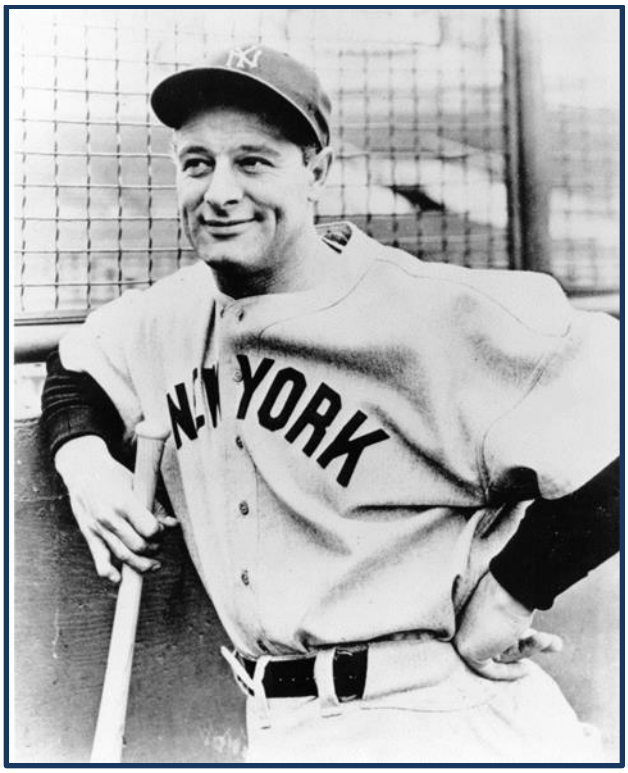
Department of Health and Human Services
Centers for Disease Control and Prevention
Agency for Toxic Substances and Disease Registry

Annual Amyotrophic Lateral Sclerosis (ALS) Surveillance Meeting



August 1-2, 2017
Summary Report

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

2017 Annual ALS Surveillance Meeting Executive Summary

Amyotrophic Lateral Sclerosis (ALS) continues to be a mysterious fatal disease with no known cause(s) for approximately 90-95 percent of those diagnosed with the disease. It is for this reason that the Agency for Toxic Substances and Disease Registry (ATSDR) established the National ALS Registry in 2010. The primary purpose of the ALS Registry is to describe the incidence and prevalence of ALS, to describe the demographics of ALS patients, and to examine the risk factors for the disease. In 2016, the ALS Registry published the second report on the prevalence of ALS in the United States in CDC's *Morbidity and Mortality Weekly Report* (*MMWR*).

Each year the ATSDR organizes the Annual ALS Surveillance Meeting to update stakeholders on the progress of the National ALS Registry, The National Biorepository, the Registry data and its implications, and to discuss strategies to further enhance the Registry for all of the stakeholders. In January 2017, the National ALS Biorepository was initiated with the primary goal of assembling the largest bank of ALS blood and tissue samples in the US and making them available for research.

Opening Remarks

Dr. Patrick Breysse, Director, National Center for Environmental Health and the Agency for Toxic Substances and Disease Registry, provided the opening remarks for the 2017 meeting. Dr. Breysse acknowledged the huge resource this meeting represents by bringing together clinicians, researchers, persons with ALS and other ALS advocates to help move the science forward. He briefly mentioned the President's budget, which reduces NCEH funding by approximately $25 million over recent funding, including elimination of the National ALS Registry funding. However, he underscored the importance of this important work and therefore hoped that the funding would be restored. Dr. Breysse also pointed out the progress that has been made by the Registry since it was launched in 2010.

Overview of the National ALS Registry

The background and methodology of the National ALS Registry was described beginning with the enactment of the US ALS Registry Act, passed in October 2008. This act directs CDC/ATSDR to establish and maintain the National ALS Registry. Because ALS is a rare and non-notifiable disease there was not a reliable method for determining the number of cases of ALS in the US, who has the disease, or other factors about ALS. The Registry was launched in October 2010 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 methodology for identifying ALS cases was described, which uses data from national administrative databases (i.e., Medicare, Medicaid, and the Veterans Administration) in addition to the information entered into the online Registry web portal by persons living with ALS. In addition to enrolling, persons with ALS can also answer questions regarding their disease and complete any or all of 17 risk factor surveys on the Registry web site. These surveys will help to answer questions about the potential risk factors for ALS.

But the Registry is doing much more than just counting cases. Some of the initiatives that are now ongoing as part of the Registry include:

- Funding to support ALS research
- Launching the National ALS Biorepository in January 2017
- Maintaining the Research Notification System to connect persons with ALS to clinical trials and epidemiological studies
- Implementing the use of a Global Unique Identifier (GUID) to link data across studies and trials PALS have participated in
- Launching a researcher data/biospecimens platform for requesting data and biospecimens for use by researchers
- Publishing journal articles including ATSDR-funded research & research that used the Registry to recruit participants
- Partnering with organizations including; the ALS Association, Muscular Dystrophy Association, Les Turner ALS Foundation, and Brunet-Garcia Advertising

Discussion about Research and Registry Activities

A high-level overview about research and Registry activities was presented, which included the next MMWR report to be released from the Registry, risk factor surveys, funded research, the Research Notification System, and manuscripts currently in development. The third *National ALS Prevalence Report* will cover the calendar year 2014. Hospice data will be included in the report for the first time, which may increase the case ascertainment counts. As of August 1, 2017, nearly 70,000 risk factor survey modules had been completed by persons living with ALS. Requests have been received from researchers for the risk factor survey data, which is now being released. These data are being made available for research with certain restrictions. ATSDR is also funding extramural research to learn more about ALS etiology and risk factors. To date, 12 research studies have been funded, with one additional study to be funded within the next few weeks. The Registry is also assisting ALS patients in locating research studies and clinical trials and determining if they meet the eligibility criteria for participation. The Research Notification System is designed to help researchers recruit for their studies and clinical trials. When a person enrolls in the Registry, he/she may choose to receive notifications about clinical trials and studies that they are eligible for. Over 100,000 emails have been sent to Registry participants thus far. A listing was also presented of 10 manuscripts that are currently under development or have been submitted to journals.

Update on the National ALS Biorepository

A brief history and update on the National ALS Biorepository was described. A pilot project ran for about four years from 2012 until 2015. The pilot study enrolled 330 Registry participants to provide biological specimens including blood, urine, hair, and nails. An additional 30 Registry participants were enrolled to donate tissues postmortem. At the end of the pilot study, a number of recommendations were made including the continuation of collecting most of the specimens collected during the pilot study. Based on these recommendations, the National ALS Biorepository was launched in January 2017. The process for enrolling in the Biorepository was described for new and previously enrolled Registry participants. From January – July 15, 2017, the Biorepository has collected 133 in-home blood and urine specimens, 30 saliva specimens, and 1 postmortem tissue donation. The process for researchers to request samples from the Biorepository was also described.

Registry Communication & Outreach

Agency for Toxic Substances and Disease Registry

ATSDR provided an overview of the communication and outreach efforts being used to increase awareness of the National ALS Registry and to encourage persons with ALS to participate in the Registry. ATSDR recognized the outstanding work being done by its partners to raise awareness. But more attention needs to be focused on understanding who the target audience is and what messages should be used. To that end, ATSDR has used many different routes this year to reach the audience. A few of these include; the creation of a new video, new digital media, and a website makeover, currently in progress. In addition to its existing partners, ATSDR is also exploring new partners who may be able to provide insights to where patients and clinicians are and can help bring everyone to the table to work together.

ALS Association

The ALS Association described the many facets of the organization that are working for people with ALS through their public policy, research, and care efforts. Between 150-180 research studies are funded each year by the Association. They are also working through the 39 chapters and over 130 clinical partners to provide outreach to support the Registry. The Association's newly created National ALS Registry Taskforce has been instrumental in revitalizing the Registry section of their website by helping to identify the need to relocate it to a much more prominent location on the Association's website. This move has significantly improved its visibility, resulting in 250,000 views per month. The use of social media to further awareness of the Registry has also been increased significantly in 2017. Also described are new and innovating strategies, some in place and others planned, to increase enrollment in the Registry such as assisting under-performing chapters to develop strategic plans and holding Best Practices meetings at upcoming ALS Association conferences.

Muscular Dystrophy Association

Kristin Stephenson, Vice President of The Muscular Dystrophy Association, explained that MDA is committed to saving and improving the lives of individuals living with neuromuscular disease. She stressed the importance of the organizations and individual stakeholders working together because each has a role to play to ensure that the Registry is successful. MDA sees its role as not only promoting the Registry, but also telling people why the Registry is important and why it is important to be part of it. She described the different disorders served by MDA, their funding commitment for ALS research and support services, and provision of care through its 150+ ALS Care Centers. MDA also advocates for public policies that impact therapy development, and provides ALS support groups and medical equipment to ALS patients.

MDA's many different channels, which are used to promote, advocate for, and to talk about the Registry to its stakeholders were also described. Some of the communication channels include social media and the more traditional print media, such as MDA's *Quest Magazine,* which can reach persons who may not be connected to the internet. Their outreach efforts employed over the last year were also presented, as well as, areas that MDA is exploring to make the messaging more impactful as it moves forward.

Les Turner ALS Foundation

The Les Turner ALS Foundation has been serving persons living with ALS and their families in the Chicago area since 1977, making it one of the oldest independent ALS groups in the world. The Foundation's mission is to: advance scientific research into the causes, treatments, and

prevention of ALS; provide people living with ALS, their families, and caregivers exceptional clinical care and support services; and to increase awareness and education of ALS. The distribution of their funding was described in the areas of research, patient care, and patient and family programs.

The Les Turner ALS Foundation uses a personalized approach to promoting the National ALS Registry, which is very consistent with the way that it approaches other ALS efforts. This approach is evident in their promotion and outreach efforts to patients and family members through clinic and home visits, support groups, annual patient education meetings, and outreach to medical professionals. Other uses of the media, educational efforts, and events, such as the ALS Walk for Life are also used to promote the Registry. The National ALS Registry Direct Enrollment Program is another very personalized effort provided by the Foundation whereby a Registry Associate works with persons with ALS in their homes to assist them with enrolling. The Les Turner Foundation also presented some of the feedback they have received directly from patients, both positive and negative about the Registry. The feedback they have received on the Biorepository has been particularly good.

Brunet- García Advertising

Brunet-Garcia has been working with the National ALS Registry since 2015 to help raise awareness of the Registry, which will lead to increased enrollment and completion of the risk factor surveys. To this end, Brunet-Garcia is continuing to work to develop and implement a strategic communications plan. One of the many underlying critical elements of the plan is to recognize the importance of helping people understand the benefits and value of the Registry. Brunet-Garcia explained the methodology and importance of ensuring that what they are doing is relevant and effectively communicates to persons living with ALS, their family, researchers, clinicians, and other audiences. Some of the highlights of their work include the following accomplishments:

- Created social media that is relevant to the caregivers as well as persons living with ALS
- Created a motion graphic video and infographics which build upon "ALS Research Counts on You"
- Worked with the Registry team to create an engaging website landing page
- Collaborated with Registry partners on a variety of articles

In all of Brunet-Garcia's accomplishments is a consistency of creating materials which communicate a very concise and clear message to a variety of audiences.

Under-Enrolled States Outreach Project

This project was initiated based on recommendations from the 2016 Annual Meeting. The previously conducted Georgia Pilot Project was reviewed in terms of its purpose, methods, results, and implementation. An update was provided on the pilot project and the strategies to increase Registry enrollment in the seven states through partner collaboration with the ALS Association, MDA, and the Les Turner ALS Foundation were presented.

The objectives of the Under-Enrolled States Outreach Project are to provide data which may be used to target outreach activities to increase Registry enrollment in specific areas of states that are enrolling persons with ALS at a lower rate than the average rate for the US. The data are now available for distribution to the ALS Association, MDA, and the Les Turner ALS Foundation. The next steps are to develop plans, to focus outreach efforts on under-enrolled counties within

the seven states for a six month period, and to evaluate the impact on enrollment for these states.

Open Panel Discussion

An open panel discussion session was held to focus on answering the questions of:

- What works and does not work when it comes to enrolling patients?
- How can Registry awareness be better raised among minority groups, persons living with ALS, and rural providers?

The presenters for this session responded to the questions from the meeting participants and the participants offered their insights into approaches that are working or appear to have promise. There was a healthy discussion of the barriers to enrolling, such as cultural issues where some races may find it difficult to enroll and provide their data to the federal government, and barriers where populations do not have internet access and populations who are living in rural areas. There was agreement on the need for simple metrics. The discussion also included concerns such as the lack of access to enrollment data that informs the local chapters and clinics of which specific cities or counties are under-enrolled. Another area is the need to enhance education about the Registry for neurologists and their staff. There was also discussion regarding when would be the best time to discuss the Registry with newly diagnosed patients.

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

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

Update From Pharma

Mitsubishi Tanabe Pharma America

Dr. Jean Hubble, Vice President, Medical Affairs, reported on the background and studies related to RADICAVA™. Dr. Hubble's presentation is not available for dissemination because it contains unpublished data.

Cytokinetics, Inc.

Dr. Sarah Kulke, Senior Medical Director, presented on two investigational products currently under development for ALS at Cytokinetics, Inc, Tirasemtiv and CK-107. Neither of these compounds are approved for the US at this time. Tirasemtiv is in a Phase 3 clinical trial. The findings of the Phase 1 trial were that muscle function could be improved with this compound. The Phase 2 clinical trial was also described. There were some findings that were encouraging, but there were also some tolerability issues with Tirasemtiv. The findings of these trials encouraged the investigators to move forward to the Phase 3 trial. Cytokinetics, Inc. recruited for the Phase 3 study through the National ALS Registry's Research Notification System. The results of the Phase 3 trial are anticipated to be presented at the ALS-NMD meeting this year.

Cytokinetics, Inc. also recently began the Phase 2 treatment study, Functional Outcomes in a Randomized Trial of Investigational Treatment with CK-2127107 to Understand Decline in Endpoints – in ALS (FORTITUDE-ALS). CK-107 is known to have the same mechanism of action as Tirasemtiv, but it is known not to cross the blood-brain barrier (BBB). The theory is that would lead to less of the tolerability or side-effect issues.

National ALS Registry Data Update

Outside researchers may now request data for use in their research studies from the National ALS Registry. The data that is available has been collected through five of the Registry's 17 risk-factor modules including: demographics, occupational history, military history, smoking/drinking history, physical activity, and family history of neurological diseases. The application process that researchers are required to follow in order to request the data was described. Once the application is approved, ATSDR provides the researcher with a unique de-identified dataset, as well as a matching data dictionary.

Open Panel Discussion

Ms. Janine Cory, Acting Director of Communication, pointed out that this session would serve as a very helpful reminder for everyone that each point of data on a slide represents a patient, and that it is important not to lose perspective about why this Registry exists and what is important. With that in mind, this panel was comprised of persons living with ALS and their families who shared their perceptions of the National ALS Registry.

Funded Research Update

Research is a critical component in learning more about the etiology of ALS and its risk factors. ATSDR provides funding to support ALS research studies to help the ALS community learn more about the disease and to also help prioritize new risk factor modules for the Registry. The following ATSDR-funded studies were presented by their principle investigators during the 2017 Annual ALS Surveillance Meeting and further information can be found on the National ALS Registry website.

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

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

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

Identification and Validation of ALS Environmental Risk Factors

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

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

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

Next Steps: Recommendations/Strategies for Strengthening the Registry

In this session there were six panelists, consisting of a representative for: the National ALS Biorepository, the ALS Registry, persons living with ALS, researchers, the pharmaceutical

industry, and ALS advocacy organizations. Each panelist shared their observations about how the Registry could be used to advance research and the future directions he/she would like to see.

In addition, this session attempted to review all of the suggestions and recommendations which had been offered from the attendees throughout the meeting, to determine if any had been missed, to add any additional recommendations, and to prioritize them.

This session was also opened for meeting participants to ask questions and to provide expert advice and guidance to Registry staff pertaining to challenges encountered by the Registry, strategies, and recommendations to maintain and further enhance the Registry.

Closing Remarks

Dr. Paul Mehta thanked the participants for their attendance and closed the meeting.

Table of Contents

Acronyms Used in this Document

Acronym	Expansion
AAN	American Academy of Neurology
ALS	Amyotrophic Lateral Sclerosis
ALS-CBS	ALS Cognitive Behavioral Screen
ALS-CBS-CG	ALS Cognitive Behavioral Subscale Caregiver Portion
ALSA	Amyotrophic Lateral Sclerosis Association
ALS COSMOS	ALS Multicenter Cohort Study of Oxidative Stress
ALSFRS	ALS Functional Rating Scale
ALSFRS-R	Revised ALS Functional Rating Scale
ALS TDI	ALS Therapy Development Institute
ARREST ALS	ATSDR Risk Factors Epidemiologic Studies in ALS
ATSDR	Agency for Toxic Substances and Disease Registry
BBB	Blood-Brain Barrier
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CMS	Centers for Medicare and Medicaid Services
CNS-LS	Center for Neurologic Study-Lability Scale
COWAT	Controlled Oral Word Association Test
CReATe	Clinical Research in ALS and Related Disorders for Therapeutic Development
CSF	Cerebrospinal Fluid
DME	Durable Medical Equipment
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DTHHS	Division of Toxicology and Human Health Sciences
ECAS	Edinburgh Cognitive and Behavioural ALS Screen
EHR	Electronic Health Record
EHSB	Environmental Health Surveillance Branch
FSTA	Fast Skeletal Muscle Troponin Activator
FBI-ALS	Frontal Behavioral Inventory
FDA	Food and Drug Administration
FTD	Frontotemporal Dementia
FVC	Forced Vital Capacity
GABA	Gamma-Aminobutyric Acid
GUID	Globally Unique Identifier
HHS	(United States Department of) Health and Human Services
HSP	Hereditary Spastic Paraplegia
IRB	Institutional Review Board
JAMA	*Journal of the American Medical Association*
JHU	Johns Hopkins University
KDE	Kernel Density Estimation
LAENALS	Latin American Epidemiology National ALS
MDA	Muscular Dystrophy Association
MedPAR	Medicare Provider Analysis and Review
miRNA	microRNA

MMWR	*Morbidity and Mortality Weekly Report*
MMSE	Mini-Mental State Examination
MND	Motor Neuron Disease
MOH	Ministry of Health
MTA	Material Transfer Agreement
MTPA	Mitsubishi Tanabe Pharma America
MTPC	Mitsubishi Tanabe Pharma Corporation
NCEH	National Center for Environmental Health
NDI	National Death Index
NDRI	National Disease Research Interchange
NEALS	Northeast Amyotrophic Lateral Sclerosis Consortium
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIV	Non-Invasive Ventilation
NMD	Neuromuscular Diseases
NOAA	National Oceanic and Atmospheric Administration
OMB	Office of Management and Budget
ORISE	Oak Ridge Institute for Science and Education
OS	Oxidative Stress
PALS	Persons with Amyotrophic Lateral Sclerosis
PI	Principal Investigator
PII	Personally Identifiable Information
PLS	Primary Lateral Sclerosis
PMA	Progressive Muscular Atrophy
RDCRN	Rare Disease Clinical Research Network
RDCRC	Rare Diseases Clinical Research Consortium
RN	Registered Nurses
RNA	Ribonucleic Acid
SES	Socioeconomic Status
SMA	Spinal Muscular Atrophy
SOD-1	Superoxide Dismutase 1
SOP	Standard Operating Procedure
SPH	School of Public Health
SRC	Scientific Review Committee
SVC	Slow Vital Capacity
TICS	Telephone Interview for Cognitive Status
TIV	Tracheotomy with Invasive Ventilation
UK	United Kingdom
USC	University of South Carolina
VA	(United States Department of) Veterans Affairs
WGS	Whole Genome Sequence

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

Minutes of the Meeting
August 1-2, 2017

Welcome and Introductions

Robert Kingon, MPA, Facilitator
Carter Consulting, Inc.

Mr. Robert Kingon called the meeting to order at 1:30 PM. He explained that the meeting would be streamed live and he requested participants sign the release form included in their meeting packets. He described ground rules for the meeting, reviewed housekeeping items, and led participants in a round of introductions. A participant roster is appended to the end of this document.

Opening Remarks

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

Dr. Breysse indicated that he had been serving as the Director of NCEH and ATSDR since December 2014. He comes from an academic background, having spent his career at the School of Public Health (SPH) at Johns Hopkins University (JHU) in Baltimore, Maryland as an Environmental Health Researcher. As a result, he appreciated what a tremendous resource this meeting represented. The fact that they could assemble clinicians, researchers, and people impacted by the disease all to help move the science forward represented a huge contribution. He expressed his excitement at being able to play a small part in that as the Director of ATSDR, and that the agency could play a major role through the National ALS Registry in helping to defeat this devastating disease. Many if not all of them have friends or family afflicted by this disease. One of his best friends lost her brother to the disease a few years ago, so he could attest to the devastation it produces. At the end of the day, operations such as this are invaluable in getting ahead of this disease. The success of the Registry depends on everyone working together. The ALS Registry is a groundbreaking registry, which is truly unique in many ways. The fact that everyone can work together toward a cure is something to be proud of.

The President's budget included limits on funding across the federal government, including CDC and NCEH. The President's budget reduces NCEH funding by approximately $25 million over recent funding, including elimination of the National ALS Registry funding. Dr. Breysse said he works for the Executive Branch and supports the President's budget, but also was happy to say that the House's budget mark-up included resources for the ALS Registry. He said he could attest to his own personal interest in making sure this important work continues, and his hope that the funding will be restored.

In terms of progress, the ALS Registry will be publishing the third report of ALS prevalence in the summer of 2017, which is a crucial report that helps to lay the groundwork for why ATSDR is doing this, why the disease affects so many people, and why the Registry is important. ATSDR is also excited about the ALS Biorepository, which also is truly a unique resource. This is an incredible resource that offers researchers access to tissues and blood samples for patients with ALS. These samples can be paired with risk factors that are known about people, and represent an untapped resource. ATSDR is looking forward to updates from its funded researchers across the country and internationally, and also is working on internal research papers through the ALS program that summarize ALS mortality, disease progression, survival modes, comparison of the Registry with state and metro surveillance projects, and other risk factors. This is an important contribution ATSDR makes with its intramural and extramural work.

Dr. Breysse recognized ATSDR's partners, the ALS Association (ALSA), the Muscular Dystrophy Association (MDA), and Les Turner ALS Foundation for providing important support to ATSDR and an update during this meeting on their important initiatives. The Registry Communication Team is also working to increase awareness of what the ALS Registry does. The Registry has been very well-received by researchers. To date, 27 institutions have utilized the Registry data for clinical trials and epidemiologic studies and over 90% of the registered persons have opted in to receive notification from the Registry about research for which they are eligible.

In closing, Dr. Breysse welcomed everyone to Atlanta and offered them great wishes for a productive meeting.

Discussion Points

Dr. Horton inquired as to whether Dr. Breysse had any sense about when the Senate would have their marked-up budget completed.

Dr. Breysse replied that his optimistic hope was that it would be completed before the summer recess, however, that is not going to occur. They will share any information received so that it can be relayed more broadly to others. ATSDR is looking carefully at those resources. The funding for the ALS Registry is allocated to NCEH, and NCEH forwards those funds on to ATSDR for the ALS Registry. ATSDR's budget comes through a different path from Congress.

Overview of the National ALS Registry

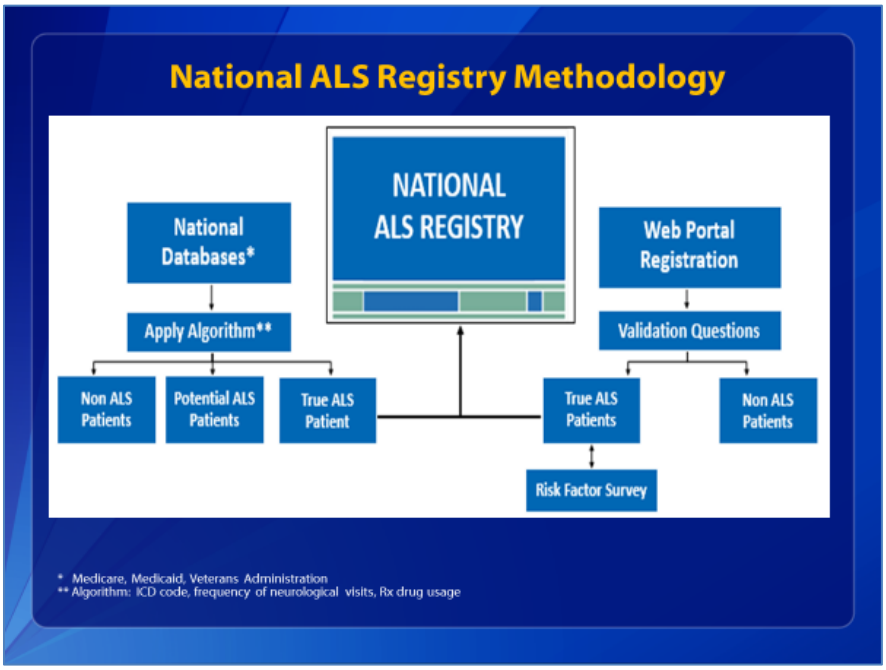
D. Kevin Horton, DrPH, MSPH
Chief, Environmental Health Surveillance Branch
Division of Toxicology and Human Health Sciences
Agency for Toxic Substances and Disease Registry

Dr. Horton welcomed everyone and thanked them for their attendance and taking time out of their busy schedules to attend, especially Persons with Amyotrophic Lateral Sclerosis (PALS) given the difficulty involved in attending. He emphasized that ATSDR greatly values PALS' input. He also welcomed those attending via Livestream. While Dr. Horton recognized that some participants may have heard his presentation previously, he pointed out that they were in a situation in which not everyone in attendance was familiar with the ALS Registry. He

explained that ATSDR is the US health agency that is charged with protecting Americans from toxic and environmental exposures. As part of the Department of Health and Human Services (HHS), ATSDR is co-located with its sister agency, the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia.

In terms of the background and methodology of the National ALS Registry, the US ALS Registry Act (Public Law 110-373) was passed in October 2008. ALS organizations and persons living with ALS are directly responsible for the passing of this Act. ATSDR certainly would not be working on this Registry if not for the hard-fought efforts of the people in the room. The law directs CDC/ ATSDR to create and maintain a population-based ALS registry for the US. The National ALS Registry launched in October 2010, after pilot-testing and development. As specified by the Act, the purpose of the Registry is to describe the incidence and prevalence of ALS, describe the demographics of ALS patients, and examine risk factors for the disease. Although Lou Gehrig was diagnosed over 75 years ago and a lot of progress has been made on the science front, many questions remain about the disease, especially for sporadic cases. One of the primary goals is to determine what leads to sporadic ALS.

Because ALS is a non-notifiable disease, the Registry needed novel approaches to track ALS cases. That is, when a doctor diagnoses someone, he or she does not have the responsibility to notify the state health department which in turn notifies CDC. Therefore, nothing was known about these cases and ATSDR had to develop a novel approach to identify ALS cases in a country the size of America that now has 320 million people. They are often asked why they do not go to Congress or each state legislator and mandate that they make this a reportable disease. In reality, that would make their job a lot easier. However, it does not work that way. There are thousands of diseases and many other disease organizations that want their particular disease to be reportable or notifiable. Dr. Horton emphasized that while he was not suggesting that they should not try to do this, the fact is that this places a major burden on state health departments. Given that, ATSDR had to develop a methodology that would allow them to identify cases of ALS. To that end, the Registry takes a two-pronged approach for identifying cases of ALS as depicted in the following graphic:



An algorithm was created during the pilot-testing phase for identifying ALS cases from large national databases from federal agencies. The algorithm separates people into three categories: Non-ALS Patients, Potential ALS Patients, and True ALS Patients, who are automatically added to the Registry. The algorithm includes elements such as the International Classification of Diseases (ICD)-9 code for ALS, Rilutek prescriptions (the only treatment at the time, though there is now a new drug on the market), and frequency of visits to neurologists or ALS clinics. Based on pilot testing and other previous studies in the literature, ICD codes alone cannot be relied upon because there is a lot of miscoding. While the bulk of cases can be captured using ICD codes, it is not possible to capture all of them in that way. All of the components on the left side of the above algorithm are done behind the scenes, so that persons with ALS do not need to do anything on that side. The majority of cases are captured through the left-hand side of the algorithm.

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

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

The Research Notification System is ATSDR's attempt to help pharmaceutical companies and other researchers conducting clinical trials or epidemiologic studies to help recruit for these particular research endeavors. There has been tremendous outreach by patients indicating that they want to take part in clinical trials. ATSDR is very happy to partner with anyone who is interested in using the Registry to recruit for their research. Partners are another critical part of the Registry. ATSDR cannot do this alone. They are a small group sitting in Atlanta behind computers trying to make this entire effort work. The ALS organizations are vital as they represent the ALS stakeholders and are essentially a mouthpiece for the Registry. Without ALS organizations, the Registry would not be where it is at this point. Patients are also critical, because there would be no Registry if they did not enroll. Neurologists are also critical partners. They are a highly valuable source of information to their patients, and are a very important resource for informing patients about the Registry.

In terms of 2016 accomplishments and activities, the goal is to publish a new report annually. The first report was published in 2014 and covered largely 2011 data. The second *Morbidity and Mortality Weekly Report* (*MMWR*) published in August 2016 covered January 1, 2012 through December 31, 2013. The data soon to be published in the third report will include calendar year 2014. Each year, additional enhancements are made to the Registry and the

algorithm is being modified to make it as sensitive and specific as possible to ensure that no one is excluded. Over time, the numbers of people captured in the Registry are increasing. That is not necessarily because more people are being diagnosed. In 2012 and 2013, there were 14,713 and 15,908 persons identified as definite ALS, respectively. Estimated ALS prevalence rates were 5.0 cases of ALS/100,000 persons in 2013 and 4.7 cases of ALS/100,000 persons in 2012. ALS continues to be more common in whites, males, and persons 60 through 69 years of age. The lowest number of ALS cases occurs in those 18 through 39 and those over 80 years of age. Males had a higher prevalence than females based on all data sources. The increased prevalence is likely due to better case ascertainment and increased Registry awareness.

Another accomplishment is that ATSDR was granted approval from the federal Office of Management and Budget (OMB), which is a very lengthy and complex process. The new approval is for the next 3 years, with an expiration date of November 30, 2019. This will allow for the continuation of data collection activities. As mentioned, the National ALS Biorepository is now live. Also implemented recently is the Global Unique Identifier (GUID). This is an important activity in that it allows ATSDR to track people in the Registry to determine what other studies and clinical trials they have participated in. Knowing this information can help ATSDR and other researchers. Now when people enroll, they have the opportunity to create their own GUID. Those who already have enrolled can go back into the website to create a GUID.

ATSDR also has launched a researcher data/biospecimen platform so that researchers can submit an application online to request specific deidentified data to use for their purposes. The same platform also houses the biospecimens in the new Biorepository, where investigators can complete a request form. ATSDR tries to be as efficient and timely as possible and is happy this platform is now available. As mentioned, the Registry is also being used to recruit for ALS clinical trials and epidemiological studies. ATSDR is trying to partner with as many people as possible, including pharmaceutical groups. ATSDR has had some interactions with a couple of pharmaceutical companies. Three additional research grants have been funded. Research is critical for understanding what causes ALS.

ATSDR tries to publish as much as they possibly can. This includes publications from researchers the agency is funding, or even researchers the agency is not funding but helps recruit. Any time a paper is published, ATSDR buys the right to it immediately and then posts it on the website. ATSDR's opinion is that they need to post this information as soon as possible so that ALS stakeholders can read about it and not have to wait a year or two before it actually clears the constraints for publishing it. There are a number of articles already posted on the website. ATSDR is also trying to publicize the registry through scientific meetings, conferences, and abstracts. Abstracts have been presented at the American Academy of Neurology (AAN), the Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS), and the International ALS/Motor Neuron Disease (MND) Symposium. A sample of a few of the journal articles that were published in 2016 follows:

2016

Horton DK, Kaye W, and Wagner L. **Integrating a Biorepository into the National Amyotrophic Lateral Sclerosis Registry**. Journal of Environmental Health 2016, 79(4): 38-40.

Roberts A, Johnson N, Chen J, Cudkowicz M, Weisskopf M. **Race/ethnicity, socioeconomic status, and ALS mortality in the United States**. Neurology 2016; doi.org/10.1212/WNL.0000000000003298.

Mehta P, Kaye W, Bryan L, Larson T, Copeland T, Wu J, Muravov M, Horton D. **Prevalence of Amyotrophic Lateral Sclerosis – United States, 2012-2013** MMWR Surveillance Summary 65(SS08);1-16.

Marin B, Boumediene F, Logroscino G, et al. **Variation in worldwide incidence of amyotrophic lateral sclerosis: a meta-analysis** Int Journal of Epidemiology 2016; doi: 10.1093/ije/dyw061.

Su F, Goutman S, Chernyak S, Mukherjee B, Callaghan B, Batterman S, Feldman E. **Association of Environmental Toxins With Amyotrophic Lateral Sclerosis.** JAMA Neurol. Published online May 09, 2016. doi:10.1001/jamaneurol.2016.0594. Open access not currently available for this journal.

Bryan L, Kaye W, Antao V, Mehta P, Muravov O, Horton K. **Preliminary Results of National ALS Registry Risk Factor Survey Data**. PLOS One 2016, April 28:doi.org/10.1371/journal.pone.0153683.

ATSDR staff have attended 11 conferences and ALS patient symposiums with platform presentations, including the following:

- ALS Clinical Trials Guidelines 2016 Workshop, March 16-19, 2016 in Warrenton, Virginia
- MDA's Clinical Conference, March 20-23, 2016 in Arlington, Virginia
- Greater Sacramento ALS Symposium, April 2, 2016 in Sacramento, California
- AAN 68th Annual Conference, April 15-21, 2016 in Vancouver, British Columbia
- ALS Association's National ALS Advocacy Day and Public Policy Conference, May 8-10, 2016 in Washington, DC
- 15th Annual NEALS Meeting, October 5-7, 2016 in Clearwater, Florida
- 6th Annual Educational & Scientific Symposium, October 26, 2016 in Chicago, Illinois
- 2016 ALS Association Clinical Conference, November 3, 2016 in San Diego, California
- 11th Brain Research Conference, 4th RNA Metabolism in Neurological Disease November 10-11, 2016 in San Diego, California
- Society for Neuroscience's 46th Annual Meeting, November 12-16, 2016 in San Diego, California
- 27th International Symposium on ALS/MND, December 7-9, 2016 in Dublin, Ireland

These conferences offer another way to promote the Registry. ATSDR also is engaged in official partnerships with a communications group, Brunet-García, and the Les Turner ALS Foundation. The Les Turner ALS Foundation is a critical partner for ATSDR. They cover the Chicagoland area and represent a number of ALS patients. Brunet-García helps ATSDR market the Registry externally.

In terms of the Research Notification System, when patients enroll in the Registry they can check a box agreeing to be notified about any clinical trials or epidemiological studies for which they may be eligible. When a researcher informs ATSDR that they have a new clinical trial or study for which they are recruiting, the agency can sort the data to match the criteria in which they are interested. ATSDR can send an email blast to the patients with information about the study, letting them know they are eligible and providing them with the Principal Investigator's (PI's) contact information. It will then be up to the patient to contact the PI. ATSDR does not take part in these studies, but acts as the "middle-man" in an effort to help facilitate study

recruitment. Over 90% of Registry PALS want to participate in research, and over 25 domestic and international institutions are using the tool for recruitment purposes.

ATSDR is funding extramural research to learn more about ALS etiology and risk factors, with 12 research studies to date and new awards pending. The information gleaned also will help ATSDR prioritize topics for future risk factor surveys. Dr. Horton noted that many of the PIs were in attendance, and encouraged those present to seek them out for further discussion. In addition, he directed everyone to the website where there is a line listing of these research projects. ATSDR will continue to fund funding opportunity announcements (FOAs) for researchers so long as funds are available. As Dr. Breysse mentioned at the outset of the meeting, they are not certain what will occur with the budget, but assuming that Congress continues funding, ATSDR will make funds available as possible.

As mentioned, the Biorepository is now live. This began with tremendous outreach by researchers who thought it would be a great idea to stand up a biorepository. There are several biorepositories throughout the country; however, ATSDR wanted a central biorepository that was open to anyone and everyone. Other biorepositories tend to have samples that are left over from other studies. The National ALS Biorepository contains pristine samples that are collected specifically to disseminate to researchers who are interested in acquiring specimens. This will be a rich source of data, given that ATSDR can pair the survey data with the biospecimens. The sampling scheme is nationally representative. He requested that everyone in the room let others know that the biospecimens are available and ATSDR wants people to use them.

In terms of how the Biorepository works, ATSDR tries to make it as easy as possible for patients. If a patient who is enrolled in the Registry wants to contribute biospecimens, ATSDR will send a phlebotomist out to their home to collect the specimens. This includes blood, urine, and saliva. Patients are not asked to present to a clinic or drive 100 miles to contribute. The Biorepository has a post-mortem aspect as well. The annual sample collection goals for the Biorepository include the following:

- 675 in-home collections
- 325: saliva, urine, blood (requires phlebotomist)
- 350: saliva kits (mailed to PALS)
- 10 post-mortem collections

Researchers can currently request data, biospecimens, or both. They do have to fulfill some specific requirements, such as having Institutional Review Board (IRB) approval and scientifically valid aims. ATSDR has a small external committee that reviews applications. If the committee has concerns about an application, ATSDR will discuss with the submitter on how they can improve their application. Another FOA will be published in 2017 through which one to two awards will be funded in the next couple of weeks. As soon as these awards are made, ATSDR will announce them through social media and will include them in the list of funded studies on the website.

Another 2017 activity is updating of the Registry website. CDC is going through responsive design, which entails making the website mobile-friendly so that it is not skewed when opened on a mobile phone or tablet. User testing has begun and launch is anticipated in September 2017. In addition, a new Registry informational video is being developed that describes the benefits and facets of the Registry to persons living with ALS and caregivers. Again, one of the primary challenges for ATSDR is promoting the Registry, especially to people who are newly

diagnosed. ATSDR does not expect neurologists or researchers to have patients register at the time of diagnosis. Many neurologists provide a packet of information to newly diagnosed patients and oftentimes that will include Registry information.

CDC holds Grant Rounds once a quarter. ATSDR was fortunate to be a part of the April 18, 2017 Grand Rounds. The topic was "National Amyotrophic Lateral Sclerosis Registry: Impact, Challenges, and Future Direction." The Registry had a good showing with the following four presentations:

- Kevin Horton, DrPH: History, Purpose, and Need for the Registry
- Paul Mehta, MD: Epidemiology, Research Initiatives, Biorepository
- Edward Kasarskis, MD: Neurologist Perspective
- Edward Tessaro: Patient Perspective

There were over 20,000 Facebook live viewers. Post-reach was 222,729 viewers, which is 27% above the average reach of a Facebook post from CDC. A total of 209,506 unique people received the post. This offered a very good opportunity for ATSDR to promote the Registry.

In summary, the National ALS Registry is the first and only population-based ALS registry for the US. ATSDR is doing its best to fulfill the Congressional mandate to determine the incidence, prevalence, demographics, and risk-factors for ALS. The Registry has added the National ALS Biorepository that contains a sample collection from persons with ALS that are disseminated to researchers. The Registry has added a GUID, continues to fund research on ALS risk factors and etiology, and seeks to have a larger internet presence. A number of tools have been developed for people to download to their websites, such as web buttons that take people directly to the Registry website. It is important to realize that the Registry continues to improve over time. Anytime a new registry is begun, the first couple of years are probably going to be under-representative. This registry is no different, but as the case-findings methods evolve and the Registry is promoted to an increasing number of people, more patients will enroll. Dr. Horton emphasized that it is not just ATSDR. Everyone is in this fight and must pull together to help ATSDR describe the Registry to patients, especially ones who are "on the fence" about enrolling. ATSDR recognizes that some patients may have reservations about entering data online, but the website is extremely secure. ATSDR is grateful for everyone's help and support.

Discussion Points

Regarding identifying cases, Dr. Finger recalled that Dr. Horton used the term "true ALS" but then later used the term "definite ALS." He wondered whether that is a confusing term given the common usage in the community. Now that the Registry and site are live, he wondered whether there is a targeted run rate for the number of expected/hoped for registrations per year.

Dr. Horton replied that ATSDR hopes to see 100% participation, but realizes that will not occur because not everyone has access to a computer and/or the internet. The current incidence rate is 2/100,000 population or 5000 cases per year. While ATSDR would like to have 5000 registrations a year, the Registry requires further promotion. In addition, it would be beneficial for ALS organizations and family members to help people enroll. This is not unique to the ALS Registry. Promotion of any registry is a major challenge.

Discussion about Research and Registry Activities

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

Dr. Mehta welcomed everyone to Atlanta, extending particular appreciation to those with ALS. He emphasized that ATSDR is the caretaker of the Registry, but it belongs to those with ALS. ALS research counts on those living with ALS, especially because there remain more unknowns than knowns about ALS. Progress is being made and ATSDR feels that the Registry is critical in promoting ALS research nationally. During this session, Dr. Mehta presented a high-level overview of the 2014 *MMWR* report, risk factor surveys, funded research, the Research Notification System, and manuscripts in development.

The third *National ALS Prevalence Report* has been submitted to the *MMWR*. The report covers the calendar year 2014 and the anticipated publication timeline is in the Fall. ATSDR is awaiting finalization and validation of data from the National Death Index (NDI) of the prevalence cases. This is for cumulative prevalence, meaning that if a case is an ALS case in 2011 or 2012, it carries over. It is important to ensure that prevalence is accurate, so ATSDR verifies through the NDI whether someone has passed away. New with the 2014 report is that hospice data are included from Medicare, which most likely will increase the case ascertainment counts. Initially reviewing the data, the prevalence appears to be increasing. However, this does not mean that the number of ALS cases are increasing nationally. It is just that the Registry is capturing more ALS cases from the databases.

The risk factor surveys are progressing smoothly. To date, there are almost 70,000 completed surveys as shown in the table below:

Survey (n=17)	Release Date	No. Completed
Demographics	October, 2010	7659
Occupational history	October, 2010	6969
Military history	October, 2010	6843
Smoking and alcohol history	October, 2010	6730
Physical activity	October, 2010	6481
Family history of neuro. diseases	October, 2010	6326
Disease progression (ALSFRS)	October, 2010	6358
Clinical data (e.g., devices used, body onset)	November, 2013	2428
Open-ended etiological questions	November, 2013	2220
Lifetime residential history	May, 2014	2541
Lifetime occupational history	May, 2014	2499
Residential pesticide use	May, 2014	2338
Hobbies with toxicant exposures	August, 2014	2099
Caffeine consumption	August, 2014	1971
Reproductive history (women)	August, 2014	1130
Health insurance status	December, 2014	1513
Head and neck injuries	December, 2014	1493
Total (as of 7/24/2017)	---	**67,915**

The 17 surveys are taken by persons with ALS when they enroll in the Registry and log in to the online portal. The surveys are wide-ranging, including the ALS Functional Rating Scale (ALSFRS) disease progression survey that allows patients to report how they are doing over time. Data requests are being submitted for the risk factor surveys and releases have begun. Thus far, risk factor survey data has been released to the following:

- ❑ Rick Bedlack, MD, PhD at Duke Medical Center who is working on ALS Reversals and received demographic data
- ❑ Bjorn Oskarsson, MD at the Mayo Clinic in Jacksonville, Florida who received data from Surveys 15 (Health Insurance Status) and 17 (Clinical Module) and will review these data together with ATSDR
- ❑ Heather Jordan, PhD at Rutgers University received data from the open-ended survey so that she can analyze patients' theories about what may have caused their disease
- ❑ Ted Larson, MPH with the National ALS Registry who is examining disease progression using the ALSFRS module data

Data are available through 2015. The data from 2016 and 2017 are anticipated to be available sometime in 2018. Data release does have some conditions from the IRB and OMB perspectives. For example, once the data are provided to a partner they may not be reconstituted such that patients can be identified. Dr. Mehta encouraged everyone to apply for these data and to let their colleagues know that they are available. ATSDR is funding extramural research to learn more about ALS etiology and risk factors. To date, 12 research studies have been funded. The recipient for TS17-001 funding, which focuses on using Biorepository pilot samples, will be awarded within the next few weeks. The hope is to fund one to two awards in Fiscal Year 2018 (FY18) depending upon the amount of funding available. ATSDR is also collecting input from researchers regarding research priorities. As always, awards are always subject to the availability of funds. The following table lists extramural research funding that ATSDR has awarded:

Study Name (n=12)	Institution	Investigator	Funding period
Epidemiology of ALS	Harvard University	Marc Weisskopf, PhD, ScD	2012 - 2013
Large-scale genome-wide association study of ALS	National Institutes of Health	Bryan Traynor, MD, PhD	2012 - 2013
Gene-environment interactions in ALS	Northwestern Univ.	Teepu Siddique, MD	2012 – 2013
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	2013 – 2017
Identification and Validation of ALS Environmental Risk Factors	University of Michigan	Eva Feldman, MD, PhD	2013 – 2017
Ecologic Study to Evaluate Spatial Relationships between ALS and Potential Environmental Risk Factors	Dartmouth College	Elijah W. Stommel, MD, PhD	2014 – 2016
Prospective study of biomarkers and risk factors for ALS incidence and progression	Harvard School of Public Health	Alberto Ascherio, MD, DrPH	2014 – 2015
Case-Control Studies Nested in National ALS Registry to Evaluate Environmental Risks	Columbia University Medical Center	Hiroshi Mitsumoto, MD, DSc	2015 - 2018
Antecedent Medical Conditions and Medications: Associations with the Risk and Prognosis ALS	Stanford University	Lorene Nelson, PhD	2015 - 2018
ALS Risk in Latin Americans- A population based case control comparative study with 3 European population based cohorts	Trinity College – Dublin, Ireland	Orla Hardiman, MD, PhD	2016 - 2018
A Population-Based Ohio ALS Repository and a Case-Control Study of ALS Risk Factors	Dartmouth College	Elijah Stommel, MD, PhD	2016 - 2018
Environmental risk factors and gene-environment interactions in ALS risk and progression	University of Miami	Michael Benatar, MD, PhD	2016 - 2018

Patient recruitment for research can be difficult, so ATSDR is committed to helping researchers and pharmaceutical manufacturers recruit for their studies. There is no fee for researchers to use the Research Notification System tool for recruitment purposes, and they can recruit locally or nationally, although local or geographic-specific recruitment can be limiting. This is a simple system that is less cumbersome than clinicaltrials.gov. When patients enroll in the registry, they receive an automatic notification regarding clinical trials and studies. The number of notifications sent has increased annually. Over 100,000 emails have been sent to ALS patients since the system's inception. Those who are interested in trials or studies can contact the researchers to determine their eligibility. In terms of recruitment of persons living with ALS by researchers, national recruitment is best. Currently, over 8,000 persons with ALS will receive notifications via email at one time. This yields a greater pool of potential recruits. Researchers do need to be prepared for volumes of inquiries by ALS patients. The feedback received from researchers has been positive. In terms of the annual number of notifications sent to persons with ALS by year, 40,000 were sent in 2015. While that decreased to 20,000 in 2016, it should increase for 2017 because there are some applications in the pipeline. The 27 trials/studies for which ATSDR has helped recruit follows, with those in red being clinical trials:

Study Name (n=27)	Institution	Investigator
Risk Factor Analysis in ALS	Medical University of SC	David Stickler, MD
Phase II/III 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
Spatial Analysis of ALS in Florida, Ohio, New Hampshire, and Vermont	Dartmouth-Hitchcock Medical Center	Elijah Stommel, MD, PhD
Mexiletine treatment of muscle cramps in ALS	University of California, Davis	Björn Oskarsson, MD
Epidemiologic Risk Factors &Genetics of ALS	University of Michigan	Eva Feldman, MD, PhD
Exp. 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 Institutes of Health/NINDS	Mary Kay Floeter, MD, PhD
Developing a Satellite ALS Center at a Remote Site Incorporating Regional Resources &Telemedicine	University of Kentucky	Edward Kasarskis, MD, PhD
Evaluating Ibudilast MN 166 in subjects with ALS	Carolinas Neuromuscular AL Center	Benjamin Rix Brooks, MD
Prospective Epi. Study in a Large National ALS Registry Cohort to Identify ALS Risk Factors	Columbia University Medical Center	Hiroshi Mitsumoto, MD, DSc
VA Biorepository Brain Bank ALS Study	VA Boston Healthcare System	Neil W. Kowall, MD
Questionnaire of cramps and pain in ALS	University of California, Davis	Björn Oskarsson, MD
Assessing pain in ALS	Penn State Hershey Medical Center	Zachary Simmons, MD
NeuRx® Diaphragm Pacing System™ (DPS) study	Barrow Neurological Institute	Jeremy M. Shefner, MD, PhD
An online questionnaire for research into ALS	University of Sydney	Roger Pamphlett, MD, MB
ALS and Genetic Testing: A Perspective from the ALS Community	The Ohio State University	Jennifer Roggenbuck, MS
Speech Motor Impairments	MGH Institute of Health Professions	Jordan Green, PhD
RDCRN Contact Registry for the CReATe Consortium	University of Miami	Michael Benatar, MD, PhD
Study to Evaluate the Sensitivity, Specificity, and Overall Accuracy of an ALS Diagnostic Test	Iron Horse Diagnostics, Inc.	Andreas Jeromin, PhD
Phase 2 Pharmacodynamic Study of Ezogabine on Neuronal Excitability in ALS	Massachusetts General Hospital	Brian J. Wainger, MD, PhD
VITALITY-ALS (Ventilatory Investigation of Tirasemtiv and Assessment of Longitudinal Indices after Treatment for a Year)	Cytokinetics, Inc.	Jinsy Andrews, MD
Methodology Study of Novel Outcome Measures to Assess Progression of ALS	Biogen, Inc.	Nazem Atassi, MD
A Phase 2 Study of NP001 in Subjects with ALS and Evidence of Elevated Systemic Inflammation	Neuraltus Pharmaceuticals, Inc	Gilbert Block, MD, PhD
Biospecimen Collection to Investigate the Causes of ALS	Mayo Clinic Jacksonville	Kevin Boylan, MD
Microbiome Assessment in People with ALS	Massachusetts General Hospital - Neurological Clinical Research Institute (MGH-NCRI)	Katharine Nicholson, MD
ALS Testing through Home-Based Outcome Measures	Barrow Neurological Institute	Jeremy Shefner, MD

ATSDR is very excited to work with researchers and pharma to help them use the Registry for recruitment purposes. A Food and Drug Administration (FDA) guidance document is under development that encourages researchers to use registries in general for recruitment for clinical trials.

A number of manuscripts are in development and/or have been submitted to journals, including the following:

- *MMWR*: Public Health Grand Rounds
- Access to ALS care, using ALSA and MDA clinic locations
- ALS disease progression modeling
- National ALS mortality, 2011-2013
- Assessing accuracy of US death certificates for classifying ALS
- Comparison of Registry data to state and metro data
- Capture/Recapture
- Educational and promotional outreach activities to general neurologists (non-referral)
- Open-ended survey: What caused my ALS?
- Genes analyses of pilot Biorepository samples

In conclusion, the National ALS Registry continues to mature and improve in terms of case ascertainment. This is evident with release of the 3rd *MMWR* report. In addition, the Registry has added a National ALS Biorepository. ATSDR continues to fund research on ALS risk factors and etiology. The Registry is about more than just counting cases. It is assisting with clinical trials and epidemiological studies, collaborating with ALS researchers nationally and internationally, and disseminating research findings.

Discussion Points

Dr. Brooks asked whether the prevalence of veterans is increasing, decreasing, or staying the same among identified cases. He also wondered how the Registry would assist them in determining whether ALS is increasing among veterans.

Dr. Mehta indicated that for 2014 this most likely will be an increase in terms of what is being captured from the administrative databases. However, as far as they can determine, this does not reflect an actual increase in ALS among veterans. ATSDR also believes it is important to work with partners who work with the military population and the Department of Defense (DoD), which specifically funds studies for veterans. One of the next potential FOAs that will be published will be to assess etiology in the veteran population.

Dr. Kaye added that they may be able to answer this question in about a year, given that the Registry is stabilizing. It takes a registry or surveillance system about 3 years to stabilize. At that point, it will be possible to examine trends in terms of various groups.

Dr. Mehta pointed out that many of the cancer registries waited nearly 5 years before publishing any data. Given that ALS is unique, ATSDR published the first report about 3 years ago so that there was not a 5-year lag time.

Dr. Kasarskis asked whether ATSDR has tested the accuracy of the patient self-registration portal versus NDI, hospice data, and death certificates. He noted that the algorithm for registration was modeled on the VA system, which was validated as the best it could be against chart reviews.

Dr. Kaye replied that about 8% of those in the Registry are identified only through the portal and have no other data source. About 50% who come through the portal also have some other data. All of them are compared to the NDI.

Dr. Mehta added that the premise for someone to answer the questions in the Registry is very specific regarding ALS. If they are answered in the wrong way, the responder will be kicked out. In terms of the actual validation of the questions, there is a smaller percentage of the population entering through the portal as opposed to the national databases where the majority of the cases lie.

Dr. Feldman noted that some of the 17 surveys had more robust responses than others. She wondered whether that was because some surveys were newly added, and if there is still an opportunity to add new surveys. For example, there was discussion earlier in the day regarding the potential effect of previous diseases.

Dr. Mehta responded that there is a higher completion rate for the surveys released in October 2010, while those completed later are new and have a lower completion rate at this point. Pursuant to the OMB requirements, the burden permitted is 90 minutes. That is, from start to finish, it can take someone no more than 90 minutes to complete all of the surveys. In order to add another survey, one must be taken down. In order to change any surveys whatsoever, ATSDR must go back to OMB for approval. There are strict rules to which they must adhere.

Dr. Feldman observed that all of the surveys appear to be one-and-done. She wondered whether there was any longitudinal value to that in terms of disease progression.

Dr. Mehta emphasized that Survey 7, ALSFRS, allows them to assess exactly how patients are progressing. This survey is taken upon enrollment. Subsequently, recipients receive an email every 3 months or so to inquire about their status.

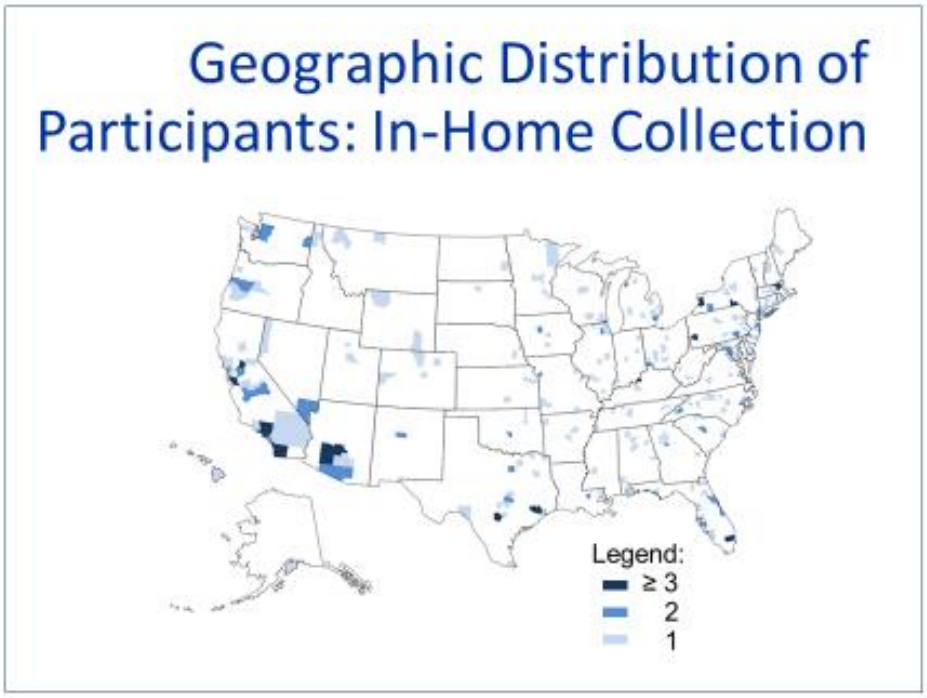
Dr. Feldman expressed concern that this appears to be a glitch. The Les Turner ALS Foundation is hearing from their patient population that they are not receiving the repeat requests, especially for disease progression.

Dr. Mehta indicated that ATSDR has a dedicated information technology (IT) team who handles these types of issues, and they will verify to make sure that notices are being sent. It is possible that email from the Registry is landing in people's spam or junk mail.

Update on the National ALS Biorepository

Wendy E. Kaye, PhD
Senior Scientist
McKing Consulting Corporation

Dr. Kaye presented a brief history and update on the National ALS Biorepository. A pilot study was conducted that lasted for about 4 years from September 2012 through September 2015. The first year was largely paperwork and IRB approvals, with collections beginning in 2013. At the conclusion of the pilot study, 330 Registry participants had been enrolled to provide blood, urine, hair, and nails. Specimens were collected on two occasions approximately six months apart. Participants were recruited to be geographically representative, with at least one person being recruited from every state by the end of the pilot study. In addition, 30 Registry participants were enrolled to donate tissues postmortem. The geographic distribution of participants who provide blood, urine, hair, and nails is illustrated in the following map:



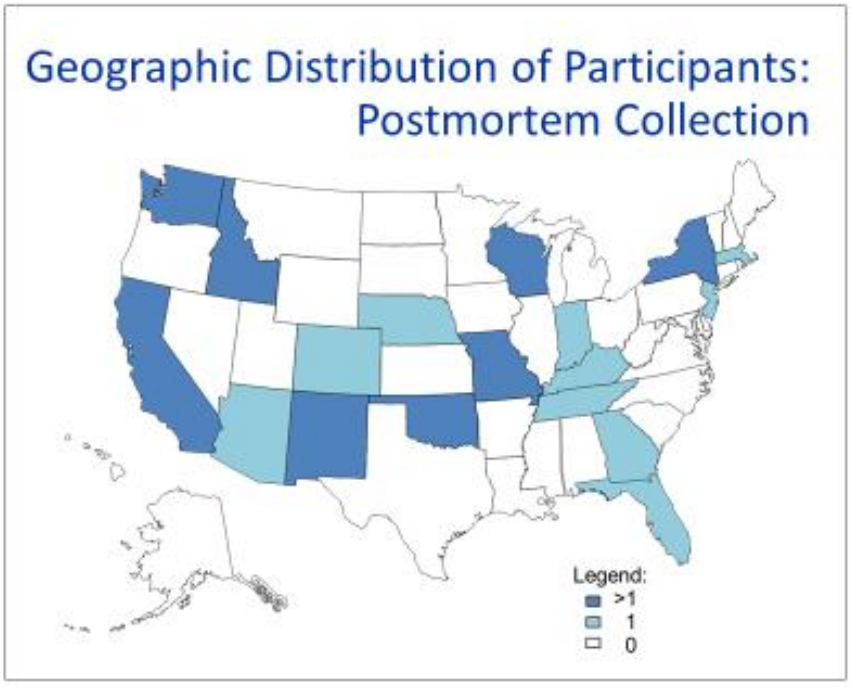
The legend depicts the number of enrollees in each area. Some enrollees were in very remote areas of the country, and finding a phlebotomist to travel to someone's home did prove challenging. The age distribution of those who gave specimens largely mimics the presentation of ALS, with slightly more males than females and most individuals are 60 years of age or older.

Once received, the specimens are processed as follows:

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

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

There has been less rigor in making postmortem participants geographically distributed becaues there are only 30 people. However, the distribution is fairly well-dispersed across the country as illustrated in the following map:



Equal numbers of women and men consented to postmortem collection. Thus far, 21 participants have donated postmortem samples consisting of brain, spinal cord, cerebrospinal fluid (CSF), bone, muscle, and skin. Three participants withdrew and did not donate.

Once received, brain and spinal cord are fixed and frozen, CSF is spun and frozen, bone and muscle are stored in formalin, and skin is made into fibroblast lines.

At the end of the pilot project, the following recommendations were made:

- ❑ Make learning more about donating specimens to the biorepository a choice after enrolling in the National ALS Registry

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

- ❑ Continue selection of participants from those who express interest to maintain geographic representativeness

- ❑ Add more people, but collect specimens only one time

- ❑ Continue collecting blood and urine
  - ➢ Extract DNA from one blood tube during the processing, create aliquots, and freeze DNA
  - ➢ Extract RNA from the PAXgene tubes, create aliquots, and freeze RNA

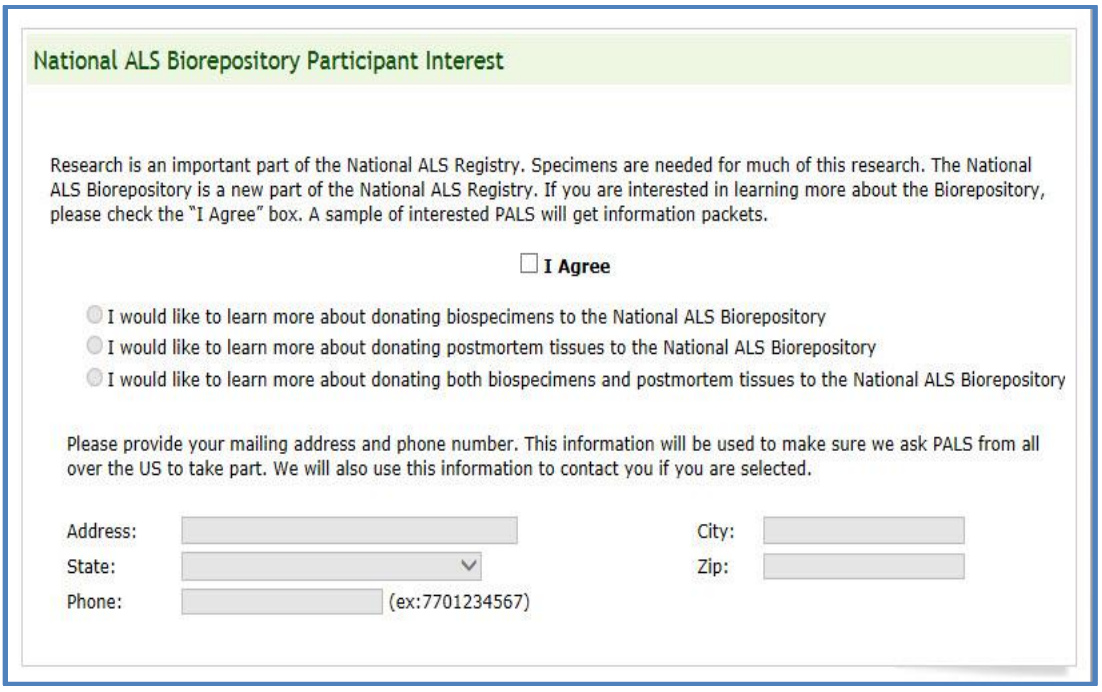
- ❑ Stop collecting hair and nails until demand for specimens is assessed (while not that difficult to obtain, there is a cost to storing that does not make sense if nobody is going to use it)
  - ➢ Add collection of hair and nails for a limited time when current specimens are depleted

- ❑ Continue collecting saliva specimens from those who cannot give blood
  - ➢ Process saliva kits to extract and freeze DNA aliquots

- ❑ Continue collecting brain, spinal cord, and CSF

With these recommendations taken into consideration, the National ALS Biorepository has now been launched. The first step was to integrate the Biorepository into the protocol for the National ALS Registry to make it part of the Registry. This required an amendment to the IRB protocol to include the donation of specimens, given that the pilot study was not conducted through the CDC IRB and needed to be moved to CDC under one master protocol. The OMB package also had to be amended to include specimen donation. The timing was actually convenient because it was time to renew the Registry OMB package, which must be done every three years. The Biorepository was rolled into the Registry OMB package renewal.

The computer system was updated for National ALS Registry registration to allow enrollees to receive more information about the Biorepository, and to allow those already registered to update their account to indicate their interest in participating in the Biorepository. The National ALS Registry website also was updated with application materials for researchers for the use of samples. When people register, they now see the following sign-up screen:



In terms of the process, ALS patients enrolled in the National ALS Registry can sign up to learn more about the Biorepository. New enrollees can agree to receive more information about the Biorepository during registration. Previously enrolled participants in the Registry can update their accounts. McKing Consulting Corporation receives a list of enrollees interested in the Biorepository on a monthly basis. Enrollees are selected to receive more information about the Biorepository. Selected enrollees are mailed packets, and potential participants are called approximately one week after the package is mailed to answer questions, go over the consent form if interested, and schedule an appointment to give blood or mail a saliva kit.

OMB approval was received in November 2016. The Biorepository went live on January 4, 2017. Participation from January 4, 2017 through July 15, 2017 follows:

Number Consented
- ❑ 178 In-home blood and urine (20 more had consented at the time of this meeting)
- ❑ 33 Saliva only
- ❑ 19 Postmortem

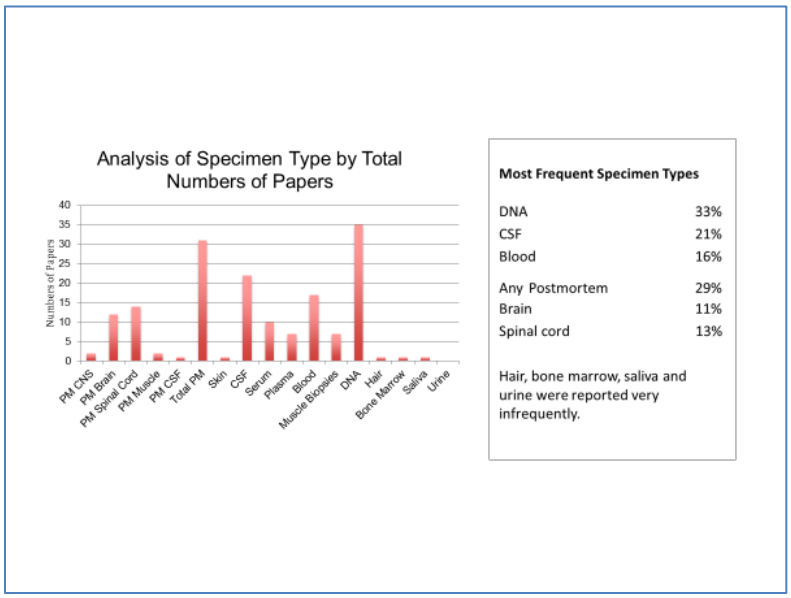
Number of Specimens Collected
- ❑ 133 In-home blood and urine
- ❑ 30 Saliva only
- ❑ 1 Postmortem

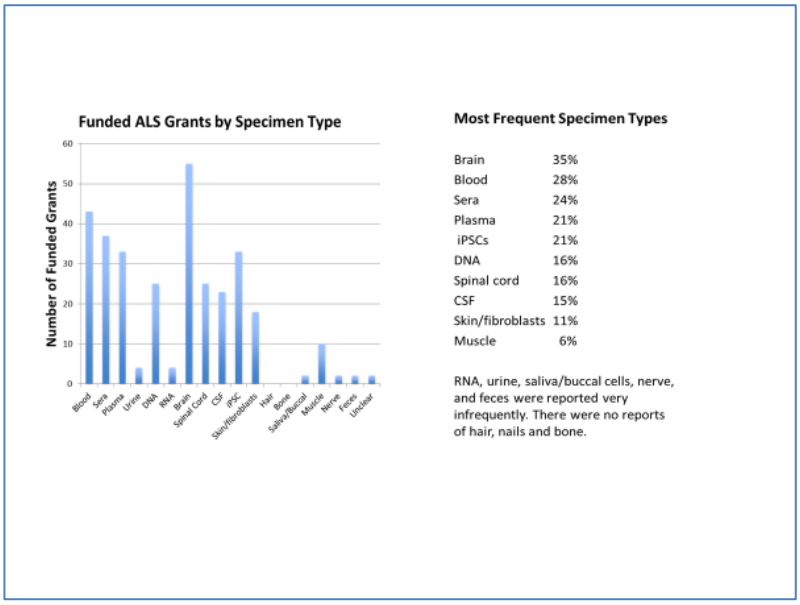
Demographics
- ❑ Those who have consented live in 44 states and Puerto Rico
- ❑ 62% are male
- ❑ The age distribution aligns with the distribution of the age at diagnosis of persons with ALS

In addition to that, McKing Consulting Corporation is responsible for evaluating specimen demand. Multiple approaches are utilized to do so, including:

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

Based on an analysis of the literature, historical use of specimens from persons with ALS and use of specimens from persons with ALS in funded ALS grants are depicted in the following two charts:





McKing Consulting Corporation is also responsible for sample distribution. Researchers can request samples for their ALS Research, for which the application process is outlined on the website. Researchers must submit a research application form, cover letter, full protocol, and sample request form(s). The application and all supporting documentation are submitted online. A completed application goes through multiple reviews, including a laboratory review (to verify specimens and quantities are available and if the approach is reasonable) and a scientific review through an ATSDR review committee. After approval from ATSDR, the researcher signs a Material Transfer Agreement (MTA), pays a nominal fee to have the specimens pulled and shipped (there is no cost to participants for collection of the specimens), McKing selects the appropriate samples, and the laboratory ships the samples to the investigator. Researcher requests received are shown in the following table:

Description of Project	Group Conducting Analysis	Number of Samples Requested
Metals analysis	CDC/ATSDR	1905
Genomic analysis	NIH/ATSDR	317
Micro RNA	Columbia School of Public Health	514
Role of FUS protein in inflammation and neurodegenerative disease	Icahn School of Medicine at Mount Sinai	360

Discussion Points

Dr. Feldman inquired as to whether the biospecimens can be linked to the surveys. She also wondered why the decision was made not to collect repeat biospecimens, given that the timing of assessing changes in some of the parameters over time is so important. With that in mind, she asked whether sub-studies could be conducted among a small sample of patients from whom samples are collected every six months over the course of the disease.

Dr. Kaye responded that they can link samples with survey data. When researchers request specimens, they can indicate what additional survey data they want to go with it. McKing Consulting Corporation is working out a process for how this will be done. In terms of sample collection time, she indicated that funding is one issue. They could either collect samples at one time point from 300 people or two timepoints from 150 people. They were never collecting more than two samples per person, and there was concern that having only two samples six months apart may not be worthwhile. In terms of the potential for a sub-study, the list of possibilities is open. The protocol and consent form would have to be modified for a sub-study of patients, but it is doable depending upon funding.

Dr. Pioro recognized that collecting the postmortem tissue is very beneficial, but is also very challenging. He requested Dr. Kaye speak briefly about the challenges they have overcome, those with which they continue to struggle, and costs.

Dr. Kaye replied that costs are pretty high. McKing Consulting Corporation is working with the National Disease Research Interchange (NDRI) that originally began procuring specimens for the National Institutes of Health (NIH) through a small R01. NDRI has now branched out and is also collecting for others, including the National ALS Biorepository and the VA ALS Registry Brain Bank. Once someone is consented, NDRI must pre-arrange a diener and a location where the collection can be done. The kits are supplied to the dieners in advance, which also is challenging. During the pilot study, one kit was burned in a fire, one was flooded, and one disappeared. These are large boxes, so it is unclear how one can be lost. In addition, there are strange state laws. For example, New Jersey does not permit organ procurement in a funeral home. If a hospital in New Jersey would not allow the diener to use their facilities, the body would have to be transported to another state in order to collect the donation. Another problem that has occurred is that the manufacturers of some of the components in the collection kit have changed dimensions, but not the part number because they viewed the change as minor. Changing an item by even a quarter of an inch can impact whether the kit fits together properly and the box closes.

Dr. Mehta added that the cost of postmortem collection is approximately $30,000. This is part of the Biorepository funding. No cost whatsoever is incurred by the patient or family for the donation.

Regarding assessing the Registry in terms of its maturity, Dr. Brooks wondered whether there was any prior work in terms of how the Biorepository will be assessed, how large it has to be before it can be effective, and what the metrics are (number of samples sent out, number of samples that offer positive insight to a cause, et cetera).

Dr. Kaye responded that everyone wrestles with this issue. They want the specimens to be utilized. There is no use in collecting them if no one is using them. McKing Consulting Corporation also is responsible for marketing the Biorepository, so she and Ms. Wagner spend a lot of time attending conferences, sending mailings to researchers, and engaging in other types of outreach to inform them about the Biorepository, how to apply for specimens, and complete their applications online so that they will use the specimens. One metric pertains to a combination of whether the Biorepository is collecting specimens people will use, and whether people are actually using them.

Dr. Mehta added that ATSDR's ultimate goal is to make the National ALS Biorepository one of the largest collections of ALS pristine samples for research of etiology, possible biomarkers, possible genetics, and so forth. If within the next 3 to 5 years this could be the seminal source of ALS samples across the country, if not the world, that would be great.

Registry Communication & Outreach

Agency for Toxic Substances and Disease Registry

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

Ms. Cory noted that she had the privilege of speaking with several ALS patients throughout the day, and was just speaking with Becky Kidd who graciously provided her with the perfect opening remark, which she paraphrased, "You have this Registry, but if people don't know about it, you really can't use it and you can't do anything with it." That makes a lot of sense. With that in mind, she briefly discussed some of ATSDR's efforts in terms of communications and outreach so that all ALS patients have an opportunity to see what the Registry is doing and know they are a part of it. Sometimes they think they are doing a great job, but what they have in their minds may not be what is best. Scientists tend to think that the more data they give people, the more they will respond and the better they will know about a project. However, several patients have told her that it can be overwhelming. Therefore, consideration must be given to how messages are being conveyed. To illustrate, Ms. Cory shared one of her favorite signs:

In very large print, the sign cautions about sharp edges. Ironically, very low down at the bottom in extremely small print the sign states, "Also, the bridge is out ahead."

One problem is that focus may have been lost on what is important and making sure that the message is disseminated about ALS awareness and the Registry and Biorepository. ATSDR's partners do an amazing job on increasing ALS awareness, but additional thought needs to be given to who the target audience is and what messages fit. How can ATSDR make sure that its message is not buried? Part of that is understanding the target audience and tailoring messages and making sure they make sense. The way she speaks to researchers to tell them about the benefits of the Registry is very different from the way she might speak with a patient. The end goal is the same, but it is important to tailor messages and ensure that communication is effective.

ATSDR has been pursuing many routes to reach people this year in terms of outreach and education, including the following:

- ❑ Motion graphic (video)
- ❑ Clinician outreach and education, going where the clinicians are
- ❑ Infographics
- ❑ Conference presentations and booths
- ❑ Publications on research
- ❑ Pursuing new digital media opportunities
- ❑ Matte articles and other ALS Awareness Month activities
- ❑ Website makeover (coming soon!), CDC home page feature and internal CDC Connects
- ❑ Social media (tweeting, Blogs, Google ad searches)
- ❑ Grand Rounds with thousands of people watching virtually, and an archived version that can be continuously accessed

Another way to go where people are is through partnerships, and ATSDR is exploring new partnerships. While the agency already has many good partners, consideration must be given to how to expand those partnerships. It is important to work better together and to utilize partners who may know where patients and clinicians are, and can help bring everyone to the table to work together:

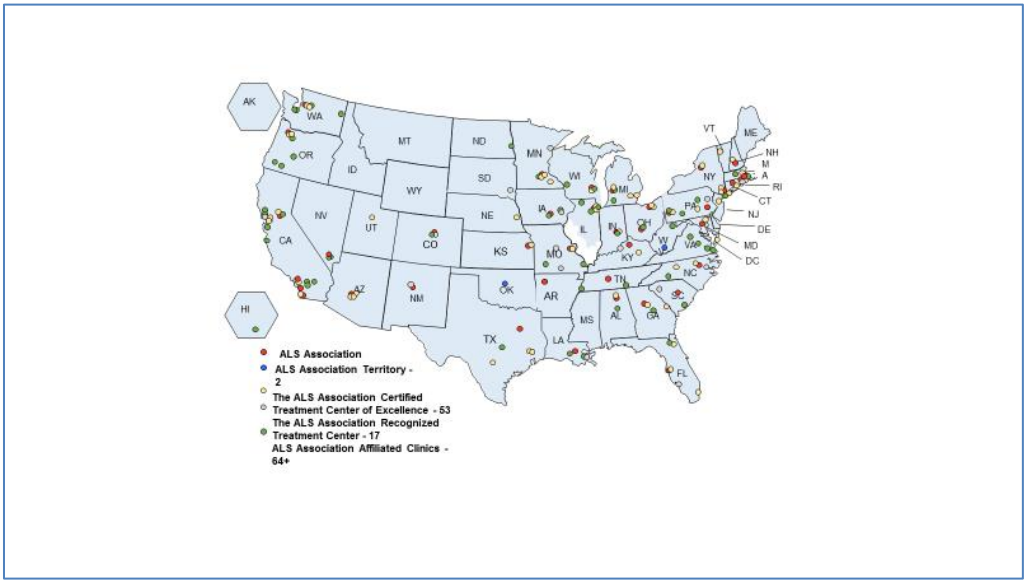
Everything takes teamwork!

ALS Association

Calaneet Balas, MBA
Executive Vice President Strategy
The ALS Association

Ms. Balas indicated that the ALS Association is the largest patient advocacy organization that is explicitly focused on working for people with ALS in terms of public policy, research efforts, and the Care Service Team helping people on a daily basis. Just under a year ago, the ALS Association relaunched the research portion of its website. It highlights all of the research the ALS Association is funding, as well as many of the clinical trials that are available. This was done in an effort to make the site more patient-friendly, more user-friendly, and easier to navigate. The ALS Association is currently funding approximately 150 to 180 research studies annually in 11 countries across the globe. They like to say that the world is their lab and they would like to keep that going. They try to ensure that the clinical trial information is updated regularly by pulling that information from the Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS).

Through its chapter services platform, the ALS Association serves over 19,000 people on an annual basis. They have a wide reach in the US and are very proud that they get to work with so many people on a regular basis. The following map shows the 39 chapters and 130+ clinical partners with whom the ALS Association is engaged in continued outreach to support Registry enrollment:



The chapters work diligently to reach the 19,000 people with whom the ALS Association works. The clinical partners are comprised of certified or recognized treatment centers. This offers a lot of power for the ALS Association to talk about the value of the Registry and why it is important. These clinical partners and chapters are the access point to reach out to people. There are large clusters on the East and West Coasts as would be expected, and some throughout the Midwest. However, there are populations who they do not get to see too often. When Dr. Kaye was speaking earlier about the Biorepository, Ms. Balas observed that Dr. Kaye's map closely aligned with this map.

In terms of the ALS Association's current efforts to support Registry enrollment, they took some time at the beginning of the year to reflect on what they have been doing, value ads, and what they should be doing moving forward. To that end, they created their own focus group known as the National ALS Registry Taskforce. This taskforce is comprised of a group that is inclusive of board members, people living with ALS, chapter executives, and the Care Service Team that was assembled by Lauren Stanford. One thing the taskforce said loud and clear was that the Registry section of www.alsa.org was not a part of the ALS Association's website, but instead was a microsite that had all but gone dormant at that point. They decided to repurpose the great information that was there and place it directly on the ALS Association's website in order to highlight it. This was done in the second quarter of 2017, and now that component of the website receives approximately 250,000 views per month.

The ALS Association also has increased its social media presence. In the second quarter of 2016, there were 2 dozen Registry-related tweets and retweets. In the second quarter of 2017, there had been 17 dozen. This increase of 15 dozen or so tweets increased visibility by over 27,000 people who are following these Twitter handles. They did the same thing on their Facebook in terms of increasing their posts about the Registry trying to explain it. This resulted in 261,398 views of posts just in the second quarter of 2017.

Moving forward, the ALS Association is working on new and innovative ideas in addition to updating websites and social media. They decided that improving and leveraging clinical partnerships is very important, because they engage the ALS Association's services. They are meeting people who have just been diagnosed with ALS on a regular basis. They decided to promote some work with chapters. To that end, the ALS Association is helping chapters that are under-performing create strategic plans. They are also working to increase the number of risk factor survey modules filled out. They found that a lot of patients might enroll, but they do not necessarily complete the survey tool. While 90 minutes sounds laborious for anyone, for a patient it can be even more so. Part of the strategic planning is to train staff to assist patients in getting through that entire survey process.

The taskforce generated some other ideas as well, some of which have begun and others of which will be launched in the future. While the ALS Association is a large organization, the clinical staff are busy. Sitting with someone to explain what the survey is, get them signed up, and go through the survey is time-consuming. Thus, consideration is being given to launching a

volunteer program in the future. There also are plans to host a couple of best practices meetings coming up attached to the ALS Association's clinical conference in February 2018, as well as a meeting attached to the ALS leadership conference. This will offer an opportunity for those within the chapters and other stakeholders to share best practices to improve this program and to educate the clinicians who will attend the clinical conference on what is occurring with the Registry. Consideration is also being given to a webinar series. The ALS Association finds that when they hold a webinar series, they hear from hundreds of people, and people have the opportunity to replay those. In addition, increased strategic collaboration is planned with Registry partners.

In terms of the strategic communications plan, when they began to look at what is relevant, they realized that people are confused. Sometimes when people join and register with a local chapter, they presume they have also registered in the Registry. It is a nomenclature issue such that people do not understand that the National ALS Registry is different. Therefore, the ALS Association is focusing on explaining what the Registry is and why it is different from some of the other registries, especially those that are taking blood samples and other biorepositories. They will be geotargeting this campaign to the under-enrolled areas, and it is anticipated to launch in the next few months. They are also working on testimonials and other communication efforts that will be part of the plan going forward.

Those interested in further information may contact Lauren Stanford at the following email address: lstanford@alsa-national.org

Muscular Dystrophy Association

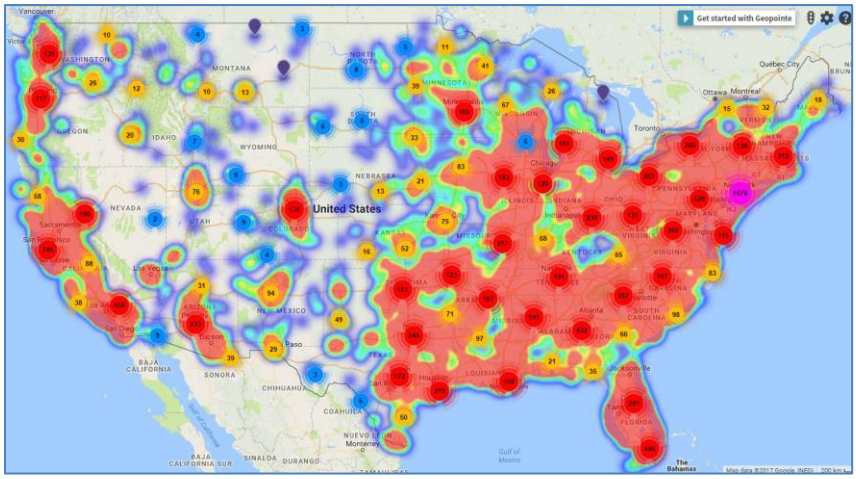
Kristin Stephenson, MHA, JD
Vice President, Policy & Advocacy
Muscular Dystrophy Association

Lauren Webb, AM
National Director of Clinical Services
Muscular Dystrophy Association

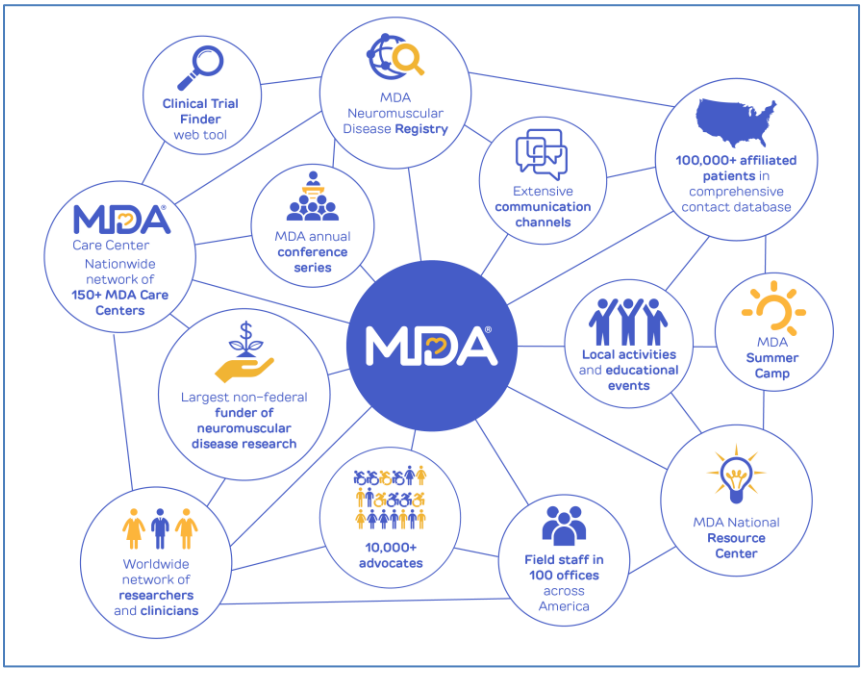
Ms. Stephenson explained that MDA is committed to saving and improving the lives of individuals living with NMD. MDA works with institutions, families, industry, and Care Centers with the idea being that each has a role to play in everything everyone is trying to achieve. One of the themes she heard several times throughout the day is that they are all working together to accomplish many, if not most, of the same goals. This is an apt meeting in which to have a working together conversation, because the Registry will not succeed to meet its aims if they do not work together. She already sees a lot of great collaboration occurring and believes this is an exciting opportunity to bring disease organizations and individual stakeholders together to promote and advocate for a common goal that serves a common good. MDA sees its role not only as promoting the Registry as it exists, but also helping people understand the "why" behind the Registry. In other words, it is not just about telling people the Registry exists. It is about telling them why it is important and why it is important to be part of it. That carries over into advocacy for federal appropriations all the way to talking to an individual patient on a Care Center visit to encourage them to sign up and complete the survey modules in the Registry.

MDA is an umbrella organization that serves 43 different disorders, including ALS, the muscular dystrophies, spinal muscular atrophy (SMA), and a myriad of other disorders. While they do focus on a lot of different diseases, specific efforts are in place for ALS. MDA tries to accomplish its goal of saving and improving the lives of individuals with NMD by focusing on Cure, Care, and Champion which they refer to as "The Three Cs." From a cure standpoint, it is

MDA's commitment to fund biomedical research and therapy development. As of 2016, MDA supported 34 active ALS research grants of more than $9 million. In the last five years, MDA spent nearly $29 million on ALS research. Since 1950, MDA has invested more than $363 million in ALS research and support services. From a care standpoint, more than 12,000 individuals with ALS have access to MDA ALS Care Centers. There are 43 designated MDA ALS Care Centers out of the 150+ MDA Care Centers. From a champion standpoint, MDA advocates for public policies that impact therapy development; offers ALS support groups for people with ALS, their caregivers, and children; and makes available much-needed durable medical equipment (DME). The following is a heat map of individuals living with ALS who MDA serves:



The following graphic offers a quick overview of some of MDA's key attributes:



These attributes are relevant to the discussion because a lot of these are channels through which MDA promotes, advocates for, and talks about the Registry to different stakeholders.

There are opportunities to communicate about the Registry in Care Centers, regional and local events, national conferences, working directly with field teams, and working through various communication channels. One of the newer supports is a Clinical Trial Finder webtool, which is a web-based tool that allows individuals to find clinical trials close to them or that meet specific search criteria that would match them up with clinical trials which they might be interested in learning more about or participating in. Another is a National Resource Center that can be reached by email or at 1-800-572-1717, which allows individuals who are living with an NMD an opportunity to reach out and ask questions. To the extent that the Care Center folks cannot help them, they aim to direct them to someone who can.

In terms of getting information out about the national ALS Registry, several of the ways MDA does this are focused on leveraging MDA's communication channels. Some are digital, such as mda.org (300,000 visits per month), Facebook (125,800 followers), and Twitter (18,800 followers). MDA also has more traditional hard copy ways to communicate that help them capture and reach out to some of the folks who may not have access to the internet, or who may have access to the internet but are not plugged into social media channels or are not getting these messages directly from MDA. One example of that is *Quest Magazine* which is disseminated quarterly every year to about 800,000 addresses. Included in that is information about the National ALS Registry.

MDA's National ALS Registry outreach efforts over the past year have included the following in terms of getting the word out about the Registry:

- ATSDR Booth at MDA Scientific Conference, March 2017
- Email to monthly clinical partners about the Biorepository, May 2017
- Strongly Blog guest blogger living with ALS, June 2017
- Monthly updates on under-enrolling states
- Weekly posts on national social media pages
- *Quest Magazine* (Quarterly print)
- Enhancing internal MDA staff training
- MDA National Resource Center
- Incorporating Registry outreach into regional events
- Lunch and Learn for MDA staff nationwide, December 2016
- Link to the Registry and the Biorepository on MDA.org (advocacy and research pages)

In terms of future state considerations and thinking about how to make the messaging more impactful and fine-tune it moving forward, the following seemed like areas that would make sense to explore together when they engaged in open discussion later in the day:

- Personalizing messaging where possible, given the restrictions and criteria that govern the way the Registry can be discussed
- Incorporating more language about current use of the data
- Considering what statements of support from the stakeholder community might play in future messaging
- Assessing IRB requirements in terms of opportunities to template some things so that this process can be streamlined if possible
- Discussing surveillance expectations in terms of how many people ATSDR would like to register every year and achievable goals

Discussion Points

Mr. Tessaro said he thought the way MDA simplified some very scientific information is very good, and is one of the best websites he has seen in this field. He congratulated them on making good ideas simple, expressed appreciation for this, and emphasized that there is genius in that.

Ms. Cory stressed that this raised an excellent point that they would come back to, which is telling the story. Sometimes that is not just personal stories, but telling the story of the research can be important as well.

Les Turner ALS Foundation

Andrea Pauls Backman, MBA
Executive Director
Les Turner ALS Foundation

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

Ms. Backman thanked ATSDR, researchers, partners, public health professionals, and especially the people and families living with ALS (PALS) who were there to help them do their jobs better. Les Turner ALS Foundation is one of the oldest independent ALS groups in the world and has been Chicago's leader in research, patient care, and education about ALS since 1977. This being Les Turner ALS Foundation's 40th year is good news/bad news. They wish they were not still here, but they will keep doing this until there is no longer a need. While they are a local group, they have national and international impact, so they tend to take a different approach in terms of how they work specifically in this field.

Les Turner ALS Foundation's mission is to: 1) advance scientific research into the causes, treatments, and prevention of ALS; 2) provide people living with ALS, their families, and caregivers exceptional clinical care and support services; and 3) increase awareness and education of ALS. They have raised $67 million to support ALS since 1977, beginning with funding one of the first ALS research laboratories in 1979. Over $55 million of that has been used to fund ALS research and clinical care.

In terms of program funding, 80¢ of every $1 spent in 2016 directly funded programs. About 48% is spent on the Les Turner ALS Research and Patient Center at Northwestern Medicine and includes all areas of ALS research. There are 3 fully staffed laboratories, and other areas of ALS research throughout parts of Northwestern Medicine and other collaborative research. This also includes the Lois Insolia ALS Clinic at the Les Turner ALS Research and Patient Center, which is the only fully multidisciplinary ALS clinic in Chicago, which was established in 1986. There are approximately 75 clinicians and researchers at the center, all of whom are working on an integrated basis toward solving ALS.

About 28% is spent on patient and family programs, with a very unique hands-on approach to how Les Turner Foundation works with patients and families. There is a Home Community Team that consists of 8 Registered Nurses (RNs) and Social Workers who are working with patients and families not only during their clinic visits, but also in their homes and throughout their support groups. They are meeting with patients regarding equipment issues, speech-generating devices, et cetera. Les Turner Foundation prides itself on this very personalized

approach. It is because of this personalized approach that they felt they should treat the promotional efforts of the National ALS Registry on very much a personalized basis.
Les Turner Foundation's National ALS Registry promotional efforts are very similar to the efforts of other national partners, including the following:

- ❑ Print Newsletters
- ❑ E-news and Website
- ❑ Home and Clinic Visits (over 3200 discrete visits with patients and families in 2016 to talk to them about the National ALS Registry and why it is in their interest to be a part of this)
- ❑ Support Groups
- ❑ Annual Patient Education Meeting
- ❑ Outreach to Medical Professionals
- ❑ Annual Research Symposium on ALS and NeuroRepair
- ❑ Community Education/Expos
- ❑ Social Media: Facebook and Twitter

In terms of the feedback they hear, participating in the Registry is not a priority for people who are so encompassed with their healthcare needs. Les Turner Foundation believes that the very personalized approach they take makes a difference. They help people understand the reason for the Registry and the benefits to them. There is Registry promotion via the Les Turner Foundation website as well, which was redesigned last year. Although the Registry had always been part of the website, they made it more prominent and have found that this definitely increased hits to the website as a result. The Les Turner Symposium on ALS and NeuroRepair takes place every November and is attended by approximately 200 ALS researchers, clinicians, and people with ALS. The Foundation is also promoting the Registry through social media (Twitter, Facebook). In addition, they promote the Registry through the ALS Walk for Life. This may be the largest ALS gathering in the country, with over 7000 attendees every September. They are very excited that Dr. Mehta will attend to speak and meet with people during the September 2017 Walk for Life. This is a tremendous opportunity for people to learn about the Registry and to celebrate hope and research, which is the primary purpose of the walk.

Ms. Gallagher reported that in April 2017, Les Turner Foundation hosted an educational seminar during which Dr. Mehta attended. He spent the first day informing people about the Registry and answering questions, and the second day touring Northwestern Medicine and meeting with researchers and clinicians. During the seminar, patients living with ALS and their families were invited to meet with Ms. Gallagher and get enrolled in the Registry. She also went to the homes of individuals asking for more assistance to help them complete the surveys. As another way to promote the Registry, they have sent over 400 letters and promotional materials to local neurologists to assist them in explaining the National ALS Registry and National ALS Biorepository to their patients. They also let neurologists know that the Foundation's National ALS Registry Associate is available to assist doctors in helping PALS enroll.

Basically, Ms. Gallagher's role is to educate people about the Registry and get them enrolled. When the RNs and Social Workers are meeting with patients and their families, those who express an interest or would like more information are referred to Ms. Gallagher. She has been with the Foundation for about 8 months, during which there has been a significant increase in the amount of interest in the Registry as well as making enrollment as easy as possible for families. In the past 6 months, they have spoken to over 60 families about being registered. She has assisted with 28 enrollments, while other families have been able to continue on their own with her assisting them via telephone or through emails.

In terms of enrollment concerns, personal computer assistance has been one of the most important services they can offer families. It is great that the Registry is available via the internet and a simple link, but many caregivers/family members do not have the time or energy to assist in enrollment and some families do not understand and/or have access to the technology. As mentioned, medical needs become a priority over enrollment. A lot of times she calls families to offer her assistance in enrollment, but they have too much going on in their lives to do this. She typically will follow up with families about 3 weeks later to try again to go to their homes to assist them. While initial enrollment is time-consuming and is a concern, this is eased by Ms. Gallagher visiting families and helping them enroll. The number of modules can be overwhelming, and they have realized that vagueness of some of the survey questions does not allow for more detailed responses. Some of the positive feedback from PALS about the Registry has included the following:

- ❑ "I'm helping to make a difference"
- ❑ "I hope to gain information about new treatments"
- ❑ "I'm looking to participate in trial studies"
- ❑ "The surveys made me think of my lifestyle choices and potential causes of disease"
- ❑ "ATSDR's phone assistance to reset passwords and recover usernames is helpful"

PALS have indicated that they have received few notifications from the Registry, no correspondence regarding usage of data or current findings, and no information on the number of researchers using the data. PALS would like to see some follow-up on disease progression (i.e., longitudinal study). It would be beneficial to provide quarterly feedback on Registry progress to enrollees regarding the number of new enrollees and the availability of trial studies. It also would be beneficial to add a survey on disease progression.

Ms. Backman reported that the Foundation has had great success with the Biorepository. Judy Richman, the Foundation's Director of Patient Services, has been working directly with Laurie Wagner who has been terrific to work with on the process. In terms of feedback regarding the Biorepository, PALS and their families feel that registration is easy, paperwork requirements are manageable for patients and their caregivers, they are very pleased to make the donation because it provides a deep sense of contributing to future ALS research, and postmortem tissue donation offers hope for rapid advancement of scientific findings. They have had very good feedback from the postmortem donations they have been a part of. The families are grateful and are happy that at such a difficult time, this last piece can be handled efficiently and so well.

Brunet- García Advertising

Kathy Lacivita
Senior Marketing Strategist
Brunet-García Advertising

Francie Lefkowitz
Account Coordinator
Brunet-García Advertising

Ms. Lacivita indicated that Brunet-García began its work with the Registry in 2015 creating branding, visual identity, and key communication messages. It is their pleasure to continue this work, and she thanked all of the partners. It makes them very proud as they listen to everyone's presentations to see the use of the web buttons and icons Brunet-García created, which is great for the Registry in terms of maintaining the consistency of the brand.

Brunet-García works with the Registry to help create and implement a strategic communications plan. While they want to raise awareness and engagement, they have heard from a lot of people that it is really important to help folks understand the benefits and value of the Registry. In addition to that is actually compelling them to engage, enroll, and begin the dialogue and process of assisting the Registry with its goals. It is important to provide value to persons living with ALS. This is a complicated subject matter and a lot of individuals living with ALS and their families/caregivers are not necessarily in a place to process very scientific and sometimes complicated material. Brunet-García works with the Registry and partners to simplify this complex information, and speak to persons living with ALS and their families/caregivers in a voice that provides comfort. In addition, Brunet-García serves as a liaison with the Registry and its partners to help the Registry ensure that messages are targeted appropriately, whether they are to persons living with ALS, caregivers/family members, researchers, or clinicians.

It is important to ensure that what Brunet-García is doing is relevant and communicates to target audiences in their voice and in a manner that they will understand and be receptive to. Part of Brunet-García's process for the communications plan is to listen, analyze, understand, and communicate. They are continually looking to gather information in a variety of ways. They assist with reviewing materials to make sure that what is being utilized is relevant or if amendments are needed. They attend strategic marketing workshops with stakeholders, have had in-depth conversations with stakeholders and partners, and work as an extension of the

Registry's communication team to ensure that Brunet-García is providing value and is communicating appropriately. The annual surveillance meetings are very important to Brunet-García. Not only do they offer a great opportunity to collaborate, but also they hear from all of the stakeholders (persons living with ALS, families, researchers, clinicians, partner organizations) about the state of affairs each year. That helps Brunet-García formulate its communications plans and determines what they will do moving forward.

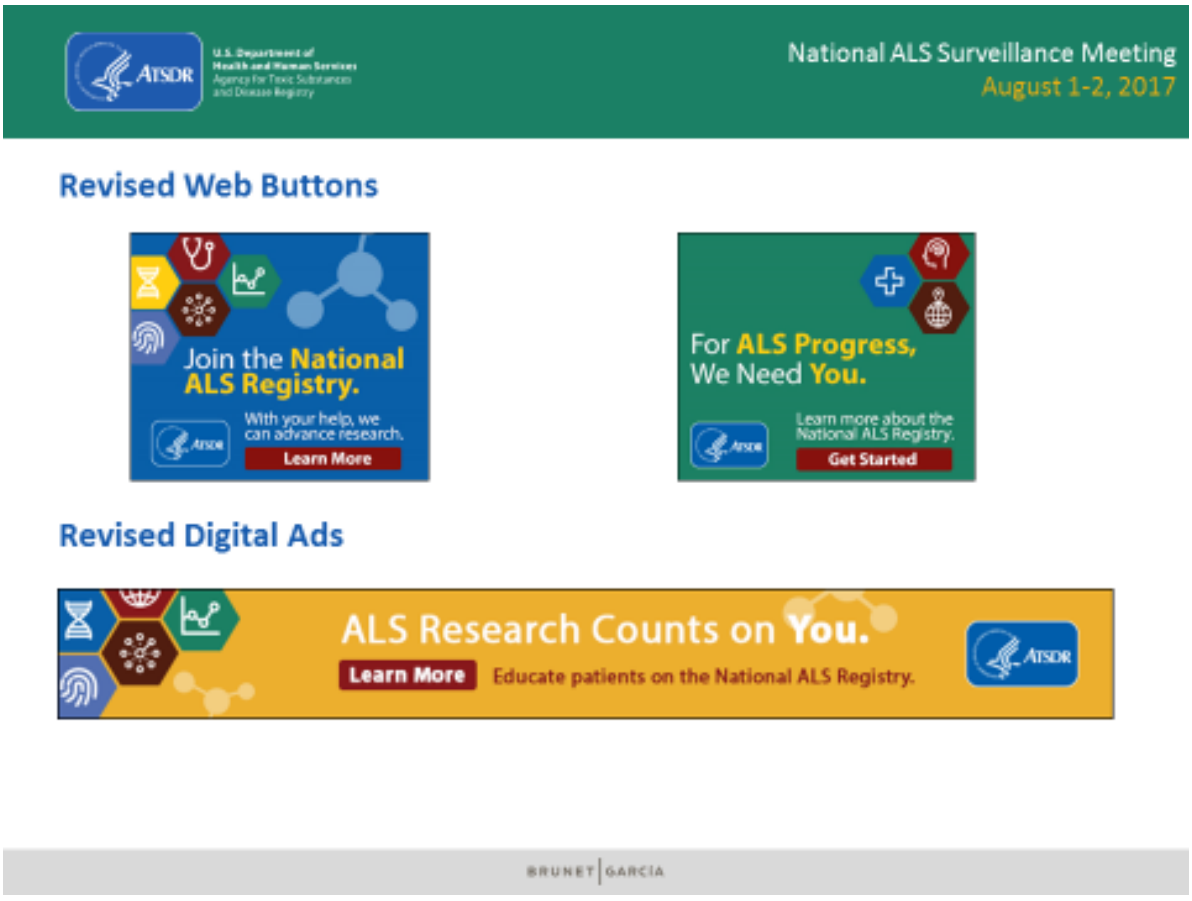
Given that Brunet-García engages in a continual Q & A analysis, they wanted to share highlights of some of their accomplishments that they felt worked and were successful. One of their main tasks is content development. In terms of the materials Brunet-García pushes out from a marketing standpoint, they need to make sure these are relevant, concise, and communicate with each individual target audience. They have heard from everyone that all partners use social media posts. Brunet-García has found that caregivers in particular engage with social media, so a lot of the targeted messages might be more in tune to their needs. They created a motion graphic video and infographics, are working with Dr. Mehta and his team on the website landing page, and have collaborated with partners on a variety of articles that have been published in *Quest Magazine*, the ALSA newsletter, et cetera.

Building upon what Ms. Lacivita discussed, Ms. Lefkowitz emphasized that one strategy Brunet-García focused on this year was article development. Two of the major efforts were a CDC feature and a blog article that the partners used. The CDC feature offered an amazing opportunity for the Registry to be featured prominently in all of CDC's work. For about a week

when anyone went to CDC's home page, they would see the article. This increased awareness and built upon existing awareness. There were several aspects to this article. One was that they interviewed Dr. Sorenson, who was kind enough to offer his time. They thought this would

help bring a face to a name for the Registry. They have heard that some people may not trust the government in terms of entering their information, so it is important to put a face with a name and show that there are people behind the Registry numbers. However, the numbers are also important so they included some of the findings from the report released in 2016. Also included was the announcement of the Biorepository launch. The article was also translated into Spanish in order to expand the reach. Biorepository information is also included in blogs, social media, and other venues. For the second article, Brunet-García engaged with the partners to work on the tone and make sure that persons living with ALS and their families would get information in different places. They may not go to CDC's home page, but may go to the partners' sites. This is another way to spread the messages more widely. They also took into account the visual aspect and not just the content. The goal is to grab people's attention and get messages across. By focusing on certain aspects and highlighting key messages, they know that certain concepts are definitely getting across.

Brunet-García did some reframing a couple of years ago and continue to build upon that. They use input from ATSDR and partners to modify their icons, messaging, and key phrases. They have adjusted previously used icons and created completely new ones based upon discovering new needs and levels of understanding. They also find that maintaining consistency is very important, so they want to make sure that if the target audience sees Brunet-García's materials in different places, they will know quickly that they are about the National ALS Registry without having to dig too much and that this is a trusted brand. Optimizing content and tone is also important to persons living with ALS and their families in that there is certain information that they want to learn more about and certain language with which they resonate better.



Ms. Lacivita indicated that Brunet-García recently completed the video she mentioned earlier. The goal was to be able to communicate to a wide variety of audiences, and be able to put a very concise and clear message in front of everyone they are talking to, whether it is persons living with ALS, researchers, reporters, someone seeking more information, et cetera. They wanted to ensure that the video was very clear as far as the action item that someone needs to complete at the end of the video, and demonstrate the value that the Registry provides to all of its key target audiences. It is a very simple motion graphic that introduces the additional icons completed this year, and offers straightforward information presented in a compelling manner that they hope has resonated with folks thus far. Ms. Lacivita played the video. The partners will be using this video, and it can be used during presentations and clinics to run in a continual loop. The goal was to be informational and engaging, and it builds upon "ALS Research Counts on You."

In terms of next steps, Brunet-García will continue to collaborate and mine the partners for their wonderful insight and continue to identify opportunities and touch points they have, especially with persons living with ALS and their caregivers and family members. They also plan to implement a testimonial quote collection plan, which will allow them to go one step further in putting a face to the Registry. They will be working with partners to talk with persons living with ALS. This plan has been approved by the IRB. Hopefully, as they gather more testimonials, they will be able to create new content and materials, and ultimately provide these to the partner organizations. Brunet-García also plans to focus on increasing awareness in the under-enrolled population, particularly in the rural areas that are very hard to reach. They also will continue to develop new materials to increase engagement.

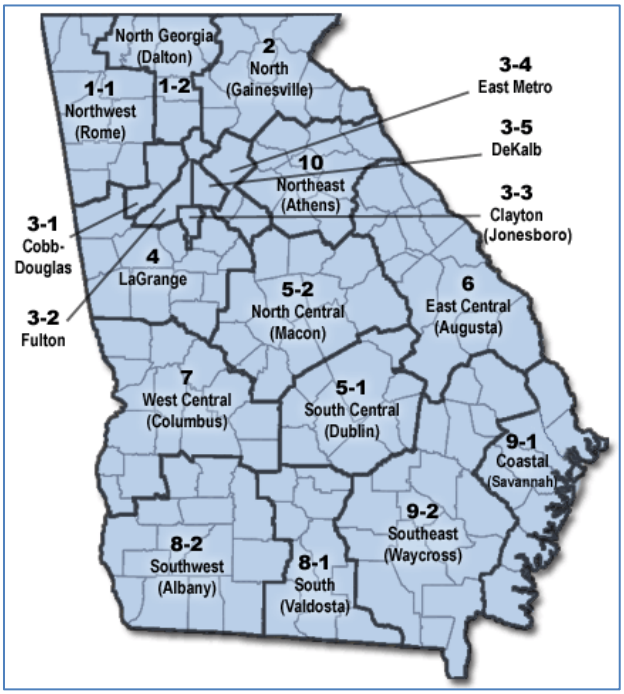
Under-Enrolled States Outreach Project

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

Ms. Punjani reported on a project she has been working on known as the Under-Enrolled States Outreach Project. This project was initiated after the recommendations from the 2016 Annual Meeting. During this session, she reviewed the previously conducted Georgia Pilot Project in terms of its purpose, methods, results, and implementation; provided an update on the outreach states pilot project for seven states; and discussed strategies to increase Registry enrollment through partner collaboration with the ALS Association, MDA, and the Les Turner ALS Foundation.

The objectives of the 2015 Georgia Pilot Project were to help target outreach activities for the Registry by identifying areas smaller than a state to focus on under-enrollment that were reproducible in other states and met the restrictions imposed by OMB; provide a qualitative assessment of Registry enrollment; and test the methods using Georgia data. Portal data are received based on cities, which are then categorized into counties. Because of OMB restrictions, the counties had to be categorized into Health Districts.

This map shows the Georgia Health Districts:



Of the 159 counties, Georgia is divided into 10 Health Districts. After the Health Districts were identified, the number of people enrolled in the Registry were compared to the expected number of cases. This analysis found that the highest area of enrollment was in Health District 3, which is Metropolitan Atlanta. The areas of under-enrollment included Health District 1, Northwest corner of Georgia bordering Alabama and Tennessee; Health District 6, which includes Augusta; Health District 7, which includes Columbus to the Alabama border; and Health District 9, which is South of Augusta to the Florida border. With this Georgia project, not only was the Registry data being compared to the expected number of cases based on Census data, but it was also compared to data received from the ALS Association Georgia Chapter regarding the number of people enrolled in the Registry. This comparison also found that Health Districts 1, 6, and 7 were under-enrolled based on the ALS Association Georgia Chapter's records.

Subsequent to the Georgia Pilot project, there were several implementations using these data by the ALS Association Georgia Chapter. First, Registry information was provided to new patients at the clinics. Also, Registry flyers were distributed at clinics and tablets were provided to help patients enroll. The second strategy included outreach to support groups by having peer speakers discuss the purpose and ease of the Registry. Outreach efforts also were conducted at annual chapter events, such as the ALS Educational Symposium and the Walk to Defeat ALS. Finally, the ALS Association Georgia Chapter conducted follow-up steps by reaching out to new patients to enroll them in the Registry. Through these implementation strategies, the goal was to focus on existing patients in under-enrolled areas to increase enrollment. This goal was achieved because Registry enrollment increased following implementation of the outreach strategies. This moved Georgia from being in the Red Zone of under-enrollment to no longer being an under-enrolled state.

The Georgia Pilot Project was led by Dr. Kaye and Ted Harada, who set up the methods that Ms. Punjani was able to use for the Under-Enrolled States Outreach Project. The goal of the

Under-Enrolled States Outreach Project is to focus on under-enrolled states and identify Health Districts within those states which could benefit from increased Registry outreach. The under-enrolled states include: Hawaii, Mississippi, New York, Utah, West Virginia, Wyoming, and Illinois. While Illinois is not an under-enrolled state, it was included because ATSDR's partner, the Les Turner ALS Foundation, is based out of Chicago.

The data utilized include the portal data, which includes self-enrollment into the National ALS Registry by county. Though collected by city, the data were geocoded so that it would be based on county. The other data available for use were the Census data for 2010. These data were used to calculate the expected number of cases per Health District. Unlike the Georgia Pilot Project, which only compared the data to the ALS Association Georgia Chapter data, this project included registration numbers by county from the ALS Association, MDA, and the Les Turner ALS Foundation. The methods were to identify six under-enrolled states and Illinois; categorize counties from seven states into health districts; compare the number of people in the Registry per health district to the number of cases expected, and compare Registry enrollment data to data received from the ALS Association, MDA, and the Les Turner ALS Foundation. Of the seven selected states, the states with the highest under-enrollment include Hawaii, New York, and Utah.

The under-enrollment in these states could be due to several reasons such as: having more rural versus urban areas, or other factors that would need to be further explored in detail to understand under-enrollment.

Now that these data are available to distribute to ATSDR's partners, the next steps for this project are to:

- ❑ collaborate with Registry partners to develop outreach plans to increase enrollment,
- ❑ focus outreach on under-enrolled counties throughout the seven states,
- ❑ conduct outreach for six months, and
- ❑ compare enrollment for the same six-month period for the previous year to evaluate the impact.

This project illustrates how ATSDR and all of the partners can collaborate to achieve the same goal of increasing enrollment in the Registry.

Open Panel Discussion

Moderator: Janine Cory, ATSDR
Panelists: Calaneet Balas, ALS Association
Kristin Stephenson, MDA
Andrea Pauls Backman and Cara Gallagher, Les Turner ALS Foundation
Kathy Lacivita and Francie Lefkowitz, Brunet-García
Reshma Punjani, ATSDR

Ms. Cory led this open panel discussion session, which focused on the following primary questions:

- ❑ What works and does not work when it comes to enrolling patients?
- ❑ How can Registry awareness be better raised among minority groups, persons living with ALS, and rural providers?

Discussion Points

Dr. Bradley asked what the denominator is in terms of under-enrollment. That is, is it the projected number of cases that the incidence forecasts for a Health District or the mean for the nation as a whole in terms of enrollment in the Registry?

Ms. Punjani replied that the under-enrolled states were identified based on the overall US population. The number of portal cases are compared to the projected expected number of cases per health district to determine the percent expected average. This percentage is then compared to the national average to determine under-enrolled health districts in the selected states.

Ms. Newhouse pointed out that it is important to recognize that in terms of under-enrollment and diversity, culturally there are people of some races who find it difficult to register in something where their data are housed at the federal government level. Further consideration needs to be given to how to enroll these individuals. In addition, there has been misguided information published about the partner organizations in terms of the amount of money they receive and not being able to justify how it has been spent. It would be helpful for CDC to develop some talking points about how much these efforts cost. For example, the postmortem collections cost of $30,000 each. Others agreed that expressing the value ad is extremely important to consider and convey.

From a strategic communications standpoint, Ms. Lacivita indicated that Brunet-García is entering its planning period for the next year ahead and they have spoken with Dr. Mehta and his team about engaging specific communities, including African Americans, Hispanics, and Pacific Islanders. The Brunet-García team has experience in reaching diverse cultures where they live, so they will be looking to include those communications in the upcoming year, and will be turning to their partners to ensure that they are leveraging resources and gathering intel they may have to make sure Brunet-García is in synch with the partners.

With great respect to Ms. Gallagher and others like her who go into homes, Ms. Newhouse emphasized that there are a lot of cultures that are not going to accept a Caucasian male or female coming into their homes to capture that information.

Ms. Kidd found this to be very helpful and expressed her appreciation for the amazing work everyone has invested from their various perspectives. Les Turner ALS Foundation having someone dedicated to helping people enroll in the Registry is phenomenal, and she highly recommended that to the ALS Association and MDA. She understands that this has to be modified based on culture. She emphasized that as they lay out their plans, it is very important to have a metric. What is the goal and what is the metric? What are they trying to achieve? If they could articulate that, then breaking it down into a specific action plan is much more manageable. She also stressed the importance of simplifying. Living with ALS is overwhelming enough without having to sort through the science. They must articulate information as simply and impactfully as possible on the web pages and in clinics. She did not join the Registry for a couple of years because she did not understand that it existed. She assumed every time she went into a clinic, they took all of her data and she was signed up for everything she needed to be signed up for. She was receiving *Quest Magazine*, newsletters from the ALS Association, et cetera. It was not until much later that she realized the Registry existed and she was not in it. It is important to integrate the work from all organizations to make sure that everything looks and feels as simple, straightforward, and unified as possible.

Regarding the funding for the Registry, Dr. Mehta emphasized that ATSDR is completely transparent and has no problem presenting that information. The bulk of ATSDR's funding is allocated to research. In terms of partner groups, it is very important to understand that this is no different from other government institutions. ATSDR cannot do everything alone. They are at the 30,000-foot level working behind their computers, giving talks, and raising awareness while the partners are "boots on the ground."

Ms. Newhouse stressed that her intent was not to put anybody in a defensive posture. She just believes that some of these points can help to tell the story in a better way that can help to increase enrollment and help in the social media context.

Ms. Lacivita said she thought this was an excellent point and was something Brunet-García could take into consideration for the evolution of the communications. Now that the message is out there and the partners have been so collaborative in terms of sharing the messaging in a consistent manner, it makes sense for the next step to address some of the funding issues in a global way.

Ms. Backman said she thought they had done a great job of getting the word out. For those people already in the Registry, it would be helpful if Brunet-García could develop follow-up emails to keep people updated on what is occurring.

Dr. Mehta reported that ATSDR is in the process of developing a survey that will be available on their website. This is a start for people to be able to tell them how they are doing. He reminded everyone that for a formal survey, OMB approval is required for them to talk to more than 9 people.

Ms. Backman clarified that she was talking about a push email notification. Research notifications are going out, so an update on the Registry to those who are already enrolled should be disseminated in the same way.

Dr. Mehta replied that ATSDR currently sends notifications and emails to the patient list itself. Approximately 8000 emails are distributed at a time. When a new article is published, for example, the IT team sends a notification about these as well. Perhaps there needs to be a component on the website titled "Latest News" or something similar. The email is only as good as somebody opening it.

Ms. Backman said she understood that ATSDR is doing this, but it is not what they are hearing from their membership.

Dr. Mehta acknowledged that it is important for ATSDR to know if their correspondences are not being received and/or read. Plain, simple emails are distributed. Perhaps they need to spruce them up to be more visually appealing.

Dr. Kaye added that many of the email addresses are incorrect and are bouncing back. She emphasized that the partners need to encourage their memberships to ensure that their emails are correct in the system.

Ms. Cory suggested that perhaps the partners could help to promote stories through their newsletters.

Ms. Backman replied that they have been doing this, and asked what the bounce backs look like in terms of what would be expected.

Dr. Mehta replied that while they have not actually looked at this, a lot of the bounce backs are from patients who have passed away because their emails are no longer active. However, if patients are looking at their emails and are not receiving emails from ATSDR at least once a quarter, they must assess this internally to ensure that people are receiving emails. Enrollees must opt in to receive notification, and about 95% of enrollees do opt in. Enrollees who have not opted in will not receive notifications about clinical trials or studies. The majority of the partners' members probably did opt in, so it is important to look into why they are not receiving emails from ATSDR.

Dr. Brooks would like to know the number of patients per year since 2010 to better understand whether that is increasing, staying the same, decreasing, or fluctuating. He recalled that during last year's meeting, ATSDR reported the percentage of people entering through the web portal versus those who were not.

Dr. Kaye replied that it is about the same each year, with approximately 25% of people diagnosed each year enrolling. However, the people who register are not the people who are newly diagnosed so it is unclear exactly how to check that lag. People sometimes register 2 years after they are diagnosed based on the diagnosis dates being entered. She clarified that the number being shared is the incidence of ALS not prevalence.

Dr. Mehta added that it is important to keep in mind that the actual survey rates are pretty good at about 51%, which is above the norm for traditional surveys.

Dr. Finger said he thought with these presentations, there seemed to be an "all of the above" type strategy. Obviously, with the budget and a country of this size, they cannot afford "all of the above." If they are trying to get from 1000 patients registering to 1500 or 2000, it seemed like there needed to be some idea of where the "low-hanging fruit" is. Is it that the word is not out and people do not know about the Registry? Is it that people go to the Registry site, open it up, and do not complete it? Not understanding that information is a waste of money. They talk about patients not being realistic about cost, but ATSDR has an obligation to state that they are using limited funds in the best way possible. Paying someone $60,000 a year to register 50 people is not going to get them there. He asked what is being done to figure out how to do this better. This whole conversation is about more than just counting cases.

Dr. Mehta agreed that Dr. Finger made a very valid point. He emphasized that the Registry is not just about counting cases. If it was, ATSDR would not be funding all of the research. At this point, approximately 80% of case ascertainment comes from the databases. The other portion comes from the online portal where they have to improve the number of people enrolling and taking the surveys. This is where they need to address people not having internet access, being leery of the government, et cetera. It is important to help people understand that ALS research counts on them. NIH is not examining risk factors for ALS. They are looking for treatments for ALS. It is difficult to figure out treatments if the cause of the disease is unknown, which is what CDC is trying to do.

Dr. Finger agreed and recognized the value in the surveys and understanding risk factors. However, that does not occur with 80%. It will only occur if they can do a better job of finding cases and getting people enrolled.

Dr. Kasarskis said he thought they were missing something. ATSDR is probably already capturing the "low hanging fruit." Every year, there is a new cohort of ALS patients diagnosed and a turnover in the pool of ALS patients. He submitted that the ALS patients in the room represented the "low hanging fruit." They are upper middle class, computer savvy, or have young children who are computer savvy if they are not. The "low hanging fruit" has come to ATSDR because they are getting their care through the service organizations and they are medically sophisticated and oriented. He would submit that the first 500 patients registered every year are probably a lower classed item than getting the remaining isosmotically 500 patients in the pool of ALS patients. Every data point has a dollar sign attached to it. For every ALS patient in the country, it becomes progressively more expensive to enroll. While that is a speculation, it is probably the case. Coming from the relatively impoverished state of Kentucky, some people's families are working two jobs, making minimum wage, may come from under-educated backgrounds, and do not have a computer. Research publications are like a foreign language to them. These individuals may be the most informative in terms of environmental exposures, but this remains unknown. He did not think ATSDR should run away from the concept that they would be spending a ton of money to register some of the more challenging patients.

Dr. Mehta replied that they know that populations of lower socioeconomic status (SES) do not have internet access and who are living in rural areas are most likely not enrolled. The question regards how to get them registered. What can ATSDR and its partners do to get these individuals registered? There are barriers as mentioned, but hopefully they can help convince these individuals to enroll in the Registry on the portal end.

Dr. Horton emphasized that until his dying day, Ted Harada helped ATSDR with the Registry itself. That is a testament to how passionate patients are about this work. He often thinks about Ted and all of the good work he did. Ted did not have to do that. Ed Tessaro does not have to do that, but he is there year after year. About 3 to 5 years ago, ATSDR purchased tablets and hotspots for the ALS Association and he assumed those are still being used by people in the field to enroll patients. He asked if purchasing tablets and hotspots for MDA and the Les Turner ALS Foundation in order to enroll more people in rural areas would be beneficial.
Ms. Stephenson said it would be worth assessing for MDA and conducting some data collection in terms of where the opportunity lies. This may be an opportunity to engage with the ALS Association on lessons learned and determine whether there is a 2.0 version of that type of consideration that might allow them to impact greater enrollment.

Ms. Backman indicated that the Les Turner ALS Foundation already does this. This is exactly Ms. Gallagher's role. She is in the field with a tablet and a hotspot in people's home regardless of where they are.

Recognizing that certain clinics are better than others at promoting the Registry, Dr. Horton asked how to make promotion more uniform across clinics.

Ms. Balas responded that this is very easy to do. They have 39 chapters across the country. Within California, they have 4 chapters. Getting a report that states that California is under-enrolling is a very difficult starting point. Is it Northern California? Is it San Diego? Is it Sacramento? The more the data points can be expanded, perhaps by health counties, this will help target under-enrollment. As the ALS Association considers launching a national volunteer program to train volunteers who are interested in helping to enroll more people into the Registry, they can use their hotspots in a more targeted fashion as opposed to constantly going to Atlanta, which is doing very well. It is pretty easy to say that the rural area is under-enrolled,

which is probably true, but her gut says there are probably many other areas that are under-enrolled that are not being targeted. From her perspective, as they think about mobilizing the 39 chapters and 130+ clinics, the more data points they have to go after, then Lauren and her team can make a targeted effort. They have to understand where they are going, and she does not think they are clear on that yet.

Dr. Horton said he knew that some chapters and clinics have folders that they give to people who are newly diagnosed, but not everybody does that. He presumed that if he was newly diagnosed and was reading this, and he came across the Registry pamphlet, he would consider enrolling. But if he did not get that packet, he would not know about the Registry. He wondered how they could ensure that all clinics are providing similar packets to individuals who are newly diagnosed. It seemed like this would be easy enough to do. Whether a patient takes the step is a different story, but at least the packet would be made available and they would read about it.

Ms. Balas indicated that the ALS Association has three levels of certification. Perhaps they could make that part of the certification process, so that this information is something that they agree to be handing out on a regular basis.

Dr. Mitsumoto expressed appreciation for the organizations and volunteers who are doing a wonderful job. He thought they also needed to talk about the importance of the neurologists. They were all so fortunate to attend the meeting to find out what is occurring with the National ALS Registry, but there are many other neurologists dealing with ALS who are not well-informed. It is extremely important to enhance education for the neurologists.

Dr. Horton said they have data to suggest that the non-referral clinics that are not associated with the ALS Association or MDA do not know about the Registry. How to target these folks is somewhat tricky. At one time, ATSDR purchased a mailing list from the American Academy of Neurology (AAN) of 25,000 neurologists. However, they did not know which of those focused on ALS versus something else. That was a shotgun approach, which may not have the intended result desired. This has been a challenge from the beginning.

Dr. Mitsumoto said he thought most neurologists are referring patients to ALS centers, which is what the guidelines recommend. While there are some rural areas where there is not an ALS clinic and that is a problem, even in urban areas with large centers, it is not clear whether neurologists are doing this all of the time. There are almost 100 centers, but he believes there is still a large proportion of ALS clinicians who are not involved as much. They must be educated continuously.

Dr. Mehta replied that it has been their experience that there are some ALS doctors who promote the Registry a lot more, while others are indifferent or are not aware. He agreed that they must build relationships with the proportion who are not engaged.

Ms. Stephenson said she thought the point was well taken about working with the clinician community. MDA has been aiming to increase their engagement with clinicians, and has been ramping up over the last few months in terms of communicating with care center directors. The timing issue is also critical in terms of working with providers, because a newly diagnosed scenario may not be the best time to share the information. The information about the Registry and filling out the forms is complex. It might be that there needs to be a period of time for some individuals after they have received their diagnosis before they even want to hear about the Registry. Working closely with neurologists also is beneficial because they can help gauge when the right time is for that patient as opposed to having a pre-determined time. If clinicians

understand about the Registry and truly appreciate what it can do, they can work that into the conversation with their patients at the right time in a way that the individual patient might be interested in following up. This cannot be all on the neurologists, but they are a critical piece of the overall outreach.

Dr. Feldman suggested tasking one to two people per state to be in charge of their state. Each state has a neurologic society. Task one or two ALS physicians who are prominent within their state to speak at their own neurological state society, and also put them in charge of developing a plan for outreach. One problem is that there is no clear infrastructure for doctors to get the message out. Delegating the responsibility of outreach in this way would provide an infrastructure. She agreed with Ms. Kidd about the importance of simple metrics. Her patients ask her why they should do this. If ATSDR showed her a reason why physicians should do this and what they will gain from it as physicians who are interested in research and care, she would be very interested to be involved.

Dr. Kaye reported that data from the State and Metro Project show that approximately 25% to 30% of people are not going to referral centers. While there is a need to increase referral centers and some are ambivalent about providing the information, they are still only reaching about 75%. Consideration must be given to how to reach the remainder who, for whatever reason, are not following the guidelines.

Dr. Brooks challenged Dr. Finger to develop a simple plan for a tax credit for entry into the Registry and MDA, the ALS Association, and the Les Turner ALS Foundation to go to Congress to push that through. It would not cost the country that much to pay for these data through a tax credit.

Mr. Tessaro agreed and said he thought they had wasted the majority of this discussion trying to run after people. Over 5000 people will be diagnosed this year who will go to a clinic at least once. However, he bet they would not get 1 out of 4 of that group. He would not spend funding sprucing up emails and going after people who have already been let out the door. Most of the effort should be focused on the time of diagnosis. While he understood that this is a difficult time and he has been in that situation, but nobody at Emory ever asked him to be involved in the Registry. He believes they let neurologists and family doctors off the hook by accepting the fact that they do not sell the Registry. It does not have to be at diagnosis in that moment of horror, but it could be during that first meeting. It is not because neurologists are not doing important work, but they are not thinking about the Registry. Within the first meeting is when neurologists own the patient and can get them to do anything at that point. After that, they will just be running after patients who are now involved in a series of activities. Efforts should focus on what to say at the time of diagnosis and during the first clinic. This is not about handing them a packet, but instead should focus on having patients enroll before they leave. He acknowledged that this is difficult and time-consuming, but that is when they will get the patient to do something that is important.

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

Robert Kingon, MPA, Facilitator
Carter Consulting, Inc.

During the end of the day wrap-up session, Mr. Kingon noted that they had a full agenda planned for the next day. Before closing out the first day, he opened the floor for final questions, comments, and discussion.

Discussion Points

Dr. Benatar said he was hearing that about 20% of the registrants are coming through the portal. He wondered for what proportion of those patients who have been surveyed they have a near complete dataset. He wanted to get them beyond the goal of trying to enroll people, which he saw as a means to an end. What is that end? He requested that someone summarize the status so that that they have some perspective on the data coming out.

Dr. Mehta responded that they do know that when people enroll, they will take surveys and will come back to them. Sometimes enrollees do not complete all of the surveys in one setting, and they are sent reminder emails to go back in to complete the surveys.

Dr. Kaye added that this is somewhat difficult to determine, given that surveys have come on line at different times. For those who participated in the Biorepository for whom they have DNA samples, close to 85% completed the surveys.

Dr. Benatar emphasized that they need to know this. It pertains to the metrics in the sense of converters, which they spoke about last year. They must take it one step further in terms of how to move from enrollment to a near complete dataset. While he understood that different surveys have come on line at different times, it would be good to know what proportion of people have completed surveys in order to have a sense of the quality and completeness of the data.

Dr. Kaye responded that of the people who enroll, about 50% take surveys. Of those who take the surveys, most complete them. However, it is not possible to tell the difference between the takers and non-takers by sex or demographics.

Dr. Brooks asked how they know when someone who enrolled in the Registry has died, and what the survivability is of people who enter the portal and those who do not. This is a potential selling point of participation.

Dr. Kaye replied that they know someone has passed when they send the data through NDI. Mr. Ted Larson is currently assessing the survivability of people who enter the portal and those who do not. Enrollees provide their date of diagnosis when they enroll.

August 2, 2017

Update From Pharma

Mitsubishi Tanabe Pharma America

Jean Hubble, MD
Vice President, Medical Affairs
Mitsubishi Tanabe Pharma America

Dr. Hubble reported on the background and studies related to RADICAVA™. Dr. Hubble's presentation is not available for dissemination because it contains unpublished data.

Cytokinetics, Inc.

Sarah Kulke, MD
Senior Medical Director
Cytokinetics, Inc.

Dr. Kulke emphasized the difficulties in conducting clinical trials in patients with ALS. She pointed out that everything she was going to talk about during this presentation were investigational products, none of which are approved for the US at this point. She said she has the very good fortune to work for a company with very deep scientific expertise in muscle biology, and a great ability to identify potential compounds that might impact the way that muscle is able to function. Cytokinetics, Inc. has two compounds in development for ALS, Tirasemtiv and CK-107. Tirasemtiv is furthest along in a Phase 3 clinical trial, while CK-107 is just completing a Phase 2 trial in SMA and has just started a Phase 2 trial in ALS.

In terms of what is known about Tirasemtiv in ALS, its mechanism of action is very well-defined. The basic contractile unit of muscle is the sarcomere, which is made up of proteins. One of those proteins is troponin. Tirasemtiv binds to troponin and in that way, is able to impact and activate the muscle. It is known as a fast skeletal muscle troponin activator (FSTA). Tirasemtiv is known to improve grip strength, hang time, and running time in a mouse model of ALS (SOD1G93A). These animal data gave Cytokinetics, Inc. some encouragement to examine what this might look like in humans.

In a Phase 1 clinical trial in healthy subjects, they were able to demonstrate that Tirasemtiv is able to increase the force with increasing concentrations of the drug. The force is measured by the ability of the foot to pull up on a bar when the nerve is stimulated. In addition to increasing concentration producing increasing force, increasing frequency of stimulation also increased force. This was the proof of principle that muscle function could be improved with this compound.

That led Cytokinetics, Inc. to design a Phase 2 trial in ALS, BENEFIT-ALS. This was a very short trial of 12 weeks in duration. It had an open-label lead in of Tirasemtiv and then went to treatment randomization of 1:1 either placebo or Tirasemtiv. Tirasemtiv was allowed to be titrated up from 125 mg BID all the way up to 250 mg BID. That study did not meet its primary endpoint, which was change in ALSFRS-R total score from baseline to the average of the

scores obtained after 8 and 12 weeks. However, there were a couple of findings that were encouraging. They were able to demonstrate that there was a difference in decline in percent of predicted slow vital capacity (SVC), which is a measure of breathing. The theory is that the Tirasemtiv may have been able to potentiate the musculature responsible for breathing, and therefore the investigators were able to pick up on a difference. In terms of muscle strength, a difference was demonstrated over the 12 weeks as measured by the muscle mega-score. In terms of the SVC seen over time, there was maintenance of the separation of curves even after withdrawing treatment. Again, encouraging but not proof. There also are some tolerability issues associated with Tirasemtiv. Tirasemtiv had a higher rate of patients feeling dizzy, fatigue, and nausea. The hypothesis is that these tolerability issues are an off-target effect centrally mediated through the gamma-Aminobutyric acid (GABA) receptor, though that is not yet positively confirmed [Shefner JM, et al. Amyotroph Lateral Scler Frontotemporal Degener. 2016;17:426–435. ALSFRS-R, Revised ALS Functional Rating Scale; BID, twice a day].

Those two pieces of information encouraged the investigators to move forward with a large Phase 3 48-week trial that is currently underway known as the Ventilatory Investigation of *Tirasemtiv* and Assessments of Longitudinal Indices after Treatment for a Year in ALS (VITALITY-ALS). This study is being conducted in 81 sites in 11 countries, many of which are the same sites used for the BENEFIT-ALS Phase 2 trial. Because of the tolerability issues with Tirasemtiv, this study was begun with an open-label phase to preserve the blind of the trial. If everyone started on Tirasemtiv and then were randomized to placebo, they would be less likely to notice the difference of being on placebo versus tirasemtiv. The target doses were placebo versus 250 mg, 375 mg, or 500 mg per day of Tirasemtiv. If patients did not tolerate moving up to the higher dose, they were permitted to return to a lower dose. The VITALITY-ALS trial is nearing the end. Enrollment was completed on 19 August 2016, with randomization completed on 2 September 2016. Of the patients, 25% are from Europe and 75% are from Canada and the US. The results are anticipated to be presented during the ALS-NMD meeting in Boston this year [Andrews JA, et al. Poster presented at the 2016 MDA Clinical Conference; March 20–23, 2016; Arlington, VA, USA].

All of the patients from VITALITY-ALS are given the option to continue treatment in the Ventilatory Investigations in Global Open-label Research in ALS (VIGOR-ALS) Phase 3 study that shares all of the same sites as VITALITY-ALS. Cytokinetics, Inc. recruited for the VITALITY-ALS study by sending out notification through the National ALS Registry notification system. In addition, Cytokinetics, Inc. recently announced the opening of the Phase 2 treatment study, Functional Outcomes in a Randomized Trial of Investigational Treatment with CK-2127107 to Understand Decline in Endpoints – in ALS (FORTITUDE-ALS). CK-107 is known to have the same mechanism of action and is also an FSTA, but it is known not to cross the blood-brain barrier (BBB). The theory is that would lead to less of the tolerability or side-effect issues. However, this is a long way from making its way through. There are several years to go before knowing how well this one does. This is a smaller Phase 2 study, so there are not as many sites. There are 56 sites in 2 countries, Canada and the US. There are 8 sites in Canada, all of which are working with Cytokinetics, Inc. on other ALS studies. There are 48 sites in the US, 41 of which are working with Cytokinetics, Inc. on other ALS studies and 7 of which are new sites.

Discussion Points

Dr. Brooks noted that epidemiologically speaking, Cytokinetics, Inc.'s approach seemed to be different from the MTPA approach in terms of looking at a wider net of patients versus a specified population. He wondered to what degree Dr. Kulke thought they would need other epidemiological information to plan these types of studies.

Dr. Kulke said she thought the distinction could be that Cytokinetics, Inc.'s mechanism of action is quite different. BENEFIT-ALS was a very inclusive trial. In VITALITY-ALS, there was a limit of 24 months in terms of time before diagnosis. BENEFIT-ALS was able to demonstrate the change in SVC significantly different with that broader group, so they did not feel they needed to narrow the population more. Given Cytokinetics, Inc.'s mechanism of action, they are hopeful that having a broader, more inclusive group will be sufficient to work for them. Understanding the mechanism and conducting the pre-work in terms of figuring out where they might be able to go can help with this. Their inclusion criteria are similar to the inclusion criteria that Biogen used for their Phase 3 study.

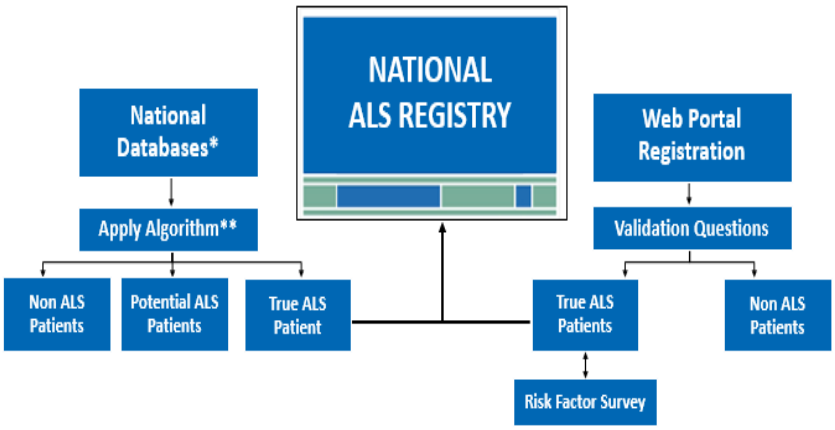
In terms of the notifications being sent out for VITALITY-ALS through the Registry, Dr. Finger asked if Dr. Kulke had a sense of the number of responses.

Dr. Kulke responded that there are many rules about pharma companies not being allowed to know anything about the patients in their trials. It is very important that that information remains separate such that they do not know any identifiable features. She is not doing the actual clinical development, so she is quarantined and guarded off. Therefore, she was able to see people asking about the study. She received many emails, which she sent to the clinicaltrials.gov site, which followed up with the site directly. While Cytokinetics, Inc. sent out the notification, it was in no way appropriate for them to track whether those patients did or did not enroll.

National ALS Registry Data Update

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

During this session, Ms. Raymond discussed data requests for the National ALS Registry analytical dataset. She explained that ATSDR uses the administrative datasets from Centers for Medicare and Medicaid Services (CMS), Veteran's Affairs (VA), and the web portal data from the website and applies the algorithm that is published in the *MMWR*. This results in the National ALS Registry. The following graphic shows all of the data that go into the National ALS Registry:



Outside researchers may now request Registry data for their own research studies. These data are collected in the risk factor modules or surveys. Some data requested may not be available because, for example, it could be used in conjunction with other data to identify a participant. Part D of the application form offers more information about the types of data collected by the Registry. All information is located on the website link below, and the Registry should be contacted before submitting any request so researchers can be provided with the information that is available:

https://wwwn.cdc.gov/als/ALSRegistryResearchApplicationInfo.as

Risk factor modules currently available for which data may be requested include the following:

- ❑ Demographics
- ❑ Occupational History
- ❑ Military History
- ❑ Smoking/Drinking History
- ❑ Physical Activity
- ❑ Family History of Neurological Disease

Upcoming modules anticipated to be released shortly include the following:

- ❑ Disease Progression
- ❑ Clinical Data (e.g. devices used, body onset)
- ❑ Lifetime Residence History
- ❑ Lifetime Occupational History
- ❑ Residential Pesticide Use
- ❑ Hobbies with Toxic Exposures
- ❑ Caffeine Consumption
- ❑ Reproductive History (women)
- ❑ Health Insurance Status
- ❑ Trauma History

The timing of each module becoming available varies, but the hope is that within 18 months, all risk factor modules will be available to request. It is important to remember that some modules or particular risk factors within a module cannot be combined with other modules or part of

another module which may possibly identify an individual. This pertains to currently available and soon to be released modules.

The application process opened in January 2017 on ATSDR's ALS Registry website. The application requirements needed for the data request include the following:

- ❑ Who is conducting the study
- ❑ Who is sponsoring the study
- ❑ Study objectives and procedures
- ❑ IRB recruitment materials
- ❑ IRB approval letter

ATSDR reviews the application for data availability, completeness, and privacy/confidentiality. If Biorepository information is requested, there will be another review for specimens. The Scientific Review Committee (SRC) reviews applications for scientific validity and the contribution to ALS research. If an application is incomplete or the SRC has any questions or concerns about the request, an email is issued to the Principal Investigator (PI) and conversations continue until all questions are answered and a consensus is met on the data request. The SRC will provide a recommendation about approving applications, and the final decision rests with ATSDR.

Once approved by ATSDR, the data request is provided to Ms. Raymond. She will then create a unique dataset for the PI, as well as a matching data dictionary to help the PI read and understand the dataset. Both the dataset and the data dictionary are checked not only for accuracy, but also to ensure that the dataset matches the request from the form. Lastly, the ALS team has established a secure, encrypted ftp site to transfer sensitive files out of ATSDR. Once the dataset and data dictionary have been finalized, ATSDR will contact the PI about the dataset and send information regarding the ftp site. From there, the PI will be given a folder on the ftp site where the dataset and data dictionary will be placed. The PI can then download the dataset and data dictionary to their secure drive.

Discussion Points

Dr. Brooks inquired as to whether a patient can update a previously completed form, or if it is locked once submitted. He also asked whether each form has a text field for free text information.

Dr. Mehta replied that once the surveys have been submitted, there is not an option to update them.

Dr. Kaye added that if someone accidentally submitted a form that they had not completed, for example they submitted their residential history and then realized they left out a few addresses, the team can basically un-submit the module and put it back in their queue. This is only done under certain circumstances. Each form does not have a text field for free text information. Some forms have choices and an "other" category, but have limited space for text. Survey 16 has open-ended questions related to an enrollee's point of view about causes of their ALS. There is free text space where enrollees can write whatever they like.

Dr. Brooks suggested that in terms of improving the Registry in the future, an announcement could be made to inform people that they could change and add to the Registry. There does not seem to be any sense of getting patients in and giving them opportunities to change their data.

Dr. Kaye explained that there is a definite bias in allowing people to do that. People do accidentally submit modules before they are completed. Under those circumstances, the administrative staff will unlock it for them. But that is the only reason for unlocking it.

Ms. Factor-Litvak pointed out that as the course of disease progresses, it is very likely that some of these variables being collected, such as occupational history, will change. That may be very important in terms of studying determinants of progression. Therefore, she supported permitting the forms to be completed/submitted multiple times should a patient wish to do so. She asked whether data dictionaries are currently available that show exactly what is being collected. That would be useful to have on the website or distributed to people who are interested in using the data from the Registry.

Dr. Kaye replied that they cannot make the forms available more than once without modifying the OMB application, because that would represent an increase in burden. The total annual burden is already about 90 minutes. Just as they do not make the survey information public, they would not want to publish a data dictionary on line. ATSDR can make arrangements to show researchers who are interested in acquiring data the variables that are available.

Dr. Horton pointed out that for any surveillance system, data are cleaned, de-duplicated, et cetera. Then the data are locked and analyzed. If the modules are kept open and are continuously changed, this will create issues. The data from most of the modules are not meant to be longitudinal. The only module that captures longitudinal data is the ALSFRS module that tracks people over time. The others are intended to be one-time surveys.

Open Panel Discussion

Moderator: **Janine Cory**
Panelists: **Rebecca Kidd**
Alan Alderman
Renee Olcheski
Ed Tessaro

Ms. Cory pointed out that this session would serve as a very helpful reminder for everyone that each point of data on a slide represents a patient, and that it is important not to lose perspective about why this Registry exists and what is important. With that in mind, this panel was comprised of persons living with ALS and their families who shared their perceptions of the National ALS Registry.

Rebecca (Becky) Kidd

Ms. Kidd said she thinks the Registry is absolutely essential. It is the only single database available to collect data as it relates to people living with ALS. The progress made since the Registry was introduced in 2010 is terrific and everyone should be applauded for that effort. However, there are a couple of key issues that they must keep driving at to make the Registry as powerful and effective as possible. One is obviously participation, but there are so many people living with ALS who do not have access to the Registry. It is important to continue to focus on those who are not the "low hanging fruit." Second, it is important to set a goal. Performance is always measured based on goals. They must set a goal to indicate that participation has to grow by X% a year in order for the data to flourish and be powerful. She

encouraged them to set a goal before the end of the meeting to articulate the percentage by which they would like to grow participation in the Registry by this time next year. While this is complicated and will not be easy to do, it is key. The marketing team is doing great work. There should continue to be a focus on simple, effective, powerful, compelling communications. If possible, perhaps ATSDR should acquire the email addresses of all MDA, ALS Association, and Les Turner ALS Foundation members and start doing blasts to discuss what the Registry does, what has been produced, and the good things they have done. Some type of incentive is critical, such as a tax credit as mentioned earlier, that would encourage people to join. Those with slow progression who have the time, resources, access, and motivation may not need this. However, others need some type of incentive to take the time to complete the modules. Because Ms. Kidd comes from an IT background, she finds the Registry to be fairly straightforward and easy to use, but she understands that not everyone would. She stressed her key points as being metrics, goals, and continuing driving up the powerful communications. Communications must be patient-focused and must land in the heart of a person living with ALS such that they will feel compelled, motivated, and inspired to help ATSDR. That is not easy when living with a fatal disease and she understands that they are unlikely to reach 100%, but they must set some goals for the future. The Registry is already producing great results, and will only grow in the power that it provides. She thanked ATSDR very much for everything they have done in this area.

Stephen Finger

Dr. Finger indicated that until this spring, he was an Economist at the University of South Carolina (USC). Because all of his research was empirical, he understands the importance of data, collecting good data, and the power it brings. The ability to learn about this incredibly difficult disease is so dependent on being able to collect good data. The purpose of the Registry and what it has accomplished so far will be valuable going forward. That said, as an Economist, especially on the data side, most of the training is focused on dealing with imperfect datasets. Given that they will never have 100% participation in the Registry for many reasons that have been highlighted throughout the meeting, it is important to think carefully in terms of the analyses with regard to how to treat the biases from a statistical perspective. They are never going to spend $100 million capturing everybody; therefore, when they produce reports it is important to ensure that they do not portray that people who are rich and have internet access get ALS. He looks forward to seeing the reports improve in that respect. In terms of the surveys, Dr. Kaye mentioned earlier that there are takers and non-takers. Dr. Finger said he originally was a taker, but then got to one survey that was very onerous to complete. He spent 20 minutes on it but had completed only 10%, so he stopped. He did not just stop for that survey. He stopped for all surveys. If some surveys are not getting good completion rates, perhaps they should not be included so early in the list. Consider moving them further down in the list so that their complexity does not lead to other survey modules not being completed. This pertains to the idea about how to use what they are learning, look at response rates, look at marketing campaigns, et cetera in terms of whether they are actually getting people to enroll. If this was 2005, it would be okay to say they are getting X impressions. However, in 2017 that is not good enough. With electronic marketing, they should be able to tell a better story and really know what leads people to go to the site and to actually enroll and take the surveys. When he watched this meeting two years ago, that was discussed. They must make sure that they are not just discussing, but are implementing because time runs out. He knows the power of the Registry and what it is capable of doing, and he has high hopes for it. They must do the best in their power to make sure on the recruitment and analysis sides they are getting as much as possible out of the Registry.

Alan Alderman

Mr. Alderman said that while he does not have the resume of Dr. Finger and a lot of his information is more anecdotal, he does have the perspective of being around the ALS community for a very long time as he is coming up on 16 years since his diagnosis. That fact that he is even alive makes him an oddity in this community. Living independently and traveling around the world on his own makes him even more of an oddity. He thanked everyone in the room for all that they do for people like him. He has had the opportunity to attend many meetings like this around the world, including the International ALS/NMD Symposium for the past 10 years. He will be in Boston again this year, and this marked his second time attending an Annual National ALS Registry meeting. He emphasized that he is not a doctor or a scientist and does not have a lot of initials after his name, so a lot of the information is in his head. What he really gets from these meetings is hope, for which he thanked everyone. He gets a lot of hope knowing that people much smarter than he is have dedicated their lives to helping him and others fight this terrible disease. For many years, he has heard the conversations about people not participating in the Registry. His state, Utah, is always on the under-enrolled list and he said that quite frankly that pisses him off and really upsets him. After last year's meeting, he went home and spent the next three months at the ALS clinic every Wednesday talking to patients. He would take a laptop or iPad and go into their rooms to talk about the Registry and offer to enroll them right then. Per capita, Utah has one of the highest rates of access to the internet in the nation and the population is predominantly white, Anglo-Saxon, and highly educated. At their clinic, every time a new patient comes in, they are given a packet with information about the Registry and they have MDA and ALSA representatives speak with patients about the Registry. It was unclear to him why Utah is always on the under-enrolled list, so he went out and asked patients. The single thing they told him was that it is not clear why they should enroll in the Registry or how it is helping them. He emphasized the importance of doing a much better job of informing patients about why it is important to enroll and how it is helping them. He did not know until the previous day that there are 27 institutions that have used the Registry data in their research. ATSDR must let people know about this. He has a group he texts and he sent that information to them, and they were all very excited about it. Knowing that, Mr. Alderman does not think a tax credit is needed. While they cannot hold people hostage at the clinic until they enroll, they can give them feedback about the important ways the Registry is helping people with ALS. When he was diagnosed the doctor said, "Alan, this is your ALS, not mine. I'm here to help you. You will know what you need before I ever know." It is his ALS and he wants to take charge of it. Most patients he talks to feel the same way. Again, feedback is critical. Let people know why the Registry is important and how it is being used and more people will enroll.

Renee Olcheski

Renee and Bill Olcheski participated in this meeting for their daughter, Rachel Doboga, who was unable to attend. Rachel's mom presented on her behalf. She said that Rachel is an ALS Advocate, Blogger, Huffington Post Contributing Writer, and a True Warrior. Before ALS, she was very active. She liked to canoe with her husband. She participated in Zumba®. She danced for the Russian Ballet, who asked her to dance with them in one of their Nutcracker performances. She went to St. Petersburgh University in Russia to study. She loved to travel and spoke multiple languages. Her life now is quite different. She has lost her teaching career. She is losing the use of her arms and legs, and she has almost lost her voice. She relies on a feeding tube for the majority of her nutrition and hydration. Rachel's mom said that she looked forward to sharing Rachel's ideas to improve outreach. While she was not able to answer questions on the topic, Rachel will be happy to field questions, discuss the ideas presented, and

receive feedback via email. Rachel's mom and dad provided Rachel's business cards during the meeting for those wishing to contact her. Her contact information follows:

Rachel.doboga@gmail.com
www.howilivewithALS.com

Here is Rachel's story as read by her mom:

In my life before ALS, I was a 5th and 6th Grade English teacher. I felt like the luckiest person in the world. I could think of no better way to spend my days than talking to children, helping them become passionate readers and skilled writers. I asked for their feedback after every unit so I could tailor upcoming assignments to their interests. I knew that the way to their hearts was in showing interest in what they cared about and respecting their learning styles. As a result, my classroom was a joyful place that students were reluctant to leave when the bell rang. The only time our smiles disappeared was when we reached the grammar and vocabulary portion of the lessons. The stories and essays they wrote were delights to read. Some were fascinating peeks into the students' inner lives and most formative experiences. Others were so hilarious, I kept a copy to share with my husband. No matter how amazing the stories and essays were though, the grammar mistakes and limited vocabulary would distract the discerning reader and prevent their work from being published in the school literary magazine. I reminded them again and again of the consequences of not checking the grammar and vocabulary lessons seriously. Still, when I asked them to take out the textbook, their groans were more like those appropriate to soldiers wounded in battle than 10-year-olds in English class.

I finally found a way to break the pattern when a fellow English teacher shared her trick for getting the kids invested in grammar and vocabulary lessons. Every day she displayed a sentence on the board that needed corrections. Each sentence was part of a story which caught the students' interest and kept them engaged. I wondered how I hadn't thought of this before. The parts of class we all enjoyed most were when the students had a chance to immerse themselves in a good book or write their own stories. Of course, storytelling was the solution to our grammar troubles. The next day, I displayed a sentence on the board that needed major corrections. When the students came in, I explained the new routine. Every day we would correct a sentence and get a bit more of the story about magical children facing down wicked teachers and solving mysteries. I was a little nervous about how the kids would react. Nothing is more awkward for a teacher than staring at a sea of blank faces praying for someone to raise a hand while minutes drag by. It occurred to me as I stood at the front of the class that if the grammar lessons of the past few weeks hadn't landed, this whole exercise would fall flat. Finally, a hand slowly rose. Then another. Then another. There were 5 errors to be corrected and 11 students raised their hands. I called on the shyest student and the others dropped their hands with huffs and muttered complaints.

I couldn't help but smile. My smile grew even wider when 4 out of the 5 volunteers made the right corrections. I realized they had been listening to my lessons. The textbook was just too dense and overwhelming to allow my students to take their knowledge to the next step by applying it in new scenarios. I had been so frustrated with the class for not responding to my lectures on the importance of grammar and vocabulary, I even became dejected when I graded the quizzes the teacher copy of the textbook provided, certain that they weren't studying. Now though, I watched students throw their whole bodies into raising their hands and making the most hilarious sounds of enthusiasm to get my attention and have a chance to make a correction on the board. They clearly cared and apparently always had. It was obvious in the adept way they transformed each wreck of a sentence into a smooth proper collection of

clauses. This whole time, they were studying and trying their best, but I wasn't meeting them halfway—not until I adjusted our practice to seize their interest and abilities.

Those of us who have contributed to the National ALS Registry and Biorepository are not so different from my students and their struggle with the grammar and vocabulary textbook. We understand the importance of the Registry's work. However, for a multitude of reasons, engaging in a deeper way is difficult. Consequently, the current outreach program is not meeting the Registry's goal of attracting a significant, consistent audience. The major obstacle I see is that we are not being told the story of how our information and samples are being used. We want to know what happens next, what progress you are making, and what opportunity you can provide in a way of connecting us with clinical trials. Unfortunately, we are not seeing regular updates and the material we do find is often too dense to be accessible and educational.

A successful outreach program should have regular, accessible, highly visible updates. The most natural effective way to accomplish this would be to improve outreach by using social media. Having a Twitter account and Facebook page specific to the Registry that people can subscribe to would instantly get you a vast invested audience. However, I understand that there are some constraints around opening and maintaining social media accounts. Fortunately, I learned a thing or two from my students about working around rules. The sliest, most creative creature on earth is a 12-year-old with an agenda.

To achieve better outreach without relying on social media, I recommend a website overhaul. If your website is engaging and easy to use, the content you publish is more likely to attract visitors who will check back regularly and share your content on their own social media accounts, in ALS blogs, and in online support groups. Let's look at some numbers and get a sense of the size of the audience you can reach. Here is a list of popular ALS organizations with thriving Facebook pages. The number beside each group indicates the number of subscribers to the page. As you can see, the opportunity for outreach is enormous [slide missing].

There are four key elements of a successful website:

- ❑ Element # 1: A menu or guide to direct visitors to content most relevant to them
- ❑ Element # 2: A prominent mission statement
- ❑ Element # 3: Feature stories accompanied by media elements such as photos or brief video interviews
- ❑ Element # 4: How people can get involved

First, the website should be navigable. Right now, it is difficult to tell which links are meant for doctors, scientists, and people living with ALS. Clarifying that would make the website infinitely more user-friendly. One way to achieve this would be to include a menu bar or a visual guide to direct visitors to content that is relevant to them. The ALS Association website uses eye-catching icons:

A highly visible mission statement such as the one on the ALS Treatment Development Institute website will give readers an immediate sense of what the Registry is about:

Feature stories accompanied by media elements such as photos or brief video interviews will be key to storytelling elements. This is where you will share the amazing work the Registry does. The features will be the piece of the website that visitors share, so updating them regularly is vital:

The media accompanying the text should help explain the content. This piece, which was recently published by the *Harvard Gazette*, includes a photo that primes the reader to process the information below. Plus, it ensures that even if the readers can't understand the precise definition of RNA, they can still grasp the basic concepts being discussed.[article slide missing]. Finally, the information on how to get involved should be prominently displayed:

The ALS Worldwide website meets all of these criteria. At the top of the page, a menu helps visitors get where they want to go quickly and easily. Scrolling down a bit, we see vibrant feature stories that would look wonderful when shared on Facebook and Twitter. Embedded in the attention-grabbing array of stories is the all-important "How to Help" button. Just below this section, the mission statement is presented so visitors gain an immediate preliminary understanding of the organization's work. Right now, the National ALS Registry website looks like this. Let this be your starting point as you work to improve outreach.

I am passionate about the work the Registry does to unravel the mysteries of this cruel disease, and ultimately find a way to defeat it. My dream is that you improve your outreach and ignite that passion in all people living with ALS by welcoming them into the story of the Registry. In this way, you will become a part of the community you serve. Thank you.

The last slide says: Thank you for your time. Now clap for my mama!

Ed Tessaro

Mr. Tessaro began by noting that his remarks would be very brief, because he could not match the eloquence or the compelling stories that he just heard, except to acknowledge how true they are. He said he was thinking of Ted Harada and Rick Isaacs. Ted Harada worked so hard on this Registry and seeking out these rural areas, and was part of a committee that worked on that effort. Mr. Tessaro expressed his sorrow that Ted was not there to see all of the work that has been done. He expressed his gratitude to everyone working on the Registry for taking two days out of their schedules to update everyone, which he thought was extraordinary. As a recipient of what all of this may mean at some point, he thanked them from the bottom of his heart. The only tactical point he wanted to address were the two ways to capture patient information in the Registry. Patients in the diagnosis room and in their first clinic represent a captive audience. They will never have a better chance to sign up 100% of the people diagnosed than they will right then. They had spent most of their time during this meeting talking about running after these individuals after they go away and are settled in whatever their symptoms dictate. While they discussed a lot of ways to capture these individuals, he recommended going back to the diagnosis and first clinic visit with a 100% goal of capturing these individuals at that point. There is no reason not to get them at that point, and it is not that hard. As mentioned earlier, there should be a point person at every clinic. There should be a person tasked in an ALS clinic to help patients with the Registry on their first visit, if for no other reason than to let them know they will be contacted in a month. Once patients leave, they are gone. Mr. Tessaro bet they could make a sea of change on enrollment success if they could figure out the point at which the audience is captive and enroll them right then.

Funded Research Update

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

Michael Benatar, MD, PhD
Chief, Neuromuscular Division
Department of Neurology
University of Miami

Dr. Benatar reported on a project that was funded in the fall of 2016 in terms of its status and plans, explaining that no data will be available until next year. He noted that he was reporting on behalf of himself and Dr. Marc Weisskopf of Harvard, as they are undertaking this project together.

The idea that underlies this project is that the risk of disease, including age of onset, and the age of disease progression are likely separable phenotypic aspects of this disease. It is not believed to be the case that if disease is developed at an earlier age, disease necessarily progresses more quickly. Insufficient thought may have been given to this issue in terms of the potential role of environmental factors. To offer an example from biology to drive home this point, looking at a genetic form of this disease, the most common SOD1 mutation in the US, which is the A4V mutation, it is known that this disease can affect people in their 20s and in their 70s in terms of disease onset. But once disease is developed, the average survival is about 12 months. This is just an example from the genetic landscape of where there must be some factor that is differentially affecting when disease is developed that is quite apart from the rate with which that disease progresses. It is that idea that underlies the proposal Drs. Benatar and Weisskopf proposed to ATSDR that was funded.

In terms of what is already known, here is the landscape of some putative predictors of prognosis:

Age (older)	Riluzole use
Gender (female)	Uric acid (lower)
Onset (bulbar)	Creatinine (lower)
Body mass index (lower)	Albumin (lower)
Latency to diagnosis (shorter)	Living without a partner
Initial ALSFRS-R (lower)	UNC13A (rs12608932 minor allele)
El Escorial category (higher)	Specific genetic mutation (e.g. SOD1 A4V)
Presence of FTD	

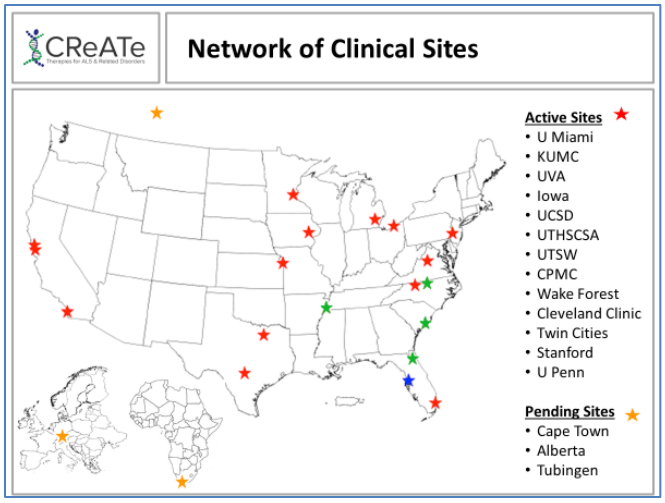
These are not necessarily determinants of prognosis, given that the difference between a determinant and predictor is not known. These are the sorts of factors that have been published in the literature typically in multiple studies, and generally portend a poorer prognosis. There is some controversy around some of these. Dr. Benatar emphasized that his goal was not to put these up and debate them, but was instead to illustrate that something is known about things that predict prognosis, but probably not enough.

There have been very few studies of the impact of environmental exposure on the rate of disease progression, and perhaps even less is known about the potential interaction between gene/genetic and environmental factors and how they might impact the rate of disease progression. With that in mind, the specific aims of the study are to:

1. Examine the influence of non-genetic factors on the progression of ALS (primary aim)
2. Explore the influence of gene-environmental interactions on the progression of ALS (primary aim)
3. Use case only analysis to investigate the influence of gene-environmental interactions on the odds of developing ALS (exploratory aim)

This approach is very relevant to what is being done in the National ALS Registry. It is important to remember that the Registry is a case only collection. There are no controls. Therefore, there is interest in developing methods that could leverage or take advantage of the type of data that are being collected. The Registry includes self-completed risk factor surveys, and as the Biorepository grows and there are DNA samples available, the methods to be developed through this study have the potential to have a lot of relevance to what is being done in the Registry. One potential drawback within the Registry is the limited depth of phenotypic data and limited longitudinal data, so there is a richer dataset in the small subset they are examining. However, something to think about as the Registry grows and continues to mature is trying to obtain more phenotypic and longitudinal data in order to try to understand the impact of environmental exposures on how disease progresses.

The study is being conducted under the context of the Clinical Research in ALS and related disorders for Therapeutic Development (CReATe) Consortium, which is an NIH-supported Rare Diseases Clinical Research Consortium (RDCRC). NIH has had this program for about 15 to 20 years in what is known as the Rare Diseases Clinical Research Network (RDCRN), which is a network of about 20 different consortia that are studying a range of rare diseases. ALS and related diseases is one of the newest members of this group. This is a sizeable undertaking that includes not only research projects, but also training opportunities, biomarker pilot projects, and establishment of a repository of biological samples mostly oriented toward helping promote biomarker discovery and validation. CReATe has a network of clinical sites throughout the country that continues to grow as depicted in the following map, with the red stars representing active sites, green genetic sites, and orange pending international sites. There is also a single data management center for all of these consortia:

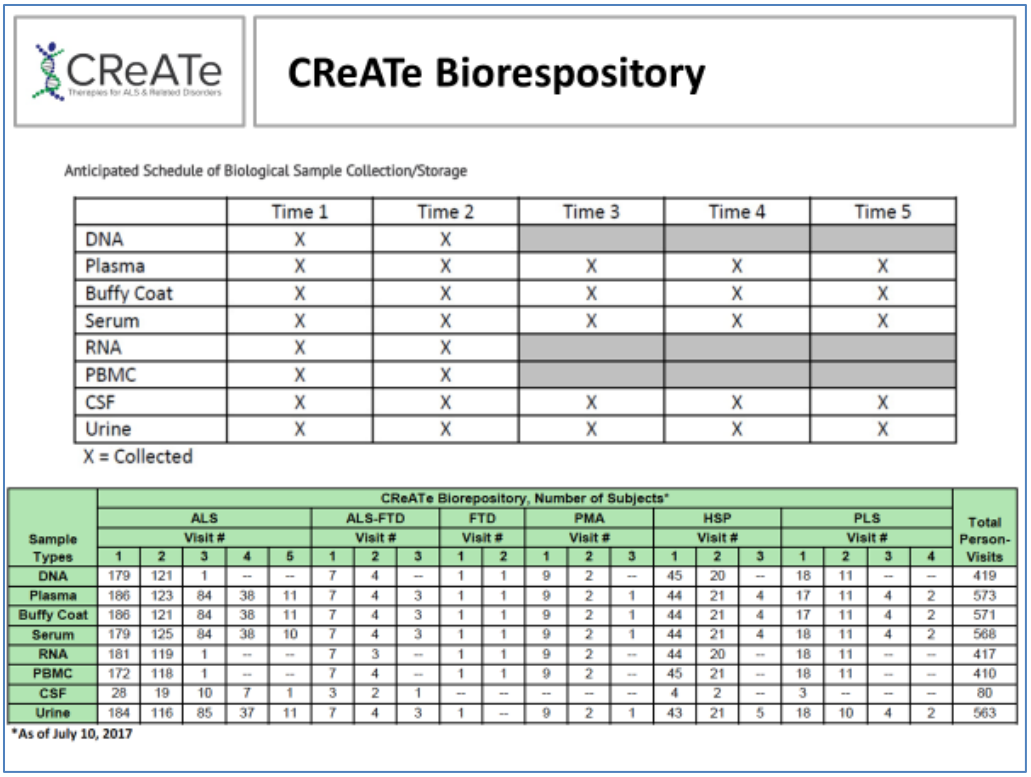


The inaugural protocol (NCT02327845) is a prospective study of phenotype, genotype, and biomarkers. The plan is to enroll approximately 700 patients with ALS, primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), hereditary spastic paraplegia (HSP), and frontotemporal dementia (FTD). Longitudinal data will be collected on phenotype, both cognitive and motor. Everybody will have whole genome sequence (WGS) data, and there will be an extensive repository of biological samples that go along with this. As originally conceived, there was no collection of environmental exposure data. That was something missing that support from ATSDR offered an opportunity to flesh out.

The study takes a very detailed approach to phenotyping, collecting the following motor, cognitive, and behavioral data:

- ❑ Identifiers – GUID
- ❑ Demographics
- ❑ Family history / pedigree
- ❑ Medical history and medications
- ❑ "Onset" and "diagnosis" phenotypes
- ❑ "Progression" phenotype – longitudinal:
  - ➢ Neuromuscular examination
  - ➢ Spirometry
  - ➢ ALSFRS-R, SPRS
  - ➢ Cognition and behavior
- ❑ Staging

In terms of progress, baseline evaluations have been completed for the first 326 patients who have been enrolled. The WGS pipeline is operational, with the first 195 genomes sequenced. They have a partnership with the NIH NeuroBioBank to collect brain and spinal cord tissue postmortem. The NIH NeuroBioBank is a network of six contracted centers to collect postmortem tissues, which is relevant to some of the efforts heard about throughout this meeting. A fairly extensive biological specimen repository has been established for biological samples to be collected longitudinally, which will be made available to the broader scientific community. There is a value in longitudinal samples, perhaps much more so than cross-sectional samples. This is the schedule of what CReATe is trying to collect, along with a snap shot of the status as of July:



CReATe Biorespository

Anticipated Schedule of Biological Sample Collection/Storage

	Time 1	Time 2	Time 3	Time 4	Time 5
DNA	X	X			
Plasma	X	X	X	X	X
Buffy Coat	X	X	X	X	X
Serum	X	X	X	X	X
RNA	X	X			
PBMC	X	X			
CSF	X	X	X	X	X
Urine	X	X	X	X	X

X = Collected

Sample Types	CReATe Biorepository, Number of Subjects*																			Total Person-Visits
	ALS					ALS-FTD			FTD		PMA			HSP			PLS				
	Visit #					Visit #			Visit #		Visit #			Visit #			Visit #				
	1	2	3	4	5	1	2	3	1	2	1	2	3	1	2	3	1	2	3	4	
DNA	179	121	1	--	--	7	4	--	1	1	9	2	--	45	20	--	18	11	--	--	419
Plasma	186	123	84	38	11	7	4	3	1	1	9	2	1	44	21	4	17	11	4	2	573
Buffy Coat	186	121	84	38	11	7	4	3	1	1	9	2	1	44	21	4	17	11	4	2	571
Serum	179	125	84	38	10	7	4	3	1	1	9	2	1	44	21	4	18	11	4	2	568
RNA	181	119	1	--	--	7	3	--	1	1	9	2	--	44	20	--	18	11	--	--	417
PBMC	172	118	1	--	--	7	4	--	1	1	9	2	--	45	21	--	18	11	--	--	410
CSF	28	19	10	7	1	3	2	1	--	--	--	--	--	4	2	--	3	--	--	--	80
Urine	184	116	85	37	11	7	4	3	1	--	9	2	1	43	21	5	18	10	4	2	563

*As of July 10, 2017

As of July 2017, there were a little over 550 person visits with a good number of longitudinal samples that they are now trying to get into the hands of investigators for biomarker discovery and validation.

Through the support from ATSDR/CDC, they are now collecting detailed environmental exposure data via self-completed questionnaires. These are largely cross-sectional at time of the baseline visit, but with some effort to collect longitudinal data as well on diet, caffeine consumption, alcohol consumption, et cetera. The environmental modules will attempt to collect the following:

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

*Reduced set of questions will be asked again over the course of follow-up

An effort is being made to separate out people's exposures before developing disease and exposures after developing disease. This is challenging because it is not clear when exactly disease begins. It is known when symptoms appear, although even that can be hard to define.

In terms of progress, the environmental questionnaires have been designed in an electronic data capture system. A lot of time has been spent assessing user acceptance of these questionnaires to make them as user-friendly as possible to minimize the burden, make them intuitive, and enable people to save as they go along and come back to make a decision about whether they feel a module is complete before submitting it. IRB approval has been obtained and about 120 patients have been consented. They are just beginning to collect environmental exposure data. One of the elements they have put into the electronic health record (EHR) module developed with Epic is, "Have you asked people to sign up for the National ALS Registry?"

Discussion Points

Dr. Mitsumoto expressed confusion about whether this is a CReATe study or National ALS Registry study.

Dr. Benatar explained that these are all people who are enrolled in the CReATe longitudinal cohort who are in the process of being re-consented in order for CReATe to also collect environmental exposure data from them directly. A subset of these individuals is likely in the National ALS Registry. While the intersection is not currently known, with GUIDS that will be establishable. These are environmental exposure data that are being collected separately. Here is an issue that has been discussed previously. When they made this proposal originally, they wanted to know if there was a way to use either the same environmental exposure questionnaires that are used in the Registry or to use the environmental exposure data being collected in the Registry and link it back to participants that CReATe is enrolling. Because those linkages were not available, they are having to collect the environmental exposure data separately.

Dr. Feldman requested further information about what patients are being asked to do, how often they have to go back into the portal to respond to questionnaires, whether they are the same questionnaires each time or if they become more targeted as more of their information is gathered, and if they are looking at medications.

Dr. Benatar clarified that a reduced set of questions will be asked to collect longitudinal data for Traumatic Brain Injury, Cigarette Smoking, Alcohol, and Caffeine. People are attending medical visits every 3 months, so they are already collecting longitudinal information about medications, evolving medical history, and disease phenotypes. This is in addition to all of that, which is already available.

Dr. Mehta indicated that ATSDR helped Dr. Benatar recruit for the CReATe program as well through the notification system.

Dr. Benatar added that they track this and get good analytic reports. Every time the National ALS Registry sends out a notification, they see a spike. While he did not have the exact numbers with him to show, it is very clear.

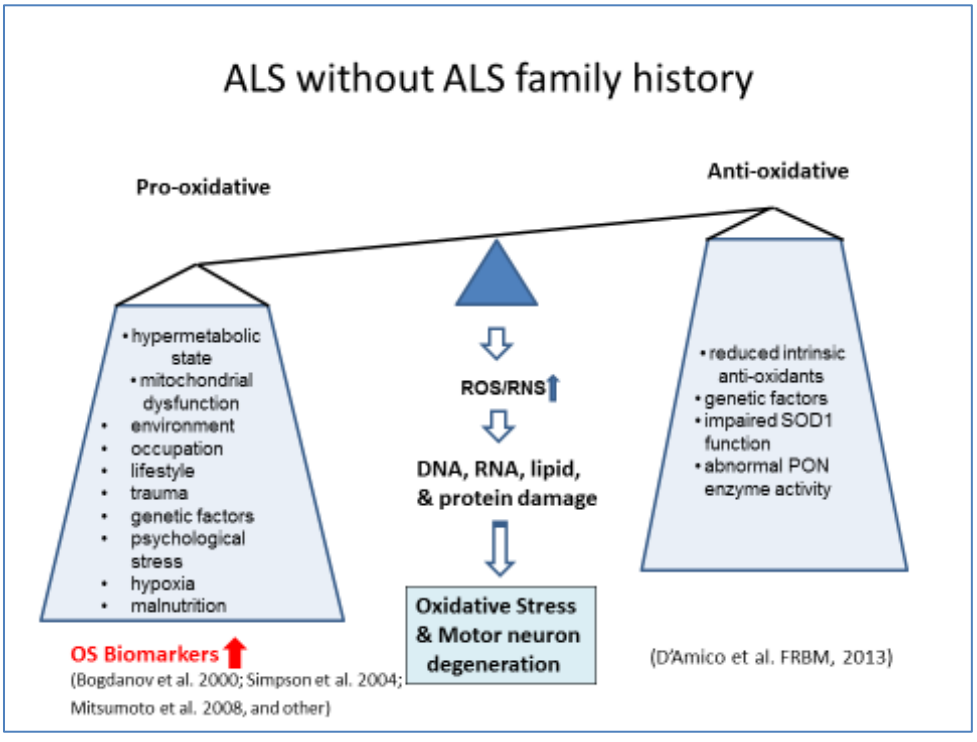
A Prospective Comprehensive Epidemiologic Study in a Large Cohort in the National ALS Registry: Identifying ALS Risk Factors

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

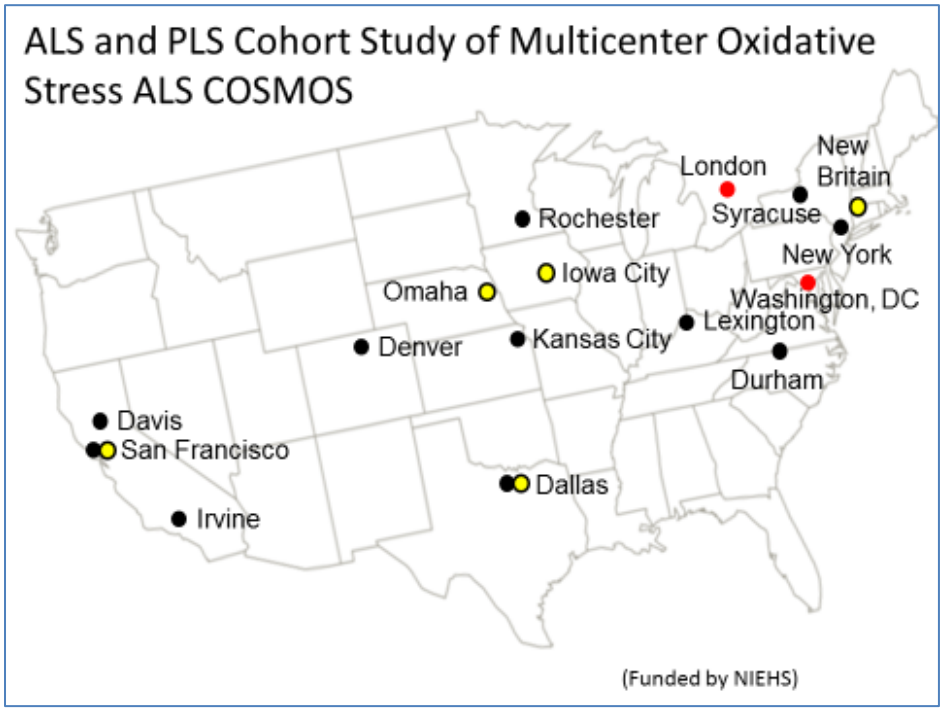
Dr. Mitsumoto discussed the project titled ATSDR Risk factors Epidemiologic Studies in ALS (ARREST ALS), which is an epidemiology study of ALS that is based on the ALS Multicenter Cohort Study of Oxidative Stress (ALS COSMOS). The National Institute of Environmental Health Sciences (NIEHS)-funded ALS COSMOS 16-center cohort study is based on the hypothesis that for patients with more oxidative stress, disease progresses faster. The hypothesis for the ALS COSMOS study was that oxidative stress (OS) is associated with the progression of sporadic ALS without ALS family history. There are a tremendous number of exposures, internally and externally, that result in oxidative stress. The principle hypothesis of the ALS COSMOS study is that OS may be associated with the progression of sporadic ALS. The specific aims will determine:

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

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



The 16 study centers are shown in the following map. The black dots are original sites, yellow dots are new sites, and red dots are PLS-only sites:



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

Publications from ALS COSMOS Study

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

(Biomarkers, Disease Progression and Survival, ALS Subsets, and Others are Pending)

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

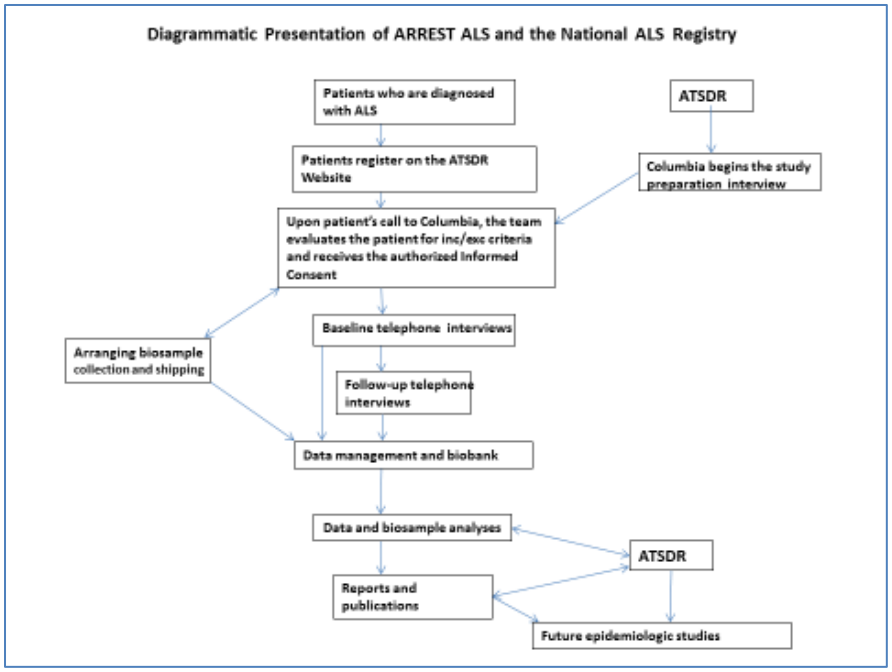
- ❑ Expand the multicenter study on a national level through the National ALS Registry
- ❑ Increase the sample size for effective analyses of the relationship between environmental risk factors and disease progression
- ❑ Possibly study gene-environmental interactions
- ❑ Recruit 420 additional patients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

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

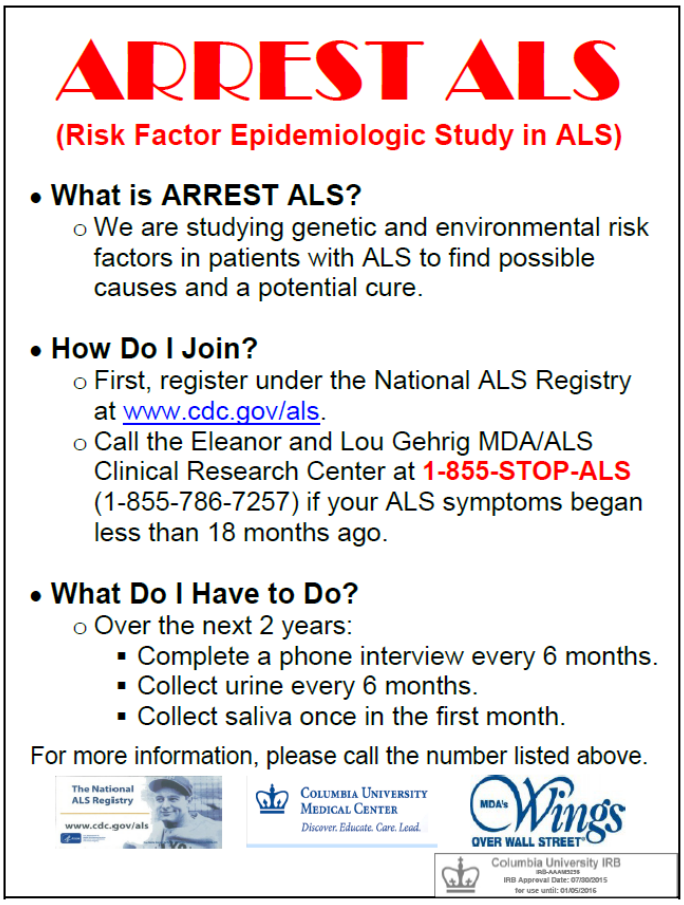
Description of Questionnaire Data Collected: Items Related to Oxidative Stress

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

The following diagrammatic presentation illustrates the process:



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



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

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

Some tests were modified so that they could be used over the phone. Equivalence Testing was performed for in-person and telephone tests that had the same scales (ALS-CBS, WVFT, COWAT, FBI-ALS, CNS-LS). These statistical methods are rigorous alpha-level analyses used by the FDA to compare generic drugs to standard drugs. For tests with different scales (MMSE/TICS, ALS-CBS Caregiver Portion), percent of total values were used for analyses. Intraclass correlation coefficients (ICC) were calculated as secondary analyses. Sequence effects also were analyzed. The findings are shown in the following table:

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

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

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

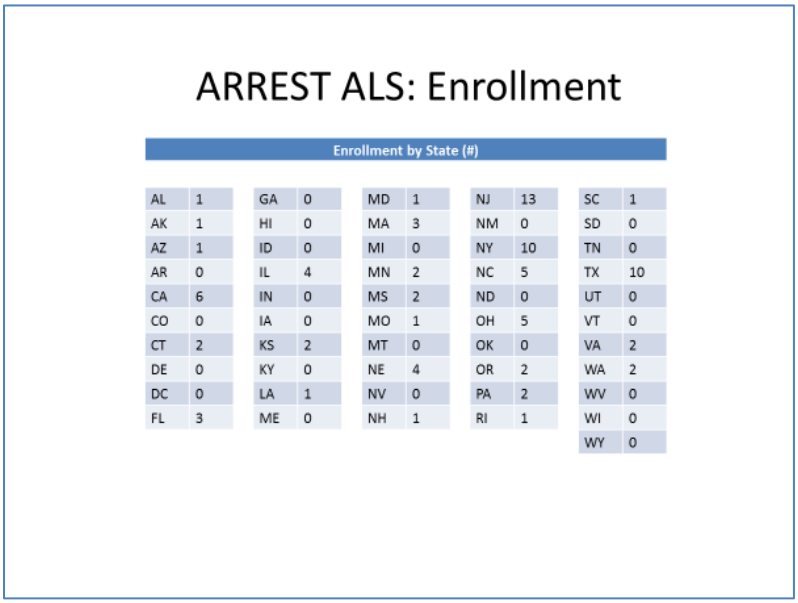
In terms of ICC, the ALS-FBI and WVFI still failed to show significant levels of agreement, while other instruments corroborated previous analyses. Possible reasons include practice effects, sample size too small, test-retest reliability not established, et cetera. No sequence effects were found across testing. The study suggests that the telephone-based version of the ALS-CBS, ALS-CBS Caregiver Portion, COWAT, and CNS-LS may offer clinicians valid tools to detect frontotemporal changes in the ALS population. Development of telephone-based

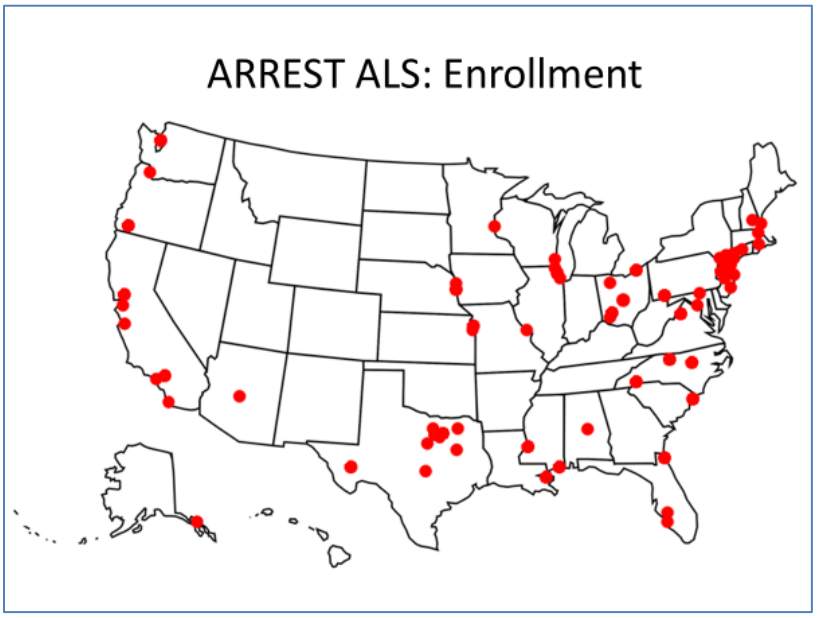
cognitive testing for ALS could become an integral resource for large population-based research in the future.

In terms of enrollment, of a total of 137 patients screened 58 patients were enrolled in 2016 and 88 were enrolled in 2017. The average age is 63, with a range of 34 to 81 years of age. Of the subjects, 60.2% are males and 39.8% are females. Race and ethnicity are as follows:

Race (%)	
White	96.6%
African American	2.3%
Asian	0.0%
Other Race	0.0%
Race Unknown *(Interview Not Yet Completed)*	1.1%
Ethnicity (%)	
Hispanic / Latino Origin	5.7%
Ethnicity Unknown *(Interview Not Yet Completed)*	1.1%

In terms of disease duration at screening, average disease duration was 13.4 months with a range of 4 months to 25 months. Subjects 4 and 85 were mistakenly enrolled into ARREST ALS despite disease duration being greater than 24 months at the time of screening (39 months and 25 months, respectively). They currently are following 50 patients. Of these, 6 have completed all tasks. Of the enrolled patients, 9 withdrew, none have gotten non-invasive ventilation (NIV) or tracheotomy with invasive ventilation (TIV) at this point, 19 are deceased, none were lost to follow-up, and 4 were lost prior to baseline. ARREST ALS enrollment by state is shown in the following table and map:





Sources of the 180 patients screened include 126 (70%) from the National ALS Registry,19 (10.5%) from the brochure, 30 (16.7%) from CUMC; and 5 (2.8%) from ALS forums. They certainly could enroll more patients, but they do not want to skew too much from one location, so they are pacing themselves. The number of patients followed longitudinally are shown in the following table:

Subject Progress (#)	
Baseline	77
6 Month Follow Up	46
12 Month Follow Up	25
18 Month Follow Up	14
24 Month Follow Up	8

Challenges in 2014 regarded whether the investigators could generate enough publicity to encourage newly diagnosed ALS patients to register and call Columbia University. This remains a major challenge. Also of concern regarded whether the telephone interview would be sufficient for collecting all of the needed information. Most national ALS registries and the CReATe project developed by Dr. Benatar collect patient information through the internet. For ARREST ALS, the structured interview is conducted by telephone with the patient. Whether that major difference makes a difference remains to be seen. They have diagnostic certainty through medical record information and have been able to collect basic physical data, so it appears that they collect the needed information by telephone. They also have been able to obtain the needed biosamples quite successfully. They could not collect blood. The ALS COSMOS study had a much more extensive biomarker program, but ARREST ALS had limited funds. However, the samples were obtained as planned.

In an attempt to improve enrollment, the new brochure was mailed to MDA and ALSA ALS Centers. A few willing centers were asked to encourage patients to register. In addition, disease duration was expanded from 18 months to 24 months. Improvements in enrollment are shown in the following table:

Screening / Consent	July 2015	July 2016	July 2017	Recent Change
Total Subjects Screened	73	137	180	+43
Total Subjects Eligible, Currently Pending	9	27	8	-19
Total Subjects Enrolled	35	58	88	+30

Future plans are to:

- ❑ Reach enrollment of at least 100 ALS participants by the end of the grant period, and they have been approved for a no-cost extension and will continue enrolling as many patients as possible
- ❑ Make certain that patients with disease duration of less than 24 months do not differ in demography and disease characteristics with those with less than 18 months
- ❑ Study whether the results of telephone cognitive screening tests utilized for the first time in ARREST ALS have a similar distribution in cognitive impairment compared to that of the ALS COSMOS study
- ❑ Investigate whether the patient population in the ARREST ALS project is comparative to that of the ALS COSMOS study in demography, cognitive impairment, disease characteristics, diet, and nutritional and environmental exposures
- ❑ Analyze whether the results based on self-reported environmental exposure in the National ALS Registry and those based on structured interviews provide the same conclusions for the same patients
- ❑ Incorporate exome and genome sequencing in ARREST ALS patients into a larger effort led by Dr. Matthew Harms at Columbia University

Discussion Points

Ms. Backman said she was happy to report that the Les Turner ALS Foundation is now actively recruiting for ARREST ALS as well. Regarding Dr. Mitsumoto's mention of wanting to recruit 100 more participants, she asked when the end of the grant period would be.

Dr. Mitsumoto replied that they have 88 patients and the grant will end in September 2017. The no-cost extension will offer additional, though limited time of less than one year, to reach a total of 100 patients.

Dr. Feldman thought the cognitive testing over the phone was very interesting, and she wondered how long it takes and if it is completed during one telephone call.

Dr. Mitsumoto indicated that the call takes about 30 minutes, but it depends on the patient.

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

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

Dr. Bradley provided a broad overview of a population-based Ohio ALS Repository and a case-control study of risk factors funded by ATSDR to illustrate how this fits into the work he has been doing with Dr. Elijah Stommel at Dartmouth and this grant in Ohio. In terms of the basis of this study, for about 7 or 8 years, they have been conducting epidemiological-environmental studies in the Northern New England area. Under the CDC contract (200-2014-59046), they have been doing the same extended into Florida. Dr. Bradley first shared some results from the now completed contract to provide an idea of how the grant that has been running for about 9 months in Ohio is going.

The CDC contract was a 2-year contract to examine epidemiologic-environmental exposures in ALS patients, and it collected a database of about 400 ALS patients in Northern New England, a mixed random control population group of about 380, and a clinic-based control population group. Florida has a database of about 1450 ALS patients, with no control patients in that area. A number of studies have been or are in the process of being published from that questionnaire-based study, including the following:

1. Angeline S. Andrew, Tracie A. Caller, Rup Tandan, Eric J. Duell, Patricia L. Henegan, Nicholas C. Field, Walter G. Bradley, Elijah W. Stommel. Environmental and Occupational Exposures and Amyotrophic Lateral Sclerosis in New England. Neurodegener Dis 2017; 17: 110–116.
2. Angeline S. Andrew, Celia Y. Chen, Tracie A. Caller, Rup Tandan, Patricia L. Henegan, Brian P. Jackson, Brenda P. Hall, Walter G. Bradley, Elijah W. Stommel. Fish consumption, mercury levels, and amyotrophic lateral sclerosis (ALS) risk. Muscle & Nerve, 2017 submitted.
3. Thomas Kuczmarski, Elijah W. Stommel, Kristen Riley, Rup Tandan, Vinay Chaudhry, Lora Clawson, Tracie A. Caller, Patricia L. Henegan, Walter G. Bradley, Angeline S. Andrew. Medical history of chemotherapy or immunosuppressive drug treatment reduces risk of amyotrophic lateral sclerosis (ALS). J Neurol, 2017, https://doi.org/10.1007/s00415-017-8564-2
4. Nathan Torbick; Beth Ziniti; Elijah Stommel; Ernst Linder; Angeline Andrew; Tracie Caller; Jim Haney; Walter Bradley; Patricia Henegan; Xun Shi. Assessing Cyanobacterial Harmful Algal Blooms as risk factors for Amyotrophic Lateral Sclerosis. Neurotoxicity Research. 2017 May 3. doi: 10.1007/s12640-017-9740-y. [Epub ahead of print].
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7. Xun Shi, Nathan Torbick, Allegra C. Codamon, Patricia L. Henegan, Bart Guetti, Angeline S. Andrew, Elijah W. Stommel, Walter G Bradley. Association between Amyotrophic Lateral Sclerosis and Water Quality in Northern New England. 2017 In preparation.

Regarding some of the environmental risk factors identified from these data, exposure to chemicals and working in industries with toxic exposure risk factors for the development of ALS, 2 to 3 times as many ALS patients record those exposures as do the control population. Exposure to water, which contains cyanobacteria either through water sports or in identified water bodies with algal blooms, is also a risk factor. Again, the number of ALS patients recording those exposures may be 2 to 3 times as much as those in the control population. The summary of the findings follows:

- Self-reported exposures to chemicals [1]
  - OR 2.51, 95%CI 1.64-3.89
- Work in industries with high toxicant exposure [1]
  - OR 3.95, 95%CI 2.04-8.30
- Frequent participation in water sports [1]
  - OR 3.89, 95%CI 1.97-8.44
- Exposure to waterbodies with cyanobacteria [4]
  - OR 1.48 when Phycocyanin concentration 100 µg/L
- Positive association between Phycocyanin concentration in waterbodies >8 hectares and risk of ALS extends up to 10 km [7]

They also examined biosamples for toenail mercury levels, estimated annual mercury consumption, and history of prior chemotherapy treatment. Both toenail mercury level and mercury consumption through fish showed an increased risk in the ALS patients compared to the controls of about 2- to 3-fold. The findings for prior chemotherapy was, to some extent, a surprise to the investigators. They found that if the subjects had a prior exposure to cancer with chemotherapy, then that was protective with an odds ratio of about half. That is, it lowered the risk of getting ALS. The summary of the findings follows:

- Toenail mercury level [2]
  - OR 2.32, 95%CI 1.1-5.4 per log µg/g
- Estimated annual mercury consumption in fish >1000 µg [2]
  - OR 2.53, 95%CI 1.13-5.89
- A history of prior chemotherapy treatment was associated with a decreased risk of ALS [3]
  - OR 0.46, 95%CI 0.50-1.02, p=0.23

Returning to the current grant, Dr. Bradley and colleagues were fortunate to be funded by ATSDR to conduct the same study in Ohio, with the specific aims to:

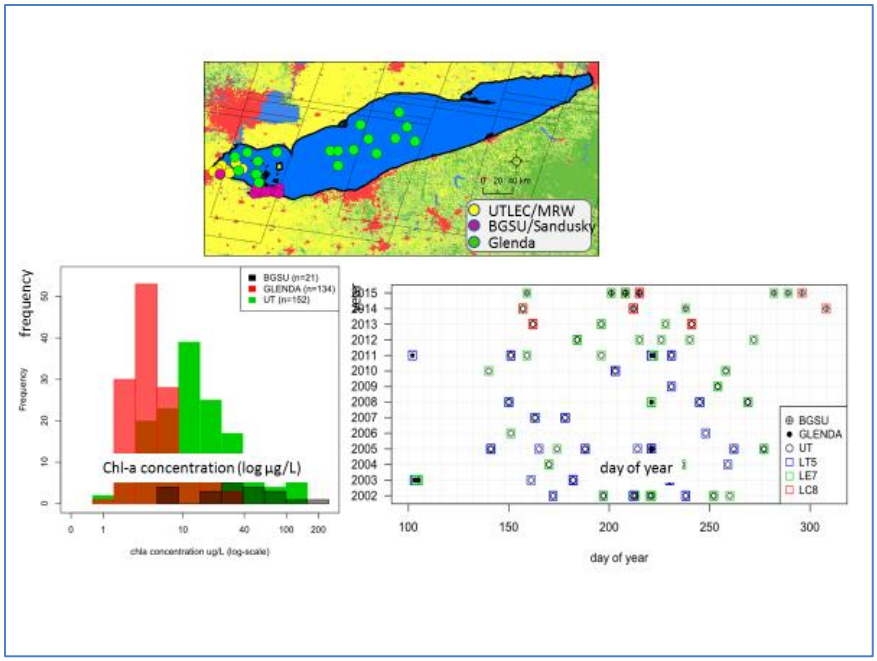
- Assess ALS incidence by developing the Ohio ALS Repository: a comprehensive, population-based ALS registry for newly diagnosed residents of Northern/Central Ohio
- Identify ALS risk factors by comparing questionnaire data on exposure to environmental toxins and toxicants between ALS patients and controls

- ❑ Perform geospatial analyses of potential environmental exposures to toxins and toxicants in relation to the risk of developing ALS

The rationale for the study of environmental risk factors for ALS in Ohio are several-fold. Northern Ohio is a region with a long history of industrial pollution of the environment. There is a large amount of agriculture that exposes the population to agricultural chemicals, particularly pesticides. The lakes in Northern Ohio, particularly Lake Erie and Grand Lake St. Marys, have a long history of recurrent massive toxic cyanobacterial blooms that have led to, for example, emergency shut-down of the domestic water supplies of Toledo and Carroll Township in recent years. There are ongoing blooms because of eutrophication due to the amount of nitrogen and phosphorous that get into the water and provide the nutrients that foster these algal blooms. This seemed to the investigators to be an ideal state in which to validate the results of the New England studies.

In terms of progress to date, given that the funding for this grant was reduced from 3 years to 2 years as CDC did not have the funds for 3 years, the catchment area was expanded to the whole of Ohio. The ramp-up of recruitment of ALS Centers and patients has been what was forecasted for a 3-year grant, but is slower than forecasted (total for the 2-years ~370 patients). Recruitment of cases to the Ohio ALS Registry is underway. Links with Ohio MDA and ALS Association chapters/clinics were established. As of July 2017, 11 Ohio neuromuscular centers were contacted and IRB and contracts were all in process. It takes time for contract development and IRB approval, and the investigators are still working their way through that rather slow process. Thus far, about 44 ALS patients have been recruited and questionnaires have been collected from 16 of those patients to date. That is about what would be expected in terms of the proportion of patients. This is expected to begin ramping up as the contracts and IRB approvals come through, and the investigators are relatively happy with how that is progressing. Approximately 130 questionnaires have been received from the postal collection of random population controls, so there is a good control population basis for making comparisons with ALS patients, moving forward. This will continue through the second year of the project.

The investigators are doing very well in terms of the collection of environmental pollutants and exposures. They have identified all of the landfills, municipal incinerators, Superfund sites, and Brownfield sites, that are the sources of the potential pollutants. They are well ahead of schedule in terms of collecting data on the cyanobacteria content of Lake Erie and other water bodies, and are now in the second year of direct sampling and calibration of satellite remote sensing data of water quality of every water body in Ohio greater than 8 hectares. Geocoding sources of environmental toxicants for Superfund and Brownfield sites is 86% complete; landfills and municipal incinerators is 100% complete; pesticide databases is 99% complete, with work being done to refine to sub-county application levels; and paraquat is 1% completed. The geospatial analyses are reflected in the following graphics:



This technique is fascinating, and these can be calibrated by direct samples from the water. The investigators have collaborations with various programs such as the National Oceanic and Atmospheric Administration (NOAA) and other programs to examine these algal blooms in collaboration with Drs. Nathan Torbick of Applied Geosolutions LLC, and George Bullerjahn of Bowling Green State University. From all of this, they will be able to produce the concentration of cyanobacteria in the water bodies over the entirety of Ohio for a timeframe of 20 to 25 years and can then make a comparison with where people live in terms of how much they may be exposed to cyanobacterial toxins. To finish this piece, Dr. Stommel and his colleagues have been collecting data on how much cyanobacterial toxins and cyanobacteria themselves are distributed from water bodies people live near. One of the tasks of that study is to demonstrate that cyanobacteria are aerosolized and do distribute at a distance from the lake containing cyanobacteria. The wave action aerosolizes an amazing amount. It is known in Florida, for instance, that the Red Tide produces respiratory symptoms in patients for up to 4 or 5 miles away from the waves and sea blooms of these red algae.

In terms of Legionnaire's Disease, which is another airborne exposure disease, people can be up to 10 kilometers away from the source of the *Legionella*. Another study that is very fascinating is that Dr. Stommel and colleagues have been collecting lungs of people who have lived within a quarter of a mile of a water body with cyanobacteria, which they identify as high-risk cases, or more than a quarter of a mile away, which they identify as low-risk cases. They find cyanobacteria in the upper lobes of those patients who come to autopsy within 5 days of dying in a hospital. They find cyanobacteria in the lungs of those individuals at a much higher rate in the high-risk versus low-risk individuals. In fact, what they find in the high-risk individuals is that there are an increased number of individuals with ALS or Alzheimer's disease compared with lower risk individuals who, had no such incidences of those neuropathological diseases. This is an ongoing study, but it is a proof of principle of the risk of exposure to cyanobacteria. While this is an ongoing picture, it is beginning to contribute to the validation that cyanobacteria is one of the risk factors involved in producing this very complex disease called ALS.

Discussion Points

Dr. Mitsumoto asked for clarification regarding whether the study is case-controlled or just random controls.

Dr. Bradley clarified that they have two populations of controls, one of which is random population-based controls from the entire state, and the other of which is a clinic-based control group that is known as the "recall bias" control group. Both of those groups will be compared with the ALS population group and are matched for age, sex, smoking, et cetera.

Dr. Brooks observed that this is serendipitous. Ralph Bunche at the University of Cincinnati conducted a county-level study of Ohio in terms of exposures and ALS several years ago. He asked whether Dr. Bradley's data were latitude/longitude coded.

Dr. Bradley replied that the IRB at the Cleveland Clinic would not allow them to have the actual GPS latitude/longitude coordinates. They did allow dithering, which is computer shuffling of latitude/longitude coordinates, which prevents absolute identification of individuals but nevertheless provides enough geographical specificity for distance exposure quantitation. They are using kernel density estimation (KDE).

Identification and Validation of ALS Environmental Risk Factors

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Dr. Goutman emphasized that the partnership between the University of Michigan and the Registry has been tremendous not only in terms of grant funding, but also in terms of recruitment through the use of the notification tool. At the University of Michigan, they believe that in order to have a comprehensive ALS research program, they need to take information they gather from the clinic, use the medical record to allow them to collect data, understand what the environmental risks are, understand how genomics and epigenomics influence disease and how that can link back to any imaging data, and how the immune system plays a role in all of this. This is the approach they are taking, and the two aspects he and Dr. Feldman discussed during this session pertained to their work on the environment and microRNA (miRNA).

In terms of the project background, the investigators were curious as to why Michigan has a higher burden of ALS compared to other states. Like Ohio, Michigan is a more highly industrialized area with perhaps more pollution or the risk of having more pollution in the environment. The investigators are aiming to understand the gene-time-environment hypothesis and interaction, in which it is understood that everyone has some genetic burden for disease and that a sufficient amount of environmental exposures may tip someone over the edge into a self-perpetuating process or a disease such as ALS. To that end, the study goals are to:

- Identify potential environmental risk factors associated with ALS, including environmental and occupational exposures to toxins as well as physical exertion

- Utilize measurements of persistent environmental pollutants to evaluate exposures based on questionnaire and environmental assessments

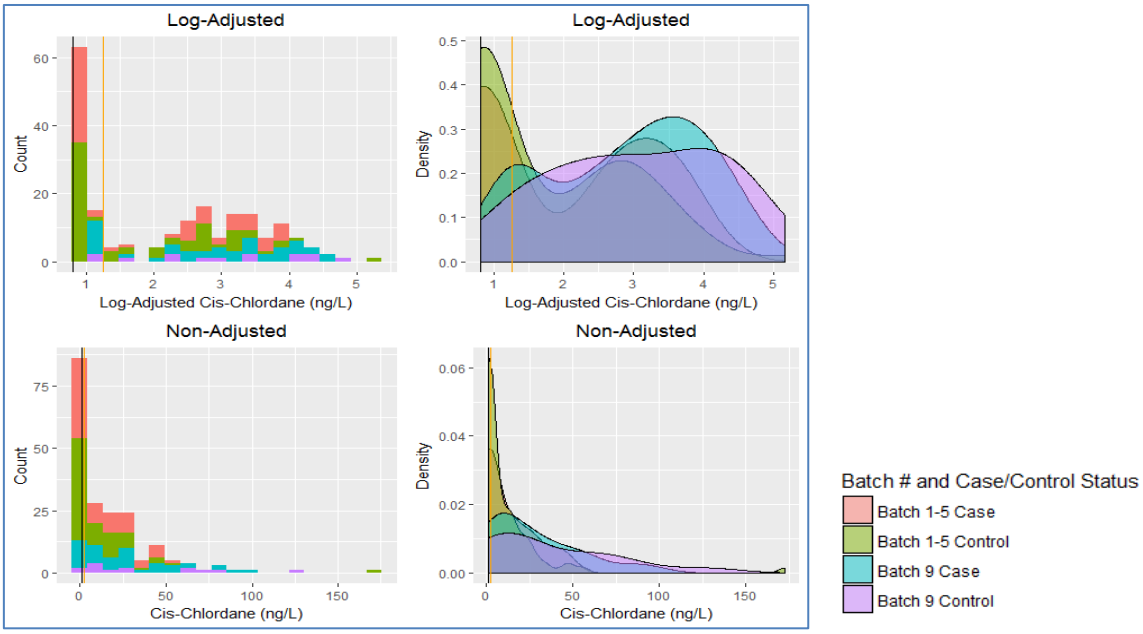
The University of Michigan has a very robust biorepository comprised of individuals with ALS and controls. The repository includes demographic data, clinical data, biofluid samples, fibroblasts, and autopsy tissue (brain, spinal cord, teeth). They have published on this in the last couple of years. The demographics for the cases and controls are similar in terms of the numbers of individuals, gender, age, and non-smokers. There is some difference between the cases and controls in terms of the distance people live from the University of Michigan, which is a challenge in terms of generating a good control population.

The investigators are very interested in understanding exposure window and whether there are periods of unique disease susceptibility that make one likely to develop disease, and at what period of time that occurs prior to the onset of disease. They separated this out into <10 years, 10 to 30 years, and >30 years. Two of the risk factors they have observed include working in the Armed Forces and reported occupational exposures to pesticides. Interestingly, some of the protective factors include a greater than college degree; occupational exposure to lead in the entire window, but not necessarily in the individual exposure windows; and working in healthcare and a combination of food services.

The next major component of this project is to measure the concentrations of organochlorine pesticides in this case in the blood of individuals with ALS and control subjects. Measuring these pollutants is a challenge, not only from the perspective of the measurement methods, but also in terms of understanding how to interpret the data in the overall context of what it means. Everyone has a likelihood of being exposed to multiple pollutants and toxins, so the goal is to try to understand which of these is likely to contribute to disease susceptibility and how they may influence the progression of disease. Univariate modeling shows a number of organochlorine pesticides and how they may increase one's odds of having ALS. When all of these pesticides are measured as a whole and some of the chemicals being measured, the investigators are starting to get some idea of how perhaps these chemicals may work to increase one's odds of having ALS. They continue to work on this to understand how this may influence ALS disease susceptibility.

One of the other aspects the investigators considered for all of the work that they are doing regards concordance; that is, when someone reports an exposure to a chemical and whether this actually appears in samples of blood. They have observed modest correlations between storage of pesticides and lawn care products in the garage in terms of the organochlorine pesticides being measured. There is more work to do in terms of understanding how this looks when some of the newer samples come online for analysis, but this may have some influence on the way questionnaires are designed and analyzed in the future.

Since presenting last year, 144 cases and controls have been added. The existing population was used as a discovery cohort, and now the investigators are interested in trying to validate these with separate group of individuals. That will allow them to assess some of the data they have already published to understand disease progression and how the measurements they are seeing align with survey data. Here is an example of cis-Chlordane, one of the pesticides of interest for the investigators:

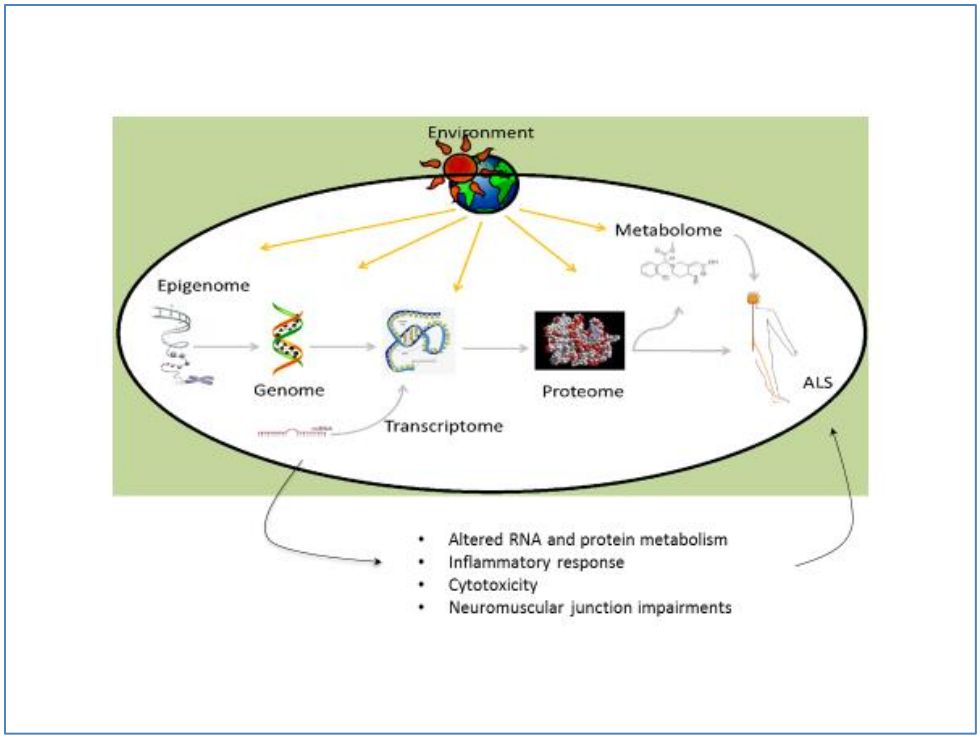


Batches 1-5, which are the pink and green, were the initially reported pesticides. Batch 9, which are the turquois and violet, overlap. So, they are seeing fairly good concentration consistencies from batch to batch. There are some challenges in terms of understanding how the concentration differ from group to group.

Dr. Feldman noted that their CDC funding ended the previous day for the study in which they examined occupational exposure within their patient cohort and via a survey, and then correlated those exposures to log measurements of the patients. With this funding, they also established a robust repository that has many other patients biofluids. As an adjunct study to the CDC-funded study that Dr. Goutman presented, they were able to obtain philanthropic funding to begin to examine other aspects of the exposure. That is, from conception to death, individuals are clearly exposed to chemical agents, biological agents, radiation, psychosocial components, and physical activity. In the gene-time-environment hypothesis, how does that influence disease progression?

Their research group has been very interested in what is known as the epigenome. Everyone is born with one set of genes, but everything individuals do (breathing the air, having a cup of coffee, being exposed to environmental pollutants, et cetera) changes the genetic make-up. That is, genes can be modified by daily activities from birth until death. Exactly how that impacts the onset and progression of ALS is of great interest to this group. There are many ways that one's genome can be changed.

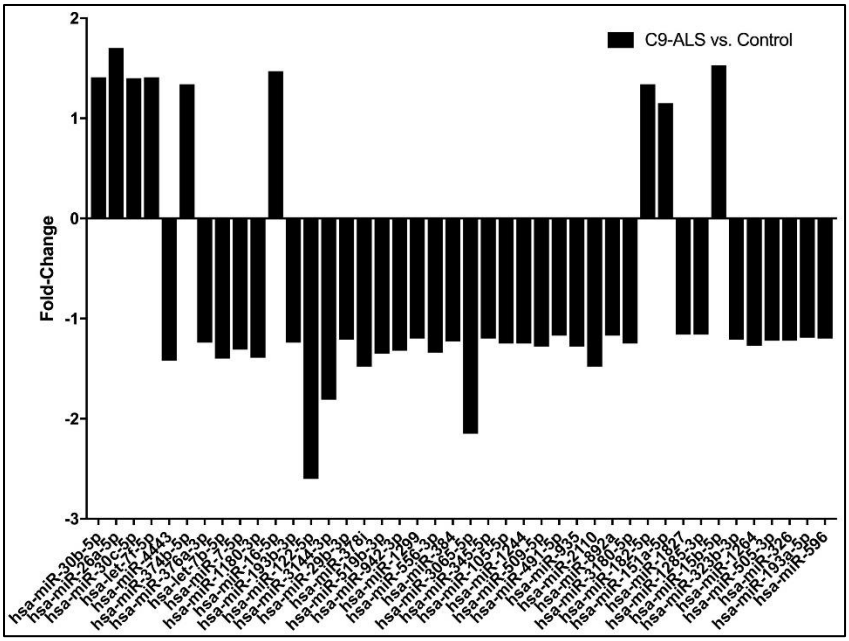
During this session, Dr. Feldman discussed one way known as an epigenome change by miRNAs depicted in the following graphic:



miRNAs are very small non-coding RNAs. Each person has about 1000 miRNAs circulating in the bloodstream. miRNAs bind to RNA and cause it to be silent, so they are known as gene silencers. If RNA is silenced, it cannot produce the protein it usually produces. In very simplified terms, the more miRNAs one has, the more RNAs are silenced and less proteins of certain classes are made. The investigators were very interested in understanding how the environment might affect the miRNAs that are circulating among everyone and how that could correlate with disease progression in ALS.

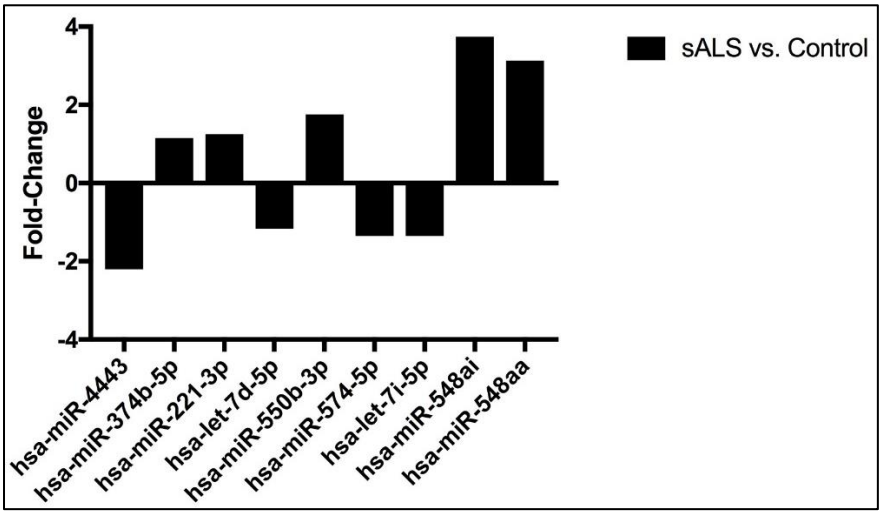
The objective of this ancillary study was to identify ALS-specific miRNA as candidates for diagnostic tools and measurements of disease progression. The investigators hypothesized that they could find disease-specific signatures that differentially express miRNA that would exist in ALS. One of the reasons they are so interested in this is not only because they think miRNAs could serve as novel biomarkers, but also miRNAs can be targeted and are druggable. There are three clinical trials in cancer in which miRNAs are being targeted with what look like very salutary benefits in terms of disease progression. Not only could miRNAs serve as a biomarker, but they could also be therapeutic targets.

The experimental workflow is very simple. Samples that were collected as part of the biorepository for the CDC-funded study in parallel underwent miRNA profiling and the results were separately verified. In terms of the data, this has been done on spinal cord, brain, fibroblast, cultures, skin samples, blood, and plasma. Comparing blood from patients with familial ALS compared to age/gender matched controls, there is a long list of many interesting miRNAs as depicted in the following graphic:



What is important to note is that most of the miRNAs are decreased in ALS. That means that that RNA is not repressed or silenced and is free to make proteins. The proteins being made when miRNAs are not repressed are primarily proteins that promote inflammation, changes in muscle functions, and changes in cell death properties.

Interestingly in sporadic ALS, this is about 50-50. Some of these involved in inflammation are decreased, while there is an increase in some of the miRNAs that actually promote cellular injury:



This is very interesting and helps to understand not only disease causation and identification of important pathways, but also hopefully identification of biomarkers and druggable targets.

In summary, the investigators have examined miRNA in blood, plasma, fibroblasts, spinal cord and brain and some of this work has been published. They have found that there is a clear differential regulation of miRNAs in ALS, and these miRNAs clearly are involved in neurodegeneration, skeletal muscle differentiation in terms of how muscle normally functions, and inflammation and stress-induced responses. The investigators are very excited and are grateful to CDC. Because of the establishment of the initial grant and the biorepository to study the environmental factors, they have now been able to perform this miRNA work. They are hoping to continue this work to examine and compare specific environmental exposures from patients with their specific miRNA profiles.

In terms of future directions, Drs. Feldman and Goutman think these miRNAs can serve as candidates for future ALS biomarker testing. They want to profile samples from the cohort of the 144 additional patients for whom they just finished entering as part of the CDC contract, and then as a correlation of the environmental scores and dysregulation of circulating miRNAs. These data offer new pathways that are implicated in ALS pathogenesis. They are also very excited that miRNAs provide druggable targets.

In conclusion, there are clear reported exposures to pesticides that are associated with ALS. There is a 5-fold greater odds ratio that a patient with ALS has been exposed to pesticides than an age/gender matched control. That is just an association and is not causation, but that is a fairly robust finding. Measured organochlorine pesticides are clearly associated with ALS. Collectively, the investigators feel that their data continues to support the idea that environmental toxic exposures play a role in this disorder. She emphasized that their CDC funding had been instrumental at the University of Michigan to boost and continue their interest, efforts, and understanding of ALS pathogenesis. She also announced that Dr. Goutman received a grant on June 1, 2017 from NIH/NIEHS to support his salary for the next 5 years to continue to do this important work.

Discussion Points

Dr. Wright asked what the key inflammatory mediators are that they find upregulated correlated with the downregulation of the specific miRNAs, if there were any changes in NF-kappaB, and if there were changes or mitigating effects related to dietary intake that would change or offset the inflammatory response pathways.

Dr. Feldman clarified that these are pathways and it is important to remember that these miRNAs control specific genes involved in inflammatory pathways. Again, this is association and they need to show causation. They find some very interesting regulation of the interferons 4 and 10 in particular. There is also interesting co-regulation of interleukin. Interestingly, there were no changes in NF-kappaB. Though they thought that would be part of the story, so far it is not. They do not have any dietary intake data, though it is an excellent question and one that needs to be explored in ALS. They have a paper in press in the *Journal of the American Medical Association* (*JAMA*) *Neurology* that examines particular subpopulations of inflammatory cells in ALS, which is funded by CReATe.

Dr. Stommel observed that the fact that pesticides are lipid-soluble and persist for long periods of time is scary in itself, knowing that farmers are spraying fields on a yearly or bi-yearly basis and most households have pesticides such as Raid®. With that in mind, he requested further information about exposures and the idea of persistence.

Dr. Goutman replied that essentially all of the pesticides he discussed have since been banned. However, they do persist in the environment for decades and hundreds of years. This creates an opportunity to be constantly exposed to them, though that exposure is hopefully decreasing over time. The half-lives of the newer pesticides and chemicals are not as long so they are trickier to measure, but certainly may have detrimental biological effects. This is why this risk factor is believed to be modifiable. If there are areas of pollution or toxins in a state or near a lake, it is possible that clean-up efforts could lower one's likelihood of developing ALS or other neurodegenerative diseases.

Dr. Mitsumoto requested clarification about who the controls are.

Dr. Goutman explained that they recruit controls through the University of Michigan outreach programs for individuals interested in participating medical research.

Dr. Feldman added that this is a longstanding, very robust program at the University of Michigan that reaches the entire state. Individuals enter the outreach program, click the studies that interest them, and are then contacted and enrolled. Of note, the University of Michigan is now called Michigan Medicine.

Dr. Finger found this to be incredibly promising, and stressed that anything that suggests targets is exciting from his perspective. He requested clarification with regard to whether the collections are done in tandem with the ALS Biorepository, and if it is separate whether if it was begun now they could have leveraged that resource instead of collecting their own samples.

Dr. Feldman responded that they began collecting biorepository samples prior to their CDC funding in attempts to obtain funding from the DoD for a very similar study. They were not successful in acquiring DoD funding, so the biorepository was limping along until they received CDC funding. That allowed them to collect the samples Dr. Goutman discussed. They now have over 380 ALS samples, over 200 control samples, and 60 autopsies because of the CDC funding. That also allowed them to have biofluids to perform the ancillary work she discussed that was funded with philanthropy. The partnership between federal and philanthropic funding is very important. They are not yet connected to the ALS Biorepository. They are discussing whether it would be feasible to share specimens, particularly autopsy specimens, with the ALS Biorepository. Both parties are very interested in doing this, but it is a matter of logistics.

Dr. Goutman added that one important aspect in terms of the biorepository is that exposures and measurements change over time. One of the benefits of the Michigan biorepository is that they have longitudinal samples. As they acquire more funding, they would like to examine how these exposures change over time. That is a slight difference between how the Michigan biorepository operates and the National ALS Biorepository. The other difference is that essentially, all of the participants in the Michigan repository are seen by Dr. Feldman or himself, so they have longitudinal clinical data to be able to correlate to what they are seeing in the biofluids. What is really important is that given the scope of the work that they are doing in Michigan, which is a limited population compared to all individuals with ALS across the country, is that they can add some very important context to the National ALS Biorepository and the Registry. If they can understand what they are seeing in a small population that is easier to follow, that can provide some great insight into what is being seen in the national sample. That is one of the goals Michigan hopes to pursue.

Dr. Horton added that one of the goals of the National ALS Biorepository is to have a national representative sample, capturing as many biospecimens as possible from all 50 states moving forward.

Ms. Newhouse asked at what point do they take the work Michigan is doing and the work of the National ALS Biorepository and look for a relationship between the two, knowing in particular that Michigan also has a huge amount of the latter.

Dr. Feldman noted that the evening before, Ohio and Michigan had a great dinner together during which they spoke about what they would like to do in the future. She requested that Dr. Bradley describe what they are discussing.

Dr. Bradley indicated that they have been speaking for about 3 to 4 years about collaborating. If CDC, perhaps through a new grant process, might be able to sponsor some of this consortium interaction, it would enable them to be able to harmonize their clinical questionnaires and examine the existing databases of biosamples.

Ms. Newhouse requested that they keep the ALS Association in mind as they are going through this process. Thinking about when pesticides came out and the algae studies going back at least to WWII, she suggested they figure how to tie what is being observed with the DoD and veterans into this as well. She wondered whether they would see less ALS in people who grew up pre-pesticides versus what is being observed now, and if there is any correlation.

Dr. Feldman responded that whether there is less ALS in those growing up pre-pesticides is a great question, they cannot answer it, particularly for pesticides. However, they have some insight in terms of metals and why they collect teeth.

Dr. Goutman said that they are interested in susceptibility windows. Certainly, they can only go back so far when looking at things like pesticides and reported exposures. Getting at what Dr. Bradley was discussing earlier, some satellite and remote environmental sensing data can go back even further. Teeth offer a window into early childhood exposures to metals within the first 15 years of life, so they are in the process of finalizing some data that he thinks are going to be very exciting in helping to understand how early childhood exposures to metals increase one's likelihood or odds of having ALS. They can even look at up to 10 to 14 metals and how the absorption of metals changes over those 15 years, and the combination of those metals and how they drive ALS risk. This is very interesting and needs to be expanded.

Ms. Webb said that as a person who grew up in Toledo, Ohio one mile away from the border of Michigan, she stressed that harmonization is very important. Regarding controls, family members really want to participate. She asked what Dr. Goutman's and Dr. Feldman's thoughts were on inclusion of family members as controls.

Dr. Goutman emphasized that this is not easy in a case-control study. They have excluded family members. Depending upon the hypothesis and design of a study, the control population may differ. Family members, siblings especially, are likely to have similar environmental exposures during early childhood and as they are growing up. That may be an experimental question in terms of understanding how things differ regarding genetics. But if trying to understand differences in environmental exposures, it may not be suitable to include people who have been living together because their exposures may overlap. They have not included individuals who have a family history of ALS or other neurodegenerative diseases, but certainly there is a significant need to develop more robust ways of collecting groups of controls to help

understand ALS and other neurodegenerative diseases. They have not been recruiting spouses or significant others as controls for this study.

Dr. Feldman added that they are conducting a microbiome study and are changing their IRB in order to recruit family members.

Dr. Nelson pointed out that if the cases are coming from throughout Michigan and those referred to the center and controls are from the local University Michigan pool, they would expect to see a positive association with pesticide because the people from the more distant rural areas are more over-represented among cases. The inverse association observed with lead could be due to the people in the more industrial regions being more exposed to metals. That makes it look protective because those controls are over-represented in the samples.

Regarding the inverse association, Dr. Goutman clarified that this was the whole exposure window and the individual exposure windows did not show that association with lead. Ann Arbor is an interesting area. One can drive 5 minutes and be in a highly agricultural area or drive another 5 minutes and be in more of an industrial area. Because it is a limitation and controls are so important, they did perform sensitivity analyses. They looked at smaller groups of populations and excluded people who lived further way. They saw similar directionality of effects, but more work needs to be done.

Dr. Feldman added that a reviewer asked them the same questions, so they performed an extensive set of sensitivity analyses.

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

Marie Ryan, MD
Trinity College
Dublin, Ireland

Dr. Ryan presented on behalf of Dr. Orla Hardiman from Trinity College, who was unable to attend in person but joined by teleconference for this session.

Very little is known about the epidemiology of ALS in South America. A systematic review was done in 2013, but little has changed since that time. In comparison to the amount of studies and breadth and knowledge of ALS epidemiology in Europe, there is very little known for South America. That said, even though 80% of studies in this review were of European extraction, there is still some evidence that ancestral knowledge may be important in the incidence and prevalence of ALS. This is important to the US because the US is classically and currently described as a nation of immigrants. Ideally, it would be preferable to conduct the study in the US. However, as alluded to by some of the panelists earlier, while the ALS Registry is an excellent resource and is excellent at capturing the majority of the prevalent cases in the US, it does have some limitations in ascertaining some cases, particularly minority cases. That is probably a result of the underlying US healthcare structure. Therefore, the investigators decided to take the study to Latin America.

At present, they are able to say that the incidence and prevalence of ALS may not be uniform as was demonstrated in the systematic review. While this may be due to differences in methodologies used in the studies, other things that should be considered as possibilities include genetics, environmental exposures, and gene-environment interactions. In terms of the current genetic evidence, everyone is aware that the C9orf72 gene is a common mutation causing ALS in European populations. The C9orf72 gene is also present in Asian populations, albeit at a much lower incidence rate. What does this mean?

The investigators would hypothesize that part of the reason for the heterogeneity in incidence and phenotype of ALS may relate to population genetics and oligogenic inheritance. A combination of susceptibility genes may occur with greater frequency than expected in ALS. This would predict lower rates of ALS in admixed populations. In homogenous populations, it would be expected that there would be a higher risk of shared at-risk genes, combinations of which would increase the risk of developing ALS. Conversely, in admixed populations, there would be less shared at-risk genes and thus lower rates of ALS would be predicted.

Studies conducted in the US by McGuire and Annegers have shown that there is a difference in incidence rates stratified by ethnicity, and that there is an apparent or real lower incidence rate in Hispanic populations. Interestingly, for Texas, the overall incidence rate is lower than would be expected in the European non-Hispanic white population for males of 1.4 (1.0-1.9) and females of 1.3 (0.9-1.7). Rates in European populations are typically between 2.6 to 3/100,000. This has been backed up by mortality studies, which have clearly shown some evidence as far as stratification by ethnicity. In terms of ethnicity as a possible risk factor in ALS, all that can be said at present is that the available data are imperfect. The investigators feel that the incidence of ALS is probably not uniform outside of Caucasian populations. They hypothesize that admixed populations may have reduced frequency of ALS.

For this reason, the investigators took their study to Latin America. One reason for doing this is that Hispanics represent the largest minority in the US and this continues to grow. By clinically characterizing the disease and determining the incidence, prevalence, and clinical outcomes in this population will have a direct impact on healthcare planning in the US. They chose 3 countries to study: Cuba, Chile, and Uruguay. Chile is a country with an admixed population with a background of Spanish and local South American ancestry. Uruguay is a country of predominantly European ancestry, while Cuba is admixed with equal parts European ancestry and African and Native American ancestry. These countries were chosen because there already are some data on these populations. A population-based mortality study from Cuba by Zaldivar showed reduced ALS rates in admixed populations. There are also population-based mortality studies in Chile (Valenzuela) and a longitudinal and incidence and prevalence study in Uruguay (Vazques). The other advantage of these countries is that they can answer more questions than one. For example, Chile and Uruguay are in the same latitude but have different population structures. In contrast, Cuba is a country of a different latitude and different population structure.

At present, to answer all the questions of interest there are insufficient data for analysis. For example, it is not possible to state what the true population-based frequencies are, because they are not adjusted for population structure. Phenotypes are poorly characterized, the frequency of cognitive and behavioral impairment is unknown, and the genetic signature in these populations is not characterized as of yet. So, the Latin American Epidemiology Network of ALS (LAENALS) came to be. This is in conjunction with three teams of researchers undertaking population-based studies in the countries outlined earlier. The hope is to achieve a standard clinical evaluation, ALSFRS, and appropriate neuropsychological batteries. They are

also collecting family history studies, exposure studies, regular follow-up for survival, and DNA collection.

In terms of the first study aim, which was to determine incidence and clinical phenotype of ALS in three genetically distinct Latin American populations, investigators and sub-investigators have been trained and a Latin American database has been established. In terms of deliverables, training of a South American network for standardized case ascertainment representing a population of approximately 33 million people has been achieved, and the euroMOTOR database has been adopted to allow data collection from Chile, Cuba, and Uruguay. The second aim is to establish the quantitative exposome in population-based cohorts from South America and the Caribbean, and identify environmental risk in three Hispanic populations of different ancestral origin and to compare those with risks in European populations using standardized methodologies. In terms of the deliverables for Aim 2, training, standardization, translation and validation of job exposure matrix-based (JEM) questionnaires has been achieved. In addition, the automated data-entry database has been constructed. The comparator populations euroMOTOR study was completed in 2016 and clinical, epidemiological, exposomic, and genetic information have been collected on over 15,000 ALS patients and 3000 controls.

A kickoff meeting was convened in Chile on October 19-20, 2016. While the CDC grant was awarded to Trinity College in April 2016, they received review comments in October 2016 that were rebutted in December 2016 and final approval was received in February 2017. In the meantime, in summer 2016, the final review of data in the euroMOTOR study was ongoing. Based on this, some adjustments were recommended to the euroMOTOR questionnaires, particularly the sections on alcohol consumption, smoking, and hormone exposure. These were subsequently translated to Latin American Spanish. During the kickoff meeting in Chile, they went through a line-by-line review of the translated questionnaires to ensure that nothing was off in the translation. Subsequently, the questionnaires had to be further adjusted to ensure that they were culturally appropriate. For example, in the euroMOTOR study, they were not collecting data routinely on cigar usage, but this was bound to be something that was relevant to the Cuban population.

During the meeting in Chile, everyone thought it was important to ensure harmonization of clinical and demographic evaluations. Therefore, standardized operating procedures (SOPs) were developed for the clinical evaluation, family history collection, and exposures. The SOPs were translated into Latin American Spanish, and were then back-translated into English for accuracy before they were finally disseminated in February 2017. The investigators also had to acquire ethics approvals for each individual country, as well as overarching ethics approval in February 2017. All of this took quite a bit of time and beyond that, there was the issue of developing the consortium agreement. The draft agreement was completed and translated into Latin American Spanish in March 2017, and all of the signatures were gathered between April 2017 and July 2017. Funding transfers will be made in August 2017. Field work is due to begin September 1, 2017.

In the meantime, they have provisional pilot data. In Chile, the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) has been completed for 10 ALS patients to test the questionnaires and train the neurologists and psychologists in the usage of these tools. Pilot data was collected from a clinic in Havana, Cuba; ALS specialists have been recruited in other regions; field worker training that was scheduled in May 2017 was deferred until September 2017; the research team has been recruited; additional training is scheduled for the fourth quarter of 2017; and 9 patients were tested using ECAS. The most interesting results are some

genetic data from Cuba of known genes, which show a relatively low frequency of C9orf72 mutation and absence of the SOD-1 mutation. In Uruguay, staff have been identified and training is underway. Data Collection is to commence immediately after funds are drawn down. Additional training is scheduled for the fourth quarter of 2017.

Some of the barriers have been the logistics of contract negotiations across 5 countries and 2 continents, though these have now been resolved; the logistics of drawing down funding, also now resolved; and delays in the timelines, resulting in deferral of the start time to September 1, 2017. However, everything is now in place and they are ready to begin at that time.

Discussion Points

Dr. Mitsumoto asked whether Brazil is included in the study. He noted that in Japan, C9orf72 is rare. Portuguese people came there in early 1400, so that gene came from Portuguese populations. The Portuguese moved to Brazil, so he supposes Brazilian C9orf72 must be very low and it would be interesting to assess Brazil as well.

Dr. Ryan replied that Brazil is not included at this time, but it is possible that the study will be expanded at some point. She agreed that it would be interesting to compare to the other countries.

Dr. Stommel said he thought that Guadalupe, which is not very far from Cuba, has a very high incidence of ALS.

Dr. Benatar requested information about the strategy for case ascertainment given the paucity of multidisciplinary clinics in these countries.

Dr. Ryan responded that the investigators have worked with the Cuban team to try to build a multidisciplinary team, but it is an issue. At this time, each patient is registered with a family doctor in Cuba, who is then supported by a polyclinic, which is supported by a regional hospital. All patients who are diagnosed with ALS go through their family doctor, and receive the formal diagnosis via the neurologist. The data are collected by the Ministry of Health (MOH). In terms of the other countries, 80% of the Chile population are in the public health system and the other 15% are in the private healthcare system. The MOH collects some data there as well. Uruguay is collecting data from 19 regions using a similar methodology to the study she described earlier. There is a possibility that every patient will not be captured in these countries, but the hope is that they will capture the majority of them.

Dr. Benatar asked whether that meant that the investigators are going to the MOHs to identify people, and how they are reaching back out to get in touch and acquire permission to contact people. The flow of the logistics was not entirely clear.

Dr. Ryan responded that some of the patients come in directly through the research collaborators' clinics, and they are approaching the MOHs to search to determine whether there are any other patients with ALS. Most patients have been referred to a neurologist in the country, and the investigators are trying to link all of the neurologists in the country to try to ascertain any patients going through them. A check is then done through the MOHs to ensure that no one is missed and give the investigators an idea of how well they are doing in terms of data collection.

Because ethnicity/ethnic heritage is such an important variable and because these countries were settled centuries ago, it was not clear to Dr. Factor-Litvak how the investigators would assess ethnic background, especially since there is likely to have been a lot of intermarriage and gene mixing in the population. There are genetic markers of ethnicity.

Dr. Ryan replied that a lot of the studies thus far have been used to determine ethnicity, but there are limitations with that. For example, in Cuba people report as being white, mixed, or black based upon skin color. About 86% classify themselves as white and of European origin, 6% classify themselves as black and of African origin, and about 20% of those who classify themselves as mixed are of African origin. The investigators are using a combination of self-reported measures and will correlate this with the genetics as well.

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

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Dr. Mitsumoto reminded everyone that ALS COSMOS and ARREST ALS are both cohort studies without appropriate controls. The purpose of these studies is to investigate the relationship between oxidative stress (a summation of environmental exposures, dietary factors, and psychological stress) and disease progression/survival. To determine if any risks or factors are associated with the disease (etiology), it is necessary to have appropriate controls to compare with ALS cases. For this reason, the investigators proposed to conduct ARREST ALS control studies nested in the National ALS Registry to evaluate environmental risks. For patients who register for ARREST ALS, patient siblings and population-based controls will be utilized to examine environmental and all other factors. There are 2 controls per patient who are matched by sex, age (± 5 years), residential area, and race/ethnicity. The information will control for environmental, dietary and psychological risk factors. The purpose of these studies is to examine the relationship between OS and disease progression. The key hypothesis is that more OS means more environmental risk, and these individuals may have faster disease progression and shorter survival.

In order to determine whether any risk factors are associated with disease, it is necessary to have appropriate controls to compare with ALS cases. This study has two types of controls as mentioned, population-based and sibling controls. The investigators asked RTI International to identify these control subjects. Sibling controls are included if the patient has willing and able siblings. Siblings of the same sex and of the closest age or the next closest age are considered first. If no same-sex siblings are available, the sibling of a different sex that is of the closest age will be selected. The investigators believe that disease could begin as early as gestational age. This information would provide control data for environmental and health risks at early developmental ages.

In terms of the status of the ARREST Control Study, confidentiality and business agreements were finalized in Year 1 between Columbia University and RTI International, IRB approval was obtained for RTI International's involvement in the research study, and IRB approval was obtained to reconsent patients already in ARREST ALS. Given that when ARREST ALS was begun, there was no plan to have a control arm, which meant that reconsent was necessary. It

was a time-consuming process to obtain reconsent from subjects and begin to consent controls. The agreement between the Columbia University and RTI International IRB approval seemed impossible in terms of agreeing on patient confidentiality. This took 9 to 10 months to achieve and get the agreement signed, which substantially delayed identification of the control subjects. Recruitment of sibling controls commenced in November 2016, and recruitment of population-based controls commenced in April 2017. Thus far, 29 siblings and 7 population-based controls have been recruited.

In terms of critical assessment of the project, there were administrative delays with setting up agreements between Columbia University and RTI and reconsenting existing ARREST ALS patients to allow for control recruitment as mentioned. RTI-identified control participants are sometimes not perfect candidates. For example, there were unrecognized diseases present in candidates or their families; a lack of interest in ALS and/or medical research even with compensation; and difficulty connecting with controls consistently (e.g., at work, traveling, et cetera). Approximately 1/3 of controls are not perfect, so RTI had to be asked to identify more controls. The ultimate goal is to enroll 200 controls. Dr. Mitsumoto emphasized the importance of identifying the correct controls, which is critical to conduct meaningful epidemiological studies.

Regarding plans for next year and future considerations, the investigators will continue to maximize recruitment for the ARREST ALS and ARREST-Control studies. The case-control designs appear to be the best design for identifying environmental risks at this point. In the future, a genome/genome sequencing study may be able to identify specific "risk genes" for environmental exposures. For genetic development in the future, case-control studies are and will be essential in providing basic environmental risk information. This study is too small to provide clear clues, but hopefully future studies will be larger and more comprehensive. They hope to obtain more funding in the future, given that they have proven that this is a good way to identify environmental risk.

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

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Dr. Nelson presented an overview of a study supported by ATSDR that has the purpose of examining antecedent conditions and medications before the clinical recognition of ALS, and how they affect the influence of developing ALS. Several factors have been associated with ALS risk, including hyperlipidemia (statins), autoimmune diseases (immunosuppressants), diabetes (antidiabetic drugs), and cardiovascular conditions (ACE inhibitors). Diabetes has been shown to be inversely associated with ALS risk in that people with diabetes appear to have a lower incidence of ALS. It remains unclear whether people with ALS are more or less likely to have hyperlipidemia prior to diagnosis. The role of statins in influencing risk remains an open question. Previous studies have suggested that autoimmune diseases and/or treatment with immunosuppressants may be associated with ALS.

Therefore, Dr. Nelson and her colleagues decided to design a study in the Medicare population during the years 2007-2013 using an ambidirectional design to investigate the etiologic and prognostic factors in terms of what role these factors play. The primary research question is, "Do antecedent medical conditions or medications used to treat chronic medical conditions increase the risk of developing ALS and/or influence the length of survival after ALS diagnosis?" The specific aims of the study are as follows:

1. *Investigate the association between antecedent medical conditions and the risk of developing ALS.*

   We will determine whether diabetes, hyperlipidemia, cardiovascular or autoimmune disorders are associated with the risk of developing ALS.

2. *Investigate the association between medications used to treat antecedent medical conditions and the risk of ALS.*

   We will examine the association between several classes of medications (diabetic medications, lipid-lowering medications, immunosuppressants, ACE inhibitors) and the risk of developing ALS.

3. *Determine whether medical conditions or medications present at diagnosis of ALS adversely or positively affect survival with ALS.*

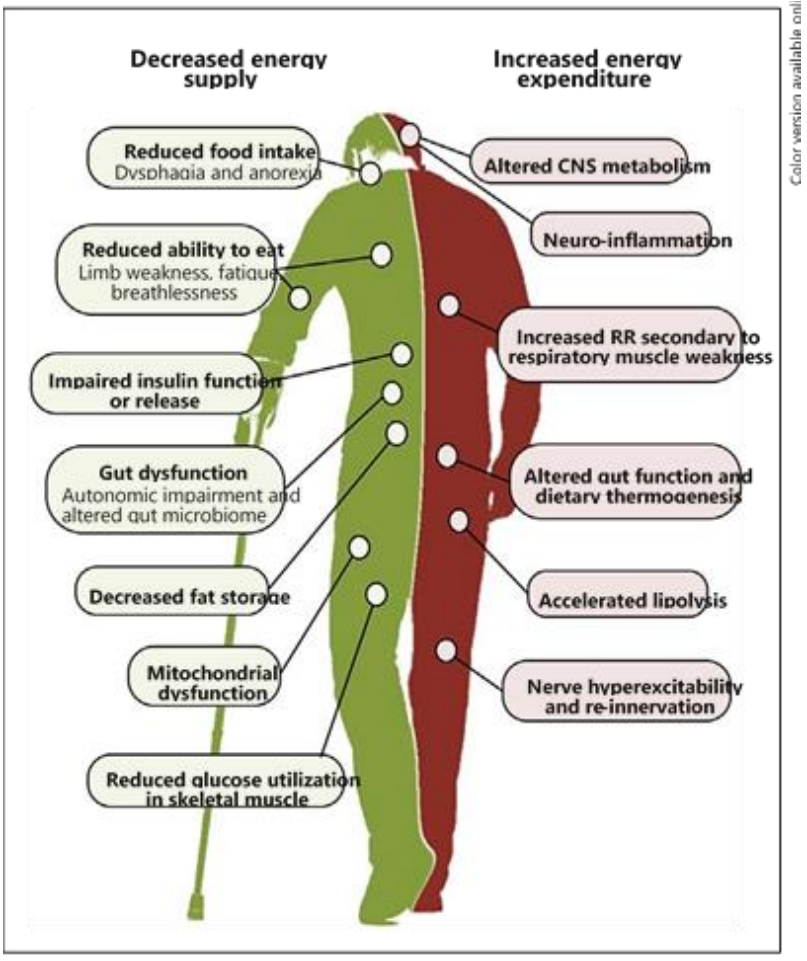
   We will test the hypothesis that the medical conditions in specific Aim #1 or the use of medications to treat those conditions, are associated with length of survival with ALS.

There have been two very influential and well-done studies recently showing an inverse association between diabetes and the risk of developing ALS. That means that people with diabetes seem to have a lower incidence of ALS. One study showed that the age of onset of ALS is about 4 years later for patients who have diabetes. A study from Denmark on which Dr. Marc Weisskopf was the Senior Investigator examined 3650 ALS cases and 100 times that number of controls (N=365,000) in cases ascertained from 1982-2009 in Denmark. An adjusted analysis was performed in which diabetes and obesity were adjusted for each other, so these are unconfounded by one another. The diabetes odds ratio is 0.61, remembering that an odds ratio of 1 means that there is no association between that factor and the risk of ALS. Thus, an odds ratio above 1.0 means that the factor increases the risk of ALS and an odds ratio below 1.0 indicates that it decreases the risk of ALS. The diabetes ratio of 0.61 indicates that having diabetes reduces the risk of ALS by about 40% and is highly statistically significant. The association with obesity was also in the inverse direction, but the confidence limits overlapped 1.0, so the finding for obesity was not statistically significant. When those two were in the model together, diabetes was most important.

Another study was conducted in Sweden around the same time for the years 1991-2010 using the national claims databases with associated diagnostic codes for individuals in their countries that are in a unified healthcare system. These investigators also found an inverse association between diabetes and the risk of ALS. The overall odds ratio was closer to 1.0 at 0.79, which might suggest that there is a 20% reduction in the risk of ALS, at least from this study's estimate. These investigators were careful to note that there was some heterogeneity about the past history of diabetes and what actually was associated with an inverse risk. When the insulin-dependent individuals who were diagnosed with diabetes before age 50 were removed, most of whom the authors expected had juvenile onset insulin-dependent diabetes that has

more of an autoimmune cause, that was associated with an increased risk of ALS with an odds ratio of 5.4. If this was stratified, the odds ratio of 0.79 gets even further away from 1.0 when those individuals that have an odds ratio of 5.4 are removed. That final risk estimate was very close to the Denmark risk estimate in terms of diabetes of presumed adult onset not autoimmune in nature.

There is a story emerging in that, while the studies are somewhat inconsistent, some studies have suggested that people who have increased vigorous physical activity are at possible increased risk of ALS. Those who have a lower body mass index (BMI) are at increased risk of ALS. It looks like people who do not have diabetes have an increased risk of ALS. This highlights the point made earlier that it is important to differentiate factors that occur before and after onset. In an interesting review performed by a group in Australia and a pictorial showing that there are many possible things that alter the energy balance in ALS after disease onset in terms of increased energy needs and decreased energy supply in patients:



It is very important to tease out an etiologic factor (something that increases the risk of developing ALS) from prognostic factors (those that are associated with the speed of progression once ALS is developed). As Dr. Benatar pointed out earlier, it could be that these are two different factors, which likely happens in many instances. But Dr. Nelson emphasized that it is also important to recognize that ALS is an insidious process and the underlying pathology has been occurring for some time prior to the clinical presentation of symptoms, so

factors that influence the risk of developing ALS may also influence the speed with which it progresses.

Dr. Nelson and colleagues used an ambidirectional study design in which the study is being conducted in the US Medicare population aged 65 years and above. In terms of the study design for Specific Aims 1 and 2, a case-control study will be conducted of incident ALS cases adapted from the National ALS Registry case definition criteria, nested within aged in Medicare cohort. This is a nationwide sample that is matched by age, sex, and geographic region. There is a ratio of 10 control subjects for every case. Also assessed are history of diabetes, hyperlipidemia, and autoimmune conditions and the medications used to treat those. Entry to the cohort occurs at the time of beneficiary's first visit to a clinical provider. The investigators will have to start at ALS onset with the 2500 cases and determine whether conditions present at that time actually affect the length of time the person survives with ALS. For Specific Aim 3, a retrospective cohort study will be conducted of incident ALS cases, followed until death or censoring (end of study). The Medicare data request included research-identifiable files from CMS as follows:

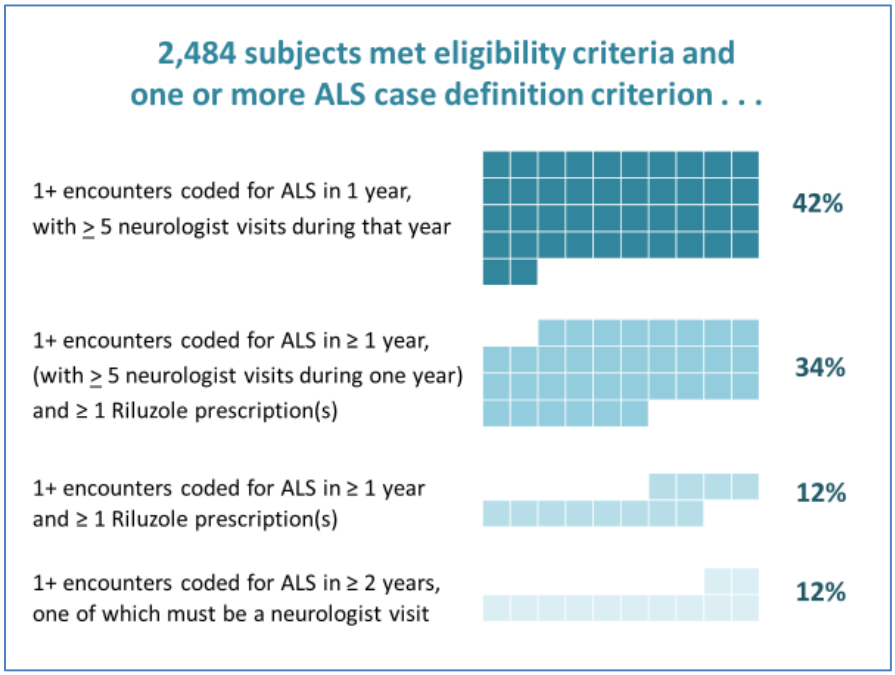
- Part A: Medicare Provider Analysis and Review (MedPAR) claims, including inpatient (hospital) services, skilled nursing facility care, hospice care, home health care services
- Part B: Supplementary medical insurance, including outpatient claims, carrier (physician/supplier) claims and services, DME
- Part D: Outpatient drug claims file (available from 2006 forward)
- Medicare Denominator File: Beneficiary demographic characteristics (age, sex, race, et cetera), date of death, program eligibility/enrolment dates

The investigators identified all *possible* ALS cases from CMS for the period 2006-2013, and determined who met case definition criteria using the National ALS Registry criteria applied to Medicare data. Individuals were required to have a minimum of two years of Medicare utilization data prior to the first diagnostic code for ALS or MND in order to have an adequate history with which to judge which conditions were preexisting. Those 8 years of data for which CMS provided anybody's records if they had one or more of these ALS-related codes resulted in 57 million individual records, which had to be reconstructed into datasets for analysis. These are claims data so they are the ICD-9 codes used for billing and procedure codes, so they constructed a longitudinal medical history record from those administrative data for each individual case or control just as the Sweden and Denmark investigators did. The following case definition criteria were applied:

- One or more encounters coded for ALS** in ≥ 1 year, and one or more prescriptions for Riluzole; ***or***
- One or more encounters* coded for ALS (ICD-9 335.20) in ≥ 2 years, one of which must be a neurologist visit; ***or***
- One or more encounters* coded for ALS (ICD-9 335.20) in 1 year, with five or more neurologist visits during that year.

*Adapted from National ALS Registry case definition criteria
**International Classification of Diseases, Ninth Revision, 335.20

This is a pictorial of the 2484 subjects who met the criteria:



In terms of the age and sex distribution of the cases, there were 1356 males and 1128 females. The earliest age of the cases was 67 years. The disadvantage of this study is the inability to study those younger than 65 years of age, because the only people in the Medicare data younger than age 65 are those who have end-stage renal disease or who have established disability by virtue of having ALS. While the investigators would like to include those people, they do not have appropriate controls for them.

It is important to be very careful when performing these types of analysis because ALS onset is not clear. It would be beneficial to know the pathological onset of ALS, but there is not an ability to know that. It is possible to know the first clinical recognition as reflected in these records, and they do want to look at antecedent history in order to exclude anything that occurred after the clinical recognition because that could not be a risk factor. The investigators had the date that each individual case first met the case definition criteria. There was often an earlier period where individuals had a number of codes for ALS or related MND, so they decided the best ability to date onset clinically would be to use the date of the first ALS, MND, or riluzole prescription. They decided further to allow another 1-year gap in order not to include the 1 year prior to the first clinical recognition from the consideration of antecedent history.

Dr. Nelson concluded that while they are in the middle of data analyses, data restructuring is a major challenge. It is very important to conduct these types of investigations because the age of onset of ALS or the age range affected is also an age when there are many chronic health conditions present in the underlying population, some of which may influence the risk of developing ALS either positively or negatively. It is especially intriguing that adult onset diabetes appears to be associated with a lower incidence of ALS, and it is very important to study this further and closely examine the medications that are used to treat diabetes and how they modify that risk. It is very difficult to conduct these types of studies. Every epidemiologic study presented in the last couple of days has challenges in terms of control selection and so forth. Although the control selection for this study is straightforward, incredible attention must

be given to detail in terms of the way the records are constructed in order to have exactly the same amount of time for cases and their matched controls for whom the clinical history is being captured so that there is not a difference in terms of the duration of the epic being characterized.

Discussion Points

Dr. Bradley noted that their study, which was much smaller than Dr. Nelson's, showed the relationship with prior chemotherapy. In that small study, they did not see an association with immunosuppressant agents or autoimmune diseases. He wondered whether Dr. Nelson's group would be able to examine that as well.

Dr. Nelson replied that they would be able to study that. A lot of chemotherapeutic agents are also immunosuppressants, so it will be important to parse that out.

Dr. Brooks asked what proportion of the subjects are on riluzole, and how they account for censoring.

Dr. Nelson responded that she did not believe they could go strictly by who met that criterion because they may have met the criterion one year and continued to receive riluzole. It appears that about 46% (34% + 12%) for certain are on riluzole, which is consistent with the 50% they observed in the VA and Kaiser data they analyzed. In terms of censoring, patients are followed as long as they are alive and are continuing to have utilization in Medicare or they passed away. Some sensitivity analyses will be performed based on using tracheostomy as an endpoint. Many studies have performed sensitivity analyses in which they allow survival up until tracheostomy, death, or censoring as the factor.

Dr. Benatar requested additional information about how they define or operationalize disease onset, and if anyone knew what the average delay is from diagnosis to someone going on Medicare. One could push the date back to try to get at the distinction between exposure before and after disease onset. He wondered about the national average of latency between symptom onset and diagnosis. If they knew, for example, that it took 6 months from diagnosis to get into Medicare, one could try to compute when disease onset really was.

Dr. Nelson responded that the only thing in the record are the diagnostic codes, so the only way they can do this is with the earliest presence of an ICD-9 code that is consistent with either ALS or one of the related MND that was probably in the differential diagnosis before they ended up having ALS. In terms of the average of latency between symptom onset and diagnosis, Medicare reflects the first actual submission of claims for a MND-related diagnosis. But Dr. Benatar was saying that a person could have related symptoms, be seeing a neurologist, and not actually have any indicator, so he would like to add those two together and exclude it from etiologic consideration. She asked the neurologists in the room whether they thought that excluding the 1-year period prior to the very first indication in the record is long enough. They are planning to perform analyses that look at Epic in order to exclude 2- and 3-year lags and still look at the same associations.

Dr. Benatar said he was not sure of the answer because the length of the pre-symptomatic phase is unknown, but it seems that one could safely reasonably add at least a year before a patient first appears in a record in terms of how long it takes people to get a diagnosis. He imagined that people who do not show up in Medicare while being evaluated and would seek Medicare coverage and be in a Medicare database after being diagnosed.

Dr. Nelson clarified that they require a full two years in the Medicare system before a patient can enter this cohort at all.

Dr. Factor-Litvak pointed out that there likely would be neurology claims for neurologists. Dr. Nelson said they could perform some analyses to determine whether there are other indicators even earlier that do not have associated diagnoses. They are including all incident cases who have two years in the system with no indication of ALS at all.

Dr. Kaye clarified that Dr. Nelson has excluded everybody who is only in Medicare by virtue of the fact that they have ALS.

Dr. Mitsumoto asked whether the investigators are separating congenital diabetes which is autoimmune from adult onset diabetes which is not. Diabetes has been noted in relation to ALS for more than 30 years, and he wondered if Dr. Nelson had any idea why diabetes is an ALS marker.

Dr. Nelson said they are going to do the best they can with these records, but that is one of the challenges. She does collaborative work with the Medical Director of Medicare who is looking at things like diabetes related to pancreatic cancer risk, and they have quite a bit of methodologic work to say how to best tease out what is juvenile onset insulin-dependent diabetes from the more usual adult-onset metabolic syndrome type diabetes. In terms of why diabetes is an ALS marker, an interesting study was conducted by the same group who conducted the Sweden study that had a longitudinal cohort of 600,000 people in Sweden from whom they drew blood at about age 45 on average. They were then able to retrospectively determine who developed ALS later. This is one of the few studies that had pre-morbid blood samples on average measured 14 years prior to diagnosis. They found the same thing. People who have elevated blood glucose 14 years on average prior to diagnosis have a lower risk of developing ALS. There is also the physical activity association that everyone is always puzzling about. People who are more physically active are going to be leaner and possibly have lower blood glucose levels, which may be associated with an increased risk of ALS. These are all possibly interrelated factors.

Next Steps: Recommendations/Strategies for Strengthening the Registry

Moderator:	**Wendy Kaye, PhD**	**Biorepository Representative**
Panelists:	**Paul Mehta, MD**	**ALS Registry Representative**
	Ed Tessaro	**Person Living with ALS**
	Hiroshi Matsumoto, MD, DSc	**Researcher**
	Sarah Kulke, MD	**Pharma Representative**
	Calaneet Balas, MBS, MS	**ALS Advocate**

Session Overview

Dr. Kaye explained that this was an experimental session during which they planned to have each panelist, representing his or her particular group, share their observations about how the Registry could be used to advance research and the future directions they would like to see.

In addition, the recommendations made throughout the meeting were captured. The plan during this session was to review them to determine whether anything was missed, needed to be

added, and/or there were gaps. They would then spend some time prioritizing the recommendations. The recommendations captured were categorized as follows:

Communication	
Recommendation	**Suggestions**
Create better messaging	Why is joining the Registry important Tell the story of opportunities through the Registry
Provide better feedback on data usage to advance research	Why the GUID is important
Provide readily accessible, easy to understand updates	
Provide information on how the Registry is using money	Create a graphic such as a pie chart showing the amounts spent on categories such as research
Overhaul the Registry website	Make it more eye-catching Make content less dense Have clear channels for patients vs researchers/physicians

Outreach	
Recommendation	**Suggestions**
Identify best practices for obtaining Registry participation	
Give states or clinics a grade on outreach recruitment	
Set goals for recruitment	Consider incentive for registration
Enhance neurologists' education about the Registry	Add Registry to neurology practice parameters for ALS
Enhance knowledge about using the Registry to help with recruitment	

Research	
Recommendation	**Suggestions**
Develop a consortium of researchers doing environmental epidemiologic studies	Identify overlapping data elements Identify overlapping sample types If possible, create a merged data set to increase power for analyses
Create a database of studies	Describe what was collected e.g., survey data, clinical data, biological samples
Evaluate the completion rate for individual Registry survey modules	Move surveys that are less likely to be completed to the end Develop strategies and outreach messages to increase completion

Panelist Observations

Dr. Mehta said they had heard a lot regarding recommendations and all of the research that the Registry funds and promotes. They would like to expand the opportunity for promotion of the Registry and collaboration with researchers in the future pending availability of funds. It was very important for ATSDR to hear feedback from participants over the last two days regarding how they can improve the Registry. There was a lot of discussion about outreach and ATSDR was taking notes and listening to what everyone was saying, especially the patients whose voices are very important.

Ms. Balas said it had been an interesting two days from the ALS advocacy perspective. Based on discussions during the meeting, a theme emerged regarding communication, clarity, and understanding to the advocacy organizations. The advocacy organizations agreed that if they can collaborate and ensure consistency in the communications they are all putting out together, the communication plan will be much stronger than them each having individual platforms. Additionally, there was significant conversation regarding value and making sure that people understand the value of the Registry. The ALS Association is working on a much larger platform with regard to patient preference, and have been speaking with Dr. Mehta and his colleagues regarding how they can leverage the Registry within that. That is another way to express value not only to the patients, but also to Congress. As they continue the conversation around communication and value, they will be able to leverage the entire Registry going forward.

Dr. Mitsumoto observed that there has been incredible progress since 2008, for which he complimented ATSDR. Nevertheless, they identified a number of problems. However, he believes those problems can be improved. In terms of what the investigators can do, not all ALS investigators have the same level of knowledge as those in the room and working on this regularly. Some investigators may know about the National ALS Registry, but nothing more. It is important to inform them and improve their knowledge. With that in mind, he proposed that the day before the next International NMD Symposium that ATSDR convene a 3-hour meeting with the neurologists in attendance. Drs. Horton and Mehta could present information about the Registry and the researchers could present their projects to show other ALS doctors what is being done. He also proposed that the ALS Association, MDA, and Les Turner ALS Foundation tell their clinic leaders to attend the meeting. Perhaps the pharmaceutical companies could fund the meeting space and lunch, given that the government cannot ask them to pay. It is imperative to improve the base knowledge about National ALS Registry enrollment.

Dr. Sarah Kulke thought the idea of such a meeting was a great idea. She thinks there are many researchers who have no idea how much research is underway with the Registry, and they may not realize the access there is to data. Knowing that and that they could access the data and use that to further the work they want to do would be very compelling. At the crux of it, it is those data that become so very valuable. She attended the meeting last year, and it was great to attend again and see the progress that has been made. In terms of the things that work really well, she was able to use the notification system as have others. This is a value ad that is working. The number of research projects discussed this year compared to last year and the depth and results of those projects this year compared to last were fantastic. Those things are really working. They heard that a lot of people would like to see the size of the Registry grow in terms of participants and surveys completed, and they heard from the patients that all patients do not understand why the Registry is valuable. Yet, those participating in the meeting had the opportunity to see the things that are really working. They heard again that a story would be really helpful in terms of helping patients understand how this is valuable. She could see all of

that coming together in a story being written about the benefits of notification service or the benefits of all of the research being done. That story could be fed through all different social media and be picked up by MDA, the ALS Association, the Les Turner ALS Foundation and other groups. In addition, she agreed that getting more physicians involved would go a very long way. She also agreed with establishing a goal, even if it is really small. Even if they do not achieve it, they can at least have had a goal and said where it went.

Ed Tessaro observed that the group of patients and their families in attendance certainly did not need anyone to summarize for them what they said. He thought Becky Kidd was right on the money with the idea of numerical goals, which Dr. Kulke just followed up on. He thought they must always be driven by the objective, and it is a great way to focus the mind. Stephen Finger's and Alan Alderman's comments about how complicated the forms are, such as spending 20 minutes trying to complete a module and only being 10% finished, must be addressed. That is daunting and in consideration of the patient community, the process probably needs to be more streamlined and easier to fill out in a shorter time. Many patients do not have the skills to do that, even if it is just keyboard or keypad skills. Alan Alderman's long history was very instructive. Rachel's Mama shared a good story and he got a lot of lessons out of that. He then summarized what he said he knew all of them were feeling at the moment, and that was gratitude because they were privileged to be there and not in a medical environment, which is daunting enough. They were there to think about the future and the people involved in the Registry all represent that. Honestly, of all of the diseases they could study, this has to be one of the most horrific. He expressed amazement that they had made it their life's work, or at least this part of their career's work, and he offered his heartfelt thanks for that. They have been talking about sharing biospecimens for three years, and they listened to the research updates during this meeting. One of the biggest issues that he saw with science from a layman's perspective is that they do not share well at all. When people say they have been talking about sharing for three years, that in itself is a disaster. How hard is it to share biospecimens. He said he realized that as human beings, everyone is tribal and gathers around themselves that which show them in the best way. He stressed that he knew this was human nature and he was not railing against that. However, there are so many pockets of groups doing the same thing others are doing. Does that information ever come together in the same place? It is great that there are that many hotspots where somebody might find the next breakthrough, but they seem to be duplicating tons of work. That has not been one of their objectives there, and he would love for them to see the ergonomics of bringing all of this together and speaking with one voice. He planned to spend time with Dr. Glass the next day and planned to ask him why he and Dr. Feldman do not have absolutely 100% sharing. They are co-researchers on the neural stem trial that he was a recipient of.

Dr. Kaye said that they ask that researchers return results to the Biorepository. They have all of the genetics data run by NIH, which is available to go with the samples so that someone does not have to rerun all of the genetics data. CDC has just run all heavy metals on all of the specimens on urine and blood, and those also will be available so that investigators do not have to rerun them. That will allow people to spend their funding on other research rather than doing the same thing over again. That is at least a step toward what Ed Tessaro asked for.

Walter Bradly emphasized that Ed Tessaro articulated exactly what people have been saying in ALS circles for many years. He fostered that by a somewhat innocent comment. ALS patients and patients in every neurological disease have always said that researchers are not talking to one another and they are not sharing data. Drs. Feldman, Goutman, and he have data which indeed they have been talking about sharing and amalgamating. It is not because they do not want to do it. There are two reasons, one of which is that they are not identical and trying to

meld them is an enormously difficult task. He suggested to Drs. Mehta and Kaye that perhaps ATSDR can fund the development of a consortium among the environmental-genetic collaboration, because they need help to take this step. They want to find a way for their data to talk together so that they can be amalgamated. He apologized if he left a sense that they do not talk together. They are in competition obviously, because they are looking for funds. But, in fact, they are not in competition otherwise because they all have the same passion as all of their ALS patients to find the answer for this awful disease.

Open Discussion

Dr. Kasarskis asked whether it is possible when a patient first enrolls that the first module they encounter is the demographics one, with the remainder presented randomly on an individual case-by-case basis. ATSDR has statisticians who know how to randomize. In addition, he said he likes to see things graphically and visually. In terms of their conversations about whether the Registry is growing, he has never seen a timeline graphic in any of the presentations that shows the cumulative enrollment into the Registry. These data do not have a shelf life and are not getting stale. While the information is in the *MMWR* paper, it would be nice to see enrollment year-by-year. That would help people see how their individual enrollment into the Registry helped build it. They also could put on the timeline when the data went out in terms of the number of requests from researchers. They could build a series of lines that would capture in one image exactly what the Registry has accomplished.

Dr. Kaye said that they have talked about randomizing the modules and it is theoretically possible, but one issue is the CDC firewall. In terms of Registry accomplishments, they have discussed placing a thermometer on each individual's dashboard in the Registry that would be filled in as surveys are completed as is done in giving campaigns, which would offer some encouragement.

Dr. Mehta added that they also have had preliminary discussions about putting the surveys into a more digitized app format. On a tablet, the surveys are somewhat cumbersome to navigate currently. It is complex to put the surveys in an app format so that they can be completed on a mobile phone, but there are plans to take the website into a responsive design meaning that people will be able to see it uniformly on their mobile phone or tablet. The survey themselves are still static and will not be responsive, but if people can do their banking on their phone, there is no reason why they should not be able to take a survey as well. It is still very sensitive information and has not been done before at CDC, but he has had discussions about whether they can do this in the future.

Ms. Balas stressed that the patient groups have been charged with recruiting, and there has been a lot of conversation about whether that is the end goal and it is not. The end goal is completing the surveys and collecting the data. However, the patient groups do not receive any data on completers. As they continue to train the field, it is unclear how to relate that information. Their clinics see patients on a fairly regular basis every 4 to 6 weeks and could continue to follow up with them if they knew the direction in which to push, but they need that information. It would be beneficial to have some type of general sense about registration and survey completion, even if it is by state or health district. They are asking people who have more than full time jobs who are driving around large states to encourage this activity. It would be very helpful with training to be as precise as possible.

Regarding the idea of data aggregation or connecting data, Dr. Berry pointed out that a lot of the challenges in getting people to answer the questionnaires on the Registry tie back to the fact that a lot of information is collected. However, it takes a long time to report that information. People with ALS who are part of this want to maximize that, and researchers do not want to ask people to do the same thing again. Circling back to the idea of GUID, it would be wonderful to enroll someone in CReATe or another study and asked whether they have been a part of the CDC Registry. If they have answered the questions, then another group would not have to ask the questions again because they will be able to connect the data to their laboriously entered data in the Registry. That would make this hugely important for researchers and it would be very clear to patients that what is coming out of this is being maximized. Dr. Berry said he thought he understood that CReATe and NeuroBANK™ use two different GUIDs, but both are part of the Registry. Linking many potential datasets would create the opportunity for a much bigger dataset. It is only a reality if that is actually allowed. For example, he wondered whether he could request data with GUIDs. If so, that is a fundamentally exciting aspect of this.

Dr. Kaye indicated that the GUID capability was added in January 2017. It sounded like one of the messages that goes out should let enrollees know that they should visit the Registry to update their account to allow adding a GUID, which would allow for maximizing and cause less burden in terms of having to complete surveys again. ATSDR receives all of the data to be able to create the NIH GUID and can also run it through NeuroGUID. The consent form is very specific that it is GUIDs plural. It is difficult to explain to the average person that a globally unique identifier is not really globally unique. They also keep the data hashed in a way that if some other GUID appears, they would be able to generate that one as well. Researches may request data with GUIDs.

Dr. Horton asked whether the GUID data would allow ATSDR's data to be appended onto a researcher's existing data, for example. This is a major selling point for researchers and should be included in the messaging to them as well.

Dr. Kaye replied that it could, but researchers are probably not going to ask for specific GUIDs. Instead they will probably ask for ATSDR's dataset with the GUIDs on it and would match the people who they have in common themselves.

Dr. Benatar asked whether any progress has been made on how investigators out in the community can tap into the environmental exposure questionnaires that exist within the Registry. When they originally submitted their proposal to CDC, the initial model was to drive people to enroll in the Registry, receive back the environmental questionnaire data they completed, and link that to the investigators' phenotypic and genetic data. Because that was not possible, they had to develop their own set of environmental exposure questionnaires because at the time, the Registry could not or would not release even the questionnaires so they could use the identical set. He wondered now two years later if he approached the agency with this same study design they would be able to do this. If so, that means they have made progress and it is worth taking note of.

Dr. Kaye replied that the problem will be with the people who opt out of creating a GUID.

Dr. Benatar clarified that as part of the enrollment process in the study, investigators could tell people to go into the Registry, consent for a GUID, and complete all of the modules. The researchers could help the Registry collect a more complete dataset by becoming a driving force as well. That is the kind of synergy that would be very helpful.

Dr. Mehta clarified that two or three years ago when data requests were being submitted, they could not release data with the personally identifiable information (PII). They could only share de-identified data, which no one could match up to their own patients and was of no benefit to them. Use of the GUID system hopefully will alleviate that problem.

Dr. Horton added whether the reverse also would be true. That is, if a researcher is collecting data that ATSDR does not have, would the Registry be able to link to those data at this point?

Dr. Kaye said that this is possible as long as both datasets have GUIDs that were created on the same computer system, either the NIH or NeuroGUID server. This would be for a specific analysis, not to make it part of the Registry. By creating a database of who has what, an investigator might be able to obtain biospecimens are datasets from additional research cohorts by taking components from different places.

Dr. Mehta added that they could store a researcher's data separately from the Registry server, where they could be made available with a unique name.

Ms. Kidd recalled that two great ideas were proposed that she did not see on the list of recommendations. One was an incentive program to motivate people to enroll (tax credit, gift card, et cetera).

Dr. Kaye indicated that they did not include incentives because this is problematic in terms of IRBs, given that it can be perceived as coercion.

Dr. Mehta added that their hands are also tied by OMB in terms of making changes. CDC's Office of the Director (OD) asked Congress for a waiver for OMB, but there has not been much movement on that. OMB restricts the Registry in terms of fluidity and changes. ATSDR cannot change this internally.

Ms. Kidd said she understood, but wanted the suggestion captured for the record. If CDC cannot do this, perhaps MDA, the ALS Association, the Les Turner ALS Foundation, or other groups could put this forward. The other idea she did not see on the list pertained to working with neurologists to make sure that at the time of diagnosis, they use that opportunity to get people enrolled versus chasing them down. While Dr. Kaye indicated that this was included under educating neurologists, Ms. Kidd emphasized that this pertained to metrics and at the end of the day, they would get what they inspect not what they expect. She suggested including a real goal such as, "We will ask the neurologists to register their patients on the day of diagnosis."

Ms. Webb indicated that MDA would be launching a "Newly Diagnosed" diagnostic binder in September. ATSDR was kind enough to provide enough materials to include in those, which will be distributed on the day of diagnosis. When consideration is given to provider-specific materials or development, she suggested that they think about this in the context of a multidisciplinary setting versus focusing solely on neurologists. Nurses, nurse practitioners, and social workers have many unanswered questions as well and could benefit from some of the data. She thanked the families and research coordinators who were watching the meeting remotely.

Regarding the problem of getting patients to enroll and neurologists to be involved, Dr. Bradley reported that there is an ALS Practice Parameters that the AAN developed a number of years ago that was instrumental in getting the provision of riluzole to patients to be higher than it was before because it was put into the Practice Parameter that it is a standard of practice to provide for patients to receive riluzole. It is a long and bureaucratic process to get something into the Practice Parameter, but he recommended putting pressure on the community that would do that to include recommending that patients be enrolled in the Registry in the Practice Parameter. The reason the Practice Parameter is useful is because a very large number of neurologists may not be specializing in the field of ALS, but they look at the Practice Parameter to determine what they should be doing. That would offer a dramatic ability to advance registration. While it will not happen overnight, it should be a goal and he recommended working with the AAN to get this done.

Regarding adding the GUID as an update to each patient's account, Ms. Backman indicated that they had gone through this process almost a year ago with over 16,000 individual records. If the GUID was added only as of January 2017, they potentially may have lost many individuals. The ALS Association, MDA, and the Les Turner ALS Foundation are actively working with the population they are able to do outreach with. She encouraged ATSDR to work with Brunet-García in order to produce some very simple messaging that says, "If you've not yet added the GUID to your account, please do so now." The partners can support those decisions, but the infrastructure has to be in place and the message has to be very clean and simple. This would help to make the Registry more useful to the research population.

Dr. Kaye clarified that the GUID is only for the patients who are enrolled in the Registry through the portal. There is no GUID on the 15,000 who came through administrative data.

Recalling a comment earlier about it being in the patient's best interest to enroll in the Registry and complete the modules, Mr. Tessaro also heard Dr. Kulke from Cytokinetics, Inc. say that this database was helpful in terms of how they fleshed out their trial. It is known that only 10% of ALS patients are anywhere near a trial or study, so 90% of people would love to be in a trial or study if they qualify. The point is that selling the Registry is saying that someone has a better chance or at least a chance of being considered for an upcoming trial by enrolling in the Registry. The day of diagnosis is pretty tough, but within in a month by the first clinic visit, patients should be sold on the fact that enrolling in the Registry and submitting their data can be a path toward knowing about more trials.

Dr. Mehta indicated that ATSDR also plans to stratify the data to make it more user-friendly so when a patient goes to the website, they can see who is currently recruiting and link to them. The plan is for this to be more interactive, but they still want patients to enroll so that they can be sent automatic notifications as well.

Dr. Horton added that the reverse is also true. ATSDR needs researchers to let them know about clinical trials and epidemiological studies, and they need to use the Registry to recruit people. That is how the Registry notifies patients.

Dr. Kulke indicated that Cytokinetics, Inc. has notified ATSDR about additional studies, and will now continue to do this in the future. They only knew about the Registry because one of their PIs told them. Before that, they had no idea that the Registry existed.

Mr. Olcheski agreed that the collection of data is vital, but he emphasized that they must not forget the human factor. Their daughter was someone who was slipping, getting uncoordinated, who had never experienced that before. When she and her husband went in, they had the thought that the diagnosis would be ruled out. They had tried everything else and the chance was rare. She went into the doctor and basically, her whole world fell apart. She is not going to have children. She is not going to have anything. Her future is shot. To ask her to sit down and fill out a form after that is almost cruel. The reality is that patients should be given a few weeks to get their act together. When they are talking with the coordinator in the clinic and begin to realize the reality of what is happening, that is the time to tell them that there is a good chance this disease can be overcome in their lifetime and a big part of that is the collection of data through this Registry. If it is presented in that fashion, there is a very good chance of achieving a much higher rate of enrollment in the Registry. He implored everyone not to forget the human factor. Rachel's world fell apart. They could not even tell her parents until that night and requested that the family get together. They all sat there crying their eyes out. That is the reality of this disease.

Dr. Finger echoed Dr. Horton's point regarding the notification system. There are 100 different efforts underway, each of which has its own strengths and weaknesses, but it confuses patients. For the notification system to be a serious component of the Registry, it seems like buy-in is needed from an organization by NEALS to state that a part of their recommendation will be to use the National ALS Registry as well. Whether people take this up is dependent upon being able to demonstrate to them that it works. Information about CReATe, Cytokinetics, et cetera needs to be spelled out so that researchers actively use the Registry notification system such that when they go to patients, it is compelling. To him, it is somewhat misleading to tell patients to sit by their computers and wait for a notification when only 10% of trials are using this system.

At this point, Dr. Kaye pointed out that they come out of these meetings every year with a long list of recommendations and they cannot get through everything. They have a team and need to think about how to divide up the efforts, as well as taking into consideration what the high, medium, and low priorities should be.

Dr. Benatar said he thought they were going about this the wrong way. Instead, they should be thinking about where they want to be in a year's time and then decide what to invest in order to get there. That will help set the priorities. Otherwise, they will be chasing their tails. If the goal is to get more neurologists and multidisciplinary clinics signing up patients, there must be a targeted campaign to do that coupled with regular feedback to clinics about how they are doing and what progress is being made so that people can see if the fruits of their labor are yielding benefits and, if not, they can make adjustments. There must be a goal along with an investment, a feedback strategy, and a loop back to make sure the goal is actually reached.

Ms. Newhouse agreed that if they do not know where they want to end up, it is difficult to tell what the pathway is to get there. As she listened the last couple of days, it seemed to her that everything came back to the communication plan. They must figure out the endgame, the pathway, and the overarching messaging that they are sending out the door. As one of the three patient advocate organizations in the room, and as the CEO of one of those, she thought it was very important for those three organizations to be willing to set the piece about their organization aside to say that they are all going to carry the same messages with the same look and feel and move the messages out the door in the same way to get it to the people. What do they want at the end? Is it more people registered or more information shared between and among researchers and neurologists.

Dr. Brooks said one thing he learned during this meeting is that there is fantastic interaction between the University of Miami and Michigan Medical, Dartmouth and Ohio; and the University of Miami and Cleveland Clinic. He heard these people say desperately that these interactions could never have occurred without the Registry's existence and having a plan to facilitate environmental studies in ALS. That is one of the most important messages that they have to get out—that without this Registry, there would be no such studies. In terms of the literature, he does not see other countries doing this. They get the data but not the actual measurements, which has been the underlying success so far that he had seen during this meeting. He strongly and enthusiastically endorsed Dr. Mitsumoto's recommendation about convening a meeting of neurologists during the ALS/NMD December 2017 meeting. This is the US's Registry and the survival of the Registry depends upon everyone knowing the success of this Registry, and he urged the pharmaceutical companies and voluntary organizations to come together to support that symposium.

Dr. Kulke said she thought it was doable, but wondered if CDC has rules against this. She agreed that it should be the day before the ALS/NMD meeting begins.

Ms. Newhouse said that as the incoming chair of the International Alliance, there are a number of other meetings occurring simultaneously. She suggested that before they all decide something that they are somewhat unsure of on timing and scheduling, they should go back to the NMD United Kingdom (UK) and her colleagues at ALS Therapy Development Institute (ALS TDI) and ALS Hope Foundation who are this year's hosts to check the status of the various sessions. She indicated that she would send the two hosts an email before the end of the meeting.

Dr. Kulke noted that Mitsubishi, Biogen, and Cytogenetics are all collaborating on another project, so she had no reason to believe they would not collaborate on something like this as well. She did not think it would need to be a long meeting. The key thing there is to get the ALS research to provide brief research updates on all that is being done so that their colleagues realize how cool this is, which will then help to drive the momentum.

Dr. Kasarskis recalled that they began the meeting with a description of the "elephant in the room" with regard to the uncertainties of funding—the very life of this Registry. He asked whether Drs. Mehta and Horton have a plan to push out the summary statements, recommendations, status of this. While he knew that Dr. Mehta was working on an *MMWR* report keyed off of the Grand Rounds, it seemed like this was entering into the realm of serious politics in terms of future plans. In a way, the Registry's survival depends upon some forward-looking statements. They received a number of practical recommendations from patients and the research community, but it seems like there is a big job on ATSDR's part that they all hope will be successful. He wondered whether under ATSDR's rules of engagement, they are allowed to push out tweets or something to each individual Congressman and Senator. He suggested tweets versus long multi-paragraph diatribe, given that these are the people who do not even read what they vote on.

Dr. Mehta replied that certainly, everything everyone said to ATSDR during this meeting was very important. ATSDR is not permitted to push out tweets to Congressmen and Senators.

Ms. Balas added that that responsibility lies with organizations such as the ALS Association. When this meeting concludes, that information should be supplied to the patient advocacy organizations because they can push that message. They work very closely with Drs. Horton and Mehta to understand the value ad of the Registry in order to activate their grassroots to

then continue to show Congress what the value is and why they would not want this funding cut. There are very clear lines as to what ATSDR can do and advocate organizations are responsible for. The advocacy organizations have multiple channels through which they can push out information, including tweets, Facebook posts, and action alerts. All of those go out at the same time, but there are very clear lines about lobbying for individuals who work in the federal government. They are pretty clear on who needs 144 characters and who has a few paragraphs inside them.

Dr. Nelson noted that each year they talk about the website and how much it needs improvement, but she recalled that in previous years, ATSDR did not have a lot of leeway in terms of improving it. Right now, it is two full pages with a lot of boxes in the middle, almost all of which are directed toward researchers. It seems like there should be a lot more for patients.

Dr. Kaye replied that there is a major effort right now with regard to responsive design, as Dr. Mehta mentioned earlier with regard to the apps. The website has the new CDC look and all of the materials are being updated. It will be a lot nicer once it goes live.

Dr. Mehta added that the plan is to have more information for patients and a button for researchers regarding data and biospecimen requests.

Dr. Horton added that there are some constraints due to 508 compliance, the government has to make their website such that there are no blinking lights and it has to have certain colors. If they could, they would light it up like the Vegas Strip. In addition, CDC dictates what the template is going to be for ATSDR. They cannot come up with their own background, et cetera. It has to be somewhat uniform to every other CDC page. They heard the recommendations from the Olcheski's daughter about jazzing it up and they fully agree, but there is only so much jazzing up that they are permitted to do.

Dr. Berry said he thought a lot of the other pieces would fall into place if they establish a goal and the importance becomes clear. For example, the role is not necessarily to get people enrolled or to have the data in any given person's hands. Instead, the goal is to create a very useful dataset that can be a starting point for new projects added on to other projects and an independent dataset for projects. If that message was clear and those projects are conducted and begin to provide important results, researchers will see an opportunity to examine their creative ideas, and if more people go to the site, then researchers can answer the questions better, and if people with ALS recognize that if they want to be a productive part of the fight and put their data in a central location, they will become primed. At that inevitable point in the conversation, whether it is the day of diagnosis or one year later, providers will be able to say that while they do not know all the answers, they do have a successful working tool to get there.

Dr. Kulke and Ms. Newhouse indicated that they will report to Dr. Mehta once they complete their action items. She suggested that they circulate the PowerPoint of the things that they suggested should be done. That should then be shared at the beginning of next year's meeting in order to keep this going. They developed recommendations last year, but did not revisit these during this year's meeting. She said she loves being here and being part of this group, and looks forward to everything they can get done.

Ms. Balas agreed that they should revisit the goals, but that they should not wait an entire year to reflect back on whether any progress has been made on these goals.

Dr. Kaye replied that the hope was to try to create a more manageable list. Sometimes they come out of the meeting with such a long list, it is overwhelming. Hopefully, within the next month or so, they can have some discussion about who is going to tackle what piece so that they can move forward. The following is the list of prioritized goals as they stood at the end of this session, which is definitely more manageable than usual:

Goals	
Goal	**Suggestions**
Increase use of the Registry to recruit for research studies	
Increase enrollment in the Registry	
Increase collaboration among researchers to combine data and use data from the Registry	
Dashboard on progress to be shared with the working group	

Closing Remarks

Paul Mehta, MD
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Dr. Mehta thanked everyone for their attendance and a great meeting. He especially thanked the persons with ALS: Ed Tessaro, Stephen Finger, Alan Alderman, Rachel Doboga's parents the Olcheski's, and Becky Kidd and her family. This is really special and ATSDR values the input from persons living with ALS and their families, as well the researchers and partner organizations. This is an opportunity for everyone to tell ATSDR what they are doing right and wrong. He assured everyone that they would take all of the recommendations into consideration, and will provide updates. ATSDR wants to make the Registry better for persons living with ALS and their caregivers, but also for research in order to find out what causes this disease. He invited anyone with questions or concerns to email him or Dr. Horton, and thanked everyone again for coming to Atlanta and officially adjourned the meeting.

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