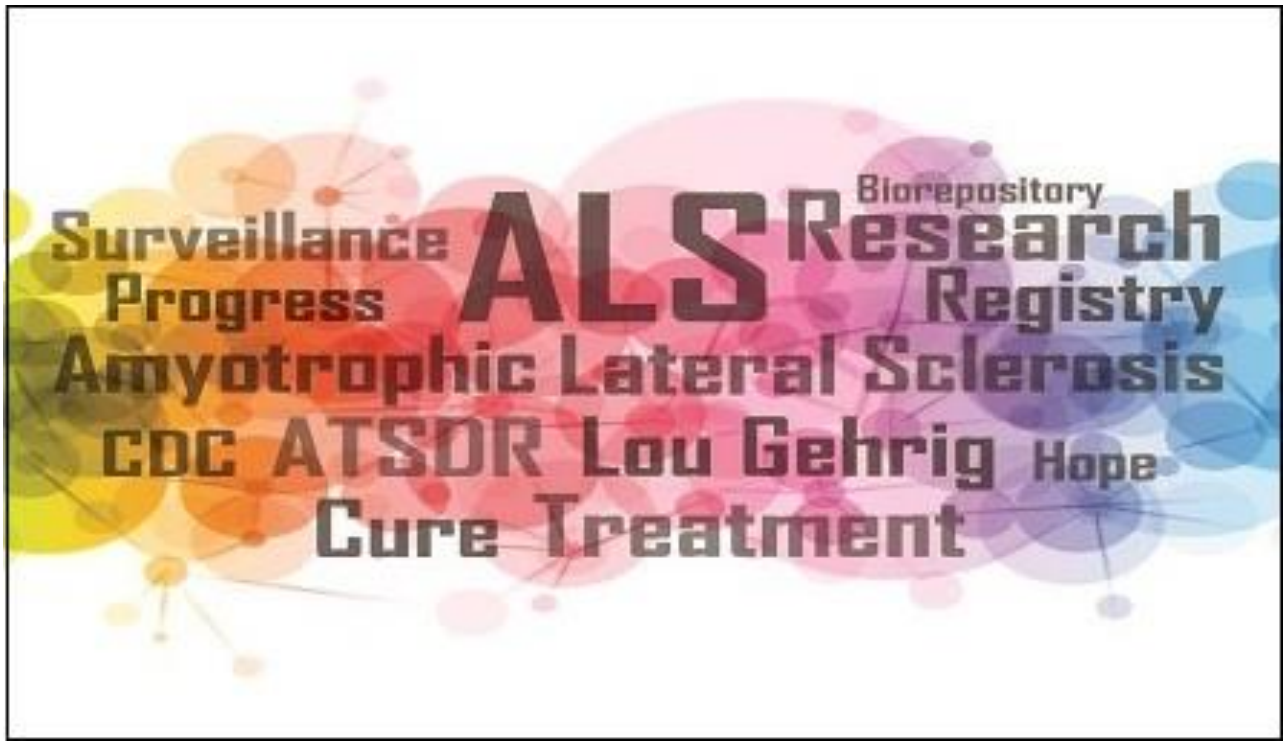
Department of Health and Human Services
Centers for Disease Control and Prevention
Agency for Toxic Substances and Disease Registry

2020 National ALS Registry Annual Meeting



August 4-5, 2020
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.

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Acronyms Used in this Document

Acronym	Expansion
AAN	American Academy of Neurology
ADA	Americans with Disabilities Act
AE	Adverse Event
AFB	Air Force Base
ALS	Amyotrophic Lateral Sclerosis
ALSA	Amyotrophic Lateral Sclerosis Association
ALSFRS	ALS Functional Rating Scale
ALSFRS-R	Revised ALS Functional Rating Scale
AQS	Air Quality System
ATSDR	Agency for Toxic Substances and Disease Registry
ATSU	A.T. Still University
AUC	Area Under the Curve
BMI	Body Mass Index
BYU	Brigham Young University
CDC	Centers for Disease Control and Prevention
CDMRP	Congressionally Directed Medical Research Programs
CIOs	Centers, Institutes, and Organizations
C_{max}	Maximum Concentration
CNS	Central Nervous System
COViMS	COVID-19 Infections in Multiple Sclerosis and Related Diseases
CReATe	Clinical Research in ALS and Related Disorders for Therapeutic Development
CSF	Cerebrospinal Fluid
CVD	Cardiovascular Disease
HBM	Health Belief Model
HHS	(Department of) Health and Human Services
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DPH	Department of Public Health
DSMB	Data Safety Monitoring Board
DTHHS	Division of Toxicology and Human Health Sciences
DUA	Data Use Agreement
ECAS	Edinburgh Cognitive and Behavioral ALS Screen
EPA	Environmental Protection Agency
EuroMOTOR	European Multidisciplinary ALS Network Identification to Cure Motor Neuron Degeneration
EVs	Extracellular Vesicles
FACA	Federal Advisory Committee
FALS	Familial ALS
FDA	Food and Drug Administration
FSHD	Facioscapulohumeral Muscular Dystrophy
GUID	Globally Unique Identifier
GWAS	Genome-Wide Association Study
HAPs	Hazardous Air Pollutants
HERV-K	Human Endogenous Retrovirus-K
HPA	High Performance Analytics
IRB	Institutional Review Board
IDV®	Symphony Integrated Dataverse®
JEM	Job Exposure Matrices
LAENALS	Latin American Epidemiology Network of ALS
MD	Muscular Dystrophy

MDA	Muscular Dystrophy Association
MDPH	Massachusetts Department of Public Health
miRNA	microRNA
MGH	Massachusetts General Hospital
MMWR	*Morbidity and Mortality Weekly Report*
MND	Motor Neuron Disease
MS	Multiple Sclerosis
MTA	Material Transfer Agreement
MTDA	Mitsubishi Tanabe Pharma Development America
MTPA	Mitsubishi Tanabe Pharma America
MTPC	Mitsubishi Tanabe Pharma Corporation
NATA	National Scale Air Toxics Assessment
NCEH	National Center for Environmental Health
NCRI	Neurological Clinical Research Institute
NEALS	Northeast Amyotrophic Lateral Sclerosis Consortium
NIA	National Institute on Aging
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIV	Non-Invasive Ventilation
NMD	Neuromuscular Diseases
NNE-OH Database	New England and Ohio Database
NOFO	Notice of Funding Opportunity
OHSU	Oregon Health & Science University
OMB	Office of Management and Budget
OS	Oxidative Stress
PALS	Persons with Amyotrophic Lateral Sclerosis
PARALS	The Piemonte and Valle d'Aosta Register for ALS
PBMCs	Peripheral Blood Mononuclear Cells
PCP	Primary Care Physician
PFOS	Perfluorooctanesulfonic Acid
PFOA	Perfluorooctanoic acid
PI	Principal Investigator
PII	Personally Identifiable Information
POP	Persistent Organic Pollutant
PPM	Parts Per Million
PSA	Public Service Announcement
RDCRN	Rare Diseases Clinical Research Consortia
REFINE-ALS	Radicava (Edaravone) Findings in Biomarkers From ALS
RNA	Ribonucleic Acid
SES	Socioeconomic Status
SfN	Society for Neuroscience
SMA	Spinal Muscular Atrophy
SME	Subject Matter Expert
SNPs	Single-Nucleotide Polymorphisms
SOD-1	Superoxide Dismutase 1
SSDI	Social Security Disability Insurance
SSN	Social Security Number
TBI	Traumatic Brain Injury
UCLA	University of California Los Angeles
US	United States
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)
2020 National ALS Registry Annual Meeting

Minutes of the Meeting
August 4-5, 2020

Welcome and Introductions

Tom Hicks, Moderator
Public Health Advisor
Carter Consulting, Inc.
Division of Toxicology and Human Health Sciences
Agency for Toxic Substances and Disease Registry

Mr. Hicks called the meeting to order at 8:15 AM and welcomed everyone, noting that this was the first virtual annual ALS Surveillance meeting. He called upon Darcy Peth from Ross Strategic to explain the Zoom logistics. Mr. Hicks then described the ground rules for the meeting and reviewed housekeeping items. A participant roster is appended to the end of this document.

Opening Remarks

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

Dr. Breysse welcomed everyone to the first ever, and hopefully the only ever, Virtual Annual ALS Surveillance Meeting. He emphasized that the importance of the National ALS Registry and its mission to determine the national epidemiology estimates and the identification of risk factors and etiologies for ALS superseded any thoughts of cancelling the meeting. Having clinicians, researchers, and especially persons with ALS (PALS) together allows feedback that helps ATSDR shape the National ALS Registry. This feedback is invaluable. Dr. Breysse said he could not emphasize enough that the success of the ALS Registry depends upon effective collaboration among many ALS stakeholders, including PALS, physicians, researchers, and other support groups. The National ALS Registry is a groundbreaking effort to help scientists identify possible etiologies and risk factors as researchers work toward a cure for ALS. The National ALS Registry is making considerable progress. ATSDR is currently working on the fifth national prevalence estimation, with a late Fall to early Winter publication date anticipated.

ATSDR also is excited about the National ALS Biorepository. The samples collected are being paired with risk factors survey data, which makes the National ALS Biorepository a very unique resource. In addition, specimens are undergoing analyses in-house at ATSDR and with ATSDR's external partners. To date, numerous studies are underway to evaluate genetic, heavy metal, organophosphate, and other risk factors. Data from the National ALS Registry also are being disseminated to researchers for analyses. ATSDR has funded 17 external research studies to date and looks forward to funding more grants this Fall. Dr. Breysse indicated that this meeting would include updates on research being conducted with National ALS Registry and

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

Dr. Breysse said that he was happy to report that the National ALS Registry's Research Notification System has been extremely well-received by Registry enrollees and researchers. To date, over 50 institutions have used this system to recruit thousands of PALS for clinical trials and epidemiological studies. ATSDR also was excited to have their pharmaceutical partners in attendance who would present on their drug development efforts, and to hear from PALS on their perspectives about living with ALS and participation in the National ALS Registry. In addition, they would hear much more about new initiatives and ATSDR's progress on the National ALS Registry over the next two days. He emphasized that as ATSDR turned to the attendees as the leading experts in ALS to continue to shape the National ALS Registry to be the best it can be, they should feel free to share their thoughts and comments throughout the meeting and afterward as well. He expressed his hope that they would see everyone in person in 2021.

National ALS Registry Update

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, thanked them for their attendance, and expressed hope that this would be the only virtual meeting they have to convene due to Coronavirus Disease 2019 (COVID-19). He emphasized that while ATSDR is the caretaker of the Registry, this is the PALS' Registry and their feedback is extremely important. It also is important to understand that ATSDR does a lot more than just count ALS cases in the United States (US). They also estimate prevalence, incidence, and mortality and anticipate publishing a paper on national incidence later in the year. ATSDR also works closely with partners such as the Amyotrophic Lateral Sclerosis Association (ALSA), the Muscular Dystrophy Association (MDA), and the Les Turner ALS Foundation to reach patients and caregivers to inform them about the Registry and its importance in the fight against ALS. Risk factor surveys also are completed by ALS patients when they enter the online portal. Over 90,000 surveys have been completed to date. In addition, there is the Research Notification System through which ALS patients are connected with clinical trials and epidemiological studies. There is a hunger for ALS research to determine what causes ALS, so ATSDR also funds various research. Another aspect of the Registry is the National ALS Biorepository.

To put federal ALS research initiatives into perspective, Dr. Mehta described what ATSDR does in comparison to other agencies. ATSDR's sister agency, the National Institutes of Health (NIH) conducts basic science biomedical research, funds clinical trials internally and externally, identifies gene mutations and cellular defects, develops biomarkers, and studies how ALS changes over time (e.g., symptoms). The COVID-19 trials that currently are underway are a great example of this. The Department of Defense (DoD) Congressionally Directed Medical Research Programs (CDMRP) examines the pre-clinical development of therapeutic agents;

completes the steps required before Food and Drug Administration (FDA) approval of a new drug; and assesses stability, toxicology, pharmacokinetics, and efficacy in cell and animal models before new agents go into clinical trials. ATSDR works with both NIH and CDMRP. ATSDR studies the epidemiology of ALS (e.g., who, what, and when) and identifies risk factors and etiologies for ALS (e.g., heavy metals, pesticides, cyanobacteria), given that figuring out what causes ALS may lead to an understanding of how to prevent ALS in the future.

In terms of accomplishments and activities since the last Annual ALS Meeting, the National ALS Biorepository was launched in January 2017 after a 3- to 4-year pilot study period. To date, over 1300 participants have been enrolled from whom blood and saliva have been collected and there have been close to 50 post-mortem collections. The National ALS Biorepository has really taken off in terms of allocating samples to researchers and collecting hair, nails, blood, tissue, cerebrospinal fluid (CSF), bone, and post-mortem samples (brains and spinal cords). The Biorepository certainly has been a very important facet in terms of biomarker, genetics, and other types of research.

Regarding communications and outreach, ATSDR launched a new user-friendly website and a Spanish mirror site. The Spanish site went live on July 22, 2019. In addition, they produced a number of assets such as videos and infographics with partners to be disseminated to patients and caregivers.

ATSDR has funded 17 research studies to date, with 2 to 3 new studies to be funded in the Fall depending upon availability of funds. To date, 51 studies have used the notification mechanism, including about a dozen pharmaceutical companies testing new drugs. All of ATSDR's data have Global Unique Identifiers (GUIDs) through NeuroBANK™ at Massachusetts General Hospital (MGH). ATSDR is working with Alex Sherman, Director of the Neurological Clinical Research Institute (NCRI) at MGH, to begin the comparison of ATSDR's GUIDs with their GUIDs. They are excited to see what comparisons they will find with this activity.

Based on patient feedback, a change was made to the password component of the Registry. When the Registry was launched in October 2010, the passwords had to be changed every 3 months. At one point, that was extended to every 6 months. Now, the passwords are user preference in that patients themselves can define when their passwords will expire (6 months, 1 year, or indefinite). This is a major improvement based directly on patient feedback.

ATSDR staff attended 20 conferences and ALS patient symposiums to present findings over the past year. To date, Registry data have been used for over 76 peer-reviewed publications on which ATSDR has been either the lead, co-author, and/or funding agency. There were 10 publications in 2019 and 4 in 2020.

ATSDR also is working with Massachusetts Department of Public Health (DPH) to compare case data. Massachusetts is the only state in the country in which ALS is a reportable disease at the state level. ATSDR worked with them earlier in the year, has Personally Identifiable Information (PII), and has begun a comparison between ATSDR's national data and what is seen at the state level in Massachusetts. This will be a very good exercise to determine completeness at the state and national levels.

ATSDR also has received Office of Management and Budget (OMB) approval for a new survey, Survey 18 (S18), that soon will be launched for the Registry. This survey is based upon specific sports in order to evaluate the role of traumatic brain injury (TBI) in sports in terms of sports played, duration, level (e.g., high school, collegiate, professional, et cetera).

COVID-19 certainly has impacted almost every facet of society, including ATSDR in terms of its activities such as data analyses and publication of the annual *Morbidity and Mortality Weekly Report* (*MMWR*) of prevalence for 2016. It is anticipated at this point that there will be a Fall or Winter publication of the report, which is approximately 80% to 85% complete. They are waiting for the capture/recapture methodology citation and journal in order to include it in the ATSDR publication. They certainly are excited about publishing the 2016 prevalence report, which will include 2 different numbers—one based upon the ATSDR algorithm and the other based on capture/recapture.

Given that patient safety is paramount, in-home sample collection of blood had to be suspended for the National ALS Biorepository in early March as the pandemic was ramping up. After considerable discussion, the decision was made to suspend collection to keep patients from being exposed to COVID-19 by phlebotomists entering their homes and vice versa. The agency is working on alternative methods for blood collection, such as potentially having patients get their blood draw at their primary care physician's (PCP's) office. They are sending saliva kits to those who do not want blood collections at this time but will circle back to collect blood samples when that is permissible. ATSDR's colleagues at the NIH have been impacted by COVID-19 as well in terms of genetic testing and whole genome sequencing (WGS) and are awaiting their laboratories to be back up and operational.

ATSDR implemented a Google campaign that was completed in July 2020, which was targeted to states such as Texas, Florida, and California that have higher proportions of minorities. Outreach efforts were impacted in terms of patient symposiums and so forth as well, including ATSDR's partners (ALSA, MDA, and Les Turner).

The National ALS Registry budget for fiscal year (FY) 2019 was $7.9 million which is allocated to research activities (61%), communications (3%), information technology (IT) and support (12%), outreach and education (13%), personnel (10%), and miscellaneous (1%).

The Research Notification System has been a very important system. Approximately 95% of patients opt in to receive information about studies. At this point, over 50 institutions have used this system. Both domestic and international partners can use this tool for their study needs. Dr. Mehta highlighted the following clinical trials and epidemiological studies for which ATSDR helped to recruit, as well as upcoming clinical trials and notifications using the Registry:

Multi-Site Clinical Trials	
Institution (Principal Investigator)	**Study Description**
Brainstorm Cell Therapeutics (Berry)	❑ Repeated dosing of NurOwn® (mesenchymal stem cells/MSC) derived from patient's bone marrow ❑ Enrollment completed
Orphazyme (Benatar)	❑ Arimoclomol, intended to extend independent breathing and improve survival, functional health, and safety
Orion Pharma (Cudkowicz)	❑ Levosimedam, ODM-109, intended to improve respiratory function
Amylyx Pharmaceuticals (Paganoni)	❑ AMX0035, intended to slow disease progression and improve muscle strength
Cytokinetics, Inc (Rudnicki)	❑ FORTITUDE-ALS, intended to slow disease progression and improve respiratory function

Epidemiological/Risk Factor Studies	
Institution (Principal Investigator)	**Study Description**
The ALS Association (Parvanta)	❑ ALS Focus Survey ❑ Evaluating patient and caregiver burden
Columbia University (Mitsumoto)	❑ Examine the relationship between oxidative stress (OS) and ALS
University of Rochester Medical Center (Heatwole)	❑ ALS quality of life analysis ❑ Manuscript development
Walden University (Jeremy van Tress); this is the first study submitted by an ALS patient	❑ Study name: *ALS Patient's Resilience, Self-Determination, and Decision-Making for Life-Sustaining Treatments* ❑ Better understanding of how PALS' experiences and their attitudes about resilience are related to their decision-making for life-sustaining treatments, such as tracheostomies and feeding tubes. ❑ Recruitment goal n=200, received 277 responses within 2 months. ❑ Survey is closed and researcher is working on analyses. ❑ Goal is 2 to3 publications and PhD dissertation ❑ Personal perspective as a researcher and person with ALS during annual meeting—ATSDR appreciates his feedback
University of Cincinnati (Macaluso); the first COVID-19 study	❑ Part of the Rare Diseases Clinical Research Consortia (RDCRN) funded by the NIH ❑ The purpose of the study is to examine the impact of COVID-19 on ALS patients in terms of comorbidities, impact on families, and interactions with treatments

Upcoming Clinical Trials Using the Registry	
Institution (Principal Investigator)	**Study Description**
Massachusetts General Hospital (MGH) HEALEY ALS Platform Trial (Cudkowicz)	❑ First ALS platform trial testing multiple treatments at once, reducing the cost of research by 30%, decreasing the trial, time by 50%, and increasing patient participation by 67% ❑ Testing 5 experimental treatments
NIH Human Endogenous Retrovirus-K (HERV-K) HERV-K Suppression Using Antiretroviral Therapy (Nath)	❑ HERV-K is found in some ALS patients ❑ Suppressed using same drugs to treat HIV

Upcoming Notifications Using the Registry	
Institution (Principal Investigator)	**Study Description**
Mitsubishi Tanabe Pharma America (Apple)	❑ Oral formulation, Edaravone ❑ Biomarker study ❑ National, multiple sites
Dartmouth Hitchcock Medical Center (Stommel/Bradley/Cox)	❑ L-Serine clinical trial
Carolinas Medical Center (Brooks)	❑ Examine protective properties of riluzole and Edaravone against COVID-19

In terms of impact, the Registry's notification system has been used by over a dozen pharmaceutical companies for their clinical trials. The review and approval of applications typically takes less than one month. Once approved, ATSDR will work with the drug company or researcher to schedule their notification. This is a completely free service for companies and academia, which is estimated to have resulted in recruitment of over 3000 patients for clinical trials and epidemiological studies. There have been 50 studies that on average have recruited 50 patients or more. This system has the largest population of ALS patients in the US and has been very popular and impactful.

Over 75 peer-reviewed publications/abstracts have been published using Registry data. The Registry pays for open-access when possible. These are presented at the American Academy of Neurology (AAN), Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS), and the International Symposium on ALS/MND. In terms of notable publications/findings in 2020, the

University of Michigan conducted a study on early life metal dysregulation in ALS that examined metal uptake during childhood in individuals who were diagnosed with ALS specifically in teeth. The results showed that metal levels of manganese, nickel, tin, chromium, and zinc were higher in cases than controls. This study reveals direct evidence that altered metal uptake in early life is possibly associated with adult-onset ALS. A Dartmouth University study of a keratinous biomarker of mercury (Hg) exposure associated with ALS risk analyzed nail clippings of female ALS patients and compared them to controls. The odds of having nail Hg levels were 2.3-fold in ALS patients when compared to controls. These findings suggest that excessive Hg exposure may be associated with the neurodegenerative health of aging populations.

ATSDR is funding extramural research to learn more about ALS etiology and risk factors. To date, 17 research studies have been funded. The information gleaned also will help ATSDR prioritize topics for future risk factor surveys. In FY2019, ATSDR partnered with the NIH for WGS of almost 300 samples from the National ALS Biorepository. That work is ongoing. The agency anticipates funding 2 to 3 awards in September 2020. Currently funded R01 grants include the following:

- Northwestern University (Siddique):
  - Looking for genetic variants of an innate immunity protein (APOL1) in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) and how it contributes to ALS.

- Dartmouth University (Stommel):
  - Investigating time periods when environmental exposures (e.g., cyanobacteria, pesticides, and polluted sites) carry the greatest risk for developing ALS.

- University of Michigan (Feldman):
  - Identifying metabolomic signatures that correlate with persistent organic pollutant (POP) exposures/risk factors and ALS progression.

- Columbia University (Shneider):
  - Evaluating toxic exposures in brains by evaluating extracellular vesicles (EVs), which can be used as biomarkers.

- University of Pittsburgh (Talbott):
  - Examining environmental toxicants in ambient air pollution by examining serum/plasma levels from the National ALS Biorepository via cases/controls.

- Trinity College (Hardiman):
  - Understanding why the Hispanic population in South America has lower rates of ALS compared to Europeans.

In FY21, grants will be funded under Notice of Funding Opportunity (NOFO) TS20-001: *Identify, Analyze, and Evaluate Potential Risk Factors for Amyotrophic Lateral Sclerosis (ALS)*. The objective of this NOFO is to identify potential risk factors for ALS in humans that are potentially associated with or contribute to the etiology, progression, and pathophysiology of ALS in humans including environmental and occupational, military service, infectious agents and viruses, nutritional intake, physical and sports activities, pharmaceutical use, and TBIs. Approximately 1-4 awards will be funding at $400,000 to $500,000 per year for 3 years, subject to funds.

This table reflects the status of recommendations from the 2019 meeting by topic area:

Communications & Outreach			
Recommendation	**Suggestions**	**Lead Organization**	**Status**
Have more materials about the Biorepository	Develop new one pager	Registry	Completed: new materials developed
Have more materials on the importance of risk factor surveys	Develop new one pager	Registry	Completed: new materials developed
Engage minority populations	Launch campaign and check internally at CDC	Registry	Completed: launched campaign targeting CA, TX, and FL
Create universal branding for ALS	New logo or image	Partners & Registry	Ongoing
ALS Prevalence Estimates			
Provide estimate of ALS prevalence that adjusts for under-ascertainment	Use novel methodology	Registry	*MMWR* report is 80% completed waiting to cite methodology in journal
Change the label of "Definite of ALS" equated with El Escorial criteria	More specific	Registry	Completed: defined in Methods section of reports
Additional Analyses with Existing Data			
Update proximity to referral centers using GIS for 2014 and 2015 data	Use prevalence data	Registry	Ongoing
Analyze survey completeness	Conduct analyses	Registry	Ongoing and update pending
Evaluate if marital status, riluzole use, impacts survey completion	Use survey data	Registry	Completed
Compare statistics for the under-enrolled states with the number identified through the admin data & time to Dx	Use survey data	Registry	Ongoing
Miscellaneous			
Randomly order surveys	In most importance	Registry	Ongoing
Have a practice test accounts for partners and clinic staff	Partners can be more familiar with system	Registry	Completed
Have a checklist or card for Registry participants to note their user ID and password	Available for partners	Registry	Almost competed, developing new Registry folder for new patients

Impact of COVID-19: A Neurologist's Perspective

Benjamin Rix Brooks, MD
Director / Professor of Neurology
Carolinas Neuromuscular ALS / MDA Care Center
ALS Association Certified Treatment Center of Excellence
University of North Carolina School of Medicine – Charlotte Campus

Dr. Brooks reported that their clinic noticed an excess of deaths in the first quarter of 2020 compared to 2018 and 2019. That led them to observe among the clinics in North Carolina comprised of approximately 1000 patients in early March 2020 1 COVID-19/ALS case that occurred in a nursing home. The way they are able to look at these issues is through a clinician-reported registry cohort being done in multiple sclerosis and through a patient-reported cohort being done primarily in Parkinson's Disease (PD).

The Fox Insight is an online clinical study for people with Parkinson's Disease, which is a patient-facing cohort that includes approximately 5000 patients with PD. This study found differences in COVID-19 symptoms and outcomes among the patients who did and did not have PD. Among the cohort, 51 with PD and 26 without the disease had COVID-19 infection. There was much higher reporting of lung comorbidity among the patients with non-PD who presented with COVID-19 [The Effect of the COVID-19 Pandemic on People with PD; Ethan G Brown, Lana M Chahine, Samuel M. Goldman, Monica Korell, Emerald Mann, Daniel R. Kinel, Vanessa Arnedo, Kenneth L. Marek, Caroline M. Tanner https://doi.org/10.1101/2020.07.14.20153023].

The COVID-19 Infections in the Multiple Sclerosis (MS) and Related Diseases (COViMS) group led by Washington University St. Louis used a clinician-facing cohort and Research Electronic Data Capture (RedCap) database in which they are collecting patient information. They have 592 confirmed MS patients among whom 380 recovered, 152 are recovering, and 38 died from COVID-19 infection. They observed that patients who were more severely affected by MS seemed to have an increased risk of death in this physician-reported cohort. They also noted that there were possible differences between the types of drugs being used among those who died and those who did not have a fatal outcome. This has not been confirmed in other similar studies in the European population [COViMS Registry. The COViMS Database Public Data Update. www.COViMS.org Access 07/27/2020].

Based on the fact that riluzole has been shown to have an antiretroviral effect and an anti-cytokine effect in clinical examinations of people treated with riluzole and reported in the literature, and also based on the fact edaravone in pre-clinical studies has shown a benefit in preventing interstitial pneumonitis, it was thought to be important to get a sense of whether patients with ALS had an increased or comparable risk of ALS. Therefore, a Quarterly Census Survey was sent out through the NEALS system to ask whether clinicians had any ALS patients who had COVID-19 and whether they were on riluzole, edaravone, neither, or both. As a denominator, responders also were asked about the number of patients they saw in the first quarter of 2020. Based on 23/150 centers returning the NEALS COVID-19 ALS Census Survey among a patient population of nearly 3000 (2926), the low was zero, the highest rate was 1 in 20, and the mean was 5.2 COVID-19 ALS cases per 1000 ALS patients with a 95% confidence interval of 0.7 – 9.6. No difference was shown in COVID-19 incidence as a function of riluzole or edaravone use. Anecdotal reports of less severe disease in ALS patients on riluzole and edaravone were reported, but final information is not available on this as it would require a more in-depth ALS-type registry.

Comparing the data from patients in Lombardy and Padua, Italy; Kings in London; and the US for PD, the case rate of COVID-19 in PD is comparable among those centers. The case fatality rate is different, but the larger numbers range from 57.1 to 76 per 1000 cases infected. Looking at the MS data for France, Holland, and the US, the case rate in France and Holland ranges from 6.2 to 14.1 per 1000 and the case fatality rate ranges from 34.5 to 46.5 in France and Holland. The data from the COViMS dataset gives a comparable case fatality rate, but they did not have the denominator for the number of patients who were in the MS clinics. For the NEALS survey, they took the 19 positive cases and divided it by the number of patients served. That is why the difference of 6.5 compared to 5.2, which is actually a mean. This is just the raw data on that.

To summarize, the attack rate of COVID-19 among ALS patients is comparable for other neurological diagnoses. The observed case fatality ranges from 0 to 20 per 1000 ALS patients. The previous evening, Dr. Brooks received a call that the first clinical trial with approximately 100 patients had 1 COVID-19 fatality associated with it. The mean incidence rate is 5.2 COVID-19 ALS cases per 1000 ALS patients [95% confidence limits = 0.7 – 9.6]. This is comparable to the COVID-19 case rate observed in European and US cohorts of PD and MS and is apparently not affected by treatment with or without riluzole, edaravone, riluzole and edaravone together, or neither. What has not been sorted out is whether there is any change in the severity of the disease.

In terms of what is needed in the short-term, the Quarterly National COVID-19 ALS Census Survey through NEALS should be repeated to determine the stability of the ALS case rate and the relation of the ALS case rate to treatment. An ALS Patient Facing COVID-19 ALS Registry should be established for web-based patient or caregiver data entry of COVID-19 details. This could be done through a CDC/ATSDR questionnaire in the National ALS Registry site and through collaboration with the ALS Association, MDA, and the pharmaceutical industry. In addition, it would be important to have web-based patient or caregiver data entry regarding the COVID-19 effects on ALS moving forward.

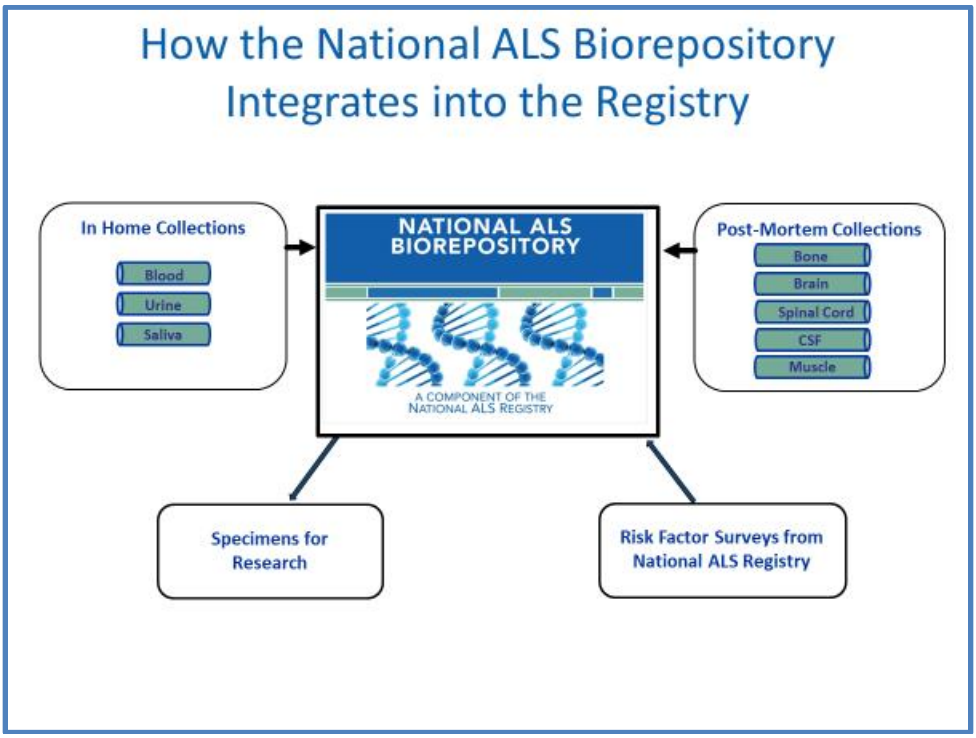
Long-term needs for COVID-19 ALS case rate / case fatality rate include: 1) an assessment of the National ALS Registry to determine the effect of COVID-19 National ALS Registry web recruitment, forms completion, data utilization, and the effects on ALS Biorepository recruitment, specimen collection, and specimen utilization; and 2) an assessment of the economic environmental effects of COVID-19 such as changes in the incidence and prevalence of ALS based climate changes and pollution levels.

Update on the National ALS Biorepository

Laurie Wagner, MPH
National ALS Biorepository Coordinator
McKing Consulting Corporation

Ms. Wagner presented a brief history and update on the National ALS Biorepository. A pilot study was conducted that lasted for about 4 years from September 2012 through September 2015 to determine the feasibility of having a Biorepository within the Registry. At the conclusion of the pilot study, this was determined to be feasible and ATSDR was funded to continue the National ALS Biorepository, which is currently being conducted. ALS patients enrolled in the National ALS Registry can now sign up to learn more about the Biorepository. New enrollees

can agree to receive more information about the Biorepository during registration, while previously enrolled participants in the Registry can update their accounts. The McKing Consulting Corporation receives a monthly list of enrollees interested in the Biorepository and sends out packets to enrollees to provide them with more information. Those expressing interest were contacted by McKing Coordinators to go over the project information, consent them, and set up appointments for the phlebotomist to visit their homes to collect samples. This diagram illustrates how the National ALS Biorepository integrates into the Registry:



Biorepository participation from January 4, 2017 through June 30, 2020 resulted in consent of 931 participants for in-home blood and urine samples, 197 for saliva samples only, and 34 post-mortem samples. The number actually collected during that timeframe included 884 in-home blood and urine samples, 202 saliva only samples, and 27 postmortem samples. COVID-19 has impacted in-home collections. On March 17, 2020, all in-home collections were cancelled and have not resumed. Pre-COVID, there was an average of 20 monthly sample collections. Since COVID-19, there have been 20 saliva and 1 blood sample collections completed. The blood sample was collected because a participant called McKing when en route to their phyisican. They already had a collection kit, which they took with them to the doctor's office where a sample was completed. The McKing Coordinator contacted the doctor's office to provide general guidelines, and the office was able to collect the sample successfully. This collection demonstrated that it is still possible for the Registry to institute alternative ways to cotinue Biorepository sample collection. Saliva kits are still being sent to participants. With the continuation of the pandemic, it is going to be necessary to consider alternative means to contact participants who are interested.

In terms of the demographics of Biorepository samples during the January 4, 2017 through June 30, 2020 timeframe, there have been participants from 50 states and Puerto Rico. In-home participantion includes 53% male and 37% female, with the age distribution as expected from participants with ALS. An effort has been made to ensure that there is an even distribution of urban and rural participants.

The Biorespository sample inventory is shown in the following table and is inclusive of pilot study participant samples as well:

Sample Type	# of Aliquots	Aliquot Size	# of Participants
DNA	22,974	2 µg	1,335
Hair	241	40 strands/vial	157
Nails	268	10 nails/vial	268
PBMCs	1,450	500,000 cells/vial	73
Plasma	9,285	.5 ml	1,151
RBC	3,854	1 ml	1,149
RNA	9,984	2 µg	1,151
Serum	7,157	.5 ml	1,143
Urine	10,046	1.8 ml	1,062
Urine with Hg Preservative	690	4.5 ml	687
Whole Blood	2,754	1.8 ml	1,133

Urine, nails, and hair are no longer being collected. However, the samples previously collected remain in the Biorepository inventory. This decision was based upon specimen demand. Each year, a survey is conducted and an assessment is made to determine what samples researchers are requesting. If there is a need and/or future demand, it would not be a problem to add these items back to the collection kits.

Post-mortem specimens include brain and spinal cord (frozen and fixed), CSF, bone (stored in formalin), muscle (stored in paraffin blocks), and skin for fibroblasts. To date, post-mortem samples have been collected from 48 participants, 6 participants withdrew and did not donate, and 10 participants continue to be followed. The samples collected from all 48 participants include brain, spinal cord, CSF, bone, muscle, and skin. Human primary cells have been collected from 28 participants. In terms of the participants who withdrew, some simply joined other registries. Regarding the demographics of the post-mortem collections through June 30, 2020 and including pilot participants, collections have been from 24 males and 24 females. There also is an even distribution of males and females among the 10 participants who continue to be followed, so there will be a good balance among the samples collected.

Regarding the researcher requests and sample distribution, the platform to distribute samples was launched in 2017 at which time researchers were able to go to the Registry web page to complete their application and request samples. There was a lot of outreach in place already, but this had to be elevated because a lot of travel has been curtailed due to the pandemic. Outreach has been done via websites/pages, attending meetings, journal ads, and referrals from other federal agencies in requests for proposals. Some of these methods also were utilized before the pandemic to engage in outreach at international conferences that could not be attended in-person. If it is not possible to attend out-of-country conferences, the Biorepository would send the 1-page flyer and/or other information to be placed in participant folders or bags.

They attended a virtual conference recently that was in Glasgow. While the times were challenging, they have had a lot of inquiries to request further information. They were able to exhibit virtually for 5 days and the exhibit will be in place until October. It is anticipated that they will move toward a lot of virtual meetings and virtual exhibits in the near future. The Society for Neuroscience (SfN) every year, which has not moved to a virtual platform at this point, but there typically has been a lot of contact from that conference. They also attend meetings such as ALSA's Advocacy Day, during which the Biorepository team has done a lot of outreach and collected samples. A few researchers have reached out because of advertisements, one of whom has been approved. Outreach has been very good and has resulted in very good feedback.

With regard to the process for acquiring samples, a researcher submits an application and all supporting documentation online (research application form, cover letter, full protocol, sample request forms). Completed applications go through multiple reviews (laboratory expert review, scientific review through ATSDR's review committee). The researcher must have Institutional Review Board (IRB) approval from an accredited IRB in order to be approved for the request for samples. After approval from ATSDR, the researcher signs the Material Transfer Agreement (MTA) and pays the invoice. McKing selects the appropriate samples and the laboratory pulls and ships samples to the investigator. The process typically takes about 2 to 3 months and varies per request. A total of 13 requests have been made since distribution of samples was implemented, some of which are from other countries. This table shows research requests in the past year, all of which have been approved but some of which have not yet been fulfilled:

Description of Project	Group Conducting Analysis	Sample Types Requested
RNA Sequencing-Based Drug Discovery Gene in ALS	Cerevance, Inc.	Serum, brain, spinal cord
Assessment of Unbound Free Fatty Acids in ALS Plasma	Center for Neurologic Study	Plasma
Biomarkers in Neuronal Exosomes for Assessment of ALS Progression	University of California Los Angeles (UCLA)	Serum
Genotyping of Samples from the Biorepository	NIH/ATSDR	DNA
LBT-3627: A Novel Immunomodulatory Disease Modifying Approach to ALS Treatment	Longevity Biotech Inc.	PBMCs
The Influence of Inflammation in the Progression of ALS	University of Vancouver	Plasma

COVID-19 has had an impact of researcher requests due to limited outreach capabilities, receipt of fewer applicants, less interest in the Biorepository since patients are sheltering in place, and inability to fulfill requests for applicants who have been approved because of shipments being on hold due to customs limitation and/or due to laboratory facilities being closed.

The take home message from the Biorepository is that it is an integral part of the National ALS Registry. COVID-19 has impacted Biorepository operations significantly in terms of sample collection and distribution. Nevertheless, researchers can continue to request samples for their studies. To date, 13 researchers have been approved and more than 8,700 samples have been distributed. However, no applications have been received since COVID-19. Persons with ALS can take part in the Registry and Biorepository even if they have donated specimens to other biorepositories/studies. The Biorepository is still running and there are still staff members who can answer questions and emails. The Biorepository will resume full activities post-pandemic.

Enrollment in the Registry & Web Portal Update

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

Ms. Raymond presented on Registry enrollment, user interface, data requests for the last 12 months, Massachusetts Department of Public Health (MDPH) collaboration, the new survey, password expiration exemption, and inactivity delay. In terms of web portal enrollment, there has been a 12% decline in registrations compared to early 2019. This is most likely attributable to COVID-19, but ATSDR is undergoing new awareness campaigns in 2020. COVID-19 has resulted in a suspension of in-person outreach activities and has been impacting partners' activities as well. As mentioned, ATSDR is in the midst of looking at new awareness campaigns in 2020. Over 90,000 surveys have been completed to date and there is demographic information on almost 10,000 patients. Survey 1 (Demographics) was launched at the same time as the Registry, so all of the years are available for this survey. Each participant is given up to a year to complete Survey 1. For the last 3 years, completion has remained fairly steady and just under 60% of those who have registered. Completion has held steady for the rest of the surveys as well. This table reflects the number of surveys completed to date as of July 9, 2020:

Risk Factor Surveys-Taken After Registration

Survey (n=17)	Release Date	No. Completed
Demographics	October, 2010	9910
Occupational history	October, 2010	8994
Military history	October, 2010	8798
Smoking and alcohol history	October, 2010	8639
Physical activity	October, 2010	8288
Family history of neuro. diseases	October, 2010	8067
Disease progression (ALSFRS)	October, 2010	8092
Clinical data (e.g., devices used, body onset)	November, 2013	3533
Open-ended etiological questions	November, 2013	3204
Lifetime residential history	May, 2014	3913
Lifetime occupational history	May, 2014	3891
Residential pesticide use	May, 2014	3641
Hobbies with toxicant exposures	August, 2014	3362
Caffeine consumption	August, 2014	3150
Reproductive history (women)	August, 2014	1702
Health insurance status	December, 2014	2843
Head and neck injuries	December, 2014	2804
Total (as of 7/9/2020)	---	92,831

In terms of ongoing and future analyses with these surveys, ATSDR is working in conjunction with Dr. Pam Factor-Litvak at the Columbia University on Survey 5: Physical Activity. The analyses have been completed and the manuscript written and is under internal review. In conjunction with Dr. Erik Pioro at Cleveland Clinic, ATSDR is working on Survey 12: Hormones. The analyses have been completed and the manuscript is in development. Two Biorepository analyses are underway. One will assess blood metal levels and the second is an analysis of persistent organic pollutants (POPs) by Dr. Evelyn Talbott and the University of Pittsburgh.

Survival analyses are being assessed for those with limb versus bulbar onset using the clinical characteristics survey. Military history and survival analyses are being examined in conjunction with Dr. John Beard at Brigham Young University (BYU). There also are a couple of non-surveys analyses underway that are examining Atlanta and Chicago metropolitan area surveillance papers.

Each year, ATSDR creates an analytical dataset and researchers can apply to receive portions of that dataset. In the last 12 months, 4 universities have applied, been approved, and received the data requested. These include the following:

- ❑ University of Nebraska: Social factors and progression; healthcare choices on ALS patients
- ❑ Oregon Health & Science University (OHSU): ALS and fungal poisoning
- ❑ Columbia University: Heavy metal water contamination and ALS
- ❑ A.T. Still University (ATSU): ALS prevalence and risk factors

As mentioned earlier, ATSDR is collaborating with NeuroBANK™ and has created a NeuroGUID™ for each patient who has consented for this project. They will be matching these up with NeuroBANK™ patients. To date, just over 4000 participants have wanted their NeuroGUID™.

Last year, ATSDR applied to the Massachusetts DPH IRB to gain data from their state registry. This was approved in November 2019. In March 2020, ATSDR received its first batch of data from the Massachusetts DPH ALS Registry. They originally received about 700 patients who had a diagnosis date between 2011-2015 and recently received 300 more. They were matched on the entire National ALS Registry, which is the web portal data, plus the administrative data. Approximately 70% of the patients from the Massachusetts DPH matched in the National ALS Registry. The majority of Massachusetts DPH cases not in the National ALS Registry were non-white and less than 60 years of age. The analyses are being finalized and a manuscript is under development, with the full results anticipated to be published by the end of 2020.

Moving on to some updates on the web portal interface, based on comments from previous meetings, the addition of a status bar to show survey completeness for PALS is currently under development. The look and feel of the surveys will be changed to make them more responsive for mobile users and easier to navigate in general. A new sports survey will be coming online soon. User testing is underway and the survey is anticipated to be launched in the next 1-2 months. The focus of this survey is on high-risk sports to assess traumatic brain injury (TBI) risk, which differs from the physical activity survey that focuses more on oxidative stress (OS).

In terms of web portal enhancements, a major complaint from patients has been the expiration of log-in passwords every 3 months. ATSDR has worked diligently to change the expiration dates to either 6 months, 12 months, or indefinitely. This will be available for existing and new patients who are registering in the portal. The inactivity reset for users is also being changed from 6 months to 1 year in the hope of capturing more ALS Functional Rating Scale (ALSFRS) scores from patients. Both enhancements will be launched before the end of August 2020. In addition, the race question was moved from Survey 1 to the Registration section of the web portal in order to allow for capture of race in the event the patient does not complete surveys.

In conclusion, the National ALS Registry values patients' feedback and is working to implement user-friendly enhancements to improve patients' experience on the website. They are constantly looking to make changes and enhancements to advance data collection practices and methods, ensure that quality data are captured, and facilitate dissemination of data to researchers.

Questions and Discussion

Darcy Peth, MS
Associate
Ross Strategic

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

Discussion Points

Dr. Finger indicated that he is a patient who was diagnosed about 7 years ago, so he has been attending this meeting for a while. He said that while he understands that it is a difficult time for everybody, he wanted to make sure they all still have their "eye on the ball." With regard to Dr. Mehta's presentation, he was a bit disappointed not to be able to see any data on how the Registry is doing in terms of enrolling patients and picking up patients in the administrative data. Everyone was told that reports would be published annually. Understandably, sometimes deadlines are missed as was the case with last year's meeting. However, they were told during last year's meeting that this paper was almost complete and to expect it in November 2019. He was very frustrated that on the first COVID slide, the prevalence paper was said to be delayed because of COVID. However, that paper should have been out by August 2019. In August 2019, they were told it would be out in November, if not early Winter. To use COVID as an excuse shows that they are just trying to push stuff under the rug and move on and this is not being taken seriously. That is his concern with the Registry each and every year. There is an annual meeting that is meant to serve as an advisory board meeting. Yet, most of the discussion is about what has happened over the past 12 years and not what has happened over the past year. The purpose is said to be about risk factors, demographics, incidence, and prevalence. But then in the update, the only thing discussed is notifications. That is not meant to be the purpose of the Registry. Getting into specific questions, everyone has waited 2 years for a capture-recapture paper. However, this technique has been used before with ALS with very mixed results. In 2013, there was a paper published by this exact same group that showed all the limitations of the method. It showed that the estimates are not reliable because of the way data are collected. Then miraculously in 2018, another paper came out that totally ignored all of the findings of the 2013 paper and said even accounting for missing cases, there are 12,000 people a year living with the disease—a totally bogus number. Instead of saying that this is a potentially flawed method and the results show that maybe it is not working right, they tried to pretend that 12,000 patients, even including missing cases, was the level. He cannot buy that. They have to do better. There has to be someone taking the responsibility to be honest about what is being found. Secondly, in terms of the Biorepository and the surveys, there was no discussion about demographics in terms of race and other socioeconomic factors. That cannot be the case. It is known they are doing very poorly in terms of capturing minorities or disadvantaged populations. The first Registry annual report said that 18 Black patients were found through the portal. Then a paper was published looking at survey responses and it was 95.5% White. Race is not reported in terms of the Biorepository or survey completion. He wondered what they are afraid of. This is not a problem specific to ALS. This is a problem with all registries, but that does not mean they can ignore it. Lastly, with the Massachusetts paper, only 70% of patients could be matched. Why is that number scary? If the majority of the 30% is non-White, that should raise enormous red flags. Enormous. That means that over 15% of the cases are non-White, yet they are working with surveys that say 95.5% of the cases are non-White. They have to be honest about that. Dr. Finger expressed his hope that throughout the

meeting, other participants on the call also would insist that they are honest about what they are doing and what they are not doing.

Dr. Mehta thanked Dr. Finger for the questions and feedbacks. He explained that regarding the 2016 prevalence report, some additional analyses had to be conducted that delayed the report. They also have to cite the methodology. They can agree to disagree with regard to capture-recapture. Dr. Lorene Nelson is the Stanford University Subject Matter Expert (SME) Professor there who published on capture-recapture on 2002-2004. Nothing was published in 2013, but they will be publishing on 2014.

Dr. Finger said that they cannot just lie.

Dr. Mehta emphasized that they could agree to disagree about capture-recapture. It is the only methodology they have right now in epidemiology that can look at existing cases and estimate the under-ascertainment of cases looking at various data sources. There are very few ways to do that. Capture-recapture has been validated. The premise is that capture-recapture is what is being used for ascertainment of the cases for 2016. ATSDR is going to publish two prevalence estimates and case counts for 2016 that will show the algorithm and the estimate using capture-recapture. He said that he understood that Dr. Finger did not agree with capture-recapture. He, Dr. Nelson, and Dr. Kaye have communicated this to him. However, that is the method that will be used.

Dr. Finger clarified that it is not that he does not like it. It is that in 2013, a paper was published with a number of ALS Registry items listed as co-authors looking at Atlanta and it used clinical data, administrative data, ALS Association data, et cetera. That paper concluded that the method was very problematic because of the way data are collected. People who show up in one bucket are likely to show up in the other bucket. Minorities are harder to deal with. It is not as if he has this problem with the method. It is that he has problem with the authors in 2013 saying it is problematic and that they have to be careful, but then in 2018 the same authors are publishing numbers that are absolutely nonsensical in saying, "Look. Proof of concept." In August 2019, they were given an apology about the delay and told the paper was expected in November. In August 2020, they were given an apology about the delay and told the paper was expected in November 2020.

Dr. Mehta emphasized that ALS is a non-reportable and non-notifiable disease. Epidemiology is not an exact science. These are only estimates of the cases they have. This is the same for Parkinson's, multiple sclerosis (MS), and Alzheimer's. ALS is non-reportable, meaning that it is not reported at the state level. It is non-notifiable, meaning that states do not report it to CDC. Because of that, what they report and have always said is that these are still estimates and it is not possible to provide definitive case counts or definitive prevalence. That is always stated in ATSDR's papers. While he understands Dr. Finger's frustration, he stressed that ATSDR is doing their best to capture the cases they can in the US with what they have. Currently what they have are the Medicare and Veterans Affairs (VA) data bases. Because of ALS, its unique qualities, and unique ability to collect Social Security Disability Insurance (SSDI) and Medicare below the age of 65, it is possible to capture those cases. Of the cases captured, 80% come from Medicare and the rest come from the portal and VA system. Across the board, the government always has been very conservative in reporting case counts. In 2015, case counts were almost 17,000. For 2016, there is a difference. There will be an increase in case counts for 2016 using capture-recapture. Dr. Mehta stressed that he wished the paper was ready 2 or 3 months ago. However, there are internal processes, internal reviews, additional data analyses, and the publication of the 2014 methodology for capture-recapture that they need. Capture-

recapture has to be published first so that ATSDR can cite it in their paper. Otherwise, they will have a question internally about what the methodology was based on. Dr. Nelson is currently working on that manuscript to submit to the journal. While he shares Dr. Finger's frustration, it is important to keep in mind that ATSDR does much more than just count ALS cases. ALS is a horrible disease and they want to make sure they are looking at the entire gamut of the disease with respect to epidemiology, biomarkers, causes, and risk factors. The clinical trial system has been extremely successful and ATSDR wants to make sure that drug companies are aware of that, because there is a hunger for clinical trials. They want to use this system to inform patients about the clinical trials that are available to them. More importantly, ATSDR is also funding research. They currently have 17 investigators and plan to add more. These are researchers from top-notch universities around the country who are conducting research on the etiology and risk factors for ALS. Dr. Mehta stressed that he shares Dr. Finger's frustration, but the report will be published.

Dr. Finger asked whether there was any response from Ms. Raymond or Ms. Wagner regarding demographics.

Ms. Raymond indicated that she could respond to the Massachusetts question that Dr. Finger asked. ATSDR is collaborating with them, but the Massachusetts registry is very different from ATSDR's. In Massachusetts, physicians are required to send the data to the department of health, whereas, CDC/ATSDR does not have that kind of mandate. If there is a private insurance patient who has not heard about the web portal, ATSDR would not get that data. They only get data from Medicare, the VA, and the web portal. There are some ways that the Massachusetts cases might be coming in that would be a way that they would never come in such that ATSDR would see them. ATSDR is continuing to analyze that data to determine differences. She emphasized that because this is not yet published, she could not release a lot of information about it. They just received the data in March 2020, so ATSDR is having monthly calls with the Massachusetts Department of Public Health (MDPH) to go over the data. They originally received 700 and now have received another 300 more cases they are trying to match up. ATSDR knows there are differences and expects there to be differences. They did not expect to get 100%. ATSDR also has cases in its system that were not in the Massachusetts system. ATSDR did not receive all of the information they asked for, such as Social Security Numbers (SSNs). They have names, gender, and month/year of birth. They did not use residence as a qualifier because they know patients can move around and they did not want to not match patients just because they have since moved out of Massachusetts, or when they registered for the portal were not in Massachusetts and have since moved. They do not have race for a significant number. There probably are going to be some matches that will not match up based on the data they received from the MDPH.

For the third time, Dr. Finger asked Ms. Raymond and Ms. Wagner about the demographics of patients in the biorepository and survey respondents and if response rates were still minuscule for minorities. Ms. Raymond indicated that survey respondents were still over 95% white. Ms. Wagner stated that even a greater percentage of patients in the biorepository were white.

Dr. Siddique congratulated Dr. Brooks for taking the lead on COVID-19 and ALS. Regarding the MS data in which Dr. Brooks showed that [fading in and out] seemed to have done better if he recalled correctly. That brings up the issue of severity of disease. In terms of incidence in case of ALS, many patients are very conscientious about sheltering at home, avoiding contact, and so forth. This raised the question of how one compares controls of a similar type. In the MS situation, Dr. Brooks said that the ambulatory cases did better. But one would think that they were more likely to be infected.

Dr. Brooks responded that the European registries that were comprised of patient- and physician-reported data used an item called "Outings" that has information about how many times people left the home. They are trying to estimate social distancing by this kind of measurement. Many people have felt, even before the American with Disabilities Act (ADA), that disease is socially isolating in and of itself. The question regards whether the rates being seen are related to the isolation caused by the disease or if it also is a public health measure on the part of the patient and the family. Those data are not in their survey because they are using the NEALS survey mechanism. They need a COVID ALS registry to get an idea of the impact of the disease on the patient and whether there are any changes in the severity of the disease as a function of the underlying status of the disease and/or its treatment.

Dr. Traynor indicated that he works at the National Institute on Aging (NIA) and thanked everybody at the Registry for their hard work. He thinks that over the years, the Registry has increasingly emerged as a serious player in the ALS sphere and now represents an impressive resource that is being broadly used across the community, with a similarly impressive list of papers that are coming out increasingly, and acting as the hub or spoke of a pattern of projects that ATSDR is undertaking. He applauded the integrity and professionalism with which ATSDR is approaching this difficult area and pointed out to the audience in general that really, if this was easy, it would have been done already. What everyone is trying to do is really quite hard and explains in many cases sometimes the delay with which these things come out. He thinks that is a very important aspect to keep in mind when addressing these issues. He asked whether the registry is making an effort to collect residential history. There has now emerged a technique for quantifying an individual's exposure to different metals and different environmental toxins based on where they have lived and where they have worked. Therefore, what was previously a qualitative measure can now be converted into pretty quantitative formats. There are registries around the world that are approaching ALS in this manner, and it would be great if these could be merged together, or at least use one as a replication of the other.

Dr. Mehta indicated that ATSDR does collect the particular aspect of where one has lived from birth to current residence. The hope is to superimpose this on the GIS data to determine where there are areas of higher activity, potentially of Superfund sites and other areas of higher contaminants around the country. This is pretty time-intensive because they have to have the GIS folks overlaying the various sorts of areas of concern. He thinks it is certainly worth exploring and is an endeavor that ATSDR would like to undertake in a year or so.

Dr. Kasarskis pointed out that ALS is not a singular thing for which there is a biomarker unless a patient happens to have a genetically-based disease. He said that Dr. Mehta's comment about estimates of disease, incidence, and prevalence is the best that can be done. It is an estimate and there is an error around clinician diagnosis. When a clinician is facing a patient wondering whether they have ALS, they do not have a biomarker or a definitive diagnostic test and cannot image their way out of it. They eliminate ALS mimics. There is an aging population and many other things that can cause progressive weakness. The only downstream marker is progressive weakness and, of course, there are many causes of that in an aging population. Compared to autopsy confirmation, neurologists do a fairly decent job of diagnosis, but it is not 100%. Every methodology has a certain intrinsic error rate. That is why Dr. Mehta's comments about using the term "estimate" is absolutely well-taken. He recalled early discussions about the Gulf War registries, during which the discussion pertained to just making a quick diagnosis based on Gulf War veterans who have ALS. Nothing is quite that simple. There must be appreciation for the fact that when looking at population estimates, these are numbers that come through a tremendous filter, so there is going to be some uncertainty about what there is that gets magnified down the line when it is finally rolled up into some sort of Executive Summary, one-

pager, or slide on a Power Point. He did not think the words were intended to be evasive, but instead were intended to be scientifically well-chosen. They must understand what the Registry can and cannot do. It starts with the phenomenology. Hopefully, that will change with further research and there will be an ALS test, just like diabetes such that there will be an A1c for ALS. That will be very helpful to doctors and patients both.

Dr. Thakur from the ALS Association said he agreed with the conversation and the points being raised about prevalence estimation and how difficult it is. He also agreed that there are errors and there can be a lot of debate on what that should be. He also was hearing that there are challenges in getting that information. Some of those challenges seem to relate to technical, workload, and internal clearance process issues. As Dr. Finger pointed out, they keep meeting and talking about these numbers. This is an advisory group or more of a scientific meeting than anything else. With that in mind, he wondered whether this was the right structure and whether the Registry is getting the oversight to help convey to ATSDR and CDC that these numbers are really important to the ALS community, that they need to be prioritized, that it is understood that they are never going to be perfect, but getting numbers out that can be debated and discussed is more valuable than having them go through a very careful process. He would love a pre-print that is labeled "Draft" that the community discusses so that everyone can be open about the challenges. He wondered to what extent the issues and processes are driven by the fact that this annual meeting is the place to provide input to CDC and ATSDR about what they are doing. He remained uncertain about whether this is the right format.

Dr. Mehta indicated that ATSDR's report is always published in CDC's *Morbidity and Mortality Weekly Report* (*MMWR*) report. The internal clearance processes are not really the issue. CDC is very rigorous in their science and wants to make sure everything is reviewed. As noted earlier, they have to wait for the citation for the capture-recapture methodology in the external journal so CDC can cite it in the actual report itself to show the methodology upon which the new estimates are based. He thinks the *MMWR* is the appropriate journal because ATSDR has a way to work internally with their colleagues in the office that handles this particular journal, and they are great to work with. The frustration is in making sure that the data they are going to be reporting is accurate, confirmed, and validated. There is certainly support internally from ATSDR and its Office of Science, so there is no question about it there. CDC is very careful when it comes to reporting information to the public, whether it is on ALS or any other disease.

Dr. Thakur clarified that he was suggesting that ATSDR/CDC should be able to put forward a draft estimate 6 months ahead of time, which to him would not undermine the field in any way. Everyone knows the final number is going to be an estimate. While he understands that ATSDR is waiting for the citation of the methodology paper that is not published yet, they all recognize that that methodology in itself is going to be controversial. They should keep the conversation moving forward rather than having drafts that are working that cannot be shared.

Dr. Mehta said he understood, but if he were to share the number which they have and cannot provide because it is currently under review and so forth, it would be like asking researchers to present their findings before they are published. Their particular institutions may be upset with that. With the way CDC's rigorous processes work for scientific review, they cannot publish any data that have not been reviewed, even if it is preliminary data. There is a possibility that they could provide some sort of ranges, but even that could be something he will have to discuss with the Office of Science and the *MMWR* editors to determine if it is possible. A number of years ago they were going to present the data generically before the report was published and were told they could not do that because "once the cat's out of the bag" they cannot put it back in. CDC is very cautious and wants to make sure everything is fine before providing approval to

publish the paper. In the past before these papers are published, they have had a meeting with the partners to let them know what the numbers would be. They probably will do this again as they get closer to the publication date.

Dr. Thakur pointed out that this conversation was getting at the crux of the issue about the governance and oversight of the Registry. The fact that this is a meeting means that he could ask a question, Dr. Mehta could provide an answer, and that effectively could be the end of the discussion. As a group that generally meets every year and generally has a pretty consistent opinion that they want this information out sooner, they do not have a formal way of advising on what they think the right course should be. If this was an actual governance committee, they would suggest that this would be an agenda item, they would discuss it, and then they would have a recommendation. However, they do not have a venue to do that. Therefore, it is Dr. Mehta taking the heat for a system that he does not control. He does not think anyone feels that they are really serving the community in the most efficient way possible, because there are numerous considerations which go beyond ALS and they are focused only on ALS.

Dr. Breysse said he would help the program in whatever way he could to address these issues going forward. While he does not think it is clearance per se, he will be happy to talk to Dr. Mehta and others if there are issues on clearance in terms of how to address that. He noted that an issue was raised during the discussion that is being discussed more broadly in the academic world about the use of pre-prints and the value of submitting a pre-print somewhere. Most recently that debate came up on an article in the newspaper about air pollution COVID that Harvard published in a pre-print journal. It was meant to get out quickly but was roundly dismissed in the policy-setting world because it was not yet peer-reviewed, which is what they are conditioned to believe. The discussion about the value of pre-prints is occurring throughout the scientific community, not just with CDC, in terms of managing expectations when drafts change in peer review—sometimes drastically.

Dr. Horton commented that when this Registry was first started 10 years ago, a decision was made that ATSDR would not have an official advisory committee. The reason behind that was because the typical federal advisory committee is very restrictive in terms of the number and type of people and various disciplines on the committee. They decided instead to establish a group comprised of the broader community of patients, scientists, and researchers in order to offer more people an opportunity to give their feedback.
In terms of the Biorepository, Dr. Dave asked whether recipients of samples are asked to report back to ATSDR about the quality of the samples to ensure that collection was done in a particular way. For example, if someone is looking at PBMCs or serum and serum protein is very low in the CDC sample, it may have been collected incorrectly.

Ms. Wagner replied that a survey is sent to the researchers every year so that they can report general information. ATSDR has open dialogue with the researchers frequently. Any researchers who are not able to process or run any of their tests would let ATSDR know and would request another sample from us. That has not happened so far.

Regarding Dr. Traynor's comments regarding residential history, Dr. Weisskopf agreed that much could be done with geolocations. It has been said that this is a difficult section because there is a long history to obtain. From the perspective of air pollutant exposures, the models do not go that far back. They go back to 1990ish at the earliest. If there is a tradeoff between time and burden on the participant versus getting information that investigators can do their best to assign exposures to, there is probably no reason that residential history is more relevant from the perspective of being able to assign a good exposure level. That is probably true for methods

that are coming out for things other than air pollution. This is just a balance to consider when thinking about participant burden.

Dr. Mehta acknowledged that the residential survey is typically one of the more complex surveys, and that it is good to know that 1990 would be the cutoff date at which to cut off the analyses with GIS and so forth.

Dr. Weisskopf noted that there are two key periods, such as births and very early childhood, that he might try to get anyway.

Dr. Traynor said he thinks that there is more to it than just air pollution, such as water quality. He thinks there is still value in trying to capture everybody's residential history. This is so sophisticated in certain European countries that with the location of where somebody lived and on what floor, their exposure to electromagnetic fields (EMF) can be calculated. Without starting data, it is going to be difficult to compare and contrast. He would favor collecting more of the residential history.

Dr. Weisskopf agreed with getting as much information as possible, but the issue pertains to what the EMF maps are good for. It is important to pay attention to the models that are going to be used to assign the exposure, because if they do not go back to 1950, there is not so much sense to collecting residential history back to 1950. Prior to 1990, maps for air pollution are not great. Water in the US is another question.

Dr. Factor-Litvak emphasized that residential history is incredibly important.

Regarding Dr. Breysse's point about the peer-reviewed literature, Dr. Finger recalled that in 2014 they were told that the annual prevalence estimates would not be put in peer-reviewed journals because of the time it took to go through the publication process and that is why they are in the *MMWR*. Now they are saying one of the reasons these results are held up is because they are waiting for a publication in another journal. To him, that sounded like the worst of both worlds. They are delaying but are not actually going to peer review the estimates.

Dr. Breysse said that he considers the *MMWR* to be peer-reviewed. It is listed in the Scientific Journal Rankings (SJR), so it would be a mistake to consider it as not being peer-reviewed.

Dr. Mehta confirmed that the *MMWR* is definitely peer-reviewed.

Partner Updates

ALS Association

Neil Thakur, PhD
Chief Mission Officer
ALS Association

Adam Baker
Manager, Public Policy Initiative
ALS Association

Dr. Thakur expressed his gratitude for the invitation to present during the 2020 National ALS Registry Annual Meeting. He indicated that he and Mr. Baker would be speaking about what the Registry means in terms of what the ALS Association does, what the ALS Association is doing for the Registry, and how this all fits together. He reminded everyone that the ALS Association funds research; provides services to over 20,000 people with ALS and their families throughout

the country; and runs a national advocacy program to help create a world without ALS. Basically, that means that they are trying to help people with ALS live the best quality of life that they can and a longer life as well by connecting people to world-class care and the most effective treatments available. When people tell him that they have ALS in their family or that they have just been diagnosed and ask what that means for their family, he does not have a lot of good information to tell them. If someone carries an ALS gene, there is not much that can be said to help them. If a gene has not been identified but someone is known to have ALS, there is little that can be done for that family to help manage their risk. What can be done to help prevent ALS, delay the onset of ALS, or prevent ALS from progressing in those who have early symptoms? Those are all really important questions, and the Registry is a key component of that.

As touched on earlier in some of the other presentations, COVID-19 has dramatically changed service delivery for ALS. There is a network of about 90 multidisciplinary clinics that the ALS Association supports around the country, almost all of which are using telemedicine to support their services in some way and have modified their service delivery. A lot of the work that the ALS Association does to engage people into the Registry happens at clinics. If people are not going into clinics. That creates challenges for enrollment. They also do a lot of enrollment through walks and events. They have had to modify those as well because of COVID-19 because it is hard for people to gather, which has changed the way that they are able to engage people. They have been making modifications and are assessing how they work.

Dr. Thakur said he wanted to frame the ALS Association's understanding of how the Registry works. The Registry is a tool that connects and impacts many other parts of the "ALS ecosystem" pipeline to a cure. The standard drug development pipeline involves the basic science of ALS, pre-clinical drug development, and Phases 1/2/3 clinical trials. There also is the public health pipeline, which pertains to taking an idea from a concept where a risk factor has been identified to turn it into information that is applied to people. That is the other part of the pipeline that NIH normally does not talk about, but that he wanted to make sure it did not get missed. The Registry is impacting almost all aspects of both the drug development and public health pipelines. The specimen repositories can help support basic science or the understanding of what ALS is and how it might work. The Registry itself in the surveys are helping to identify risk factors. Some of the funding is happening in that space as well. There also is the recruitment effort of using the Registry to help enroll people in the clinical trials. All of these parts make the Registry an integral part of the ALS research infrastructure.

Mr. Baker observed that while there are aspects of the Registry that could be improved upon, it is a valuable asset to both researchers and people living with ALS. It provides the essential connective tissue between the data that underlies research, understanding the demographics of the disease, expanding understanding of environmental and other risk factors, and helping people living with ALS understand what clinical trial opportunities might be available to them. No other ALS database has national reach, which allows the CDC to map trends and better understand the demographics of the disease. Data from risk factor surveys and the National ALS Biorepository inform early stage research funded by the registry and by the private sector. These risk factors surveys help researchers determine patterns that hopefully can facilitate future preventive activity. The National ALS Biorepository helps link the risk factor surveys and physiological indicators, is bringing a new dimension to understanding the disease, and draws in people living with ALS because it is somewhat more exciting than just filling out risk factor surveys. Finally, clinical trial notifications help fill the trials driven by the early stage research mentioned earlier.

Going into more detail about some of the specific promotional efforts the ALS Association has done with the Registry over the past year, the ALS Association periodically convenes meetings of both chapter and clinic staff to generate best practices and brainstorm around the Registry. This started with a chapter meeting in 2017, which was followed by a focus group of chapters and clinics in 2018. The suggestions generated during the 2018 focus group were sent to a larger group of clinic directors and staff in 2019 who were asked to rank those suggestions based on feasibility and effectiveness. One of the top action items was to increase the education of clinic staff. The ALS Association chose to address this through a couple webinars, both of which were hosted by the ALS Association and CDC. Both webinars took place in late 2019. The webinars covered basic information around the Registry like its purpose, different functions, some of the materials available for promotions, and general best practices. Both of those were extremely well-attended, although there was a little bit of overlap between the audiences. They have been going back and forth collaborating on ways to further refine the documents, and the CDC has been very responsive to that. Some of our suggestions included consolidating a lot of the information on the documents into a single handout that could be used more widely, and a more practically focused checklist document with a space for the password and to mark progress on surveys. This dovetails with things like the status bar mentioned earlier, which could be very helpful. The final big action item from that 2019 ranking of suggestions was a practice registry module. The test accounts are supposed to be an interim measure, with the hope that CDC will produce an instructional registration video. The test accounts are working out great in the meantime.

Another major suggestion from the 2018 focus group and subsequent ranking of ideas was to increase social media promotion, so a social media and email campaign was devised that is complementary to the Registry social media. All of the images and copy for this campaign came out of a video that was created at the 2018 National ALS Annual Meeting during which they had people living with ALS speak about what the Registry meant to them personally. Those have been used in copy and still images for social media. Pieces were created for Facebook and Twitter, and the whole video is being shown on YouTube. All of this social media has definitely had a demonstrable impact. They are still analyzing final metrics but are already at over 2200 click throughs at the halfway point in the campaign. That is definitely something they are looking forward to hearing more about. Not only is all of this having a demonstrable impact in the near term, but also it is going to lay the groundwork for future promotion because they are using these assets to create a toolkit for chapters that they can customize as they see fit so they can do Registry promotion on a more individualized level. That is something they are really excited about.

One of the ALS Association's biggest events this year, and one that is usually a fantastic opportunity for Registry promotion, was the National Virtual ALS Conference. Like so many events this year in response to concerns related to COVID-19, they went virtual for the first time from May 26-29. Programming consisted of a series of 4 90-minute webinars that were free and open to the public. While they would have loved to have experienced the sense of community and connection that this event usually inspires, there were some advantages to having a virtual event. There were over 1300 attendees across the webinars, of whom 260 were people living with ALS. That maximized the number of eyes on Registry promotion. In addition to the graphics provided by the CDC, they had individual speakers at the top of each webinar speak uniquely about what made the Registry important to them. This was a compelling form of Registry promotion, which they may want to do more of in the future.

Dr. Thakur discussed the new ALS Association survey platform, ALS Focus, which offers an opportunity for some synergy with the Registry beyond what is already happening. ALS Focus is

a survey platform that the ALS Association is creating to survey ALS patients and their caregivers at multiple points throughout the year, right now through an internet survey. The initial survey was on health insurance access, and there is a health insurance module in the Registry. This was a one-time data collection that they have the opportunity to update, as well as a small profile system. They are working on a second survey that is going to be about what people are looking for from drugs, their health status, and the things that they value in medications. It is designed to help support the patient-focused drug development activity and the advocacy program and provide a faster turnaround than what the Registry is doing. Of course, it is not focused on identification of risk factors. There are a couple of points that are important. One is all of the data will be de-identified and made available to the public. The second is that the ALS Association is working through NeuroBANK™ as is the Registry to assign a GUID so that there is the potential for interoperability between the ALS Focus survey and ongoing clinical trials and the Registry. They hope to work out some way to help remind people that if they are in Focus filling this out and are interested in participating in research, they can participate in the Registry. Focus can feed the Registry and the Registry has been supporting Focus in that they used it to help with Focus recruitment like some of the clinical studies.

The other collaboration the ALS Association will be involved with in the Fall is a small workshop with help from the Registry to develop a framework for how all of the different risk factors can be turned into guidance for people with ALS. Through its research and data, the Registry has identified a number of risk factors. Now the questions need to be answered regarding what to do with this and how to turn it into personal level information. A number of funders are involved in this process like the National Institute of Environmental Health Sciences (NIEHS), DoD, VA, and NIH. Different disciplines are involved such as clinicians, epidemiologists, and those who work to get a small group of scientists and funders together to map out this space and then thought can be given to how to support this translation pipeline more formally with funding support from the ALS Association and its government partners. This is the start of something that will build upon a lot of the work that already has been done.

There are numerous scientific, communication, and logistical areas in which everyone can work together. In terms of science, translating the findings that have come out of the Registry can have an impact on people with ALS and their families. In terms of coordination with other funders, the Registry is a small pot of money in a research space, but it is pivotal. Part of what the ALS Association thinks they can do as a group that is not in government is to help make sure that the findings coming out of the Registry are carried forward by other private, non-profit, and government funders. Some communication challenges were raised earlier in the conversation. For instance, it is important to be judicious about putting out non-peer-reviewed materials that could be misused by the community. Identifying a risk factor for ALS is something they must be very careful about. Putting information too soon before it is ready could be problematic. Consideration must be given to the tradeoffs between speed versus accuracy in everything they do because this work is so important. The ability to engage people of color in the science and into the Registry is important to understanding what is occurring with ALS. There are also linguistic and cultural barriers that need continued work. While it is great that they are starting to see some Spanish language documents, more outreach must be done with those communities. The ALS Association's partners from the Registry have been pushing them on that, which they are right to do. With regard to logistics, it is very difficult to get people in rural areas to participate in the registry. With increasing reliance on the internet to support recruitment and everything else associated with ALS, understanding prevalence, incidence, and risk will be much harder if people do not have good internet access. There is a nexus of internet, physical accessibility, and geographic problems that are in some ways intensified by COVID-19.

In addition, there are the fundamental challenges of a voluntary database. There is the example of the Massachusetts registry where reporting is required. It would help to hear more about that to ascertain the potential benefits of having a database that is not voluntary. Dr. Thakur emphasized that he did not want to miss the opportunity about the importance of prevalence estimates. He does not want those estimates to be accurate. He wants them to be ranges because he does not think it is possible to get an accurate estimate. In some ways, those are oxymoron in lay terms. Everyone will have to become comfortable with the idea that they are going to be putting out ranges. He thinks they owe the Registry a lot of gratitude for recognizing that this is an undercount and has been documenting these errors. They just need to keep moving forward in that space and get out ranges of estimates, which can help everyone with planning and the work that they all need to do. In closing, Dr. Thakur emphasized that the ALS Association would love to hear more feedback.

Muscular Dystrophy Association

Marydeth Guerin
Director of Care Center Grants
Muscular Dystrophy Association

Ms. Guerin said that she was pleased to be invited to speak about MDA's efforts in promoting the National ALS Registry through its platforms. For the past 70 years, the MDA has been committed to transforming the lives of people living with muscular dystrophy (MD), ALS, and related neuromuscular diseases (NMDs). They do this through innovations in science and innovations in care. As the largest source of funding for NMD research outside of the federal government, the MDA has committed more than $1 billion since its inception to accelerate the discovery of therapies and cures. Research that the MDA has supported is directly linked to life-changing therapies across multiple NMDs.

Organizationally, the MDA serves as a convening platform across and the muscular field bringing forth the intersection of research, care, support, and advocacy with the goal of advancing research and improving health outcomes for those living with NMDs. The MDA covers more than 43 disorders, including MD, spinal muscular atrophy (SMA), ALS, facioscapulohumeral muscular dystrophy (FSHD), and other related diseases that uniquely positions MDA to support and promote breakthroughs in research across diseases. The MDA works across disease-specific boundaries because research breakthroughs in one disease can help fuel the progress in others. There also is a strong connection between approaches to caring for NMDs and providing therapeutic interventions.

The MDA has a long history of leading and innovating in the NMD space and in the ALS community as a whole through its robust combination of programs and services. The MDA supports and advocates for all individuals affected by ALS in the US. Since inception, the MDA has attributed over $168 million to ALS research, including more than $18 million invested in the last 5 years. All individuals living with ALS have access to the MDA National Care Center Network, which includes more than 150 Care Centers, 48 of which are designated as MDA/ALS Care Centers. The MDA Care Center Network includes more than 2400 clinical providers. The MDA further supports the ALS community through offering free educational seminars for individuals living with ALS and their families and caregivers across the US.

The MDA is contracted by the ATSDR to promote the National ALS Registry by providing continuous outreach, education, and awareness to individuals living with ALS, their families and caregivers, and researchers using the MDA's channels and infrastructure. MDA remains committed to using every channel available to it to promote the National ALS Registry. This includes MDA's National Cancer Center Network, leveraging MDA staff members, using MDA's communication channels, promoting the Registry through MDA's community and educational events, and conducting research and MDA's advocacy initiatives.

The MDA's National Care Center Network infrastructure serves as a platform through which there is a unique opportunity for both MDA staff and MDA-sponsored Care Center Clinicians to connect with the ALS community regarding the National ALS Registry. MDA Care and Clinical Services staff share ALS Registry information materials and updates with PALS, caregivers, and their families as part of their MDA Care Center visit interaction. Additionally, MDA utilizes the Care Center Network infrastructure to provide promotional and educational information regarding the National ALS Registry to ALS clinicians who are then able to relay that information on to individuals living with ALS, caregivers, and families.

MDA staff members across the organization are able to directly interact and develop meaningful connections with individuals living with ALS, their caregivers, and their families. Through these connections, it is possible to empower the ALS community through promoting and educating about the National ALS Registry. MDA's Care and Clinical Services staff, which includes Care Specialists, have a number of touch points with ALS families. They are able to provide educational and promotional activities through MDA Care Center visits, focused call-out initiatives, outreach to newly diagnosed individuals with ALS, and sharing updates and information with MDA Care Center providers. MDA's National Resource Specialists provide ALS Registry information to PALS, caregivers, and families contacting MDS National Resource Hub for resources and information.

MDA is committed to equipping its staff with the knowledge and tools they need to ensure they are able to best promote and educate on the Registry. They accomplish this and seek to continuously improve upon this through a multi-point staff training plan that includes new hire training as they come on board, annual training, mandating participation in training sessions that are provided through the ATSDR team, and now leveraging the test Registry account to better familiarize staff with the Registry platform so that they are able to best assist PALS with navigating registration and ongoing survey participation.

Another large component of MDA's efforts to provide Registry promotion and education is through leveraging the communication channels available to MDA. One of the most powerful ways that MDA can support progress is through its multiple channels where they can directly connect with its patients, providers, and research communities. MDA is uniquely positioned to share knowledge and distribute information as comprehensively as possible through these channels. This includes a combination of MDA's national and local level social media accounts, including information about the Registry on our main ALS landing page on the MDA website, and including an educational page in MDA's quarterly publication of its *Quest Magazine* publication. These are all ways that MDA is working to get the knowledge and information into the hands of its community, researchers, and clinicians.

Another avenue through which MDA's promotional activities are geared to promote the National ALS Registry is through its educational and community events. MDA provides education about patient and clinician communities, incorporates educational promotional content on the Registry into MDA's educational and community offerings through including presentations during some of these seminars and events, and/or having informational booths at in-person events, and assisting PALS with registering upon their request. Several key categories at these events include MDA's Annual Clinical and Scientific Conference, MDA Engage Educational Symposia, MDA Social Events, MDA Muscle Walks, and MDA's Medical Education Webinars & Newsletters for Clinicians.

AS everyone is keenly aware, the COVID-19 pandemic has had significant impacts and continues to have a substantial impact. Although MDA has had to shift the way in which it delivers on its mission, this also has brought forth unique opportunities for MDA to reach and impact and even broader audience. MDA developed a COVID-19 landing page on mda.org which has a variety of resources and educational content to support the neuromuscular and ALS communities amid the pandemic. Many MDA Care Centers have had to make the shift to telehealth amid the pandemic to help limit potential risk and exposure, which in turn allows for many more ALS patients to continue having access to the care they need. Throughout this time, MDA Care Specialists have been supporting MDA Care Centers in their telehealth visits virtually and continuing to share Registry information through their one-on-one interaction with PALS as part of their Care Center visits.

MDA also has launched its first ever Facebook Live Event series, with the initial series focused on supporting the neuromuscular community through the pandemic and through these times of incredible uncertainty. MDA has engaged medical experts to answer the questions of the community and the families that it serves. The series featured an ALS Facebook Live Event with Dr. Matthew Harms of Columbia University to answer questions from the ALS community amid the pandemic and speak specifically to how the COVID-19 pandemic may impact the community. This is available for playback on MDA's COVID-19 landing page or MDA Facebook page.

They also have been able to successfully pivot a number of MDA programs to virtual platforms, including designated sessions from MDA's Annual Clinical & Scientific Conference; MDA Engage Educational Events; and a number of upcoming events which will be held virtually including MDA's Muscle Walk and other MDA community events. Additionally, MDA has launched a Community Survey on COVID-19 to learn more about the impact of COVID-19 on the neuromuscular community and has focused several MDA advocacy initiatives on ensuring therapeutic development and clinical trials are able to continue amid the pandemic, and joining other patient organizations in addressing Congress to protect patients through upcoming COVID-19 legislation. More information about these advocacy initiatives and the COVID-19 Community Survey on MDA's COVID-19 landing page at mda.org/covid19.

Les Turner ALS Foundation

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

Ms. Webb expressed the Les Turner ALS Foundation's gratitude to be there and began by thanking the patients, caregivers, surviving family members, researchers, and organizations that are all involved in the National ALS Registry. In particular, she thanked the participants with ALS who joined the meeting for sharing their perspective. It is important that everyone continues to do better, move forward, and identify additional opportunities. She thanked everyone for working on this effort together.

The Les Turner ALS Foundation focuses its comprehensive care in the Chicagoland area. They have ALS Support Service Coordinators who used to go into the home but who are now making their visits using computers and telephones, due to COVID. They have found that this has been a unique way to help provide comprehensive services in a more efficient manner for families, but there is a definite need to get back into the home for certain families as well, when it is safe to do so. That is something the Les Turner ALS Foundation is working on.

Something that is really important with the Les Turner ALS Foundation is that they focus on being a family and helping guide families with love, compassion, and understanding. There is a lot going on during the adjustment to understanding ALS and wanting to have more information about clinical care and trials. The Les Turner ALS Foundation helps individuals confidently navigate this disease by empowering and helping them make decisions. The Registry offers an important opportunity for people to begin their engagement with research. The focus is on the family, helping individuals become a part of the Registry, and having family members assist individuals with ALS who are not able to utilize the computer or who have technology difficulties. The Les Turner ALS Foundation works on problem-solving at the individual level to support families to ensure that they have access to the best quality care and most promising therapies, and that they get their questions answered.

In terms of the Les Turner ALS Foundation's impact, there were 1785 visits from Support Service Coordinators to the homes of people living with ALS in 2019. These are very intensive wraparound visits that include continuous conversations about the ALS Registry and assistance with in-person and remote registration. They meet with patients at the Les Turner ALS Foundation's Lois Insolia ALS Clinic for people living with ALS. They have had over 930 unique patient appointments in 2019. Oftentimes, the clinic is a diagnostic location for having a second opinion for the Chicagoland ALS population. Over 2100 people are receiving community education from the Foundation. While this is typically done in person, they are now shifting to virtual education and work in partnership with home health agencies and nursing schools to help drive the understanding and awareness of ALS. Depending on the topic, information is included about the National ALS Registry. $1.02 million in grant dollars were allocated to the Les Turner ALS Center at Northwestern Medicine and other ALS organizations in 2019.

Very importantly, the Les Turner ALS Foundation helps to support families economically through the provision of direct grant dollars to people living with ALS and their families through 4 grant programs: Walter Boughton Foundation Support Services Grant, Dan Nelson ALS Respite Grant Program, Stuart Rosen ALS Transportation Program, and the Assistive Communication Program. People want to learn more about clinical trials, registries, and participation so having the ability to communicate is critical. It is a core tenet of the Les Turner ALS Foundation's belief

system to constantly work with families as they adapt to the ever-changing nature of this disease. The Les Turner ALS Foundation served 324 people living with ALS in 2019. Some have more needs than others and the foundation works with their team to triage and incorporate that. They also run support groups throughout the Chicagoland area. Now that they are running support groups remotely, they have people joining from across the country.

The Les Turner ALS Center is a partnership between Northwestern Medicine and the Les Turner ALS Foundation that supports clinical activities, clinical research, education through research symposiums, continuing medical education (CME) credits for local providers in the area, and basic research and enrollment in clinical trials. During meetings, presentations, and individual conversations with researchers, opportunities to participate in research with the National ALS Registry are described. Ms. Webb expressed gratitude to Dr. Teepu Siddique who was awarded a $1.3 million grant over 3 years by the National ALS Registry. Dr. Siddique's research study will look for genetic variants of an innate immunity protein in ALS patient DNA and RNA, which they would hear about later in the meeting. The Les Turner ALS Foundation is grateful to have him. As part of the Les Turner ALS Center, Ms. Webb noted that he has been a tremendous mentor to her in helping her understand the various approaches to looking at ALS, caring for people with compassion, and meeting people where they are.

The Les Turner ALS Foundation's National ALS Registry/Biorepository promotional efforts very much mimic what the ALS Association and MDA are doing, which include the following:

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

The most unique feature of the promotional work done by the Les Turner ALS Foundation is its dedicated National ALS Registry Associate who works with families personally to help them register, whether it is starting them at clinic and getting them through the first demographic survey, answering questions, helping to triage problems such as access to passwords, et cetera. Having her engagement and personal touch has helped significantly to aid that process. They observed that the number of Registry discussions with people living with ALS decreased 7% from June 2018-June 2019 versus June 2019-June 2020 as the majority of the patient population had already registered. However, they are continuously identifying the problems and considering how they can do better. They have had some very frank conversations in their team meetings about new ways of talking about the Registry, so they are looking forward to increasing the discussions further. COVID-19 did impact that throughout March and June because they were working with families to address very specific needs, help them understand how COVID-19 was impacting them, and helping them triage and address specific issues that families are encountering.

In terms of website promotion, the Les Turner ALS Foundation added the Registry's Spanish component as another important part of the efforts to reach out to communities and address socioeconomic and social justice. It is critical for research to have a wide range of individuals

who are impacted with ALS. They are going to begin with building partnerships throughout Chicagoland outside of the Northwestern Medicine catchment area to help support families and make them aware of clinical trials. Equitable access to clinical trials is critical. They have a one-pager for the National ALS Registry and recently launched a clinical trial page that outlines the current clinical trials taking place at Northwestern Medicine. The page highlights the National ALS Registry and includes the Registry Associate's phone numbers. They were very excited to see the ALS clinical research dashboard that came out, so they added that to the website as well. This is a tremendous opportunity for partnerships and incorporation as they move forward on this journey.

Like MDA and the ALS Association, the Les Turner ALS Foundation is engaged in social media promotions, using its channels and working with its Communications Team to further identify different ways in which they can engage with families. Ms. Webb commended the Registry Communications Team. She has been a part of the Registry in various capacities with different organizations and really appreciates the change, the look, the graphics, and the feel. That makes a really important pathway for people to register when things are presented visually and are easily accessible.

The Registry is promoted at the Foundation's conferences to researchers, clinicians and patients and families. The Les Turner ALS Center at Northwestern Medicine hosted its annual ALS Clinical Conference for medical professionals in September 2019, with 100 attendees and also hosted 37 community education in-services with professionals. Though Dr. Eva Feldman was due to be the keynote speaker, she was not able to make it due to snow. However, it was live-streamed and another team member stepped in to present for her. They are very excited for the upcoming symposium in November 2020 for which they will provide information as it becomes available.

The team is meeting the challenge of ALS during COVID-19. In-person programming has moved to a virtual format for the foreseeable future, which includes support visits from ALS Support Services Coordinators that are now conducted via teleconference and phone calls. The 4 monthly in-person support groups are now being conducted virtually through videoconferencing. Appointments at the Lois Insolia ALS Clinic at Northwestern Medicine are largely done via telehealth, with some in-person appointments available. A lot of families are reporting there that they are very happy with the format, the way the team is providing service delivery, and the service delivery in the clinic. There has been a 24% increase in visits over last year in the first 6 months of 2020. The team is working very hard in the field and to help families.

The Les Turner ALS Foundation set up a new COVID-19 website as mentioned, which includes of number of topics to address an urgent need to support families in a holistic manner in adapting to the new realities, including:

- ❑ COVID-19 Emergency Relief Fund
- ❑ Care Recommendations for Respiratory Issues During COVID-19 Outbreak
- ❑ How to Prepare for a Telehealth Visit
- ❑ Tips for Preventing the Spread of Respiratory Disease
- ❑ COVID-19 & ALS: Frequently Asked Questions
- ❑ Home Health Care, Medical Appointments and Urgent Care
- ❑ ALS Clinical Trials and Research
- ❑ ALS Community Resources

The Les Turner ALS Foundation typically has a beautiful walk that takes place at Soldier Field, which the ALS Registry folks usually attend. There are generally over 7000 attendees. Due to COVID, they are now taking this to neighborhoods and people are going to be wearing masks and doing their own personalized walks. That is going to be a really nice way of engaging with neighbors, the community, and helping raise awareness in a unique way in the Chicagoland area.

In terms of thinking about improving and increasing the Les Turner ALS Foundation's engagement with the National ALS Registry, more emphasis will be placed on the "concierge approach" of having the National ALS Registry Associate give more details about how she can help work with families and help them understand that this tool is available to them and is a service that they give to the community in the Chicagoland area. They just hired a Community Education Manager who is going to be working to enhance the foundation's virtual engagements. They are a small but mighty organization, so they want to figure out unique ways to help families understand and drive communication around the Registry in different ways. They continue to hand out National ALS Registry materials and packets. Some people are attending clinic, so materials and toolkits are being handed out by the wonderful team at Northwestern Medicine.

Ms. Webb thanked everyone for the opportunity to share their progress and for encouraging them to look at themselves in a different way, dive deeper into the metrics, and assess how they can better support the community and collaborate with industry. When she has meetings with industry and talks about what the Les Turner ALS Foundation does, she always mentions the National ALS Registry as a possible tool for them to use for recruitment. There are a lot of areas in which they work to support the Registry, and she thanked all of the research participants currently in the Registry.

Registry Communications & Outreach Initiatives

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

Ms. Cory thanked everyone for joining them and hanging in there, recognizing that it is difficult to feel engaged virtually. She quipped that on the plus side, she may never wear dress shoes again. She appreciated hearing the partners speak first about some of the things that they are doing, and pointed out that her presentation was intended to be a bird's eye view of some of the communication efforts rather than a comprehensive description of everything. One of the key efforts pertains to how ATSDR can support the partners, which is one of the major goals of the communication and outreach initiatives.

One of the overarching goals that they had to accomplish this year was to redesign the website That started with using communication science to think about the target audience who is using the website and assessing how they utilize that information. In addition, they wanted to make the website more intuitive and less busy. There is now a grouping by target audience that includes: Patients and Caregivers, Researchers and Clinicians, Partners, and General Public. They also made it easier to register with just one click. The portals make it easier for various audiences to locate what they need.

In terms of some rough metrics, the top 10 most popular pages had about 24,000 unique visitors at the time this presentation was developed. That is an increase from just under 15,000 unique visitors at this time last year. That is a really good boost that hopefully reflects that information is easier to find. The top 10 most popular pages included the following:

1. Join the National ALS Registry
2. ALS Homepage
3. ALS Research Notification for Clinical Trials and Studies
4. National ALS Registry Conferences and Events
5. Patients and Caregivers
6. Researchers and Clinicians
7. General Public
8. Frequently Asked Questions
9. External Research funded by the National ALS Registry
10. What is ALS?

Ms. Cory invited those who had not visited in a while to go on the site to look through the information and see if they found it easier to navigate.

The other big news this year is that the Spanish website was finally translated. Now the basic pages, registration page, and all 17 risk factor surveys are available in Spanish. This is a big deal because, as they heard from the partners, there are some difficulties in outreach and education to a large portion of people for whom Spanish might be their primary language. Obviously, the goal is to increase the enrollment with the Spanish-speaking ALS patients and make sure that caregivers and patients feel like there are resources to help them understand the Registry and go through the enrollment process in the language that they prefer. This means that they also can start doing some other social media, education, and outreach that focuses on and targets those audiences because they now have the resources to support that. They look forward to seeing how the partners use some of these new items as well.

The other feature that was launched is the National ALS Registry newsletter, which is a way to reach people in a slightly less formal way to highlight some of the research. The newsletter is very popular, including the Patient Spotlight. There is an easy link on the homepage that requires one click to sign up for the newsletter. This is designed to reach patients, their caregivers, and professionals and to alert researchers and patients to clinical trial research opportunities.

A lot of thought also has been given to how to help making messaging consistent for outreach to help spread the word about the Registry. With that in mind, a train-the-trainer model was used to highlight some folks who are engaged in outreach who could share in real-time discussion. They had their first ever peer-run platform where people could share information and hear from us at ATSDR. The first Partner Training Webinar was in 2019 before COVID-19, and now it represents a new way to try to be interactive. There is a plan to have another one this year. Ms. Cory thanked Jennifer Hjelle from the ALS Association who had some concrete ideas and agreed to work with ATSDR to present those. Part of the thinking is that travel is really difficult, now more than ever. They wanted to think of ways to get people who are working at the Les Turner ALS Foundation to be able to talk to folks who perhaps are in South Georgia, for instance, to share ideas about best practices, what works, and the importance of the Registry. The first webinar had almost 225 participants. It was convened during lunch to make it easy for people to sign on and take an hour out of their day to think about the Registry as it applies to your job, particularly some of the smaller partners and local chapters that may have to cover

large areas. If people feel convinced about the importance of the Registry, they will feel more comfortable talking about it. This went really well, so it is planned again for 2020. ATSDR would love to work with the partners, so Ms. Cory invited ideas about what has been innovative and has worked. There were interesting discussions about some of the real-time barriers, generational differences among people and how that impacts the use of online platforms and use of social media, and ideas about patients having their grandchildren help with enrollment and surveys. That is a great way to engage in some intergenerational storytelling.

Some tools were developed to be customizable, which are also free. This includes presentations, tweets, social media, et cetera. Brunet-García has been helping support the design of some of these and making them very easy for the partners to use. ATSDR continues to use the CDC social media channels such as the CDC Facebook, LinkedIn, and Twitter to help push out messages and keep awareness high.

Additional outreach plans include continued support of partners in outreach and education, including additional webinar trainings for partners and other virtual options; highlighting caregivers in the newsletter; and targeted social media outreach in 2021, possibly including Facebook. Google ad words, when searching for ALS and other key words, drove over 9000 clicks to the Registry website. Consideration is being given to additional means for virtual outreach and education, not only through the website, but also through community newspapers and other venues to really dig down and get some outreach and education into the social media and traditional media worlds.

Update from Pharma

Stephen Apple, MD
Senior Medical Director, Medical Affairs
Mitsubishi Tanabe Pharma America, Inc. (MTPA)

Dr. Apple presented an update on the MTPA Radicava® (edaravone) development programs focused specifically on their biomarker study, oral development program, and real-world evidence plans. Radicava® was approved by the FDA in May 2017 and became available to US health care providers in August 2017. The FDA approval of this drug was based on a pivotal, randomized, controlled clinical study conducted in Japan showed that edaravone slowed the rate of functional loss in ALS[1] based on the ALSFRS. Radicava® is administered intravenously by infusion at clinic sites, infusion centers, or at home[2,3]. As 1 of only 2 drugs (active pharmaceutical ingredients) approved for the treatment of ALS in the US, and because the pivotal clinical studies for edaravone were conducted in Japan, there was interest in the real-world experience with Radicava® in the US [Writing Group; Edaravone (MCI-186) ALS 19 Study Group. Lancet Neurol. 2017;16(7):505-512. 2. Radicava® (edaravone injection) [package insert]. Jersey City, NJ: Mitsubishi Tanabe Pharma Corporation; August 2018. 3. Jackson C, et al. Amyotroph Lateral Scler Frontotemporal Degener. 2019;20(7-8):605-610].

When this drug was launched in the US, nobody had any experience with it. It has been 3 years now, so there is real-world evidence. Dr. Apple discussed some of the studies that were developed to capture the US and Canada experiences. The first study, Radicava®/Edaravone Findings in Biomarkers from ALS (REFINE-ALS) is being conducted in collaboration with Massachusetts General Hospital. Dr. James Barry is the lead investigator along with a distinguished and esteemed panel of investigators who are assisting MTPA as part of its Steering Committee. REFINE-ALS is a prospective observational longitudinal clinical study that

will be conducted in a broad population of ALS patients treated with edaravone in the real-world setting. The aim of this study is to improve the understanding and application of biomarkers as they relate to the use of edaravone in ALS, and particularly the potential use in patient care, research, and clinical trials. The REFINE-ALS study also is going to evaluate the safety and clinical outcomes of edaravone in the real-world setting. All of the participants need to either be treatment naïve or they need to have been off of edaravone for more than a month prior to screening. The primary objective is to identify putative biomarkers to serve as quantifiable, biological non-clinical measures of edaravone's pharmaco-dynamic effect in ALS. The study will be collecting data on a variety of biomarkers that potentially have been implicated in ALS. In addition, clinical assessments will be conducted to measure disease progression and assess the safety of Radicava® in patients with ALS.

The study is going to include a total of 42 clinical sites, of which 18 sites are currently active in the US. As everyone knows, these are trying times and COVID-19 has had an impact on everyone's lives and in the ability to conduct clinical trials—specifically observational trials. Patient visits at clinic sites are limited or they have been postponed. Unfortunately, there are very specialized assays for these biomarkers and many of the specialty laboratories that conduct them are still closed. However, MTPA has a mitigation plan in place. They are conducting site retraining when needed, amending the study protocol to include an option for study assessments in the remote setting where possible, and conducting regular meetings with sites during the restart process.

In summary, the hope is that the findings of the REFINE-ALS study may help to establish the feasibility of using biomarkers to assess the effect of edaravone in people with ALS. In addition, these biomarkers may be important assessment tools for use in patient treatment plans and future clinical programs and may provide additional insights into the mechanism of action of edaravone in people with ALS. This study will also provide additional real-world experience with edaravone to US and Canadian physicians who have not tried the drug over the last 3 years.

In terms of where MTPA is going with edaravone, they are now looking to develop an oral formulation for use in people with ALS. This work is going to be in collaboration with MTPA's Japanese partners at Mitsubishi Tanabe Pharma Corporation (MTPC) in Tokyo, Japan. Several types of non-intravenous (IV) formulations were assessed in order to develop a more convenient formulation for ease of administration of a dosing regimen. An investigative oral suspension formulation may provide an alternative option to IV edaravone and is prioritized for development in clinical trials to prepare a potential path for market authorization. The oral suspension formulation of edaravone is being developed by MTPC in Japan and MTPA in New Jersey.

Several pharmacokinetics studies have been conducted of edaravone formulations. It has been determined that a single oral dose of approximately 100 mg of edaravone appears to deliver the maximum concentration (C_{max}) and area under the curve (AUC) exposure comparable to that of the approved 60 mg/60 min IV infusion. Overall, there were no additional safety concerns with doses up to 300 mg in this study in terms of the safety and tolerability of the oral formulation at that high dose compared to what was seen in the multiple clinical trials or the IV formulation. They are moving forward with the 100 mg dose going into the clinical development program [Takei K, et al. ENCALS Meeting 2019; May 15-17, 2019; Tours, France. Abstract 2036].

The development plan for this oral formulation includes assessments for the timing of administration against the timing of meals to examine the questions: Will individuals need to take it 1 to 2 hours prior to a meal? What does the fasting component of this look like? Are there any drug-drug interactions with the oral formulation? In order to prepare for regulatory filings, they must pursue a PK bridging strategy that includes a bioequivalence study between IV versus oral edaravone in healthy subjects, as well as an open-label safety study in ALS patients, which is now being actively recruited for in the US and Canada, with population PK analyses using a 4-week treatment cycles (2-week on/off) as with the IV regimen. The first cycle of this drug will be 13 days on with a 14-day off period for looking at drug safety and tolerability. All subsequent cycles will be 10 to 14 days on with a 14-day drug free period.

In summary of the oral development program, the oral suspension formulation of 100 mg of edaravone had similar C_{max} and AUC values as the current 60 mg/60 min IV formulation. The oral suspension formulation of edaravone was generally well-tolerated at doses up to 300 mg. The clinical development plan will help establish the data needed to seek registration for marketing authorization pending ongoing discussion with regulatory authorities.

It has been 3 years since the study was originally conducted in Japan. MTPA recognizes the value of real-world data and is pursuing a significant number of initiatives to bring those real-world data to the ALS community. The objectives for assessing the real-world effectiveness data for the IV edaravone are to: 1) assess the demographics and clinical characteristics and settings in which edaravone is being initiated (e.g., home care, infusion center); 2) evaluate the economic value of edaravone, including health resource utilization and total cost of care; 3) describe treatment duration, adherence, discontinuation, and survival rates; and 4) describe real-world effectiveness in slowing functional decline as measured by the ALSFRS-R and other clinical outcomes such as forced vital capacity (FVC) and proxy endpoints in a real-world database such as time to disability milestones.

In conclusion, Dr. Apple expressed MTPA's gratitude for the opportunity to serve the ALS community now and in the future and that they look forward to many collaborations with their investigators and with PALS.

Questions and Discussion

Darcy Peth, MS
Associate
Ross Strategic

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

Discussion Points

Dr. Factor-Litvak thanked all of the presenters for their excellent talks. There has been some discussion about the lack of under-represented minorities in the Registry and likely in research studies dealing with ALS. While the presenters earlier in this session were going through some of the promotional materials for the Registry, MDA, the ALS Association, and the Les Turner Foundation, she noticed that there were very few photographs of under-represented populations in the materials. She suggested that perhaps having greater representation of under-represented populations in the promotional materials might make it more conducive for people

in these groups to join the Registry and other studies. It is a problem not only in ALS, but also in many other diseases that under-represented minorities are not well-represented in research. While Ed Tessaro is incredibly photogenic, perhaps having him alongside an African American with ALS might be a better way to approach some of the promotions.

Dr. Mehta indicated that last year, they attended a symposium in Florida where they took 70 or 80 pictures of patients who were attending. The majority of those patients were White, but they certainly want to reach out to the minority patient groups. He was giving a talk in Tucson, Arizona last year and there were 6 ALS patients of Hispanic origin. However, they did not have their cameras to take any pictures. They also need to have a release as the patients must agree to have their pictures taken and sign a release. He agreed that it was a great idea. They do want to make sure that they are showing actual patients and not just media pictures.

Ms. Cory added that it is such a good idea, they have already started doing it. These were very selective, small pictures. She referred everyone to the partners portal where they would see that there are multiple types of social media, including African Americans and just about everyone else. They want to show family members, intergenerational photographs, et cetera. As a reminder, Hispanic is not a race. It is an ethnicity and can look like anything. There are multiple things translated into Spanish featuring different people. But right now, there is just about everybody who could possibly be imagined in terms of women, men, races, and ethnicities. The materials in the partners portal are to help the partners customize. For instance, someone in North Dakota may not need to reflect the Spanish language demographic. Certainly, they are trying to broaden that and welcome suggestions. For features in the newsletter, for instance, they would love recommendations of patients who have unique stories.

Dr. Factor-Litvak suggested that perhaps they could have those photos up front on the website as well so that the first thing people see is a more diverse group.

Ms. Cory agreed that it would be a great idea to rotate some of the photos on the homepage.

Ms. Pauls Backman said she thought Dr. Factor-Litvak's comment was very appropriate and that she is glad that Ms. Cory and others involved in the promotion of the Registry are addressing this. However, it also is a much deeper issue. Within the composition of individuals who attend various multi-disciplinary clinics around the country, there is not proportional representation of people of color at those clinics. It is unfortunately and quite frankly a failure in terms of the ability to reach individuals who need their help. While she said she did not have an immediate answer for it at the moment, what they are seeing in terms of the data is a reflection of what is happening with care. It is a much bigger issue than they will be able to address, but she believes they must continue to keep in mind and determine what efforts are needed to reach under-served communities.

Dr. Brooks pointed out that having written the foreword for the first Spanish textbook on ALS many years ago, he spent a lot of time on Spanish websites. He wondered whether consideration had been given to putting a mark on other Spanish websites about the CDC Registry Spanish website. Many people go offshore, so to speak, to get information. Having a link on other websites to focus people onto the CDC Registry Spanish webpage could be very helpful. With respect to reaching patients who are Black in the US, there is a series of news outlets and websites for Black patients, African Americans, different ethnic groups, et cetera. He wondered whether consideration had been given to how ATSDR could broaden its outlay of announcing the ALS Registry to these media outlets.

Ms. Cory indicated that for some of these, they have tried to establish relationships. For example, BlackDoctor.org (BDO) allowed them to create a customized blog, story, and outreach directly. That is a popular site with African Americans, particularly those looking for health information. Pairing with health sites that have specific target demographics is a great idea. For larger sites such as the popular Telemundo Online, these are generally pay-to-play, meaning that they require payment to put up a link or something of that kind of information that would be considered marketing. They can definitely explore whether there is value to that while they continue to hit some of the "low hanging fruit." For example, they know certain CDC pages are quite popular and they have tried to put the link for the Spanish website there as well. They can do buttons and badges in Spanish that have pre-coded information about the Registry website. The partners can provide information to local affiliates as well. ATSDR is looking for ways to broaden and hit some of the target demographics.

Dr. Mehta added that Facebook certainly is a way for them to target those populations as well and is under discussion, which could be a much more selective approach.

Mr. Van Tress asked whether the ALS Association has implemented any ALS chapter level initiatives to promote and encourage people with ALS in their jurisdiction to self-register with the ALS Registry.

Dr. Thakur responded that they do quite a bit of that at their clinics and walks. They do some outreach and enrollment on a monthly basis. They also do some targeted outreach like webinars and so forth, which are more national. Every time they do a research event at a chapter, they also talk about the Registry in particular. Those efforts are all coordinated through the national office, but they are happening through the chapters.

Dr. Finger observed that based on the earlier sessions, it is obvious that the Registry is trying to do a lot of things. They all know how difficult it is to reach all of these patients who are facing such a devastating disease. On top of that, they have only about $1 million a year to market across the entire country. One thing that concerned him with all of the presentations was there was no discussion about what they are trying to accomplish. There does not seem to be an overarching goal or an acknowledgement of where they are right now. Right now, they are getting about 1000 patients a year to self-enroll out of just over 6000 who are diagnosed. That is 1 in 6 patients. If they are going to spend this money effectively, they have to think about the goal. How they spend this money could be very different if they are trying to fill in gaps on a prevalence number, trying to increase enrollment, trying to target under-represented minorities, or trying to get surveys completed. There are not enough resources to engage in an "all of the above" approach. Every single year at this meeting, Becky Kidd would bang on the table and say, "What are you measuring? How do you know what you are doing?" Dr. Finger said he did not know if there was a single metric produced in the last 4 presentations. How do they know if social media outreach is where the dollars should be going? The ALS Association does some paid media. Where is the return on investment (ROI)? They have to be thinking about using this very limited budget to get as much "bang for the buck" as possible in facing this really difficult problem. He takes exception to the idea that the portal is 95.5% White because of care and because that is what the population looks like. That is not true based on the administrative data, which is about 85% White. Even those data are skewed against disadvantaged populations. They have to make a concerted effort to reach these patients and in terms of how resources are used to do that. He recalled a presentation by Ted Harada about taking a concierge approach where he drove around the State of Georgia trying to enroll people. He was one of the hardest workers and one of the most optimistic patients Dr. Finger has ever met. However, when he presented at the meeting he said, "Sadly, this isn't a cost-effective strategy to try to increase

enrollment. It takes way too much time." Dr. Finger said he does not quite square that with the idea that they are giving $100,000 to a group who is registering 50 or 60 patients a year. They have to make real decisions about how they are going to use a very little amount of resources and what they are actually trying to accomplish scientifically.

Dr. Mehta agreed that they have a very limited budget for outreach and communications and that they need to use those funds wisely. One of the approaches they are thinking about internally is to have their partners target certain states such as Florida, Texas, and California where there are larger minority populations than in other states. By doing it that way, potentially they could reach out to more of those patients in those areas. Another approach is to utilize Facebook. The scientific rationale is that typically, they are trying to get people to enroll in the portal side of the Registry to provide their data regarding residence, occupation, military history, and so forth. In terms of enrollment not being addressed in any of the presentations, ATSDR receives numbers from every single group regarding their outreach and enrollment per month. They cannot provide names and ATSDR cannot match the names up internally due to strict rules pertaining to PII, but all 3 partner groups provide metrics monthly regarding their outreach methods.

Dr. Finger said he assumed that ATSDR could at least match those efforts to aggregate changes in enrollment. If the ALS Association undergoes a big push in a given state, ATSDR should at least be able to look at that given state and see an enrollment change. This is a point that is hammered upon each and every year in the marketing presentations but they seem to be moving further and further away from it. He could not imagine what Becky Kidd would be saying right now.

Dr. Mehta indicated that when there are campaigns conducted during the ALS Awareness Month of May, they have seen an uptick in registrations. When they attend the walks and give patients symposiums in the fall, they see an uptick in enrollment. There is "bang for the buck." ATSDR has increased spending and outreach in terms of going to walks and patient symposiums and they do see increases in enrollment afterward.

Mr. Faretra observed that there are numerous ALS groups on Facebook, but he did not see a National ALS Registry group there. Someone could go on Facebook to mine the names and information and the cost would not be very high. Facebook is a great place to data mine.

Dr. Mehta said that ATSDR is making a push to have their own Registry Facebook page and Twitter handle. There are CDC requirements. There is a Facebook page within CDC, as well as the centers, institutes, and organizations (CIOs) within CDC. ATSDR does use their Facebook pages. One of the challenges is having the manpower to have someone monitor all of the Facebook posts, Twitter posts, and so forth.

Ms. Cory pointed out that the items that pop up are paid and expressed her hope that she did not give the impression that any of their social media was paid for. That is a zero budget. Right now, they do utilize the CDC and ATSDR media accounts. However, they cannot mine personal data. They can certainly assess whether there is "bang for the buck" in paid outreach through social media channels, which is very different from organic. They do have the name of CDC and people do look to CDC as a trusted source of health information. They look to the Health Belief Model (HBM) for communications, which says that there are multifactorial elements and that a single Tweet or reading of a single article does not necessarily tip the scale to registration. They believe that there are multiple points at which someone gets information, processes it, and then may make that decision. In-person outreach and other efforts all add up and it is very hard to

tease out whether one single thing, particularly for social media that is unpaid, would equal an actual enrollment number.

Dr. Siddique pointed out that while social media is good in terms of advertising, he did not think they could approach patients or families without their consent. A proper mechanism would have to be in place.

Dr. Mehta indicated that all information, posts, and so forth are approved by the IRB to ensure that they comply with IRB regulations and that they are not saying something that they should not be saying.

Dr. Siddique clarified that he was referring to the suggestion raised about recruiting or mining patients through Facebook, for example. He did not think it would be permissible for research to approach people through that mechanism.

Ms. Cory confirmed that they cannot data mine through Facebook.

Dr. Brooks noted that one of the reasons that he and Drs. Bradley and Weisskopf went to Congress about the Registry was because of the observation that military patients were not just from one war. They were across a number of wars. Part of the argument that allowed them to convince Congress to get the Registry was by looking at a larger dataset of patients, the Registry might allow them to find the answer to the causes of ALS. He said he thought they had to focus on that, and that he was surprised that the agenda did not include any input from the military or the VA. Perhaps a restatement of the goals along the lines of what Dr. Finger and maybe other patients would identify would be important moving forward.

Dr. Mehta indicated that they have provided funding to Dr. Weisskopf in the past for research on military veterans. They also are working with Dr. John Beard at BYU who also has published extensively on military veterans. He agreed that they probably should consider inviting the VA to the ALS meetings as well. ATSDR has had some communications and dialogues with the VA through the ALS Association. NIEHS was also on the call, so they might invite their staff to Registry meetings as well. That is one of the areas on which they would like to see some applications and military veterans with ALS is one of the areas listed as priority research.

Update from Actively Funded Registry Grants: Part #1

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

Mark Heverin
Project Manager
Trinity College
Dublin, Ireland

Mr. Heverin expressed appreciation for the opportunity to speak and conveyed apologies from his boss, Professor Orla Hardiman, who was unable to attend. During this session, he presented an update on the European Multidisciplinary ALS Network Identification to Cure Motor Neuron Degeneration (EuroMOTOR) study. The PIs on this study include Professor Orla Hardiman (Ireland), Professor Giancarlo Logroscino (Italy), Dr. Abayuba Perna (Uruguay), Dr. Patricia Lillo (Chile), and Dr. Tatiana Zaldivar (Cuba).

Professor Logroscino published a paper in 2017 with collaborators showing the world age standardized prevalence at 4.5 (4.1-5.0) per 100,000 for motor neuron diseases (MND) and 0.78 (0.71-0.86) per 100,000 person years for all age incidence. The conclusion they drew was that both incidence and prevalence are low, but the burden of disease is quite massive in terms of disability and the fatality rate is obviously huge. That emphasizes the need to continue to expand the research into the condition around the world. One of the commonalities was the idea of ALS as a European condition driven by a European genetic profile. That particular study showed on the world map that the highest rates of ALS are seen in Western Europe, North America, and Australia—so European populations—and that lower than expected rates are seen in richer Asian Pacific countries like Japan, which seems to rule out socioeconomic factors as being a major factor. That was an interesting finding and was one reason they wanted to look at the Latin America area previously [Giancarlo Logroscino et al, Global, regional, and national burden of motor neuron diseases 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016, The Lancet, Volume 17, Issue 12, P1083-1097, December 01, 2018].

The idea of a European driver to the condition is supported by work by Roberts et all in 2016 which showed higher rates in the White population in the US as compared to Black and Hispanic populations. Again, they controlled for socioeconomic measures, access to healthcare, health insurance status, et cetera. That furthers the idea of being driven somewhat by a European genetic profile [Andrea L. Roberts et al, Race/ethnicity, socioeconomic status, and ALS mortality in the United States, Neurology, November 29, 2016; 87 (22)].

With that, Hardiman et al decided to look at ALS Latin America. There has not been that much research done there previously and it was an area with some European populations, but admixed in probably a different way than in the US or Europe. In terms of the numbers as they were known in these countries, part of part of the challenge of the Latin American Epidemiology Network of ALS (LAENALS) was to maybe generate more numbers, check the veracity of what they had previously, see how it pans out over time, and learn more about the numbers in Latin America in the specific countries they are looking at currently for Cuba, Uruguay, and Chile. This study has 3 teams of researchers undertaking population-based studies in these 3 countries. Throughout the study, they are collecting clinical evaluation, ALSFRS, and appropriate neuropsychological battery. There will be detailed family history studies, exposure studies, regular follow-up for survival, and DNA collection. Exposure studies are probably the biggest overlap with the previous EuroMOTOR study. DNA collection is done as a matter of course in Cuba, but they got off to a slow start on that in Uruguay and Chile for various logistic reasons.

The comparator population is the EuroMOTOR study for which the investigators collected information on over 1700 patients and around 3000 age-, sex-, and location-matched controls across the Netherlands in the study that ran between 2011 and 2015. The first study aim is to compare the incidence and clinical phenotype of ALS in 3 genetically distinct Latin American populations (Cuba, Uruguay, and Chile). To that end, the investigators and sub-investigators have been trained, cases have been ascertained using existing infrastructures supported by trained investigators; the Latin American dataset has been established, and report of incidence and detailed clinical phenotype of ALS in 3 Latin American countries has been partially achieved. In terms of the status of the deliverables for Aim 1, the team has been trained, the EuroMOTOR study database has been adapted to accommodate the Latin American data, and the EuroMOTOR study questionnaire was edited to be culturally appropriate to collect the information in Latin America as well. This this will be the first and population-based comparative study of its type in these 3 Latin American countries. They continue to collect the information at

the moment. The clinical phenotyping and ancestral origin data will be really valuable as a legacy of this study for future work on these admixture studies.

The second aim of the study is to: 1) establish the quantitative exposome in population-based cohorts from South American and the Caribbean; and 2) identify environmental risk in 3 Hispanic populations of different ancestral origin and to compare with risks in European populations using standardized methodologies. In terms of the deliverables for this aim, training, standardization, translation, and validation of questionnaires has been done. The automated database has been constructed and data entry are underway. Quantitative lifestyle data will be collected, including Job Exposure Matrices (JEM) linking questionnaires to exposure matrices (energy expenditure during physical activity, electromagnetic field exposures and exposures to dusts, particles, pesticides, insecticides, smoking). Comparison of the information in the Latin American countries and between the Latin American countries and European ones will come at the end and will be really interesting.

In terms of the results, Uruguay is the smallest country of the 3 involved with the smallest population, which is 3.5 million. Incident cases were collected over 2017 and 2018 and then a mean annual incidence of 1.7 per 100,000 was calculated. That relates quite well to previous work in 2002-2003. Care is quite centralized and that means the cases are easier to capture. Because Uruguay got off to a strong start, they have been able to start a new sub-study in which they looked at all of the incident cases this year and collected DNA samples on as many of them as possible. That will allow them to do great comparisons between Ireland, Cuba, Uruguay, and the other European populations that were part of the EuroMOTOR study. In Uruguay, they are validating the Edinburgh Cognitive and Behavioral ALS Screen (ECAS). The ECAS is used in clinical and research practice a lot in Ireland. They were advised of the possibility of a cluster of ALS in a small town in Uruguay, Empalme Olmos. They do not know much about that at the moment, but they are trying to approach those cases to apply the questionnaires to get as much information as possible on them, so that will be something interesting for the future as well.

For Cuba, the investigators had hoped to look at all 15 regions. Unfortunately, logistics prevented that so they have focused on 3 regions instead that they feel are quite representative of the country as a whole in terms of ethnicity and admixture (Havana, Cienfuegos, and Guantanamo). These represent about a third of the population overall. The Cuban healthcare system is very good and lends itself to this kind of research. They have done work with the Cubans in the past and it has always been very productive in that regard, especially when working with a rare condition like ALS. Previous work in Cuba comes back to the hypothesis that ALS is a European-driven condition. The previous work has shown the highest rates ALS in the White population and, indeed, next down the Black population. There are significantly lower rates of ALS in mulattoes or mixed populations. That develops the hypothesis of a European-driven disease and whether there is something around admixture, which is a very interesting opportunity that they have with the LAENALS consortium, because there are various degrees of admixture in all of these Latin American countries. The death rate from ALS is quite high in Havana, Cienfuegos is in the middle, and Guantanamo is the lowest of the 3. The investigators have produced some incidence rates from the 3 provinces. The information that will be collected will be vital in further interpreting these data, but the incidence rate in Havana so far has been shown to be 0.58, Cienfuegos is 0.86, and Guantanamo is 0.78. Those will be quantified as more data are gathered.

Again in Chile, they wanted to look at the whole country but this proved to be too difficult logistically because it is a vast country that is quite fractured in terms of healthcare. Instead they looked at the Santiago metropolitan area, which represents about a third of the population overall. To data, detailed assessment have been collected on about 60 people and more general descriptions of about 198 cases in total ascertained. Chili has probably caused the most difficulty so far, but they have set up the first multi-disciplinary clinic in Santiago. The biggest issue in Chile has been to get established. Dr. Lillo has had to get our name out there. She has linked up with Dr. Ricardo Hughes and they are now forming the ALS registry in Chile, which is quite exciting and is anticipated to generate numbers going forward and to help ascertain cases over time. It is the difficulty of setting up any register and in this case, even setting up study, getting the name out, and getting people to participate. Chile has been rocked with political instability from October 2019 to February 2020 and that segued directly into the COVID-19 crisis. Nevertheless, progress is still being made.

One of the interesting things they have done is to look at a comparison of the clinical populations in Montevideo, Uruguay; Havana, Cuba; and Dublin, Ireland. This was published in 2019. One of the findings was that the Cuban age of onset is significantly lower than that in Ireland, while Uruguay tends to look a little bit more like Ireland. They had DNA from the Cuban Irish samples but not the Uruguayan sample. Hopefully, they can repeat this once we have the Uruguayan DNA after their 2020 collection [Ryan M et al. Comparison of the clinical and genetic features of amyotrophic lateral sclerosis across Cuban, Uruguayan and Irish clinic-based populations. J Neurol Neurosurg Psychiatry. 2019;90(6):659-665. doi:10.1136/jnnp-2018-319838].

The big hope for the future is to add new countries to the LAENALS consortium to go beyond the life of this immediate study. The legacy of this grant will be to leave a lasting research infrastructure in these countries, and also expand that out across the region. They had a meeting scheduled for April 2020, but it was cancelled. They had delegates from Argentina, Brazil, Costa Rica, Colombia, and Paraguay all interested in joining the consortium. This will inevitably go ahead again and it will be rescheduled because there is a recognition that the infrastructures in place. The questionnaire will be translated to Latin American Spanish, is largely culturally appropriate, and is suited for combination with the European datasets.

All recruitment has been suspended since February 2020 due to COVID-19. They are hoping like everybody else in the world that things was slowly get back to normal. While their face-to-face meeting was cancelled, they will reschedule this. Their no-cost extension has been granted thanks to the CDC until September 2021, so that gives them a real chance to bring things on and move where we want to go. Data upload continues and the reports will be generated based on all of the data once it is in the database. Dissemination continues on this. In addition to the Ryan et al paper on the comparison of the clinical populations, there was a poster presentation at AAN in 2019 and a platform presentation at the ALS/MND symposium in 2019. In preparation are LAENALS – Design of the First Latin American Epidemiology Study of ALS, Cuban mortality data, and comparative incidence from 3 regions.

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

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

Dr. Bradley provided a second-year progress report on the study of critical periods of exposure to environmental risk factors for ALS and gene-environment interactions. He indicated that he was presenting on behalf of an international collaboration including Dartmouth Hitchcock Medical Center and Dartmouth College, the Cleveland Clinic, NIH, University of Miami, Piedmont ALS Registry and University of Turin in Italy, Applied GeoSolutions, Bowling Green State University, and the ALS Care Project in Ohio. The specific aims of this study are to: 1) investigate the time periods when exposures to environmental risk factors carry the greatest risk for later development of ALS in Northern New England, Ohio, and the Piedmont Region of Italy; 2) investigate the time periods when exposures to cyanobacteria and to pesticides carry the greatest risk for later development of ALS in the US; and 3) identify genetic variants conferring susceptibility to lifestyle factors and residential exposures to cyanobacteria and to pesticides as ALS risk factors.

In terms of the first aim, the investigators first made a decision to analyze the people in the larger Piedmont database (> 3,000 patients and >3,000 controls) as the initial study set and then use the New England and Ohio (NNE-OH) database (currently 333 cases and >551 population controls) to validate the Piedmont findings. The Piemonte and Valle d'Aosta Register for ALS (PARALS) database now has about 4000 ALS patients and an incidence rate of approximately 3.06 per 100,000 patient years [Chiò A et al, Secular Trends of Amyotrophic Lateral Sclerosis: The Piemonte and Valle d'Aosta Register, JAMA Neurol. 2017 Sep 1;74(9):1097-1104. doi: 10.1001/jamaneurol.2017.1387].

Regarding Dr. Angeline Andrew's preliminary findings from these studies, first they found that the odds ratio for exposure to lead as a risk factor of ALS was significantly increased with an odds ratio of about 5, particularly in terms of lead bullet-making. Casting lead bullets has an odds ratio of 4.97 and is statistically significant. They also found that the odds ratios for exposure to lead 30 and 40 years ago were significantly increased to a level of about 6. Head injuries also were a cause of increased odds ratios, with head injuries in the past being those that occurred above the age of 30, with an odds ratio of 3.31.

Moving to Aim 2 to investigate the effects of exposure for two environmental pollutants, pesticides and cyanobacteria, to study the whole of the US they are using a massive database of environmental pollutants and a large commercial national database named Symphony®, which contains 26,000 ALS patients in the US from 2003 to 2018 with locations at the Zip3 level. To study past epochs of exposure, they are using a NNE-OH database of 3677 ALS patients and the same number of controls, with geocoded residential database addresses going back 25 years and time-linked databases of environmental pollutants. The Symphony Integrated Dataverse® (IDV®) has 26,000 patients from 2013 onwards with Zip3 address at diagnosis with age and sex matched controls from the same database.

Dr. Bradley shared maps to illustrate how they map exposures of cases and controls. From this, they estimate the odds ratios of case-control exposures in each Zip3 area. Estimating the spatio-temporal exposure for past epochs for each subject in the NNE-OH database is based on the history of where the subject lived over the last 25 years and the 25-year history of release of a pollutant from a point source. He presented a preliminary study of one pesticide using the Symphony IDV® and the NNE-OH databases. Though the odds ratios of1.05 in the Symphony IDV® dataset and 1.39 and the NNE-OH dataset are small, the significance is high. In a preliminary analysis of the odds ratio for an airborne pollutant, the odds ratios are 1.09 for the whole US and 1.22 for the NNE-OH datasets for the 15-year epoch before the development of ALS. Though these odds ratios again are small, they also are highly significant.

Moving to Aim 3 to identify gene variants that confer increased susceptibility to lifestyle factors and to residential exposures to pollutants that lead to the development of ALS, Dr. Bradley shared preliminary data on genome-wide association studies (GWAS) performed by Dr. Bryan Traynor, with data analyses by Dr. Jiang Gui. In the NNE-OH database, they have looked at 578 specimens that Dr. Traynor has studied. This showed that about 20 single-nucleotide polymorphisms (SNPs) were significantly more frequent in ALS patients than in controls.

Dr. Bradley then provided a brief summary of their previously completed CDC grant to study the incidence of ALS in Ohio. Between the period of October 2016 and September 2018, they collected 333 individual ALS patients indicating a crude annual incidence rate of 1.66/100,000 patient years. They recognize that they were not able to recruit every newly diagnosed case in Ohio during the index period either because they had not recruited all centers in Ohio or because of the parts of Ohio where patients get their medical care in other states.

In terms of the age and gender standardized incidence rates for each of the 88 counties in Ohio, the incidence varied widely between counties from 0 to 13/100,000 patient-years. To address this problem of the unevenness of recruitment and correct for missing cases, they developed a new method to estimate the number of missing cases. In this, they selected cases that had age and gender adjusted incidence rates within 0.5 standard deviations of the mean adjusted rate of all 88 counties, assuming that these selected countries represented the situation where case recruitment was complete and where local environmental factors did not lead to an abnormally high incidence. There were 33 such "average" reference counties. They ran regression analyses to build the case population relationships for each age and gender category in these 33 average reference counties. They then applied the regression models to the 30 counties whose observed incidence rates were statistically lower than those in the reference counties. They hypothesized that these counties were where they had under-recruitment of patients. Using this regression model, they estimated that the total expected or missing number of cases in the 30 low-density counties was 54. Adding these 54 missing cases to the 333 individual ALS cases collected, they estimated that the total number of ALS cases in the 2-year window should have been 389 and that they, in fact, collected 86% of this total. This estimate is similar to the 76% of expected cases that Dr. Nelson and her colleagues collected from multiple national databases by the capture-recapture methodology in 2018. Thus, the corrected crude incidence rate for Ohio was 1.66/100,000 patient years and the age- and gender-standardized rate was 1.45/100,000 patient-years.

As a prelude to the presentation to be given later by Dr. Diane Re, Dr. Bradley noted a recent paper on neural-derived exosomes in ALS by Dr. Paul Cox and colleagues based on blood samples from Dr. Elijah Stommel's ongoing Phase 2b clinical trial of L-serine in ALS. Sandra Banach, Rachel Dunlop, and Paul Cox were able to separate an ALS miRNA fingerprint using neural-enriched extracellular vesicles from blood plasma. They found that eight of the several hundred miRNAs were significantly altered in ALS patients compared with controls. They proposed that these could be used as biomarkers [Open Biology 2020;10:200116].

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

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

Dr. Talbott expressed her gratitude for being invited to the meeting to present their progress for the current year. She indicated that the goal of this study is to examine environmental and occupational risk factors for ALS by conducting a case-control study of cases from the ATSDR National ALS Registry and population-based matched controls. The specific aims are to: 1a) evaluate self-reported environmental/occupational exposure to metals, pesticides, and solvents for ALS cases and controls as independent risk factors for ALS; 1b) download, link and examine exposure to ambient air pollution: fine particulate matter ($PM_{2.5}$) and ozone, using an Environmental Protection Agency (EPA) downscale modeled data from EPA Air Quality System (AQS); 1c) download, link, and examine ambient air toxics: EPA National Scale Air Toxics Assessment (NATA) data; 2) measure exposures to pesticides and solvents in samples with a battery of tests using blood concentrations of persistent environmental pollutants (pesticides and solvents) in cases and controls; and 3) among ALS cases, examine the functional relationship between environmental toxicants in human biological samples and key biological pathways and common genes associated with the development of ALS.

They used the 80 cases from the National ALS Biorepository pilot study and 80 matched controls. They most recently received permission to get 200 more cases from the National ALS Biorepository, not the pilot, and obtain the controls. The did that because they wanted to have the most complete data. They found that going forward, the surveys were more complete and they felt more confident with the data that we were getting. To be clear, the case data was provided by the National ALS Registry. They did not have to contact these individuals as they already were consented, contacted, and surveyed and the Biorepository data were obtained for PALS in the National ALS Registry Biorepository. CDC provided the survey data on the cases, the Biorepository data for 280 blood specimens, and genetic material for further DNA testing.

There are two parts of the study. There is a survey of the matched controls, which is ongoing. The second part is the blood draw that occurs at the home of the controls. Recruitment is ongoing. At the end of February or early March, the laboratory and school were shut down. However, they were quickly able to get back up to speed to conduct the interviews remotely. Therefore, they were able to continue to do the surveys and send out the consent forms. They have now reopened and consent forms are coming back from these individuals who they actually interviewed over the remote portion of their study. Exam #1 is up and operating, so they are very hopeful that with this no-cost extension they will be able to complete the requisite number of cases and controls. That is where they are with the 175 surveys, which brings it up to 184. They are now going forward with the in-home blood draw with COVID protections in place.

To briefly summarize the first 127 cases and their matched controls, cases and controls were matched on year of birth, county of residence, and gender. They also have education, although they are showing a dichotomous and very definite and precise demarcation of education. In addition, they have smoking status and will have all of the other variables on the surveys from the Registry. In addition, they have self-reported environmental and occupational exposure by case status on the first 127 cases and their matched controls. Based on Dr. Bradley's previous work, they are looking at insecticide and herbicide usage over time, solvents, lead paint, using a solder working as a welder, and a plethora of work exposures. They also have pesticide exposure at home and chemicals that were used.

In terms of progress to date, they have the daily ambient $PM_{2.5}$ and ozone for 2002-2015. As Dr. Weisskopf mentioned the previous day, good air pollution data do not go back that far. It is possible to get $PM_{2.5}$ from 1997 on. This Bayesian space-time downscale model that is available for the whole country by Census tract is a very expertly modeled database, so they were able to download 2002-2015. They were able to get air pollutant estimates for each Zip Code and are currently working with the Zip Code of the residence of the blood draw, although they do have residential history going backward that they also can assess. Air pollutant estimates were linked to each case/control by Zip Code at residence of blood draw and for the cases. CDC staff linked the ambient air database to Zip Code at residence of blood draw and sent the data file to the investigators after deleting geographic data. They also have the data for the controls, so they have a case-control comparison.

Some general exposure to ambient air pollution gathered so far at the beginning of this, they are looking at $PM_{2.5}$ and ozone. They focused on 2011 and 2014 because those were the same years that the next air toxic database modeled the data for the NATA done in 2011 and 2014. The next step is the analyses of the estimated exposure to $PM_{2.5}$ and ozone for cases compared to controls with adjustment for potential confounders. For Aim 1c, in addition to the ozone and the $PM_{2.5}$, which has starting to be looked at in Europe and other places, they are also trying to leverage the US EPA NATA data for 2011 and 2014 in order to assign exposure levels based on residence at time of blood draw for ALS cases and controls. NATA offers data on model-estimated ambient air concentrations of air toxics at state, county, and Census tract levels. Estimates are based on data sources (point, nonpoint, on-road, and nonroad source groups); and monitored data, reports, models, et cetera. NATA data has been applied as an exposure estimate in research settings.

Similar to the $PM_{2.5}$ and ozone, they are looking at 43 of 187 neurotoxicants that were collected by EPA plus the pesticides that also were modeled. Again, CDC assisted with assignment of individual residential address of the 280 ALS cases for this study, and the initial 127 cases have been liked to their controls (N=127) in order to perform a preliminary comparison of the range of the exposures. The 43 neurotoxicants and pesticides of interest are grouped into 5 categories: Metals, Aromatic Solvents, Pesticides, Chlorinated Solvents, and Other Hazardous Air Pollutants (HAPs). They have to look at the distribution and make sure that the data were all modeled in the areas they are studying, but this will offer a nice snapshot of where people were living.

For Aim 2, they are looking at the pesticides in blood. CDC set up this protocol. There is a series of E1 and E2 pesticides study being conducted in British Columbia at the SGS AXYS laboratory by Patterson. Some of the long half-lives of persistent organic pollutants (POPs) already have been linked in the literature. Many of them actually are no longer in broad use because they have been phased out. But because they are looking at half-lives and long POPs,

they really do bear looking at. Again, they have age- and gender-match controls living in the same county. Therefore, they will be able to determine if there are differences between cases and controls.

In terms of progress to date, they are up to about 130 to 135 serum specimens and they have 41 people in the hopper being scheduled for their blood draw. The results from the CDC blood specimens have been received for the 280 cases. Now they can begin to evaluate the results. The final step is the genetic analysis that will be performed by Dr. Chris Donnelly. They are interested in measuring the length of the C9ORF72 repeat expansion and considering newly identified genetic polymorphisms for familial ALS (FALS) in those individuals who reported a family history but for whom no ALS gene was identified. They have a small sample of blood from individuals for whom they can look at these newly identified polymorphisms in addition to those that have already been identified. The genetic information was received from CDC/ATSDR for the C9ORF72 positive cases, so they are continuing to work with those.

Regarding the samples tested, there has been positive detection of expanded repeats and the C9orf72 gene from blood of patients but not C9 negative controls. There is some evidence of Mosaicism of the expanded G4C2 repeat in length and size in the blood samples tested. Some have single bands, some have multiple intense bands, and some have smears. Mosaicism is found in the brain as well, but it is unclear whether this is a correlate of the disease. Dr. Donnelly will be able to answer any questions related to the fascinating results. The more newly identified genes that he will be looking at in relationship to the other results that were tested using the NeruoChip:

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

A few manuscripts have been published, some are in preparation, and others are planned, including the following:

- ❑ Talbott EO, Arena V, Rager J, Malek AM, Wu F, Buchanich J. Use of ALS cases from the ATSDR/CDC National ALS Registry and a population-based control group to investigate ambient air pollution and suspected neurotoxicants as risk factors for ALS. American *Academy of Neurology Annual Meeting*. Toronto, Canada. April 2020 (poster online). • Malek AM, Bear

- ❑ TM, Rager JR, Foulds AL, DePerrior SE, Mehta P, Raymond J, Horton K, Wagner L, Kaye WE, Vena JE, Talbott EO. Identification and Recruitment of Controls for the National ALS Registry Cases. *Northeast ALS Consortium Annual Meeting*. Clearwater Beach, FL. October 2019 (poster).

- ❑ (In Preparation) Bear TM, Malek AM, Foulds AL, Rager JR, DePerrior SE, Vena JE, Larson T, Mehta P, Horton DK, Talbott EO. Recruitment of population-based controls for ALS cases from the National ALS Registry. Amyotroph Lateral Scl Frontotemporal Degener.

- Planned Manuscripts:
  - → Environmental and occupational risk factors associated with ALS: Results of Case Control Study
  - → Exposure to ambient concentrations of air pollutants and air toxics and risk of ALS
  - → The association between persistent organic pollutants in blood and ALS: Results of Case Control Study
  - → Length of the C9ORF72 repeat expansion and newly identified mutations in ALS

With regard to 2020/2021 study completion, the hope is to finish as soon as possible during this fiscal year with the no-cost extension. For the survey data, the plan is to complete recruitment, consent, and surveys of the match controls. Most importantly, they want to collect the blood specimens on the 41 people who were surveyed during the COVID shutdown so that they are able to provide Pat 2 of the study. Then they will carry out match pair analyses and conditional logistic multivariable analyses of the relationship of the survey data, blood pesticide levels, and air toxics.

Questions and Discussion

Darcy Peth, MS
Associate
Ross Strategic

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

Discussion Points

Dr. Factor-Litvak thanked everyone for the great presentations. She asked Dr. Bradley how he plans to validate the estimates of pesticide exposure and air pollution since the data are only good since 1990. She also asked whether he had considered that the airborne dose may not be equivalent to the internal dose, and said that she was not quite sure she understood how he was estimating the missing cases. She thought she understood the underlying assumption to be that there are counties where there were low incidence rates for which he hypothesized that the missing cases are equivalent in demographics and other characteristics to the counties he hypothesized do not have more complete case ascertainment.

Regarding the airborne and pesticide applications, Dr. Bradley emphasized that the Symphony databases do not go back to the epochs of 30 and 40 years ago, which is what they would prefer. That was one of the things they wanted to do with the more limited NNE-OH databases, so that is as good an answer as he could offer to that particular question. With regard to the distribution of cases in Ohio, this is an interesting way of being able to approach this. They hypothesized that in those counties that had a low incidence rate, they were missing the cases because the cases were going to other centers or going elsewhere and that those counties that had high incidences will be interesting hotspots for later studies. They will present that paper to a journal for publication within the next few weeks, so the methods will be set out there and can be criticized as they have it. Certainly, he does not think that it matches the capture-recapture method, but it is a way of approaching the difficulty of developing a registry.

Dr. Factor-Litvak noted that all of the cases Dr. Talbott described appeared to be White. Yet, they had a long discussion the previous day about under-ascertainment of cases from under-represented minorities.

Dr. Talbott said she talked to her team about that after the meeting. The main reason is that the first 80 people who came from the pilot Biorepository were from 2012-2013 when the Registry was kicked off and they were the first people to step up. For whatever reason, most of them identified as Caucasian. There were a few who identified themselves as mixed-race. They are very aware of this. They then decided to go with the 2017-2018 sample because at that point, the Registry was up and operating and there was probably a lot more heterogeneity in the response rates. They did collect detailed information on race. They only interviewed those 80 people as part of that 127 mix. Going forward, she is hopeful that they will have more variability and more cultural diversity. With the way things are right now, they have to be very cognizant to get a representative sample.

Dr. Factor-Litvak observed that the concentrations of many of the airborne pollutants, solvents, and pesticides were almost identical for cases and controls. She hypothesized that it is because they have been matched geographically and they would need to take matching into account in the analysis, but thought perhaps she missed something during Dr. Talbott's presentation.

Dr. Talbott agreed that it was a good point. They went back and forth about this. The good news is that they do have the residential history going backward. They do not have an exact address, but they have the major town identified for their residential history. They also have air pollution going backwards and the NATA data in the past. The EPA data they have for residence is Zip Code centroid. In that regard, the Zip Codes of the cases and the controls are essentially different and there will not be matching on Zip Code. Whereas they have a county that might have 150 to 200 Zip Codes, they do have the controls and the cases coming from different parts of the mix. She believes they have enough heterogeneity for this. It is correct that they are matching on county. Many counties are very large and there are many Zip Codes, so that is what they have to work with.

Dr. Feldman requested that Dr. Bradley speak more about the Symphony database as it sounded very intriguing.

Dr. Bradley indicated that there are two large commercial databases that have been collected by organizations, Symphony® and Truven Health Analytics®. Posters have been presented at ALS/MND, ALS Association, and ANA meetings by HVH Precision Analytics (HVA) about their use of these databases for looking at pre-morbid diseases that might forecast the development of ALS later. These databases are commercially available and are tremendously powerful. They go back a fair way. While people cannot be identified by individual names, they have close addresses and things of that nature, so that is what they made use of.

Mr. Faretra asked Dr. Talbott whether they have looked at air crew members in any of their studies. He can name 4 air crew members from Charleston Air Force Base (AFB) who have ALS, probably the most famous of whom is General Mikolajcik. It is his understanding that the Airline Pilots Association union believes that they have a higher incidence rate and want to start looking into that.

Dr. Talbott indicated that they do have occupational history on all of the cases and the controls. She asked for clarification about what he meant by "air crews" in terms of whether he meant pilots or people who work around the planes.

Mr. Faretra clarified that in the cargo aircrafts, there are pilots, engineers, load masters, and the people that work the flight line who suck in a lot of hydraulic fluid. Looking at the list of toxins, that is probably not very good for them.

Dr. Mehta said he has heard about pilots, flight attendants, and others in the airline business who are potentially exposed to solvents, fuels, and so forth. This is of potential interest in terms of getting ALS. He thought it was the ALS Association that created a video on a pilot for American Airlines who had ALS. It was a very poignant story about an American Airlines pilot who got ALS, and the other pilots started carrying his bag around and started raising awareness about ALS.

Mr. Faretra said that was where he heard it. He has a brother in law who is a pilot for American Airlines.

Dr. Finger recalled that a paper was published either last year or this looking at post-Gulf War military veterans. There were enormous spikes on their crews. This is not anecdotal. It is supported by the science. (https://academic.oup.com/milmed/article/185/3-4/e501/5586481)

Dr. Weisskopf emphasized that geographic matching is important to pay attention to with regard to specific air pollutants. Some of them like $PM_{2.5}$ and to some degree ozone are rather regional. The group in the Netherlands broke their geographic matching at some point in order to handle that problem. Particularly for certain pollutants, he suggested that Dr. Talbott's group may want to consider that. The matching would be kept for other things.

Dr. Talbott pointed out that with daily levels, Allegheny County Pittsburgh is one of the worst places as far as air pollution and $PM_{2.5.}$ However, there are parts of Allegheny County in Zip Codes in the periphery of Allegheny County in the hinterlands of the suburbs where the levels are incredibly low. Downtown Pittsburgh has major problems. They are very cognizant of that, and she thought breaking was a very good suggestion.

Dr. Weisskopf added that they potentially could do things like treat geography in a different way from socioeconomic factors to account for that. The other thing that might crop up by doing that is that they might get differences in the further East they go versus further West, because the counties are so much different in size. He observed that Dr. Talbott's team found a way around the recurring issue of controls and requested more details on how they got their controls. He wondered where they were coming from, especially given that they are being asked to complete questionnaires and provide blood samples.

Dr. Talbott indicated that they struggled with this because they wanted a nationally representative sample and did not want to get all of the controls from Pittsburgh. They thought about the fact that different regions have different pesticide exposures and different occupations. Someone growing up in Iowa would have different exposures than they would have in Manhattan. They used the Marketing Systems Group (MSG), which is a national database group that generates population samples for the whole country. Because of credit unions and because everybody has a credit card, there are huge swaths of information on everyone. They have age ranges, gender, and exactly where someone is living. So they were able to generate a huge sample to whom they were able to send letters. They sent 10 letters for every control. They sent a pre-notification letter to state what they wanted, included a brochure that said they were looking for controls who did not have ALS, and then they would call them. The outpouring of people who know somebody who has this condition, know it is bad, and want to help. She has been very impressed by the excellent response rate.

Dr. Mehta added that controls Dr. Talbott and her team have enrolled will be added to the Registry. ATSDR is in discussions with Drs. Todd and Bear to potentially have them create more control groups in the future, because they have established a good method and controls are always needed. It would be good for the Registry to be able to add 500,000 controls or more.

Dr. Talbott emphasized that the hard part is having someone come to one's home to take a blood sample. What impressed her the most was that most of the individuals, even in this time of COVID, were willing to allow that. They soon have a paper coming out that was spearheaded by Dr. Malek that describes the methodology for the study.

Dr. Finger observed that Dr. Bradley has worked with the Registry for a very long time and wondered why he used the Symphony® database versus the Registry in terms of what benefits there were for his project. That would help them to think about the strengths and weaknesses of the Registry.

Dr. Bradley indicated that the Symphony® database has about 26,000 ALS patients distributed over the whole of the US. While distribution is not uniform, it is an enormous and useful database. They have any number of times that number available for controls. That was the reason for choosing it.

Dr. Finger pointed out that one of the problems with a large and skewed sample is that even the lower educated patients or minority patients may look very different from the average person with the same characteristics. For instance, a person who gets 900 on his SAT and gets into Harvard is totally different from the average person who gets a 900. He asked Dr. Talbott if she worried about this very select sample in which perhaps a bricklayer does not look like the average bricklayer.

Dr. Talbott agreed and said she thought they always had to worry about that. They do get detailed information about education and occupation. Those are covariates for which they have to adjust. In the real-world, it would be wonderful to get a completely random sample of cases from across the country and a large number. They really wanted to get the serum blood levels, which is really the novelty. This is very important because it gives not only a snapshot in time now, but also a snapshot in time in the past. That does not change whether someone got an 8th grade education, high school, or college—it is there. She is hoping that that coupled with the air pesticide and the air pollutant data and knowing what someone did for a living will allow the investigators to tease some of this information out. It is very hard.

Dr. Dave asked whether Dr. Walters or Dr. Traynor have looked at whether the 20 SNPs that have been identified that were found to have significant increases were in the coding regions of the gene, and if they fall into the gene areas that may have been shown to regulate and dysregulate TDP-43.

Dr. Bradley did not think they had any data at this moment with regard to the C9ORF72 or any other underlying genetic features of these particular patients.

Dr. Traynor added that he did not know. It is a great question and he thinks it is something they should pursue. They can do things like look at the individual genes. They are increasingly turning toward doing enrichment analysis looking for pathways that might be over-represented within those 20 SNPs. Each individual SNP on its own might not be that compelling, but looking at groups of those SNPs, different pathways start to emerge. It is something they have thought about but have just not done yet. He said he had to admit that over the years he has been rather skeptical of pathway analyses, but the recent 12 to 18 months have really shown him the value of this so he does think it is worthwhile pursuing.

Update from Actively Funded Registry Grants: Part #2

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

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Department of Environmental Health Sciences
Columbia University

Dr. Re expressed her gratitude for the opportunity to present and meet everyone virtually. She noted that she has been working on ALS for quite a long time but spent the first part of her career studying cell and animal models of rare genetic mutations in superoxide dismutase 1 (SOD1). Since becoming an independent investigator a few years ago, she decided to refocus her career in ALS on the role of environmental exposures. The data she presented during this session are part of an R01 funded by the ATSDR/CDC for which she is a multiple-PI with Dr. Neil Shneider who is the Director of the ALS clinic at Columbia University. They gathered a very interdisciplinary team for this work that includes Matthew Harms, Marianthi Kioumourtzoglou, and Beizhan Yan.

When they received this R01 a few years ago, they wanted to tackle the role of environmental exposure in ALS from a different angle and different approaches. The first aim of the study was to look at non-persistent pesticides and their role in ALS progression. In particular, they are interested in organophosphates and they decided to use the ALS Registry for hair samples. They know that non-persistent pesticides are difficult to measure in blood, but they can accumulate in hair. What they are doing now with Dr. Yan is to measure the metabolites of all of the different pesticides in the hair of 180 ALS patients at two different time points to look at their potential effects on disease progression. The second specific aim of the study was to investigate whether metals measured in central nervous system (CNS)-derived extracellular vesicles that can be found in the blood, are a better biomarker of brain metal load than classical blood metal level measurements. Dr. Re noted that she would not present data during this session on the extracellular vesicles and would focus on Aim 3. The objective of the third aim is two-fold. First, is to try to identify a common transcriptional signature between the CNS transcriptome of mice that in a controlled manner in a laboratory are exposed to a neurotoxicant and the CNS transcriptome of ALS patients. By extracting the signature of the neurotoxicant exposure, they hope to gain information on ALS etiology. The second objective in the third aim is to use this comparison of concordant of transcriptional signatures between the mice exposed to the neurotoxicant and the ALS patient to identify early pathogenic pathways that will confirm relevance to ALS underlying molecular mechanisms. Here they hope to identify novel potential therapeutic intervention.

There is a proof of concept study in Parkinson's disease from the group of Flint Beal that showed that it is possible from the CNS transcriptome of mice that were exposed to different pesticides that some signaling pathways could be extracted that also were found in post-mortem samples from Parkinson's disease patients. They thought it was a good rationale to bring the same type of approach to ALS next. They did not choose already published transcriptome data, because they had their own RNA-seq that were produced by Matt Harms and Neil Shneider from the motor cortex and spinal cord of 100 ALS and 20 control patients. In the laboratory, they are chronically exposing mice to an OP pesticide and a metal. For the metal, they selected manganese and for the pesticide they selected one of the organophosphates that they are studying in Aim 1. They selected these because there is some evidence that says they could be linked to ALS. At motor deficit onset, mouse motor cortex and spinal cord were collected and RNA-seq for comparative transcriptomic analysis. The rationale is that cell death in ALS is known to be asynchronous, they hope that they can identify some pathogenic pathways early in the mice and find some correspondence at a later stage in the post-mortem of ALS patients.

As everybody knows in this audience, ALS is sporadic in 90% of the cases and familial in 10% of the cases, but something that often is not highlighted is that even in familial cases where a genetic mutation is identified, most of those mutations are incompletely penetrant. That means that one can have the variant but will not automatically develop the disease. For example, for TDP43, only 26% of the variants are clearly pathogenic. Also, there is only 15% segregating with the disease. Something which is also interesting with the TDP43 variant is that they are found in frontal temporal dementia that can co-occur in ALS. Finally, within the same TDP43 family, disease onset can vary by up to 35 years. Therefore, they believe that this could be a role for environmental exposure in sporadic ALS, but also in familial ALS as a modifier.

The mouse model used in the study was developed by the group of Neil Shneider. It is a knock-in TDP43 mouse model. The beauty of this model as compared to previous transgenic models that were over-expressing a protein is that here, the mutation is introduced in the right locus via homologous recombination so it will express endogenous levels of protein. The variance that was introduced was G298S of TDP43, which is incompletely penetrant, and causes early onset of ALS and a rapid rate of disease progression. This mouse model was asymptomatic and there were no motor phenotypes or neuropathological features in the mice. They found a phenotype in Homo G298S confirming the relevance of this model. They felt that the Het model offered a unique opportunity to study gene-environment interaction because this mouse has a genetic susceptibility to ALS but no phenotype.

Regarding the study design, there were two different cohorts. One was exposed to manganese via drinking water, or to control water. Another cohort was exposed to chlorpyrifos via subcutaneous pellets or to placebo pellets as controls. In each cohort, half of the animals were wild-type controls and the other half were het G298S. The exposure was started at 11 weeks to place themselves more in a model of occupational exposure, adult onset exposure. The original design was to expose the mice for 6 months or when they detected a stable 25% motor deficit. Unfortunately, they had only male mice. Sporadic ALS is more common in men, and TDP43 mutations demonstrated greater penetrance in men than women, so they still believe there is some good relevance here. They had to choose which dose to use to expose the mice to manganese, they had to find a level of exposure that would not cause in the wild-type mice a neurotoxicity by itself, because ALS patients do not complain about neurotoxic symptoms before they develop the disease. So, they went to the study that showed the slightest symptoms at the level of 400 ppm by Krishna et al. They showed very mild but significant decrease in grip strength in those mice. Therefore, in the pilot study, they tried to test for several weeks chronic exposure of a reduced group of mice to 200 ppm—half of the dose. They assessed the mice

longitudinally for their motor performance and did not observe any effect on the rotarod of manganese or the gene, so they decided to move back to 400 ppm causing very mild neurotoxicity in the mice for the larger study.

In terms of chlorpyrifos for the exposure, the investigators followed the advice of the group of Pamela Lein. She made a good argument that one of the most relevant exposures to people working with organophosphates in the field was to do subcutaneous exposure, because it can be more controlled and it is safer for the personnel and is relevant to the animal exposure. One of the innovations in this study is that here instead of doing subcutaneous injection, they used pellets that are biodegradable and that are progressively releasing chlorpyrifos. The pellets are usually used for drug delivery, but the company agreed for them to put the organophosphates in the pellet.

They wanted to reach an AchE inhibition target of about 40% to 70% in the blood to replicate what was observed in a cohort of Egyptian farmers. They tested different doses of chlorpyrifos and found that delivering 0.5 mg/kg/day to the mice was achieving the goal after three weeks. So, they utilized this for the larger chronic study. To monitor consistency of exposure in animal studies, the first thing they did was to make sure that the mice were consuming water at the same rate of exposure and they did not find any difference in water consumption between the manganese mice compared to the control mice. In terms of CPS exposure, after they did a longer measure of the AchE inhibition that was reaching the blood, unfortunately they saw that after 3 weeks, the pellets were losing their activity and are bumping back in the level of AchE activity. They know now that exposure was on and off over the course of the disease. They were replacing the pellets basically every 8 weeks. So, they can debate whether exposure is even more relevant as compared to humans who are using organophosphates periodically but not continuously in the field.

In terms of the results on the weight of the animal over the study, no decrease was observed in weight over the course of the exposure. Often, weight is used in ALS as a surrogate of paralysis onset. The study never reached a stage where the mice could not eat normally and thus decrease their weight. The second thing they saw was that the Het group has a tendency to weight increase, but it became only significant upon exposure to manganese. This observation is quite interesting because the same was observed in another TDP-43 knock-in mouse model and it was linked by the authors to hyperphagia, a clinical symptom of frontotemporal dementia. Unfortunately, however, they did not measure food consumption in this study. In terms of the CPS study, they did not observe any difference among groups. But again, they did not reach overt paralysis over the course of the exposure.

In a longitudinal motor assessment of those mice by the rotarod, the wheel where the mice are running, first they did establish a baseline before the exposure started. After 11 weeks when the exposure started, all of the group were progressing in their score. Very quickly, they see that the Het group exposed to manganese is not performing as well. But because this deficit was not stable and was bumping up and going down, they decided to prolong the exposure to 9 months. At 9 months, it was still about a 25% to 30% deficit, so they stopped the study. But they observed here a clear interaction between manganese exposure and the genotype. It was a good thing for the CPS study that they extended the study from 6 to 9 months, because they were not seeing anything at 6 months for CPS exposure. Finally, at 43 weeks they started to see the Het group specifically developing motor deficits.

They also tested the mice for some cognitive aspects, such as memory by a combination of the Y maze and novel object cognition test. For the manganese study, they did not see any clear gene-environment interaction. Basically, manganese already affected the memory of mice independently of the genotype. But for the CPS study, the Het exposed to the organophosphates specifically developed memory deficits as compared to the other group, suggesting again that maybe it could be some behavioral sign of frontotemporal dementia in those mice.

Regarding biomarkers of exposure as the study endpoints, when they sacrificed the mice, for those with manganese exposure, there was about a 20% to 30% increase in all of the CNS areas they measure. There is a non-significant tendency of higher increase in the Het. At the endpoint for CPS, inhibition of AchE as expected was not seen any more in the blood because the last pellet was inserted 5 weeks before, at a time CPS lost its stability in the pellet and is not effectively delivered any more. However, there was permanent inhibition of about 30% in the frontal cortex and 10% in the spinal cord in the Het group.

The conclusions so far are that the interaction between Mn, CPS, and genotype appears quite promising for the motor phenotype. Hyperphagia and memory impairment could indicate FTD at the behavioral level. Ongoing pathology (NMJ, MN count gliosis, TDP-43 inclusions) and transcriptomic studies will confirm the relevance to human ALS and/or FTD. For continuous exposure to AchE inhibition via CPS pellets, future studies should replace pellets every 3 weeks instead of every 8 weeks.

Metabolomic Signatures Linking ALS to POPs Exposures

Stephen Goutman, MD, MS
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Associate Professor of Neurology
University of Michigan

Dr. Goutman stressed what an honor it was to be speaking to everybody, even though it was not in person. He noted that he was presenting on behalf of their group and Dr. Eva Feldman, who also was on the line. The goal of their work is to focus on metabolomics and ALS. The metabolome is a complete collection of small molecule metabolites in a cell, organ, tissue, or organism. Importantly, it includes both endogenous and exogenous molecules, as well as transient molecules. Metabolomics is an emerging tool to assess exposures, especially in circumstances where the exposure may not be known. Dr. Goutman displayed a series of articles to illustrate how metabolomics is being incorporated into exposure studies.

The hypothesis for the University of Michigan study is that persistent organic pollutants (POPs) and other exposure types will lead to unique metabolite signatures in both plasma and CNS tissue in ALS subjects and this will: 1) yield novel biomarkers of ALS; 2) inform us of past exposures; and 3) increase the understanding of disease pathophysiology. In terms of the project timeline, they are somewhat ahead of where they planned to be at the end of Year 2. The original plan was to send off samples over the course of 3 years, but a decision was made to send them in 2 phases. In retrospect, this was a good idea for batch-to-batch variability. They are ahead in terms of sending the plasma samples and now they are sitting on an abundance of data that are ready to head into Year 3 analyses.

Regarding the Cohort 1 or Phase 1 data, they have 125 cases and 71 controls. There are no differences in their age, sex, or body mass index (BMI) and their ALS disease characteristics are fairly typical of what would be expected. They wanted to look at these metabolomic differences in various accepted statistical models. These include conducting a univariate analysis that looks at the metabolite one at a time to see if it differs between cases and controls. That univariate analysis can be done while adjusting for important covariates such as age, sex, and BMI. The literature suggests that there may be some role for adjusting for some of those covariates in certain metabolites. A partial least squares-discriminant analysis (PLS-DA) can be used to look at the differences in metabolites between two groups while also accounting for the correlation between those metabolites. A least absolute shrinkage and selection operator (LASSO) model was also used to adjust for clinical covariance, but thinking about the related structure and sub-pathways of these individual metabolites. They see in their Phase 1 data that the metabolites are very clearly differentiated between cases and controls.

Looking at a high level overview of the top metabolites that they saw in terms of the relative abundance, there is a relative abundance of metabolites in the control group. There was a very clear differences in the cases, suggesting that there is a very different metabolism. The relative abundance of these top metabolites are lower in ALS and fall into different sub-pathways of metabolism, including benzoate metabolism, chemical metabolism, and creatine metabolism. They were very interested in understanding the difference of pathways involved in these metabolite differences, so we looked at this in three of the statistical models discussed earlier: Adjusted Model, PLS-DA, and the Group LASSO model. This enabled them to look at each of the significant metabolic pathways and whether they were seen as enriched in each of the statistical models. The top 10 based on the p-Values were: Benzoate Metabolism, Chemical Group, Diacylglycerol, Lysine, Sphingomyelins, and the Urea Cycle. Many other sub-pathways also were detected as being dysregulated in the ALS participants, including: Fatty Acids, Food, Glutamate, Glutathione, and Histidine Metabolism.

It is very interesting to think about what the potential roles could be. This is one of the goals of the work with enriched metabolic sub-pathways. The benzoate metabolism and chemical group are both from the xenobiotic super-pathway and they have many metabolites that contain cresol and catechol groups, which are common pesticide moieties. Diacylglycerol are bioactive signaling lipids with roles in cytoskeleton, neuronal development, inflammation, immune cell signaling, and apoptosis. Sphingomyelins are bioactive signaling molecules involved in apoptosis, autophagy, and inflammation. They include sphingomyelins, sphingosines, ceramides, and hexosylceramides. All of these are very important signaling pathways that may be dysregulating ALS pathophysiology. Lysine metabolism's connection with ALS is uncertain. The urea cycle converts ammonia to urea for elimination. Some literature suggests that this may be regulated in ALS.

They have just received back their second round of data, so they sent additional subjects. They wanted to see how well these subjects overlap with the participants in Phase 1. In Cohort 2, they also included longitudinal time points. In Phase 1 they sent plasma at only one time point, In Phase 2, they sent 236 participants that have 1 time point only. There are 73 participants who have 2 time points, 98 who have 3 time points, and 2 with 4 time points compared to 154 controls with metabolomics profiling at 1 time point. The time points do not tend to cluster together, which shows that there is a lot of heterogeneity in this disease and that there is not a clear difference in metabolites that occurs over the course of disease.

They just received these data back and wanted to see how closely Phase 2/Cohort 2 matched to the Phase 1/Cohort 1 participants. In another PLS-DA comparing cases and controls, metabolites in ALS subjects are very clearly differentiated from those in the control group. They wanted to look at how well these two cohorts shared their metabolites and they saw overall some very good agreement. There were 22 matched metabolites between Cohort 1 and Cohort 2, such as: Creatine Metabolism, Glutathione Metabolism, Benzoate Metabolism, Fatty Acid Metabolism, and others. They are seeing very good overlapping and agreement between the two cohorts, and the sub-pathways are very much in agreement with what we they saw in their initial wave of subjects and what has been published in the literature.

Part of this project is to understand how these metabolites are altered or different based off of categories of pollutant exposure. They are really just starting this analysis now that they have received their datasets back. A year ago, they presented data showing that subjects with ALS that have higher measures of POPs tend to have a faster disease progression or shorter survival. So they looked at whether there are any metabolism and differences between those who fall into the high exposure group or the highest group POP concentrations versus those that have low amounts of POPs in their blood. The PLS-DA plot shows that there is very clearly separation between those two groups, and there are 221 metabolites that are shown as being important in terms of separating those two groups out.

When they performed an enrichment analysis based off of these two groups, Sphingomyelins and Long Chain Fatty Acid Metabolism seem to be dysregulated between these two groups. These are data that they need to really further jump into and understand what is happening in these groups. That is a high-level overview of how they are applying these metabolic signatures to their POP measures.

There is another advantage of doing these untargeted metabolomic profiling studies in that different chemicals also can be seen that show up in these untargeted metabolic assays. For instance, chlorothalonil is a widely used fungicide and pesticide, especially in the Eastern half of the US. It is highly used in Michigan and along the East Coast. The metabolite of chlorothalonil is 4-hydroxychlorothalonil. The density between ALS and control subjects is of interest in that there is a higher density in the control participants. When they compared differences in the overall metabolomic signatures between those with high amounts of this metabolite versus those with low amounts of these metabolites in the ALS group alone, the PLS-DA plot shows good separation of these two groups. This is something we need to look into further.

They also had measures of perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA). These are persistent chemicals found in cookware, food packaging, stain repellents, and firefighting foams. They were in the news a lot prior to February and March. People are exposed to them through food and drinking water and there are a lot of health effects that are proposed to occur because of exposures to these chemicals. Individuals with ALS and controls seem to have similar exposures to this group, which is not a surprise given how widespread they are in the environment. Similar to the chlorothalonil measures, if the cohort is divided into those who have the lowest amount of PFOS and PFOA, clear separation is seen in these in these two groups. What they need to do now is start thinking about how these pathways are enriched between the cases and controls and if it is possible to determine whether ALS pathways are being further dysregulated by chemicals or if there are new pathways that are becoming dysregulated as part of these chemicals. This is the goal for the next year now that they have all of these data back.

Finally, one of the last aims of this study was to understand how well these metabolites match between what they saw in plasma samples and what they saw in CNS tissue. In a very preliminary look at this technique of the Matrix-Assisted Laser Desorption/Ionization (MALDI) Mass Spectrometry Imaging (MSI) which allows them to look at different metabolomic changes in certain tissue regions, so in this case the difference in gray matter between a control subject tissue and an ALS subject tissue in one case versus one control. This shows that there are very clearly different metabolic pathways in the gray matter of ALS compared to controls. Over the next year, they should be further analyzing more samples of the CNS tissue.

In terms of conclusions and future directions, they are identifying these unique signatures as hypothesized and are identifying signatures of POPs and other exposures. And over the coming year, the aim is to correlate these signatures with residential and occupational exposure histories and determine whether these metabolism signatures that are found in the plasma are present in post-mortem brain tissue. In closing, Dr. Goutman expressed that they are extremely grateful to ATSDR, the National ALS Registry, and Drs. Mehta, Horton, and Wright for all of their support and funding their work and all of their other funders at the ALS Association, NeuroNetwork, the CReATe Consortium, Target ALS, and the Michigan team.

A Novel Innate Immunity Risk Factor for ALS

Teepu Siddique, MD, PhD
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Dr. Siddique expressed gratitude for being invited to this platform to present some of the work that his team at Northwestern University is doing, ATSDR for funding this work, and his team members. He has not had the ear of his colleagues and patients in a long time, so he said he wanted to share where he was coming from. In 2012, the great pillars of ALS, Stanley Appel and Lewis Rowland passed away [fading in and out]. They applied molecular genetics to ALS and identified several genes as the cause in hereditary ALS and ALS/FTD, and identified mutations in the main protein quality control systems (UPS and Autophagosome -lysosome system) genes and the first animal model for ALS/FTD (UBQLN2 P497H). These were very important because they unified pathology for all of ALS and ALS/FTD with P-62 and Ubiquilin2, TDP-43 as a sub-pathology, and for the first time these were genes that actually had mechanisms that would be operative in ALS and pathology. There also was the discovery that the TDP-43 pathology was not pertinent to all forms of ALS.

His team has been focused on novel therapies based on pathogenesis, including gene silencing and augmentation. The problem in sporadic amyotrophic lateral sclerosis (sALS) is the knowledge gap pertaining to 85% of ALS being sporadic and without known causes or mechanisms of disease. There also is a knowledge gap in that there is a long history of clinical trials that have failed in sALS, which will continue to fail. They may find statistically different significant differences in trials but that does not necessarily mean clinically significant. They can have drugs and make them available, but they will be trivial or they will be clinically meaningless, as has happened so far. Without knowing the cause and mechanism of disease in sALS, clinical trials are likely to continue to fail. Clinical measures like multidisciplinary specialized ALS clinics, powered wheelchairs, better nutrition with G-tube, non-invasive ventilation (NIV) for respiratory support, and sleep and communication support have improved

the quality of life and possibly increased the life span. Adequate personalized professional care for ADLs is still a lacune.

ALS apparently is a multi-step process, otherwise the huge efforts that have been made in sequencing would have found huge signals like are found with APOE and Alzheimer's disease. There are now diminishing returns as more and more is being sequenced and less than less is being found in sALS. This has to be a multi-step process or a much more complex idea, process, or mechanism than they are led to believe.

Many years ago, they proposed that there would be a gene-environmental interaction and wanted to look at the variance in the genes for xenobiotic responsive elements in ALS. They conducted a very large study with the funding from NIH to whom they are very grateful because it led to the current study. In the NIH-funded study, they identified the PON cluster where the signal came from in ALS, and there were several other studies after that. Then it was forgotten for two reasons. One was that the meta-analysis was and did not seem to see the signal, but their large data were not included. The second reason they decided to move on was that they needed to find a partner environmental agent. There were many, but they were all new. They could not find anything going back years and years for decades or centuries perhaps.

This formulation that he put together is a work in progress. An environmental factor is needed that could challenge or provoke a normal intrinsic response, but that normal intrinsic response may go haywire as has occurred with COVID. It would be variable and maybe population-restricted genetically or stratified by environment, age, and co-morbidities. There is a layering of complexity here and there would be variants in the gene that modulate intrinsic response and also may be restricted to sub-populations. There may be trans factors that may be independent or cascading in the body. They would amplify, diffuse, or perpetuate the response. There also would be the element of age, because this is an age-related disease, which would be a mechanism that would modulate or later rendered senescent and would fail challenge or challenge in later life. Then there is the issue of variability between individuals for all of these different elements, but the sum total would reach the threshold to cause disease. One thing that fits this bill is innate immunity.

After they looked at the PON cluster, they found that it was carried in the HDL particle. They usually talk about HDL cholesterol, but that is just one of the elements in the particle. It affects many systems including the liver, cardiovascular disease (CVD), immunity and so forth. There are a number of other related proteins in familial disease. They started to look at this more systematically. They conducted a number of studies to show the HDL cargo, pathway, and the gene loci. They have a lot of data on all of these very interesting molecules that they found that are related to pathways in different ways. One could write a tome on them. They found a particular molecule, APOL1 that seemed to have a partner in the environment. Preliminary studies suggested that in the White population, 3 SNPs were found to be associated with sALS. They replicated that study in a larger cohort and that was sustained. This was a while back. This allowed them to then apply for the ATSDR grant.

The specific aims of the ATSDR grant are to: 1) identify *in cis* variants in the region of the APOL1 gene for association to ALS and endophenotypes in existing sALS patient samples (N=650) using custom capture targeted high throughput sequencing of a one megabase genomic region centered on the APOL1 locus; 2) test for correlation of variants identified in the APOL1 locus associated with ALS (above) and acting as *in cis* eQTLS affecting APOL1mRNA expression and/or plasma concentrations of Apol1 measured in the ALS cohorts; and 3) interrogate our own registry environmental exposure data and on acceptance of our application,

the data available from the ATSDR/CDC ALS Registry and if pertinent NEALS registry for known exposures against measured cytokines and levels of Apol1 and integrate the genomic and RNAseq data with epidemiological measures in a standard format. All studies that have been done with direct elements have not been very successful.

APOL1 is on chromosome 22. It has 398 proteins and 5 functional domains. The domain that is of importance is the BH3 domain, membrane domain, and pore forming domain. The most important thing is that it is responsive to Trypanosoma. Now they were able to find an element in the environment that is ubiquitous that coupled with these variants in the genes and other system transacting elements would be a reasonable hypothesis. They analyzed CSF samples from 29 sALS patients and 28 controls. In 19 samples, ApoL1 was not measurable by ELISA and the lack of ApoL1 was verified by SDS-polyacrylamide gel electrophoresis. All samples were positive for ApoA1 confirming that HDL-like particles were present. The ApoL1 levels were 14.2 +/- 1.87 ng/mL for controls and 12.4 +/- 1.94 ng/mL for sALS patients (p=0.51).

So is it ubiquitous. It seems to be. It has animal hosts everywhere (e.g., rat, cattle, sheep, domestic animals of all kinds, goats, sheep, monkeys, dogs, mules, horses, camels, birds, chicken, fish, and frogs). But how is it transmitted? These are not pathogenic to humans. The pathogenic ones are limited to a few species in East Africa, West Africa, Central America, South America, et cetera. Those are pathogenic and a lot of studies have been done to show that they can be transmitted. They can sit there on the skin and nobody would know they have it, but they would have the antibodies and will transmit it to other people. A person could have an infection, provoke a response and not even know it because it is not pathogenic in most cases. Of course, there could be another thing that could provoke the same response, but this is a good model.

Trypanosome is a very efficient killer because APOL1 from HDL1 enters the parasite, targets either the mitochondrial membrane, destroys the pH system, and the whole cell is destroyed by the rupture of those membranes. The same thing happens in mammalian systems. They measured it in 349 cases and 55 controls. They conducted some more studies and started to look at the difference cutoffs. Above the 25th percentile, they are all highly significant in terms of levels of APOL1. APOL1 mRNA varies among brain regions and is at least 10 times lower than in abundant tissues such as the liver, bladder, and kidney. Expression is also high in lymphoblasts. Large variations in APOL1 expression suggest regulation by both "Cis" and "Trans" factors. Looking at the various expression forms of SNPa and how they may have an effect on the expression of APOL1 or the expression of APOL1 variant on other genes, there are some very interesting genes. Of course, it self-regulates. The real elements are the ones that have the most effect in terms of the transcoding elements that come in.

Current Project: ALS Cases

- ❑ 1534 White patient samples with appropriate materials
  - → Blood > plasma & lymphoblast cell lines
  - → 17 from clinic patients since clinic credentialing approval

- ❑ 832 samples screened to date
  - → Mean age of onset 59.5 ± 13.4 years
  - → Brain & spinal cord from 50 patients
  - → CSF from 8 patients
  - → Environmental hx questionnaires from 73 patients

- ❑ 702 samples available for next phase
  - → Mean age of onset 53.5 ± 13.3 years
  - → Brain & spinal cord available from 62 patients
  - → CSF from 36 patients
  - → Environmental hx questionnaires from 135 patients

Current project : Controls

- ❑ 2150 samples from White controls: 1437 with plasma & lymphoblast cell lines

- ❑ 831 samples screened to date
  - → Mean age of onset 52 ± 19.7
  - → Environmental hx questionnaires from 4
- ❑ 1606 samples available for next phase
  - → Mean age of onset 50.5 ± 17.6 years
  - → Environmental hx questionnaires from 16

In conclusion, this is a novel innate immunity gene pathway associated with sALS and unique to humans and some primates. The proteins coded by those genes are elevated in subgroups of sALS patients. It is ubiquitous in the environment, but is usually a non-pathogenic infectious agent(s), and provokes a unique innate immunity response which is elevated in a sub-cohort of sALS patients. The protein is toxic to parasites and detected in the CSF of humans. The protein belongs to the porin family of proteins and affects apoptosis and the autophagosomelysosome and mitochondrial membranes.

Questions and Discussion

Darcy Peth, MS
Associate
Ross Strategic

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

Discussion Points

Dr. Bradley pointed out that like the cancer field, environmental exposures almost undoubtedly have to have occurred over a very long period. This is well-known in the cancer field with smoking, arsenic exposure, and so forth. In the ALS field, this is also known from the Finnish database that indicates that where people are born is a risk factor for ALS. He expressed his hope that everyone else would concentrate on length of exposure and how many years ago those exposures occurred. He noted that one of Dr. Re's specific aims is to look particularly at metals in exosomes. Even though she decided not to present these results, he asked whether she could give a brief outline of what they found in those exosomes.

Dr. Re said that they looked at different types of metals, including manganese, mercury, copper, iron, and selenium. They were able to detect most of those metals in the exosome mainly from astrocytes. They immunoprecipitate from the blood with an antibody, which is directed against a specific marker of astrocyte. When they look at enrichment of the astrocyte marker even if they find a higher enrichment of astrocyte marker, they find a lot of neuronal protein. They could detect all of those meta except selenium, which most of the time is not detected. They looked at

the meta level in the CNS of the patient, but unfortunately so far they got only seven samples that were paired between CNS and blood. For manganese, they found clearly the blood level was not predicting at all the level of the metal in the brain. Now they are screening 180 samples for which they do not have CNS at two different time points. They have ALSFRS data that were taken close to the time the blood was collected, so they look at how the metal level can predict, for example, disease progression and how it varies with disease progression. One of the original ideas was that if you look for example at lead, which was one of the first metals associated to ALS, there was some very interesting findings showing that finally it is in the ALS patients that were surviving for a longer time that the lead level was highest in the blood. This suggests that maybe metals accumulate for many years in the brain. Maybe it is a way for the body and brain to extrude metals out. That is why it is very important for this type of research to have access to blood and brain samples to try to understand the data.

Dr. Stommel asked Dr. Re whether the mice showed any symptoms of toxicity when the organophosphate pellets were inserted and if they measured levels of the organophosphates in the blood.

Dr. Re indicated that they did not measure metabolites, but they have longitudinal data. Every 8 weeks they renewed the pellets. Basically what happened was the first 3 weeks for sure they have an inhibition of about 40% in the blood. And that, they are losing disinhibition. She does not have the 4 week data, but they know at 5 weeks it is lost. It was on and off exposure.

Dr. Finger noticed in Dr. Goutman's data summary slide that patients were broken out by El Escorial criteria of Definite, Probable, et cetera. He asked whether he found it confusing at all that Definite ALS and Probable ALS are used in a different way with regard to the Registry.

Dr. Goutman said he thought that was an excellent question, but was beyond the topic of their presentation. The reason his team breaks it up that way is because they do find it to be a prognostic factor. He deferred to Drs. Mehta and Horton about the Registry.

Dr. Finger replied that respectfully, he did not think this was about Dr. Mehta's opinion. He was asking more about them as researchers in a closed forum if they think this is a good term.

Dr. Goutman said he thought Dr. Finger was asking really good and excellent questions and that a lot of them in the community have asked these questions as well. He does think it is up to them as a community to discuss this. Dr. Brooks did some work recently on those terms. Because there were other experts who could comment on the use of the El Escorial criteria in the past with the historical perspective and currently, he did want to defer that question to somebody else.

Dr. Brooks indicated that the El Escorial criteria used the terms Definite, Probable, Probable Laboratory Supported, and Possible in a sense to identify the burden of the disease pathologically as it presents clinically. The use of the word Definite by the Registry, he believes, is just to say that these people would be in a cohort of people who would have all of the different burdens of the disease. He did not think that if they properly apply the pathologically defined burden of disease and think of it separately from the epidemiological identification of the disease that there is any problem.

Dr. Factor-Litvak congratulated everybody on these very excellent presentations. In terms of Dr. Goutman's case-control comparisons of the metabolomics, she expressed concern about the "chicken and egg" problem, because certainly there may be multiple genomic perturbations associated with disease. She thought that the conclusions about the differences in the metabolomic profiles between cases and controls need to be maybe tempered a little bit for that. She also congratulated him on using the two cohorts as discovery and validation.

Dr. Goutman indicated that there was a really nice paper published recently that looked at a pre-symptomatic cohort of individuals who went on to develop ALS and metabolites and did not see any differences. That was a really excellent study that frames this idea that perhaps there is not this long-term change in metabolism that is occurring prior to the onset of disease. He encouraged everyone to look at it. His team is seeing changes that are occurring during disease. They are capturing their cohort as early as we can, so typically within 6 months of being diagnosed. Clearly there are changes in metabolism that are occurring that they are catching as part of the disease, but very clearly showing up in the case series between cases and controls. That is why they aim to do these longitudinal measures. They planned to distribute the measurement of metabolomics over the course of the 3 years based off of the budget, but made this decision to do it in two phases, which in retrospect was a very wise move, especially as we were granted year 3 of funding. It reduces some of that variability that they need to think about, but they just received these datasets back and are going over them. He does think that the longitudinal data will be very insightful.

Dr. Wright congratulated all of the speakers for their excellent progress and work on these awards. She recalled that Dr. Siddique's hypothesis is that trypanosoma infection elicits an APOL1 mediated innate immune response that if chronic, will then result in an antagonistic tropic phenotype, which then confers neuronal toxicity. She thought he was working with a North American cohort for the evaluation of APOL1 variance and Trypanosoma infection. She wondered if there was consideration for looking at, say, a Latin American cohort for a population that may have a different profile for trypanosoma infection in the past. She was thinking about how prevalent that is in North America.

Dr. Siddique said that trypanosoma is ubiquitous in South America, Central America, and Africa. There was a case many years ago in India where trypanosoma is very common and everywhere and does not cause any disease that is noticeable. But it is immediately killed by the APOL1. There was a person in India who developed it and they found that there was mutation in one gene of that individual so he could not mount a response. These are not pathogenic because of APOL1. Naive organisms may mount a very strong response and a very toxic one. There are over 200 zoonoses that they know about. In terms of the current situation, there are 4 of them that cause viruses. One of them came 1000 years ago through camels and two bats and another came 100 years ago through bats, cattle, and so forth. This is ubiquitous. It does not have to be this particular organism. It could be many other things that can mount this response and some people who will always express it. They have an African American cohort that he did not have time to present that they would really like to enlarge, because there the signal seems to be very strong. That is very important and if it is possible, they would love to do it.

Dr. Wright indicated that she would connect with him offline.

Persons Living with ALS Perspectives on the Registry

Ed Tessaro

Hi everybody. I'm Ed Tessaro and I'm in Atlanta. I have been an ALS patient for a dozen years, so I have three areas to comment on. First, the concept of gratitude, which I'll get to. Then the way we currently silo data and research versus collaborating and sharing that data is still a big question in my mind. Even given proprietary pressure on research, is there still room to share more open questions? And then number three regarding the Israeli Biotech BrainStorm. You may have seen they posted a second quarter release today. That Phase 3 trial is fully funded. I wanted your take on whether you think that ALS trial is on the cusp of something great or do you remain a bit skeptical of stem cell transfer. So, those are the three areas. The easiest is gratitude. I know all of our objectives are to leave ALS better than we found it. So, for all the work each of you are doing, I want to personally thank you. Every year, and this is 10 for me, I am inspired by the researcher, the doctors, and the work that goes into planning and managing to carry on against obviously big odds. There are so many fields where you get wins and losses in individual disease. You all picked one where we have a lot more losses. So, what could be more difficult than telling people like me and families like mine that we have a fatal disease with no cure. It takes, I think, a special toughness, maybe a special humanity, and intestinal fortitude to do this kind of work. I see it all the time from Jonathan Glass at Emory and his team. I see it in decades work at the Registry. I see it in the MDA and ALS grants and care program, from the VA campus, and other investigators. I know that we're all hardwired for survival. So, in a sense, it's easier to be me than it is my family. It's easier for me than it is for perhaps yourselves, who have to say what you have to say every time you see a new patient. So, I know it's hard work and I wanted to thank you for doing that. And to the Registry, Paul, Kevin, I don't know if you're both on or not, my gratitude extends to you because we kind of grew up together.

Ten years ago when you began this, I had been just diagnosed, and I felt like I had a really big family of very smart people who are working on this with dedication and amazing work over the long haul. And you guys have given a platform to all of these disparate opinions and the chance to go back and forth on any number of things. So, you're on 19 grants to institutions—double what they were not long ago. Your new website, which I think is excellent, and I know a little bit about websites, and even in small things. I am just thankful you're there. So, my second point about data and how so many new institutions and foundation are working on different angles, I'm interested in whether or not this is an open question. We are concerned with more silos going up around research, or whether or not you feel there is more collaboration on that research. I know MDA and ALSA years ago began to collaborate very well, but there are still many new things, you know, in Answer ALS and ALS ONE saying that they want to aggregate all the great work that's going on across the country. That's a pretty tall order, so I wanted your opinion if we're doing everything we can to bring ideas together and get faster paths to the science, to the stall or the stuff of ALS. I never say "cure." So, that's my open question. And then the last thing is about BrainStorm by Israeli Biotech. You may have seen the second order posting this morning. As I said in the lead in, they are fully funded and your opinion of whether we're on the cusp of something there or whether you're skeptical, I would welcome your opinion within the bounds that you have on commenting about such things. I would love your opinion. So, that's what I had to say and I promise I won't do any exercises while the camera is still on as I did yesterday!

Madeline Kennedy

I apologize for my ventilator, but as you know, that's part of this. I am delighted to be back again at the ALS Registry meeting. I anticipate that I will not have the strength or energy to be able to participate in next year's meeting. But I do have the experience and perspective of living with ALS closing in on 9 years now. My contemporary fellow PALS, with very rare exception, have already finished their journeys. So, my contribution today will be quite personal. As everyone here appreciates, a person's time with ALS is comparatively short. When you live with ALS, you become aware that the period of time between diagnosis and death is not only filled with neuromuscular decline, but also with diminishing energy. PALS are encouraged to focus on the here and now. I remember well that energy was described by one our clinics as a partially filled glass of water. So it's a finite amount of water, that is, energy for each of us to spend and it is diminished daily. The COVID environment has disrupted everybody's lives, ALS clinical trials, clinic appointments, support groups, and meetings. The trials are starting to accommodate remote measurement and evaluation. The ability to attract other PALS is severely reduced, so many are frustrated or exhausted with living within the Zoom screen, computer, or smartphone. The situation further isolates those of us with ALS and adds to periods of forced contemplation, which was discussed last year. How do we do better? Registering in the ALS Registry is an essential tool to collect biospecimens to facilitate the direction of the clinical research and lead to a more efficient and timely understanding of this complex and multifactorial disease. We spent a significant amount of time at last year's meeting in discussion of how to increase the participation both in terms of initial sign-up and ongoing completion of the surveys. How do we do better? We need to set the stage so that newly diagnosed patients share our vision that the Registry is essential and that joining and participating is a positive action they can take amid a sea of other actions.

I would like to focus on enrolling PALS in the Registry as early as possible at the first appointment at the multi-disciplinary clinic. Many of these new patients are pretty sure of the diagnosis, but are hopeful that it is a different disease, or a better prognosis, or an effective therapeutic intervention. The patient during the initial appointment is focused on everything the physician says. This is the time to plant the seed. The patient is looking for what they can do to—clinical trials, regimens of drugs, observational or retrospective study in clinics. You are all assailed with such questions posed by desperate patients. The physician is in a most difficult position. I understand that there is so much to discuss. I suggest the doctor look at the Registry to know what they could do. Enrolling in the ALS Registry is a positive step in contributing to solving this relentless disease. Another clinic person, perhaps an MDA, ALSA, or Les Turner representative, or someone else with clinic resources can carry the ball from there after the doctor has planted the seed and assist with the enrollment, ideally while the patient is still in the clinic. Once the patient leaves the clinic, they are researching everything from cannabis to Deanna's Protocol. There should be more user-friendly patient data collection. We risk losing them to other organizations that they confuse with the Registry. There is only one comprehensive Registry. The brochure for the Registry is good but cannot compete with on equal footing with professional interactive optimized websites linked to ALS searches.

I thank Stephen Finger for his passion for more accurate data regarding the number of PALS who utilize the essential service of the multidisciplinary clinics. How many participate in the Registry? Is it proportionate to adverse outcomes of the communities of color in the current COVID-19 crisis? This should be a wake-up call to all leadership. I have given much thought during forced contemplation time considering how to best reach the largest number of PALS, resulting in enrollment and active participation in the Registry. This current COVID-19 environment has isolated all of us patients and communities. The support groups were an opportunity for face-to-face discussion with PALS to share experiences and perspectives. Multidisciplinary clinics and many ALS support groups are the best vehicles for recruitment and for ongoing support of the Registry. The biggest Registry issues I hear this year are that it is too time-consuming. I did complete all of the surveys. It took me two years and I had a lot more energy then. Perhaps prioritizing would be a good step in the right direction. I do understand that the survey to be lengthy to get all of the needed data. Secondly, the password expiration is too often. We talked about this last year. Thank you for fixing this. I do understand that it is a security issue for the federal website. Now that it is fixed, that is a tremendous help to patients. I can't count the number of fellow patients who have been denied access and had to do the updated password.

There is a lack of updates and news. We need to give back to our members, not just seek information from them. I was thrilled to see the newsletter sign-up. I had not been aware of it before. I hope this will reinvigorate the PALS. I would encourage that a note be sent to all who have not signed up for the newsletter inviting them to participate. Clinics, with rare exception, are associated with the 3 major organizations represented here and they receive financial backing from the Registry for their support. Do we measure the Clinic of Excellence designation against the level of participation of PALS in the Registry? Are performance metrics involved in financial support levels? Distribution of the brochure does not recruit a participation as effectively unless it is distributed with other materials, such as the folder that was talked about yesterday. How about a more attention-grabbing title to the emails that arrive in our inboxes. It is certainly clear when ALSA is trying to get our attention, or the MDA. I don't know how many of you are aware that ALSA appears as one word. It is also difficult to look up or try to find a past email. Maybe something novel like the "ALS National Registry" or just "The Registry." The current one is a mouthful of gobbledygook that doesn't really represent what we want it to represent. I hope these suggestions don't sound petty. You are all experts in ALS who have treated hundreds of us. This is but one small glimmer from one who has lived it. Those who pass through their journey more quickly also don't have the opportunity to articulate the issues. The scientific presentations have been marvelous. Thank you all for the work you do and for the dedication to this most important endeavor. Thanks.

Stephen Finger

I think before I start, I want to sort of frame my comments. Today we've heard a lot of really important research that's being done and funded by the Registry. And I think this is, going forward, an incredibly important component of the project. I think most of my comments are about how we are making sure we're getting everything we can out of the 12 years of hard work and roughly $80 million we've spent building this infrastructure and trying to enroll patients. As we all know, this is an incredibly difficult problem in terms of finding patients, getting them to enroll, going through administrative data and pulling out cases—it's all very hard. But in ALS, we're used to having hard problems whether it's understanding basic science, which even now, there's so much more we need to understand. Or if it's how we translate that into drug development, how we come up with informative trials, how we set up a regulatory framework

that speeds the search for a cure. None of this is easy and there are big reasons why we don't have a cure after 150 years. As a patient, I would love to see all these problems solved, but I think my biggest concern is that we're doing everything in our power to move forward. Are we fulfilling our mandate? Are we improving our understanding of the disease? Are we building off of what we've learned so far? Because this is such a difficult problem, we know all of our methods and all of our data is going to be imperfect. And so, as we're trying these different methods, a really important part of this endeavor is taking an honest look at what is working and what isn't. That's the only way we move forward.

When it comes to the capture-recapture approach, my concern is not that this is an imperfect technique. My concern is that Dr. Nelson in 2013 wrote a paper entitled "Evaluating the Utility of Capture-Recapture in ALS," which showed that seemingly minor innocuous changes in how they use the data could lead to huge variations in the results, many of which were totally implausible. And so, my concern comes that then in 2018 the Registry staff, with Dr. Nelson, wrote a paper seeming to ignore all of these caveats and said, "Voila. Look with this technique, accounting for missing cases, there are 12,000 patients in the US in a given year." Now we know based on everything we've learned so far that 12,000 is not in the right ballpark. And so, if we're going to use this imperfect technique and we come out with a number that doesn't make sense, we have a choice. Do we try to whitewash it so that it's easier to publish a positive result, or do we dig down and stress the limitations of our approach and work on figuring out how we move forward to understand more about what's going on? And if Registry staff is on these papers, I think as patients we fully expect they're taking the latter approach instead of the former.

And then we look at what we've learned from the death certificate data. Again, it's not perfect, but it's more accurate than the algorithm in terms of picking out cases. We know that over 6000 patients a year are dying of ALS, and so that translates to an incidence of about 1.7 or a prevalence somewhere north of 7. And so as we keep producing research, it has to be in that context. The cleanest data we have says prevalence should be around 7, incidence around 1.7. If a method comes out with a number like 3.2, we have to raise our hand and say, "What possibly could have gone wrong?" And additionally, in terms of partners, trying to increase the patient momentum behind this project, we can't put out public service announcements (PSA) saying, "hey, FYI, there are 5000 patients a year being diagnosed with the disease" if we know 6000 people are dying each year. We know 5000 is no longer a plausible number. If partners are using dated data, why should patients get behind this project?

And then in terms of the state and metro surveillance project, which I still think was one of the most important pieces of this research project, where they went out covering a quarter of the country going to individual neurologists and paying them to give us cases. Right? So, we would know after the fact if the Registry is picking up people who we know have ALS. And it found that we were getting about 60% of these people. Even for people known to be on Medicare, who should have been in the administrative data, we could only pick out 70% of them with the Registry. The Massachusetts data we learned yesterday is showing us the same thing. Roughly 30% of people aren't being picked up by our methods. So, let's be honest about that when we're reporting results.

This is the problem I have with the past *MMWR* reports. They report the number of people we found, immediately jump to what that means for prevalence calculations, and it isn't until the second to last paragraph that they even can say that there is a possibility of under ascertainment. That's not honest and it doesn't move us forward.

And then we get demographics. It is very important that we are honest about what our Registry is doing and is not doing. We can't fall into the trap of saying that African Americans, minorities, and disadvantaged groups aren't being diagnosed and that's why the portal is 95.5% White. The only paper using Registry participants in today's presentations used a sample that was 99.2% White. Medicare is 85%. Medicaid is 75%. I've attended 3 different clinics: Dr Bedlack, Dr. Brooks, and now Dr. Glass. None of those would ever suggest that this 95% is due to care.

We are excusing our incompetence if we try to use that as an excuse. We have to take this seriously. And then on top of that, we know that the 85% and the 75% in the administrative data are probably over-estimating the percent of Whites because we know we're missing so many minorities and disadvantaged folks. The algorithm depends on the level of care people are receiving. In everything we know about our flawed healthcare system, we know disadvantaged groups are less likely to be picked up and we see this in the State and Metro where only about half of African Americans known to be ALS patients made it into the Registry. And so, we have to decide whether we're going to take these limitations seriously, or we're going to provide some sort of lip service.

And again, I'll go back to the 2018 capture-recapture paper where another one of their conclusions was that because so many patients came from Medicare, they suggested that you could drop the Medicaid data without substantially impacting your results. They failed to mention that because the Medicaid data is 25% minority, if you dropped it, you would drop roughly a third of your minority patients. If that matters, it should be in the paper. It should not be that we could ignore them and it wouldn't make a difference. And I think we saw that as well in the presentations yesterday. We had the Biorepository presentation and the survey presentation. They presented the age and sex statistics and there wasn't anything about demographics. I had to ask Ms. Raymond three separate times about the demographics, about race and ethnicity until she admitted that yes, we are still at 95.5% white. If this is something we care about, that should be our first thought and our discussion should not have been about how great this is. We should have said, "Look, we have all these smart people together. How do we address this?" Instead, that statistic was nowhere to be found. And we say we want minority representation. You don't see it on this call in terms of the patients who have been invited.

And so, what are we trying to accomplish here? From the Congressional mandate, from previous reports, from Dr. Breysse's remarks, we have this clear mandate that our goal and our purpose is to determine, and learn about, and improve our understanding of incidence, prevalence, demographics, characteristics, and risk factors of ALS in the US. And so, what are we doing to move ourselves toward that goal? And so, I asked Paul this with respect to the marketing. What are we doing? Why are we doing it? He said our goal is enrollment and survey completion. So, we're enrolling year-over-year about 1000 of 6000 patients. And according to Ms. Raymond from last year's meeting, our enrollment is down about 30% since 2013. And so, are we taking this seriously if this is a purpose of our project? And we talked about it's really hard to tie different marketing efforts to enrollment, but you have to put that 1000 patients a year in perspective. 1000 patients a year is three per day. 1000 patients a year is on average 1 patient every 3 weeks in each state. And so, if we're seeing many more than that in a given day, we know something worked. So, if you see 10 people in South Carolina enroll in a given week, reach out to different folks in South Carolina and see what is working and what is not. It shouldn't be that hard. I mean, you hear stories about Amazon when it was first starting and in their code they put a bell that rang every time someone ordered. Have a bell in the office. If it's only 3 a day, and this is one of the most important parts of our mission, take it seriously.

And then we get to the surveys. And we say this project is more than about counting noses and so getting the surveys completed is an enormous deal. Having someone enroll is half the battle. Getting that data is what allows us to really move forward. But this year, there was no discussion of completion rates and how we make sure people are filling these things out. I think Madeline brought up the idea that some of them are very burdensome. And people stop completing them. Doctor Kasarskis last year said, "Why are we putting them in this order? Shouldn't we at least randomize them so some of the ones down on the list gets completed?" Do we really need the smoking questionnaire up towards the top if we have already produced a couple of papers on it? We have limited resources. Patients are only going to fill out a few of these and if they get frustrated, it is a huge cost to us. And so, for the life of me, I cannot understand that even though at every meeting I've attended since 2017, this has been a major point of emphasis. Nothing has changed. Again, we included as action items in 2017, 2018, and 2019, but it hasn't changed. How can we say this is the goal and the purpose of our Registry if we're not going to do this. And then we get to the algorithm and we know it's not perfect, but how are we learning about how it's functioning? Having a delay in the *MMWR* report is disappointing, but what really makes it frustrating is that that delay was used as an excuse to share no data at all. And so, we're going to go roughly three years between meetings when we're able to talk about data. So, a project where the goal is to determine incidence, prevalence, demographics, risk factors—we get no data to discuss. We either take the role of this meeting as something that's meaningful or we don't. Even on the enrollment graph that Ms. Raymond presented, they had to white out the y-axis column. And so, we have to figure out what is working. We have to decide if we want this to be a substantive meeting or if it's just a marketing opportunity. You had Dr. Brooks presenting only data. I mean, in classic Dr. Brooks' fashion, every single slide was detailed, detailed data from a project he started a couple of months ago. Every paper presented today was preliminary data and there wasn't a fear that somehow we were going to run out of the room and use these results irresponsibly. I don't see how, at a minimum, we couldn't have looked at the administrative data, something where we could have seen if this project is improving over time.

We talk about patient advocacy. Does it matter that Stephen Finger is frustrated with how this project is moving forward? I mean, I think you look at something like the MGH platform trial. For years patients were screaming, "Hey, we are dying and the way you've setup trials, we have one shot to be in a trial because of the exclusion criteria." There's only a 50% chance we get an active drug, and then we're told to go on our way and sit tight and 4 years later, a paper will come out. We said, Do something. Do single arm trials. Do something." And so, some researchers when patients made noise said, "Look, this is the way science has been done since the late 60s. Please sit tight. We feel your pain, but this is how it gets done." And then there were other researchers who said, "You know what, there's clearly a problem here. Maybe single arm trials that you're suggesting isn't the solution, but we can come up with something better. Let's set up a platform and have open-label extensions and then it will fundamentally change your experience." And were patients irate that single arm trials weren't a part of it? No, patients are incredibly enthusiastic that efforts were made to move us forward. You look at what has happened with the DoD research program in the past couple years. For a long time, DoD and the Registry both received $10 million a year in funding, roughly. Last year, patients got very motivated and IAmALS spearheaded an effort to get the $10 million number for the DoD bumped to $20 million. This year, they're pushing to get it to $40 million. That's a lot of incredibly important research that will now be funded because patients saw the promise in the program. If we believe in the promise of this program, if we believe there's more external research, we could be funding that could make a difference, we have to demonstrate that we are good stewards of this investment and we are learning as we go.

And so, those are my comments. Oh, and then lastly, I apologize, I don't have any acknowledgement slides. That was an oversight, but I would like to acknowledge my Research Assistant, Mary Adair Finger, for her dedication in putting the slides together and formatting them nicely for a father who is not so good at that anymore.

Ron Faretra

The first problem I have with the Registry program is not so much with the Registry program, but the providers that don't tell you about the Registry. That's some of the problem. Providers need to tell you. I learned about it because I went to an ALS clinic. And in that brings up another problem that I have is that newly diagnosed people need to go to the ALS clinics. They need to go to the ALS clinic severely because you can learn there a lot of things that you're not going to learn on Dr. Google. A lot of people at the clinic will give you information. They'll tell you what they tried and what they didn't try, and what works and what doesn't work. The problem is that if you're ambulatory, you feel kind of bad about going to a clinic if there's three or four people that are in a wheelchair in that clinic. Some of them can't talk. Some of them can't get out of the wheelchair. But they give you the best information. My first clinic I met a guy named Loy Stewart. I don't know if any of you know him. He had been diagnosed 17 years ago. He runs, or owns, our owned Detyens Shipyards. And Loy's speech was very impaired. He was in a wheelchair. He had to eat through a tube. Loy told me just live every day and live it to your fullest. And I looked at this guy and I see him running a shipyard in Charleston. And of course the unfortunate part of all that is Loy passed a couple of weeks ago and he passed from COVID, not even from ALS. But to me, I'd like to see the clinics push the ALS Registry more. I'd like to see us somehow make it a reportable disease. Who do we need to talk to? What laws do we need to change to make it a reportable disease? Because if it's not a reportable disease, you have a real problem in the rural areas where a person doesn't get diagnosed until that person really is on the last leg of the journey. So, that becomes a real problem. That person is not even going to be able to get online and get registered. So it has to be made a reportable disease, whether we do it nationally or whether we do it state by state, I think a lot of efforts need to be put into that. The surveys. There's a lot of them and I'll be the first to admit that I haven't completed all of them because they are very time-consuming. So, I think somehow maybe we ought to engage the people a little more often and if they haven't completed the surveys, send them one and say, "Hey, can you complete this?" And yes, that's a little more time-consuming on the Registry staff, but it's a way to keep people occupied with the Registry. And I think that's very important because if you just go on there and you just sign in and you don't do anything else, it's not doing us any good. And with that, I'll end. I thank you for having me here this year. I hope I get to come next year. I've enjoyed it and I've learned a lot from it. Thank you.

Jeremy Van Tress

Hello, everyone. Thanks so much for inviting me to participate in the ALS Registry's annual meeting and share with you my perspective on the Registry as a PALS. I have prepared most of my remarks in advance due to the fact that I might need to speak through an assistant speech device. From both the patient and researcher perspective, I have been very impressed with the Registry. As a researcher currently finishing my Doctoral dissertation, I have benefited from the recruitment capabilities that the Registry provides. Because the Registry has a robust system, I was able to recruit participants rigorously and efficiently. I also find it invaluable that the Registry shares data and tissue samples with other researchers as it saves time and money and maximizes resources for the collective goal of finding breakthroughs. These are critical leverage points for research that must not be overlooked. From a patient perspective, I remember getting

connected to the Registry about 6 months after I was diagnosed. I was diagnosed in February of 2017 and got my tracheostomy in September of 2018. My ALS clinic discussed the Registry with me. While I was at the conference with the ALS Association, I got more exposure to it and self-registered. Since that time, the Registry has alerted me about opportunities to participate in research. I appreciate those opportunities because at this point, I don't typically meet the inclusion criteria to participate in clinical trials due to having a tracheostomy. But the Registry has given me opportunities to participate in other research opportunities, which has been very meaningful for me. In that sense, the Registry could be a great tool to help PALS of all stages of the disease to get involved in research. In hindsight, I would echo Madeline's comments that early access to the Registry, preferably at the time of diagnosis, might facilitated increased participation.

More broadly, I am grateful that the Registry has so many initiatives, including the Biorepository, internal and external research grants and projects, and surveying the ALS population to understand the risk factors associated with the disease. This type of surveillance is very challenging considering it is not a nationally identifiable disease. I appreciate the Registry's multi-pronged approach to importing from several systems that are using every other methods to identify cases. Overall, I think that is the soundest methodology available to capture and estimate the prevalence of ALS. The Registry is vital and we need to continue funding it. It is critical that we continue to explore the risk factors like any disease registry. However, I think the ALS Registry remains a work in progress. I look forward to seeing continued efforts to build off of its strengths for years to come. In that regard, one point of interest that I have is about how the Registry is dealing with increasing self-enrollment and reaching PALS from minority and under-represented populations. I think this will be a crucial element in capturing the prevalence fully. Also, from a patient perspective, I think it might help to have direct contact with the Registry once PALS self-register. A telephone call or an email from the representative at the Registry could help PALS understand what opportunities are available to increase our participation. Finally, because I am a Veteran with ALS, I have heard multiple Veterans with ALS express how they want more prevalence information about Veterans with ALS released and report it on. I recognize that my opinion is my own and I certainly do not speak for all PALS. There are various views among the ALS patient community about the Registry. Some are positive and some are not positive. While my views about the Registry may differ from others, I respect their opinions. Respectfully, I will push back on Stephen Finger's feedback that the Registry is not being honest about their data. Scientific peer-reviewed articles typically follow a prescribed method so that limitations are discussed at the end of the articles. This is consistent with virtually all other peer-reviewed articles. In every article I have read in the *MMWR*, which is peer-reviewed, the authors have been transparent about the limitations of the methodology. I would ask my fellow PALS who are critical of the Registry to consider and respect the complexity and developing nature of epidemiological work. Epidemiological work requires time, persistence, and incremental improvements and achievements. I will concede that this is time that we as patients don't have, but that does not change the process involved. Solving the ALS puzzle, in my opinion, is integral to the work that must be done as a collective body of researchers, physicians, patients, and families. Researchers need to tackle projects of all types and the Registry is just one of many critical projects. I want to express my gratitude for the researchers and staff at the ALS Registry for all the work they do. PALS everywhere appreciate what you do. Thank you for giving me some time to speak. Hearing from many voices is very important. I think the ALS Registry is a fantastic project that will pay dividends for years to come.

Next Steps and Discussion: Recommendations/Strategies, Wrap-Up, Adjourn

Paul Mehta, MD
National ALS Registry, Principle Investigator
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Dr. Mehta indicated that ATSDR had been jotting down the comments for both days to capture suggestions and recommendations, which they categorized as follows:

Communications/Outreach
- ❑ Clarify goals and develop methods to evaluate
- ❑ Increase promotion/outreach efforts, including Facebook and other social media to increase minority population representation in the Registry and Biorepository
- ❑ Represent minority groups with photos of ALS patients of all races and rotate and highlight photos on all documents not just targeted outreach efforts
- ❑ Engage with VA researchers to discuss ALS-related Veteran affairs

ALS Data and Reports
- ❑ Provide annual reports in a timely manner
- ❑ Provide demographic data including race and ethnicity for the Registry and Biorepository
- ❑ Use prevalence ranges instead of actual prevalence rates when presenting data
- ❑ Consider pre-releasing Registry data prior to publication reports
- ❑ Use residency data along with GIS data and the relationship to environmental exposures

In closing, Dr. Mehta thanked everyone for attending this conference virtually and taking time from their busy schedules to participate. Obviously, the times are trying with COVID. He offered special gratitude to the patients for being very courageous individuals and emphasized that their very heartfelt comments, thoughts, and recommendations would be taken very seriously. He recalled the words of John F. Kennedy (JFK) who once said, "We choose to go to the Moon and do other things, not because they are easy, but because they are hard." A disease like ALS can be hard, especially when it is not reportable or notifiable. However, ATSDR is committed to making the ALS Registry/Biorepository a much better, more exhaustive, and more thorough system. The program is maturing, more research is being funded, and ATSDR is considering ways to capture more data resources to make the data more representative across all demographics. He thanked the patients, presenters, clinicians, researchers, and staff who made the meeting possible and expressed his hope that they would see everyone in person in 2021.

Discussion Points

Mr. Hicks thanked all of the PALS who shared their perspectives. He emphasized that their suggestions and recommendations are taken very seriously.

Dr. Mehta called on Drs. Brooks and Bradley to provide information if they could regarding Mr. Tessaro's question about the BrainStorm clinical trial. Dr. Brooks indicated that the plan for the clinical trial was that there would be a readout in the Fall of 2020. However, he was unaware of how COVID may have affected that overall readout.

Dr. Bradley added that he has an inbuilt skepticism about any of these studies until the final answer comes out. Phase 3 means that they think they have enough data that were sufficiently suggestive Phase 2 study, but he thinks they will have to wait until the end.

Regarding Mr. Tessaro's comments about silos, ATSDR works very closely with the NIH researchers and program officers such as Drs. Bryan Traynor and Amelie Gubitz. Dr. Traynor is a great resource. He does all of the genetic testing. The DoD's Notice of Funding Opportunity (NOFO) states that investigators who would like to acquire data and samples for research should contact the National ALS Registry/Biorepository. One of DoD's new grantees contacted ATSDR about 6 months ago to request samples. ATSDR certainly collaborates with its governmental partners across the board, which is very important to them.

Dr. Finger said that he thought regarding the first bullet about evaluating progress toward the goals, he thought the 2018 meeting had a very good action item to that regard. He suggested copying and pasting that language and moving forward on that. In terms of the surveys, every year they talk about how important these are to this effort and how important the ordering and way they are presented impacts survey completion. He expressed his hope that 2020 is the year they act upon this. A 2018 action item was to disseminate a progress report sometime in the Fall on how they are doing toward the goals so that it is not a once a year effort. He expressed his hope that they re-implement that suggestion.

Dr. Brooks noted that there was a paper recently in the amyotrophic lateral sclerosis–frontotemporal dementia (ALS-FTD) journal identifying the cohort that was in a Medicare Advantage plan. They actually had a higher prevalence of ALS and obviously a higher proportion of White patients. This occurrence of different data from Medicare Advantage plans, versus Medicare, versus Medicaid, which Dr. Finger presented, is very important. He wondered whether there had been any analyses of the Truven database and the other database that Dr. Bradley presented on with respect to how they compare against the data in the Registry with respect to clinical form and the rate of completion of that clinical form. They have talked a lot about using single arm trials. Perhaps they could get more interest in the Registry and completion of the forms if they could essentially embrace their patient population to present this data so that it might be used as a potential in the future for these kinds of clinical trials. Thank you.

Dr. Mehta indicated that ATSDR has access to Truven MarketScan® data and are looking at the prevalence in that database. They talked to Optum, a part of the UnitedHealth Group, and they also have access to IQVIA. He will have to check internally to determine whether they have access to Symphony®. They are hoping to publish on Truven MarketScan® data prevalence. There are limitations in terms of these large databases. For example, Truven MarketScan® data are not available for all locations, such as rural areas.

Dr. Bradley concurred with Dr. Finger's observations about Medicaid and Medicare data. Obviously, they must find some way to be able to recruit more reasonable representation of the whole population. The Ohio study they conducted recruited essentially the same proportion of Blacks as in the whole population of Ohio, though that is a small number of patients. Nevertheless, that is the sort of analysis they are going to try to aim for, or else increase the proportion of Medicaid cases preferentially.

Dr. Mehta thanked everyone for attending and adjourned the meeting at 1:00 pm.

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