not necessarily an index of long-term exposure. BMAA in the brain is the "gold standard." Teeth are useful for measuring lead, but not for BMAA. Regarding the availability of data from water bodies, the satellite data is the most likely to be useful internationally. It is somewhat intensive to extract that data from all of the scans that are published, but it is possible.

Dr. Horton asked whether the algal blooms occur periodically and whether northern states see more frequent blooms than southern states.

Dr. Bradley answered that algal blooms are the result of an increased amount of nutrients in the water, particularly nitrogen combined with phosphate. Phosphate comes from agricultural land, and nitrogen comes from fertilizer as well as from human waste products. Blooms are more frequent in the summer than in the winter. The concern is not only blooms; for instance, cyanobacteria exist year-round in a mass at the bottom of Florida Bay. Cyanobacteria are also present on pavement after rainstorms. Harmful algal blooms have become an issue for departments of health around the country. Water bodies are regularly closed for recreational activities in the summer due to continual blooms.

Dr. Feldman asked whether the National ALS Registry surveys ask questions that address living adjacent to lakes or that address similar relevant exposures.

Dr. Horton said that the surveys do not currently address those issues. Dr. Bradley has discussed with ATSDR the possibility of creating an additional survey that relates to exposure to water bodies. Dr. Horton said that information gleaned from the research studies can be incorporated into the Registry.

Dr. Kaye said that while the surveys do not specifically ask about residence near water bodies, it may be possible to discern that information from the enrollees' full residential history. The surveys ask about lifetime exposures to agricultural areas and pesticides.

Cognition, Behavior, and Caregiver Burden in Amyotrophic Lateral Sclerosis

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

Dr. Brady described the Boston VA Research Institute's study, which was just funded and which has not yet begun. He said that it would be beneficial to talk with the other researchers who had presented, perhaps to adjust the measures to build a larger data set.

Early on, MNDs were described with motor symptoms, with less description of cognitive symptoms. Within the past decade there has been increased interest in the types of patterns of cognitive dysfunction in ALS. Recent reports have estimated rates of cognitive impairment at between 10-75%. Dementia estimates range from 5-41% (ALS-FTD – 15%). The pattern has traditionally been described as having a frontal, executive component, but some studies suggest aspects of memory and other cognitive domain impairments as well.

Thus far, the study findings have been equivocal on whether the site of onset is related to the severity or pattern of cognitive dysfunction. It has been shown that ALS with cognitive and behavioral dysfunction is associated with shorter survival. The differences in patterns across studies are probably related to the genotypes and phenotypes of the samples, whether the samples were composed or more or less incident and prevalent cases, the site of onset, and the age of the cases. A meta-analysis of 13 cognitive function studies was published in 2009. The effect size is relatively strong, with significant effects in several areas compared to comparable control studies.

Cognitive Dysfunction in ALS (Raaphorst et al. 2009, ALS)

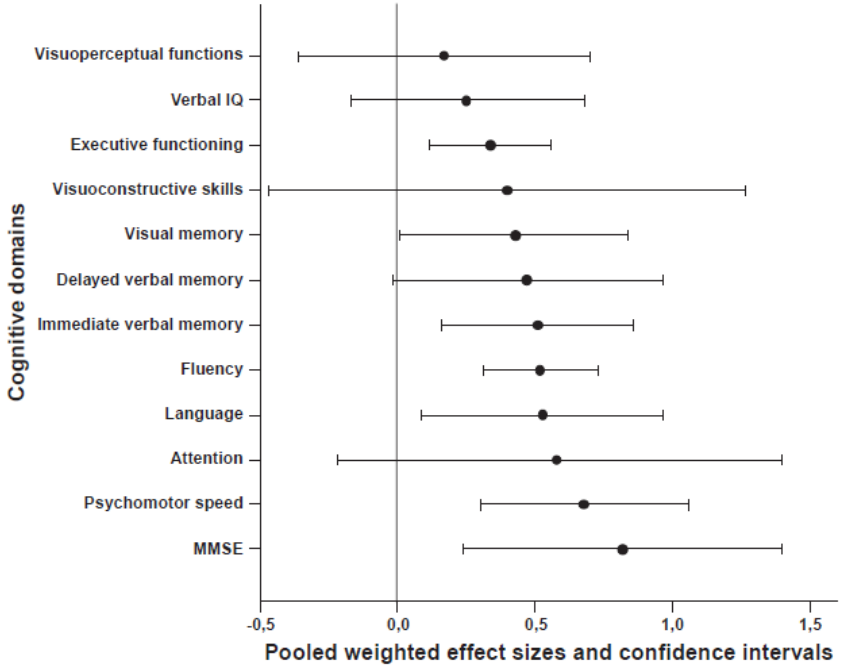


Figure 1. Pooled weighted effect sizes (●) and 95% confidence intervals of the cognitive domains calculated from available studies. A positive effect size indicates a worse cognitive performance of ALS patients compared to controls for that domain. If the horizontal line does not bracket the vertical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

Behavioral dysfunction has also been described in patients with ALS and expressed as a frontal dysexecutive syndrome consistent with emotional lability, disinhibition, apathy, and mental rigidity. The disease itself can bring psychological reactions that are consistent with these elements, and studies have attempted to decide whether the symptoms are above and beyond what would be expected as a normal psychological reaction to the impairments associated with ALS.

The cognitive and behavioral findings have been backed up by structural imaging studies that describe frontal and temporal patterns of atrophy. There is corticospinal tract decline, which is expected, but there are suggestions that white matter in other areas of the brain is affected. Some studies of ALSFRS scores show that the scores are correlated with white matter pathology. Resting and activation functional imaging studies show a predominantly frontally-associated pattern in both types of studies. Some findings suggest some reorganization of plasticity and that the brain's reaction is a function of ALS disease progression.

Some years ago, a large meeting in Canada was convened to develop consensus criteria for diagnostic subgroups in ALS patients. The group generated four subtypes:

- Classic or "pure" ALS with no cognitive or behavioral impairment
- ALS with cognitive impairment (ALSci), in which 1.5 standard deviations are demonstrated on at least two frontal tests
- ALS with behavioral impairment (ALSbi), which partially meets at least two of the Neary and Hodges criteria for ALS-FTD
- ALS with dementia (ALS-FTD), which has three subtypes:
  - FTD with behavioral and cognitive deficits,
  - Progressive nonfluent aphasia, marked by expressive language deficits and word-finding difficulty, and
  - Semantic dementia, marked by impairments in word meaning.

Caregiver burden in ALS became a point of interest for the VA Biorepository ALS Brain Bank, whose staff interacts with caregivers daily. Caregivers for PALS tend to be informal, such as spouses, relatives, and friends. A robust literature related to caregiver burden in dementia has been developed for Alzheimer's disease. That literature considers caregiver burden as it progresses over time, with activities of daily living (ADL) impairment coming later in the disease progression. The scenario is reversed in ALS, as ADL impairment tends to occur earlier in the disease progression, with cognitive and behavioral effects coming later. Caregiver burden and stress in ALS are related to the severity of ALS motor dysfunction; the mood of the caregiver tends to be congruent with the mood of the PALS; executive cognitive ability dysfunction; caregiver burden/stress increases over time; and perceived social support by caregiver is an important moderator.

Cognitive impairment in ALS is prevalent and heterogeneous, with different patterns and subtypes related to cognitive and behavioral dysfunction. Caregiver burden and stress appear to be related to cognitive and behavioral components. Studies thus far have been informative, but their results are inconsistent because they are usually conducted on local samples of relatively small size and different sample compositions. The National ALS Registry represents a chance to do work on these issues in a large sample. It is important to determine whether the

different cognitive and behavioral subtypes in ALS are associated with caregiver burden and to determine the time-course of disease progression and caregiver burden associations.

The first specific aim of the study is to characterize the cognitive and behavioral subtypes in a large national cohort of PALS and to identify risk factors for the subtypes. The second specific aim is to study cross-sectional and longitudinal relationships among cognitive and behavioral subtypes in PALS and caregiver burden, and whether these relationships are related to ALS disease progression over a three-year interval. The third specific aim is to validate the telephone and questionnaire-based assessments with an in-person PALS-caregiver dyad sample collected through the VA in the New England region. The study intends to enroll approximately 200 participants per year from the Registry for a total of 600 participants. The study will also recruit from the cohort at the VA Biorepository ALS Brain Bank. Approximately 60 participants will be recruited for in-person interviews and assessments.

At enrollment and follow-up, PALS will receive the ALSFRS, measures of cognition, and measures of mood and behavior. Caregivers will receive measures of caregiver burden and assessments for mood and behavior at enrollment and follow-up. The telephone cognitive assessment of PALS will consist of the ALSFRS-R; the Telephone Interview for Cognitive Status; and, if necessary, the Cambridge Behavioural Inventory Revised (CBI-R). Questionnaires will be mailed to PALS and caregivers to assess depression, anxiety, other diagnoses, and a dysexecutive questionnaire. Caregivers will receive the Zarit Burden Interview, the most widely-used caregiver burden interview, and the Social Support Questionnaire. The New England sample will receive all of those assessments plus an in-person assessment and an in-person interview of caregiver burden. The administration of the measures will be counter-balanced so that there will be no order effects between the telephone and in-person assessments.

The first year of the project period is devoted to securing IRB and OMB approvals. If those approvals are secured sooner, then the project will start sooner. The research will examine the relative prevalence of the cognitive and behavioral subtypes; the rates of conversion over the observation interval; and risk factors for those conversions over time. The research will also include cross-sectional analyses of PALS cognitive and behavioral symptoms and disease severity; the relationship of PALS cognitive and behavioral symptoms and patterns to caregiver burden; and caregiver burden and disease severity relationships at enrollment and over time. Longitudinal analyses will consider whether the cognitive, behavioral, and mood symptoms of PALS at enrollment will predict subsequent caregiver burden trajectory; whether initial assessments are related to disease progression; and the status of caregivers at enrollment and whether their status is related to subsequent disease progression. The validation process will consider how the telephone and questionnaire measures relate to the in-person assessments. Adjustments will be made as necessary.

Discussion Points

Dr. Lucie Brujin asked whether Dr. Brady had connected with other researchers who have worked on determining ALS and ALS-FTD tied with genetic studies.

Dr. Brady was familiar with that work and agreed that genetic analysis would be beneficial, if funding were available.

Dr. Amelie Gubitz said that the Office of Clinical Research of the National Institute of Neurological Disorders and Stroke (NINDS) has developed common data elements and recommended some instruments for cognitive and behavioral assessments. If those instruments are applicable to this study, then it would be useful to utilize them to enable future meta-analyses.

Dr. Brady replied that the measures that they selected were related to the common data elements. They have also considered the NIH Cognitive Toolbox measures.

Like many ALS patients, Mr. Tessaro visits with many families. Almost without exception, the biggest issues killing patients and caregivers, especially spouses and family members, is financial ruin. That circumstance often leads to a bad psychological state. The body follows the mind, and when someone enters a despairing state of depression, almost anything measured will be "on the downside." He hoped that the questionnaires would include specific questions about the financial effects of ALS.

Dr. Brady said that the study will consider socioeconomic status, and it will be important to assess the dynamic changes in socioeconomic status as a function of the disease.

Dr. Brooks said that one of the proposed scales does not measure eye movement difficulties. The relationship of eye movements is becoming clearer in the cognitive domain of ALS. He suggested focusing on VA patients who might be in the Registry in order to potentially correlate eye movement difficulties with telemedicine interviews.

NeuroX ALS

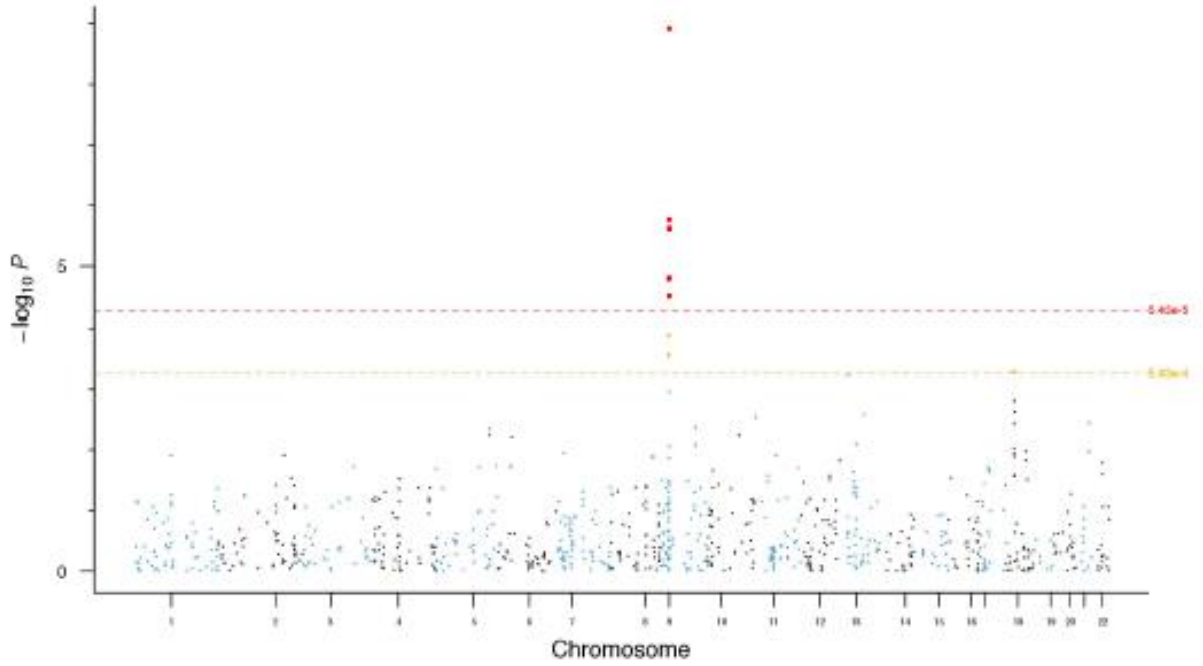
Bryan Traynor, MD, PhD, MMSc, MRCPI
Chief, Neuromuscular Diseases Research Section
Laboratory of Neurogenetics
National Institute on Aging

Dr. Traynor described the NeuroX Genome-Wide Association Study (GWAS), which was funded by CDC and ATSDR. The analysis is ongoing, and more information will be released soon. The study is unique in its use of the NeuroX gene chip, which has custom content that is specific to neurodegeneration. The study culled the literature to pull out all of the mutations and genes that are associated with Alzheimer's disease, Parkinson's disease, ALS, and other neurodegenerative diseases. Those mutations and genes were put onto the NeuroX chip. If the same genes that cause Alzheimer's also cause ALS, then the study will be able to detect it.

In addition to custom content, there is standard content of the Exome chip. The standard genome-wide association study chip has single-nucleotide polymorphisms (SNPs) scattered across all base pairs of the genome. In the Exome chip, those SNPs are concentrated in the portion of the genome that codes for proteins, which represents only 1% of the actual genome and is "heavy on rare variants." From a geneticist's perspective, this approach is different and novel. The study also took the 900 top SNPs from the recent Langerfield paper, a meta-analysis of GWAS of ALS, as a means of replication and to determine whether it is possible to demonstrate an association signal.

The study included approximately 5000 cases and 5000 controls. The populations sampled were limited to avoid population stratification, a common problem in GWAS. The results were

presented on a Manhattan Plot: the x-axis is all of the chromosomes, and the y-axis is the "strength of the signal." Each SNP that is assayed is represented by a dot on the chart, and the height of the dot represents the strength of the association. The red line must be reached in order to declare significance.



Chromosome 9 is a "skyscraper" on the plot, but none of the other 900 SNPs were replicated. The single-marker association is more dense because more SNPs are represented. The only significant element in that analysis is Chromosome 9 as well.

Next steps include continued analysis. The raw data will be made publicly available as quickly as possible, as the other GWAS and Exome sequencing data sets that have been made available. In the long term, a larger GWAS is needed, with 10,000 cases and 10,000 controls. The larger GWAS should use the OmniExpress chip, a different chip with broader coverage. Ultimately, one laboratory should use one chip and conduct all of the analyses in one place to eliminate quality control and batch effects.

The justification for a study with a larger sample size is based on experience with a study on Parkinson's disease involving 13,000 cases and nearly 100,000 controls. In contrast to the plot for ALS, the Manhattan Plot for Parkinson's disease has much stronger, and more, loci. The data come together at the 10,000 mark.

Discussion Points

Dr. Gubitz asked whether the 26 loci associated with Parkinson's disease have a significant sporadic component.

Dr. Traynor answered that most of the cases were sporadic Parkinson's disease. They can now account for the genetic etiology of about 66% of all sporadic Parkinson's disease cases. Work is ongoing to devise a mechanism by which the onset of Parkinson's disease can be predicted based on genetic loci and other factors.

Dr. Bowser commented that there were a few more "blips" on the second ALS Manhattan Plot. He asked whether smaller studies of Parkinson's disease also showed loci "creeping up" in a similar fashion, and whether it is expected that the loci that are "creeping up" in the second ALS plot will grow over the significant level in a larger study, or whether the results will be completely different.

Dr. Traynor answered that experience indicates that some of the loci will survive and grow to the point of significance, some will disappear entirely, and novel loci will emerge as well. The chip proposed for the Mega-GWAS has a different set of SNPs and different coverage, so the findings may be different. Because of the possibility of random chance, GWAS are stringent in the requirements that loci cross the significance threshold and replicate in order to be believed.

Dr. Feldman asked how other researchers can contribute DNA samples to the research.

Dr. Traynor expressed interest in talking about those details offline. The study is particularly interested in Americans. As long as the samples are de-identified, a Material Transfer Agreement (MTA) makes the IRB process relatively simple. They already have 10,000 cases and more than 10,000 controls.

Dr. Brooks said that in order to identify one gene, the whole prevalent population in the US must be screened. He asked how to address the issue of oligogenic ALS.

Dr. Traynor answered that GWAS is ideally positioned to identify oligogenic, complex genetic etiologies. GWAS identifies numerous different association peaks. As the term applies to ALS, "oligogenic" refers to familial cases when there are mutations and protein change in one gene, and protein change in another gene. The NeuroX data has enabled researchers to find instances of mutations in two genes occurring in the same sample, which is not seen often.

PALS Perspective on the Registry

Rebecca Kidd
Emory ALS Clinic

Ms. Kidd extended her thanks to the meeting participants and to people who were not present: personnel in laboratories, clinics, and offices who fight for PALS every day. She admires their work and believes that it is difficult to deal with ALS on a day-to-day basis from that perspective.

The first day of the meeting gave her an appreciation for how far the National ALS Registry has come and how much it has accomplished. She also appreciates the power that the Registry holds moving forward and is "on fire" to help build and enrich the Registry to feed additional studies. The presentations about the Registry studies were inspiring.

PALS have few options in their medicine cabinets to fight the disease. They have Rilutek® (riluzole) and, on good days, faith, a good attitude, and hope. One has to be pragmatic where hope is concerned, though, so it is not false hope. Because of her time at the meeting, she has a "bottle of hope" to take home with her.

She hoped that they would walk away from the meeting with a concrete, measurable, time-structured plan for growing and enriching the Registry.

Eric Von Schaumburg
Muscular Dystrophy Association

Josh Von Schaumburg thanked the group for the invitation to attend the meeting, and he read his brother's comments.

Eric was amazed to see brilliant people gathered in a room discussing how to solve problems that can save his life. He hoped for better incentives for PALS to enroll in the National ALS Registry and to take surveys. The stress of the diagnosis and the limited lifespan make every second important to PALS. All of the PALS at the meeting are concerned with the greater good and giving back to the ALS community, but most do not search global ways to contribute to the greater good. They are focused on saving their own lives and accomplishing their lifetime goals in just a few years.

The first time he visited the Northwestern clinic, he was asked to take a blood test for research purposes. The test would provide no information for him, but every person who takes the test may increase the chance of finding a cure for ALS or a new progression-slowing drug. He gladly took the test and assumes that most PALS will do the same. He wished for access to data from studies such as that one. He wondered why that test could be offered to him, but clinics cannot urge him to fill out paperwork and register him in the Registry. All clinics can do is provide him with a URL and encourage him to go to a computer after he has received a horrific diagnosis.

Regarding incentives for PALS to register, patients can be recognized in small ways for contributing. There are data privacy concerns, and it is difficult to secure IRB approval, but it might be possible to include a box at the bottom of each survey indicating that the respondent agrees to allow an organization to recognize them in their next newsletter for contributing to ALS research. Then The ALS Association, Les Turner, and MDA can recognize these people publicly. Facebook fan pages can recognize people on a monthly basis who have contributed by completing a survey. As the ALS demographics shift to more online-focused groups, this approach may be more useful.

The Mobile Service Locator App is a one-time download and view, with no additional use. He suggested allowing the app to provide information regarding meetings through MDA, Les Turner, The ALS Association, or other support groups. The app could have more user interaction and links to registries.

These ideas do not solve the problem of reaching people who are not online, but they can lead to gathering more data through surveys. The Ice Bucket Challenge illustrates the importance of empowering patients to show their support on social media. Mr. Von Schaumburg encouraged the researchers at the meeting to challenge the IRB to allow patients to spread the word about participating in research. The additional data will allow for answers more quickly and to connect patients with viable treatment options.

It may not be enough to encourage researchers to speak on behalf of PALS. It may be more powerful for PALS to unite and challenge the IRB to permit what they want, which is widespread information-sharing. If the Registry and its relevance are completely explained at the first visit, all PALS would sign up for it. As one's individual disease progresses, there is less incentive as PALS realize the results are not likely to affect finding a cure for one's self. PALS become understandably more selfish to their own needs as the disease progresses.

It has been frustrating to see how sharing information through computer technology has grown exponentially over the past decade, but the medical field seems stuck in the 80s in many ways. Producing a database of PALS including their demographics, environmental factors, and biomarkers through surveys seems simple from a technological perspective, given all of the data that is currently available. The fact that privacy laws drag behind technological advantages does a disservice to PALS who are "fighting our asses off on a daily basis." It has been a mental and emotional letdown to see a full room of intelligent individuals who cannot figure out the best way to legally share information across organizations to find a cure for ALS.

Mr. Von Schaumburg encouraged those at the meeting to seek out Project MINE. Josh Von Schaumburg works for Accenture, Inc. When a senior manager in the Netherlands was diagnosed with ALS, Accenture started sponsoring several different initiatives. This global company is working together as one, as the ALS community needs. Project MINE is one of those initiatives and is in the process of genetically sequencing full genomes of 15,000 ALS patients across Europe to compare data. It is important to work together with all of the available data, not just within the US, but around the world.

Discussion Points

Dr. Bradley said that it might take an act of Congress, but it would be interesting if patients were allowed to "sign out" or abandon HIPAA.

Josh Von Schaumburg said that Harvard is conducting the Personal Genome Project, which allows for sharing full genome data through different research initiatives.

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

Mr. Harada shared feedback from PALS who appreciated the live streaming from the first day of the meeting.

The National ALS Registry has come a long way. The results were highly anticipated, but they were somewhat anticlimactic, possibly because expectations were not managed. The Registry can do a better job of explaining what will happen each year, the data that will be available each year, what the data will be useful for, and what is anticipated in the future. People in the ALS community feel like stakeholders in the Registry. Not only do they work with Congress to ensure that the Registry continues to be funded, but they are also critical to the Registry's success when they enroll in it. The ALS community should be treated like stakeholders with communication, expectations, and status updates. Ultimately, the Registry is better off if it under-promises and over-delivers.

PALS are encouraged to tell their stories. In this case, CDC/ATSDR needs to tell their story. Mr. Harada suggested an open letter to the ALS community thanking them for their work in securing funding for the research and for enrolling in the Registry. The letter can list the Registry's accomplishments to date and how they will be utilized, as well as opportunities for improvement and struggles, including the OMB and IRB. This communication will help PALS understand the success of the Registry, where the number of 3.9 has less impact and relevance. People do not know what they have until you tell them. Mr. Harada related an experience from his time in management at Federal Express, which taught him the importance

of telling people what they have. CDC/ATSDR has done great things, but they are not selling themselves.

It is not possible to manage what is not measured. It is not clear whether the field efforts to build enrollment in the Registry are having an impact. The NGOs and other support organizations can set goals, expectations, and accountability related to the Registry. For instance, providing tablet computers for use in the field is a good program, but the return on that investment is not clear. It is not known how many people signed up for the Registry via those tablets. It is possible to learn from the clinics how many new patients are signed up on a monthly basis; it should be possible to verify with the clinics whether the patients have been reached to sign up for the Registry. The organizations can set enrollment goals for a given time period and hold chapters accountable for them. Neurologists have a stake in the Registry, because it is in their best interests to have strong data.

Regarding telling the story of the Registry, the funded research is a significant win and important point of information for PALS. Few PALS are aware of the funded research.

The problem of Internet access has been discussed widely, but telephone surveys are important elements of some of the research projects. It is not feasible to fund a telephone bank of operators all day, every day, but it might be possible to make an operator available during certain hours or on certain days. This approach expands the opportunity for PALS to enroll in the Registry.

Follow-up to this meeting is very important. Some of these issues and obstacles have been discussed in previous meetings. They should pick top action items to improve the Registry and map dates and responsible parties to them. He is happy to contribute in any way.

It was emotional for Mr. Harada to meet Dr. Feldman in person for the first time at the meeting. He thanked her, and the other clinicians and researchers, for their hard work. Nobody wants to be given the ALS diagnosis, but he also would not want to be in the shoes of clinicians who were trained to help people, but who have to tell patients that they have a terminal illness. Even though clinicians are exhausted after a clinic day, that experience remains an opportunity to capture PALS and enroll them in the Registry.

Discussion Points

Dr. Mehta thanked Mr. Harada for his comments. He asked whether a National ALS Registry Newsletter would be welcomed. It would have to be IRB approved but could be released twice a year or quarterly to engage PALS and inform them about funded research, activities of the NGOs, and other information in a newsletter format that can be emailed or provided on websites.

Mr. Harada said that in his professional experience, he never heard an employee complain that the boss talks to him too much. More often, there is not enough communication and information-sharing. PALS and their families are thirsty for information. He has written articles about the importance of the Registry. If the newsletter is created, then it must be timely and useful, because it will be expected.

Dr. Kasarskis asked whether social media posts, such as tweets and Facebook posts, have to be cleared through the IRB.

Dr. Mehta said that all communications must be cleared. They have some posts that are already prepared. A newsletter is doable, but it will be planned accordingly.
Dr. Kaye clarified that communications being used for recruitment must go through the IRB, but other communications may not. Therefore, communications that do not describe how to enroll in the Registry can be created. The IRB has been generous regarding Facebook and Twitter posts, which can normally take weeks to be cleared. The approval process has been shortened to less than 24 hours.

Dr. Feldman agreed with the importance of having deliverables from the meeting. She hoped for best practices or a Standard Operating Procedure (SOP) to provide structure for the states to improve enrollment in the Registry. Without such a structure, the same issues will keep occurring.

Ms. Kidd said that the newsletter idea is a good one, but a master strategy for communication is needed. The strategy would include the newsletter and its intended audience. She urged them not to under- or over-estimate the information that PALS need. Sometimes they need a simple reminder. A group of PALS or representatives from the NGOs could take on the task of formulating and actioning a communication plan.

Edward Tessaro
Retired/Philanthropy
MDA for ALS/St. Jude's Hospital/CF

Mr. Tessaro said that receiving the diagnosis of ALS is a solitary experience. As Mr. Harada expressed, he cannot imagine spending a workday meeting families to deliver the second opinion to confirm ALS. He expressed love and respect for the neurologists who do that work at least once a week, and some more than that.

Even given the solitary nature of ALS, Mr. Tessaro has never felt solitary in the six years since receiving his diagnosis. He described a community of friends, family, professionals, and clinicians. ALS patients discover things deep in themselves that may not be "better" than their previous lives, but which lead to deeper love for those around them. The clinical researchers and technical supporters are part of the same personal, physical experience. He expressed his great appreciation and thanks for their work, as their careers are focused on a condition that he and 30,000 other people have.

Next Steps and Strategies for Enhancing the National ALS Registry for all End Users: Open Discussion

Robert Kingon
Facilitator

Mr. Eric Von Schaumburg asked how registries are handled by other diseases and whether the prevalence of the other diseases are greater so that they do not need registries per se. He wondered how other less-common diseases are undertaking similar registry projects and whether there are lessons to be learned from them.

Dr. Horton answered that there are a number of different registries in "all shapes and sizes." There are not only disease registries, but also exposure registries and other types in the public

health world. The best-known registries are cancer registries, which have been in existence for decades. They have an advantage, however, because each state requires that doctors report cancer to a registry. ALS does not have similar laws associated with it.

Mr. Eric Von Schaumburg asked why ALS is not a reportable disease in all states.

Dr. Horton said that it is up to each state to dictate which diseases are reportable. Massachusetts decided to make ALS a reportable condition, but the other 49 states have not. Multiple sclerosis (MS) and Parkinson's disease are also not reportable, among other diseases. Many diseases do not have registries. The MS and Parkinson's disease communities are fighting for their own registries. He hoped that other disease organizations can incorporate similar strategies from the National ALS Registry into their registries. ALS has strong, passionate, mobilized advocates that tell the ALS story with PALS on Capitol Hill every year to secure funding for the Registry. That work moves decision-makers. In the absence of a Registry, other disease area research is based on mortality data, but that approach is not the best way to gauge how the disease affects Americans. ALS is in a unique situation, and they are fortunate to be able to create and maintain the National ALS Registry as a collaborative effort with a number of people and groups.

Dr. Kasarskis wondered how to motivate the rest of the ALS population to participate in the Registry. The PALS at the conference have gone through the shock of diagnosis, and their backgrounds and education have motivated them to become spokespeople and advocates for the illness; they represent a small fraction of the entire ALS community. Expertise in behavioral science or another area may be needed to discover how to motivate others to participate.

Mr. Tessaro disagreed with the notion that backgrounds and education are motivating factors in PALS's interest in helping people and in surviving. He said that a person's attitude and motivation are less related to education and background, and more related to whether a person is happy, is loved, and loves others. Attitude and involvement is also related to whether a person can afford an illness that insurance companies offer little help with.

Mr. Harada added that 25 people logged on to the live stream of the meeting the day before, and he has been receiving emails asking about the proceedings on the second day. There is interest in the Registry. He felt that interest in the Registry is less related to socioeconomic and more related to communication. A person with lower socioeconomic status may have less access to communication tools. The Registry sells itself if the story is told. When a person is diagnosed, several thoughts go through his mind: "What do you mean, I have ALS?" "What do you mean, there's no cure?" These questions must be processed. Most PALS, regardless of socioeconomic status, want to help even if their efforts will not help them directly. When they understand how the Registry can make a difference, they are willing to enroll in it.

Ms. Kidd agreed and added that the initiatives must be local. The national-level team cannot be expected to enroll the entire ALS community. People will be motivated by "a local touch." She did not sign up for the Registry for over a year after her diagnosis because she was in shock. Everyone's story is different, but local outreach will make a difference. Chapters should make enrollment a priority, whatever it takes. The efforts must be tied into an overall structure, with a leader at the top, and the data and work can cascade to local initiatives.

Dr. Horton agreed and added that ATSDR is a government agency. Nobody likes the government to tell them what they should or should not do. Local-level, peer-to-peer approaches will be the most effective.

Dr. Boylan was not previously aware that there may be a means for accessing Registry data regarding the proportions of people who are registered within states and districts. That information will focus efforts to improve portal registrations.

Dr. Wolff said that MDA's clinical Registry currently includes 25 clinics and three different diseases. In 2015, they will expand to close to 200 clinics across the country. The burden of disease cannot be underestimated. Enrollment in a Registry is not a priority when a person is first diagnosed, and there is a process of understanding the impact. She hoped to explore options for MDA to consent for both registries at the same time as part of their clinical care Registry.

Dr. Brooks observed that the National ALS Registry is at a tipping point that began with the first report. It is clear that better efforts are needed to "sell" the Registry, which is the only ALS registry that is national. It is a live patient registry, which is significant. Neither the MDA nor The ALS Association will send an email to an individual asking for participation in a clinical trial. Those components must be communicated in order to bring the Registry to the next level. He endorsed the idea of MDA and The ALS Association collaborating on a simple way to consent participants to join more than one registry. ALS diagnosis must be confirmed for cases to enter the MDA Registry. The Registry needs increased granularity. ALS is a syndrome, and aspects of ALS-Plus, ALS with lab abnormalities, and ALS-FTD are important elements to consider from the point of view of individual risk factors. Additionally, phenotypes and genetic efforts will have an impact on the Registry in the next five years.

Mr. Harada volunteered the Georgia chapter of The ALS Association to serve as a pilot site to develop SOPs and to work with the CDC to better capture the ALS population, especially the newly-diagnosed population. The key to this work will be developing a means for measurement.

Closing Remarks

D. Kevin Horton, DrPH, MSPH
Chief, Environmental Health Surveillance Branch, DTHHS
Agency for Toxic Substances and Disease Registry

Dr. Horton thanked the PALS for attending the meeting. Working with PALS makes the researchers and clinicians more impassioned to work even harder. Their hard work captures the spirit of PALS and their willingness to help others.

This year has been critical for the National ALS Registry. Their work is just beginning with the release of the first report. They are building evidence, and there will be more reports and journal articles detailing findings.

The Research Notification Tool is critical for linking PALS to researchers. He asked for help sharing that feature of the Registry with PALS and with ALS researchers so that they can take advantage of it. So far, nine institutions across the US are using the tool, and over 15,000 emails have been sent to PALS. More researchers need to submit more proposals to the Registry to build those numbers.

There are currently 15 Risk Factor Modules in the National ALS Registry, and more will be launched in the fall of 2014. Over 30,000 surveys have been completed, and the collection may

be the largest in the world on a number of potential risk factors for ALS. PALS must be encouraged not just to enroll in the Registry, but to take all of the surveys. Some of the surveys have already been analyzed, and additional analysis results will be shared in the fall.

Promotion and outreach regarding the Registry is a challenge. ATSDR was tasked to create the Registry, and they must tap into their partners' expertise in communications to spread the word about the Registry and to tell its story.

PALS are the Registry's priority target, but the continuing education modules represent a way to bring healthcare professionals into the fold so that they can understand, speak for, and support the Registry.

The state-metropolitan surveillance is important for the National ALS Registry in different ways. The surveillance helps determine the completeness of the Registry data. It also provides more granular information about ALS incidence and prevalence across the US.

The mobile applications are currently "one and done," but they could be expanded to have better utility. That expertise is in-house at ATSDR.

The research projects are strong and impressive, and their results will fill gaps in the literature. It is important to publicize the research funded through the Registry. The studies help explore and better understand the etiology of ALS. A Request for Proposals (RFP) may be released in the fall of 2014. He welcomed ideas for potential studies for funding.

Dr. Horton invited the group to remain for the Biorepository Meeting that afternoon. He thanked them for their attendance.

The meeting adjourned at 11:58 am.

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