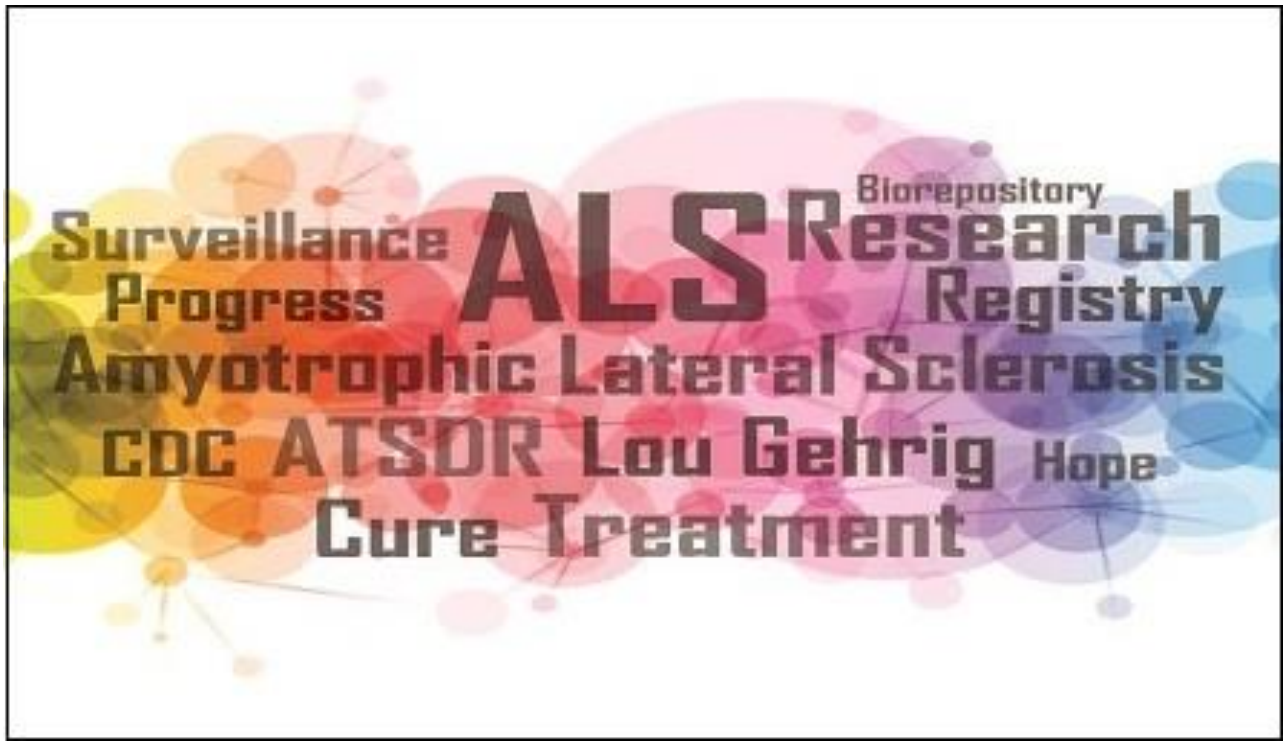
Department of Health and Human Services
Centers for Disease Control and Prevention
Agency for Toxic Substances and Disease Registry

Annual Amyotrophic Lateral Sclerosis (ALS) Surveillance Meeting



August 31-September 1, 2021
Summary Report

Table of Contents

Acronyms Used in this Document

Acronym	Expansion
AANEM	American Association of Neuromuscular & Electrodiagnostic Medicine
ADDF	Alzheimer's Drug Discovery Foundation
AE	Adverse Event
AI	Artificial Intelligence
ALS	Amyotrophic Lateral Sclerosis
ALS TDI	ALS Therapy Development Institute
ALSA	Amyotrophic Lateral Sclerosis Association
ALSFRS	ALS Functional Rating Scale
ALSFRS-R	Revised ALS Functional Rating Scale
ALSFTD	Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration
ATSDR	Agency for Toxic Substances and Disease Registry
BBB	Blood-Brain Barrier
BiPAP	Bilevel Positive Airway Pressure
BKMR	Bayesian Kernel Machine Regression
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CDMRP	Congressionally Directed Medical Research Programs
C_{max}	Maximum Concentration
CMS	Centers for Medicare & Medicaid Services
CNS	Central Nervous System
COD	Cause of Death
CRLI	Clinical Research Learning Institute
CSF	Cerebrospinal Fluid
CVD	Cardiovascular Disease
DEI	Diversity, Equity, and Inclusion
DME	Durable Medical Equipment
DMSS	Defense Medical Surveillance System
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DoDSR	DoD Serum Repository
DUA	Data Use Agreement
EMG	Electromyography
EPA	Environmental Protection Agency
EU	European Union
EVs	Extracellular Vesicles
FALS	Familial ALS
FDA	Food and Drug Administration
FMC	Finnish Mobile Clinic Health Examination Survey
FMCF	Finnish Mobile Clinic Follow-Up Survey
FOA	Funding Opportunity Announcement
FSHD	Facioscapulohumeral Muscular Dystrophy
GAMMs	Generalized Additive Mixed Models
GEE	Generalized Estimating Equation
GIS	Geographic Information System
GLAST	Glial Glutamate Aspartate Transporter
GUID	Globally Unique Identifier
HCB	Hexachlorobenzene
HHS	(Department of) Health and Human Services
HHS	(Department of) Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act

HIV	Human Immunodeficiency Virus
HMO	Health Maintenance Organization
IDK	I Don't Know
IP	Immunoprecipitation
iPS	Induced Pluripotent Stem Cells
IRB	Institutional Review Board
IT	Information Technology
JHU	Johns Hopkins University
LDEO	Lamont-Doherty Earth Observatory
LOS	Letters of Support
MD	Muscular Dystrophy
MDA	Muscular Dystrophy Association
MFS	Mini-Finland Health Survey
MG	Myasthenia Gravis
MGH	Massachusetts General Hospital
MI	Myocardial Infarction
MII	Maryland Innovation Initiative
miRNA	microRNA
ML	Machine Learning
MLB	Major League Baseball
MMWR	*Morbidity and Mortality Weekly Report*
MND	Motor Neuron Disease
MOVR Data Hub™	neuroMuscular ObserVational Research Data Hub™
MS	Multiple Sclerosis
MTA	Material Transfer Agreement
NAICS	North American Industry Classification System
NATA	National Air Toxics Assessment
NCEH	National Center for Environmental Health
NCHS	National Center for Health Statistics
NCRI	Neurological Clinical Research Institute
NDI	National Death Index
NEALS	Northeast Amyotrophic Lateral Sclerosis Consortium
NfL	Neurofilament Light Chain
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIV	Non-Invasive Ventilation
NMD	Neuromuscular Diseases
NYGC	New York Genome Center
OMB	Office of Management and Budget
OPs	Organophosphates
PALS	Persons with Amyotrophic Lateral Sclerosis
PBDEs	Polybrominated Diphenyl Ethers
PBMCs	Peripheral Blood Mononuclear Cells
PCBs	Polychlorinated Biphenyls
PDA	Physical Disability Agency
PFT	Pulmonary Function Test
PHI	Protected Health Information
PI	Principal Investigator
PII	Personally Identifiable Information
POP	Persistent Organic Pollutant
PPO	Preferred Provider Organization
PRO-ACT	Pooled Resource Open-Access ALS Clinical Trials Database
PT	Pyrethroid

QC	Quality Control
REFINE-ALS	Radicava (Edaravone) Findings in Biomarkers From ALS
RNA	Ribonucleic Acid
RNA-Seq	RNA Sequencing
RNM	Research Notification Mechanism
ROI	Return on Investment
SCD	Sickle Cell Disease
SMA	Spinal Muscular Atrophy
SMART	Symptom Monitoring for ALS in Real Time
SME	Subject Matter Expert
SNPs	Single-Nucleotide Polymorphisms
SOPs	Standard Operating Procedures
TA	Technical Assistance
TBI	Traumatic Brain Injury
TRI	Toxics Release Inventory
UN	United Nations
US	United States
VA	(United States Department of) Veterans Affairs
VASRD	Veteran Affairs Schedule for Rating Disabilities
VBA	Veterans Benefits Administration
VHA	Veteran Health Administration
VOC	Volatile Organic Compound
VPA	Vigorous Physical Activity
WGS	Whole Genome Sequence
WTC	World Trade Center

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

Minutes of the Meeting
August 31-September 1, 2021

Welcome and Introductions

Song Xue, MPH – Moderator
Public Health Analyst
Carter Consulting Inc.

Mr. Xue called the meeting to order at 8:15 AM and welcomed everyone. He emphasized that while they would love to have held the meeting in-person, due to the ongoing extenuating circumstances of COVID-19 in the country, it was necessary to resort to a Zoom meeting instead. However, they were hopeful that it would be possible to have as productive a meeting virtually as they could have had in person. He extended gratitude to Melissa Banales and Tori Bahe from Ross Strategic for providing logistics and facilitating the meeting, especially since they were on the West Coast where it was an obscenely early hour for them. He then described the ground rules for the meeting, indicated that Ms. Bahe would review housekeeping items, and noted that the meeting would be closed to the public at the end due to the proprietary nature of the presentations during that timeframe. A participant roster is appended to the end of this document.

Opening Remarks

Chris Reh, PhD
Associate Director
Agency for Toxic Substances and Disease Registry (ATSDR)

Dr. Reh greeted everyone and emphasized what an honor it was to be in front of this distinguished group to kick off the Virtual Annual ALS Surveillance Meeting. He stressed what important work the National ALS Registry is for ATSDR and how truly excited they were to be able to discuss this with the participants over the next two days. This marked the second year in a row that the meeting was convened virtually. While ATSDR preferred for the meeting to be in-person, the safety of the attendees and staff was of utmost importance given what was occurring in the nation with COVID-19. He expressed gratitude to everyone for taking time out of their busy schedules to join the virtual meeting, noting that the times were interesting at the Centers for Disease Control and Prevention (CDC).

The COVID-19 response has consumed a lot of the agency's time. While people may think of staff at ATSDR as Environmental Health Scientists or Registry and Surveillance Scientists, they also were drawn into the COVID-19 response. In fact, over 50% of ATSDR's staff at one time or another have been dedicated or detailed to the response, including himself on 3 occasions. In addition to simultaneous Southwest Border migrant health issues, National Center for Environmental Health (NCEH)/ATSDR stood up its Hurricane Ida response the previous day.

Nevertheless, ATSDR prioritized the ALS work and community. Even though they have had to respond to some of the priorities around COVID-19, they also have managed their resources such that they have kept the National ALS Registry going with the hope that there had been no blips in response or in services provided. They truly believe that this is some of the most important work that they do at ATSDR. Because of that, through their leadership and how they manage their resources, they have been able to keep the work going.

Having clinicians, researchers, and especially persons with ALS (PALS) together provides ATSDR with important and invaluable feedback that helps the agency shape the Registry. It could not be emphasized enough that the success of the National ALS Registry depends upon effective collaboration among many ALS stakeholders, including PALS, caregivers, families, physicians, researchers, support groups, and many others. 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 great progress. The previous week, the National ALS Registry published its 5th ALS national prevalence estimation, which they would learn more about during this meeting, including what actions are being taken to improve case ascertainment.

Dr. Reh said he also was very happy to report that the National ALS Registry's Research Notification System has been extremely well-received by Registry enrollees and researches. To date, over 50 institutions have used this system to recruit thousands of PALS into clinical trials and epidemiological studies that are needed to find a cure for ALS. ATSDR is also very excited about the National ALS Biorepository and its partnership with Johns Hopkins University (JHU). The samples collected are being paired with risk factors survey data, which makes the National ALS Biorepository a very unique resource. To date, 1500 patients have taken part in the in-home collection and almost 50 patients in the postmortem component. This results in tens of thousands of samples available right now for researchers to use to help find a cure for ALS. Data and specimens from the National ALS Registry are being disseminated to scientists for research. To date, over a dozen research institutions and companies have received thousands of data points from the Registry and the Biorepository. In addition, almost 100,000 risk factor modules have been completed by PALS to help ATSDR learn more about the etiology of ALS. The Registry has recently published findings on some of these surveys, which were to be discussed later in the meeting. As part of this meeting, ATSDR looked forward to updates from its funded researchers. ATSDR has funded 19 external research studies to date and looks forward to funding at least 2 more grants in the Fall.

During this meeting, Registry staff planned to go over the recommendations from the previous year's meeting and provide updates. Participants again would be asked to provide feedback on these and other topics. ATSDR's partners, who are extremely important to this effort, 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. In addition, they would 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. Dr. Reh 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 beyond. He expressed his hope that they would see everyone in-person in 2022.

National ALS Registry Research 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 to the annual meeting, thanked them for their attendance, and expressed hope that the 2022 meeting would be in-person. As a reminder, the National ALS Registry was enacted by Public Law 110-373 that was signed by Congress in October 2008. The United States (US) ALS Registry Act (the Act) directed CDC/ATSDR to create a population-based US registry. The National ALS Registry was launched in October 2010. The purpose of the Registry as specified by the Act is to: 1) describe the incidence and prevalence of ALS; 2) describe the demographics of ALS patients; and 3) examine risk factors for the disease. It is currently known that 90% of ALS is considered to be sporadic and 10% is considered familial, so it is important to figure out the risk factors for that 90%.

The Act did not make ALS a reportable disease. In the world of public health, there are "reportable" and "notifiable" diseases. Diseases that are reportable tend to be communicable diseases and are mandatorily reported to jurisdictions by individuals in the health care community, including providers, facilities, and laboratories. Not all reportable diseases are communicable, such as cancer and lead silicosis. The list of reportable conditions is maintained and disseminated at the state level and may vary among states and territories. ALS is reportable only in the State of Massachusetts, but not to the Registry. Notifiable diseases are reported to the CDC on a voluntary basis by each jurisdiction. Data are reported to the CDC by health departments. These data are reported in a de-identified format and include limited information about the patient and the case.

Given that ALS is not a reportable or notifiable disease, the Registry had to establish some novel study methodology to determine exactly who has ALS in the US. Currently, Registry cases come from the Centers for Medicare & Medicaid Services (CMS), Veterans Affairs (VA) through the Veterans Health Administration (VHA), and the National ALS Registry Web Portal where patients enter through the Registry and answer a series of questions to be added to the Registry. ATSDR is seeking to expand the case ascertainment methodology to bring in other sources.

A report was released the previous week describing the prevalence of ALS in the US for 2016.[1] The rationale for publication in *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* is that CDC has an all-hands-on-deck focus on COVID-19. Due to that, much of CDC's print space is relegated to COVID-19 topics. For this publication, the Registry identified 16,424 adult persons with ALS in the US for a prevalence rate of 5.2 per 100,000. In terms of how this compares to the 2015 prevalence report, the findings for 2016 were similar to the 2015 report. In 2015, slightly more cases (16,583) of ALS were identified than in 2016 (16,424). This is a difference of 159 cases, which is not statistically significant. The age-adjusted prevalence rate of 5.2 per 100,000 remains the same. The pattern of patient characteristics did not change for

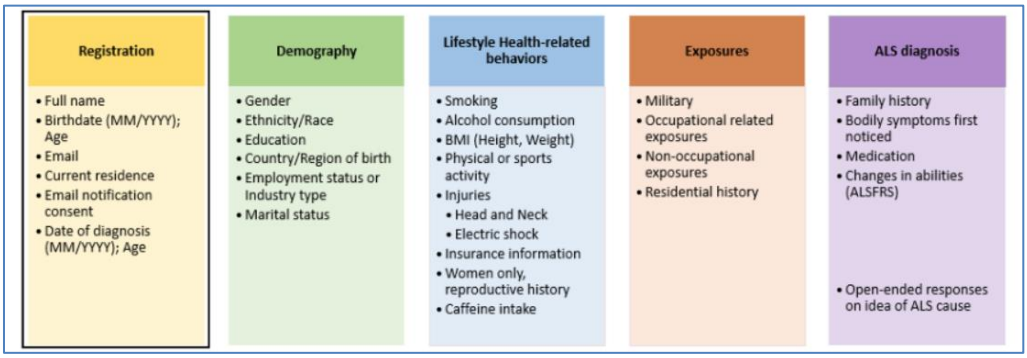
[1] Paul Mehta, Jaime Raymond, Reshma Punjani, Theodore Larson, Frank Bove, Wendy Kaye, Lorene M. Nelson, Barbara Topol, Moon Han, Oleg Muravov, Corina Genson, Bryn Davis, Thomas Hicks & Kevin Horton (2021) Prevalence of amyotrophic lateral sclerosis (ALS), United States, 2016, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, DOI: 10.1080/21678421.2021.1949021

age, sex, race/ethnicity, et cetera from previous Registry reports. ALS remains more common among whites, males, and persons 60–69 years of age.

Because ALS is not a notifiable disease in the US, it is challenging to estimate missing cases. The Registry is currently utilizing different methods to estimate missing cases, such as capture-recapture. Capture-recapture is a statistical method that measures the overlap of cases from different data sources. The 2016 report does not include capture-recapture estimates, given that the methodology is still under review for publication. Before ATSDR can include the corrective factor for 2016, the capture-recapture methodology must first be published. However, the goal is to be able to include this in the 2017 report.

A request has been submitted to the Office of Management and Budget (OMB) to add new data sources from patient organizations, including the Amyotrophic Lateral Sclerosis Association (ALSA), the Muscular Dystrophy Association (MDA), and the Les Turner Foundation. These groups serve the largest proportion of ALS patients in the country. The request also includes the Massachusetts ALS Registry and insurance companies, including Health Maintenance Organizations (HMOs) and Preferred Provider Organization (PPOs). Insurance companies service ALS patients and while there is no promise there, ATSDR certainly will try to get their cases. While discussions have begun, it will take 12 to 24 months to have agreements in place. Cases will be added prospectively, meaning that no previously published reports will be changed.

In terms of other activities, survey enhancements are underway. The Registry also asked the OMB to allow modification of the surveys to make them more user-friendly. Surveys will be replaced with name categories to make them more user-friendly and some surveys will be retired. The Registry consulted with the National Center for Health Statistics (NCHS), which conducts surveys internally across the agency, to have them evaluate the National ALS Registry surveys. NCHS recommended naming and categorizing the surveys. Instead of having patients facing 18 surveys when they come to the Registry, the surveys would be broken up into categories such as the following:



The Registry also asked the OMB to allow the release of ALS case-counts at the state-level. Cases will be able to be visualized for each state by overall counts, gender, and race. Currently, the Registry can report only on national cases due to OMB restrictions. Approval of this request would allow for better estimation of overall cases by gender and race/ethnicity at the state level for all 50 states, as well as by region. Visualization of these data on the Registry website will allow users to compare data. Caveats such as missing cases will be stated.

To date, over 60 institutions have used the Registry's Research Notification Mechanism (RNM) system to recruit for clinical trials, epidemiological studies, and future notifications such as the following:

- Clinical Trials: Mitsubishi Tanabe Pharma (oral Edaravone), Amylyx (AMX0035), Orphazyme, Brainstorm, Ionis, Alexion, Helixmith, and others
- Epidemiological Studies: ALS Focus Survey (ALS Association), Radicava (Edaravone) Findings in Biomarkers From ALS (REFINE-ALS) Biomarker Study (Mitsubishi Tanabe Pharma), Answer ALS Companion App (Johns Hopkins University - Jeffrey Rothstein)
- Future Studies: COURAGE-ALS (Cytokinetics), and Toferson (Biogen)

ATSDR estimates that thousands of persons with ALS have been recruited through the National ALS Registry, which is the only mechanism of its kind in the US that has the capability to email notifications to all patients who come into the Registry who consent to receive them. Patients' names are never released, but they can contact researchers who are seeking participants for clinical trials and epidemiological studies. All publications are posted on the publications page of the cdc.gov/als website where they can be read in their entirety. ATSDR pays for open access so that the public can read the full journal articles. Registry publications in the past year have included the following:

- *Impact of the National ALS Registry's Research Notification Mechanism (RNM) on Patient Recruitment for Clinical Trials and Epidemiological Studies* is with a journal for final review. Co-authors of this paper include: Drs. James Berry, Sabrina Paganoni, Rick Bedlack, and Hiroshi Mitumoto. Thousands of participants have been recruited. Among them, those 60-69 years of age had the highest level of participation, those 18-39 years and over 80 years of age had the lowest level of participation, and males participated at 59.3% versus females at 40.7%.

- *Risk Factors for ALS: A Regional United States Case-Control Study* (Andrew et al., Muscle & Nerve) found increased ALS risk with severe electrical burns and hobbies involving lead.

- *Case-Control Study in ALS Using the National ALS Registry: Lead and Agricultural Chemicals are Potential Risk Factors* (Mitsumoto et al., ALSFTD) focused on increased ALS risk with occupational exposure to lead, as well as exposure to agriculture chemicals.

- *Reproductive History and Age of Onset for Women Diagnosed with ALS: Data from the National ALS Registry: 2010-2018* (Raymond et al., Neuroepidemiology)

- *History of Vigorous Leisure-time Physical Activity and Early Onset ALS, Data from the National ALS Registry: 2010–2018* (Raymond et al., ALSFTD), with an overview provided during this meeting by Jaime Raymond.

Funding of grants is very important to the Registry. Supporting research institutions and academia allows the agency to figure out the potential risk factors for/causes of ALS. To date, the Registry has funded 19 research projects and funded 2 grants to Harvard University in Fall 2020. The first is *Pre-disease biomarkers of persistent organic pollutants (POPs), immune system, and ALS*. The Principal Investigator (PI) for this grant is Marc Weisskopf, PhD, ScD. This study is measuring pre-disease biomarkers by measuring the levels of POPs in PALS to determine whether pre-ALS POPs levels are associated with the risk of ALS. The second is *Serological profiling of the human virome and ALS risk in a military population*. The PI is Albert Ascherio, MD, DrPH. This study is examining blood samples collected from healthy service

members and includes persons who later developed ALS and healthy persons. Samples will be examined for antibodies against more than 400 viruses and will assess whether these the viruses were associated with ALS. This is the first study examining the military population from the Registry. The goal is to fund 2 to 3 new grants in this grant cycle depending upon funds available. Two Fiscal Year 2022 Funding Opportunity Announcements (FOAs) will be released for exploratory grants for etiology/risk factors.

In terms of new and ongoing collaborations and projects, the Registry is very excited to work with Dr. Lyle Ostrow in a collaboration between the Registry and JHU Postmortem Tissue Core to expand research collaboration in areas such as biomarkers, genetics, and disease progression. Regarding evaluation of the Registry's 11-year-old algorithm to identify ALS cases, they met with Drs. Benjamin Brooks, James Berry, Stephen Goutman, and Bjorn Oskarrson to determine if the algorithm needs to be revised (e.g., single prescription for Riluzole, redefining the categorization of patients). Any changes will be validated and peer-reviewed. The *ALS incidence for United States, 2014 -2016* manuscript is in development and is approximately 75% complete. This will be the first time administrative databases will be used for incidence. The publication is anticipated for Fall 2021/Winter 2022.

The Registry continues its collaboration with NeuroBANK™ on comparison of the Registry's Global Unique Identifiers (GUIDs). The Registry also is continuing to collaborate with the Canadian ALS Registry to compare demographics among the two countries. They are working with Dr. James Berry on evaluating whether PALS were adversely affected by COVID-19. For this effort, data were requested from NCHS, which has been approved. The data for 2020 are still outstanding, but the hope is to have it by the end of the year. The goal is to perform a comparison to determine whether the mortality of ALS patients was higher in 2020, which could be important in determining whether COVID-19 has impacted this patient group.

The Registry is working with Drs. Ted Larson, Stephen Goutman, and Neil Thakur who are evaluating the most common causes of death for patients and whether there are ways to potentially prevent common causes of death. This certainly would be an exciting publication and could be highly consequential. Jaime Raymond and Reshma Punjani are in the process of comparing Registry cases with the Massachusetts ALS Registry, an update for which Ms. Raymond would provide later in the meeting. It will be exciting to see these data, given that ALS is a reportable disease in Massachusetts. Dr. Moon Han is leading a study comparing Registry data to the Pooled Resource Open-Access ALS Clinical Trials Database (PRO-ACT) database to evaluate demographics and clinical information found in both databases. Bryn Davis is leading an effort to update the Registry's publications page to improve navigation and make it more user-friendly. There are approximately 70 publications on the website currently.

In terms of the budget for FY2020, the National ALS Registry received $7.7 million after program support. The bulk of the funding, 61%, is allocated to research activities (e.g., grants, the National ALS Biorerpository, capture/recapture, and fellows/data requests. Outreach and education receives 11%, while 13% is allocated to personnel, 9% to information technology (IT) and support, 5% communication, and 1% miscellaneous. It is important for researchers and the public to realize that the bulk of the National ALS Registry funding is dedicated to research activities to examine what causes ALS and the risk factors for ALS. Data costs money. For instance, there is a cost when data are requested from CMS, even though they are a sister agency within the Department of Health and Human Services (HHS).

Dr. Mehta reminded everyone that the Registry does more than just count ALS cases. There is a National ALS Biorepository and the Registry includes assessment of epidemiology of ALS in the US in terms of incidence, prevalence, and mortality. The Registry also works with its partner organizations, neurologists, and academia partners. There are currently close to 100,000 completed surveys in the Registry, with data published on these for review. As mentioned earlier, over 60 national institutions have used the Registry's Research Notification Mechanism. This has translated into thousands of patients recruited into studies. The research portion of the Registry is extremely important with regard to figuring out the unknowns, risk factors, and causation of ALS.

In terms of impact, the National ALS Registry is the largest database of ALS patients in the US for research. The Registry collaborates with pharmaceutical companies and academia to provide recruitment assistance for clinical trials and epidemiological studies. The Registry also partners with the largest ALS patient organizations to raise awareness and inform and educate patients and caregivers about the Registry. The Registry advances ALS research through the National ALS Biorepository on biomarkers, genetics, and environmental exposures. The Registry also funds research grants for leading academic institutions to learn more about risk factors and possible etiologies, such as cyanobacteria, heavy metals, POPs, genetics, and others. In addition, the Registry provides updated national epidemiological estimates of ALS cases in the US using novel methodologies.

Discussion Summary

Dr. Siddique congratulated ATSDR on making considerable progress. He asked what the differential in the reporting statistics was when Massachusetts moved from just laboratory reporting to ALS being a reportable disease, and how that compared to states in the Northeast and in terms of missing data compared to the National ALS Registry.

Dr. Mehta indicated that they are still working on the data analyses. The manuscript is in development and is currently out for review with Massachusetts. That will provide the full spectrum regarding the actual comparisons. In terms of comparisons of Massachusetts and the surrounding states, Massachusetts General Hospital (MGH) is a large institution and many patients likely present there from the surrounding states for their care. Massachusetts has a capture rate of approximately 90% or more. By way of background, the Massachusetts ALS Registry was stood up because Governor Paul Cellucci had ALS. In terms of the difference before ALS became reportable, Dr. Mehta did not have this information but directed Dr. Siddique to the Massachusetts website for further historical information.

Dr. Stommel requested that Dr. Mehta speak to the hope of adopting reportable registries in other states. He has been trying to get the legislatures in Vermont and New Hampshire interested in having a mandatory registry. The primary objection has been finances. For New Hampshire, the majority of cases that do not go to Massachusetts are seen at Dartmouth. There would be approximately 60 new cases per year based on the population in New Hampshire and about 20 more cases per year in Vermont. He can handle those cases along with the help of some of his colleagues in terms of verifying the cases and getting them entered into database without a tremendous amount of money being spent. If he addressed 1 case per week, he could probably get most of them. It is discouraging that the states are shy about having a registry because of the financial situation, and he does not know how to get around that.

Dr. Mehta indicated that they have had cursory information from and conversations with other states. There is a push currently for other states to stand up their own registries. There has been a push to stand up registries in the states of Vermont, New Hampshire, Michigan, and Alabama. The caveat is that standing up registries at the state-based level is a state-based initiative. While federal agencies do not get involved in these efforts, they can provide technical assistance (TA) if asked. His personal take is that anything that can help to identify more cases is certainly helpful. State finances are stretched and ATSDR's resources are limited as well. In terms of the newborn screening model at CDC, a majority of states have newborn screening for certain diseases and those are reported back to CDC. That model uses a cooperative agreement whereby funds are provided by CDC to states to report to CDC. This is perhaps a model that could be used for ALS as well.

Dr. Goutman thanked Dr. Stommel for being a leader in pushing state registries forward, which was tremendously helpful for him in approaching Michigan. It is extremely helpful to have state-based registries, which will take physician and advocacy champions from individual states to push this agenda forward. He thinks that they are on the cusp of thinking about what it takes to prevent ALS and what information is needed. As a basis of this, it is important to understand who has ALS, where people are living, how many cases there are in each state, whether the numbers are increasing or decreasing, and getting a sense of the lay of the land. Mandatory reporting systems at the state-level would help to formulate the basis of some of the prevention efforts that everyone would like to pursue in the coming years.

Given the severity of ALS, Dr. Mehta thought a case could be made that there are grounds for making it reportable. Since these are state-based initiatives, champions at the local-level certainly could be beneficial and ATSDR certainly wishes them well.

Timeline for Data Acquisitions and Registry Survey Findings

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

Ms. Raymond presented an update on the timeline for data acquisitions and registry research findings from the National ALS Registry web portal data. In terms of data collected currently, data from the Veterans Benefits Administration (VBA) are requested on a recurring basis that includes a list of names of VA patients with diagnostic codes related to ALS are received. These data are available approximately a few weeks after the calendar year ends. There have been complications with these data in the past. Despite this being a recurring data request, sometimes ATSDR must jump through hoops to receive the data requested because it contains personally identifiable information (PII), which is uncommon. Most programs will not receive PII, but because the data will have to be de-duplicated and redundant patients removed, the PII is necessary. In addition, the data must be shipped on a CD or DVD instead of the secure encrypted FTP site the Registry holds, which can sometimes cause delays.

Moving to the Veteran Health Administration (VHA), the Registry receives inpatient, outpatient, pharmacy (both in and outpatient), and demographic information from VHA. These data also are received through a recurring data request through the ALS Registry Act. These data include encounter data with ALS codes as the primary reason for the visit. The VHA data typically are ready shortly after calendar year ends, but the request can take time to be approved since the Registry is asking for PII. The complications are the same as for the VBA data. For 2018, the data request will have to be amended to include newer drugs that have come on the market.

The data received from CMS include demographic, base file, inpatient, outpatient, pharmacy, and hospice data. The data requested information comes from a Data Use Agreement (DUA) with CMS that has been in place since 2009. Encounter data are received with ALS codes as the primary reason for the visit. These data are available approximately 18 months after the calendar year ends. Complications with this data source are that data requests can take up to 9 months before approval is made, given that data with PII are requested. The data formats also change periodically, which will then require recoding in the way the data are accepted in order to match it up correctly.

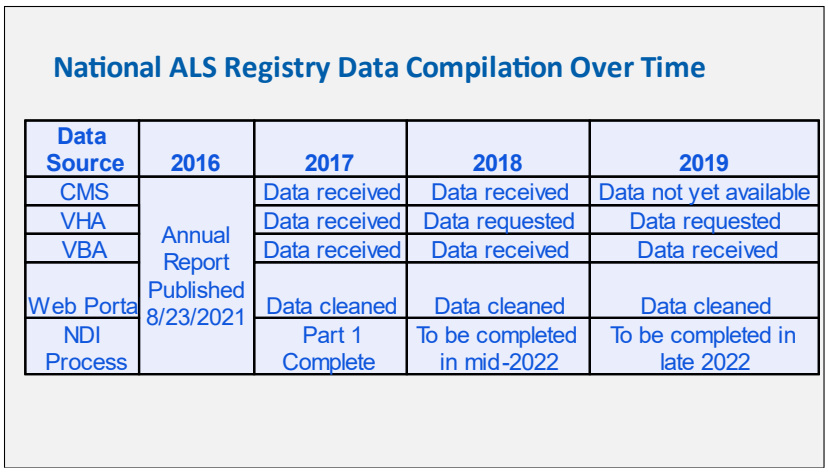
Because ATSDR receives PII, the data requests are scrutinized annually to make sure the data remain safe. Sometimes these requests are seamless and sometimes a simple change can require an entirely new request. Forms also change over the years, so a significant amount of time may be spent collecting information from different parts at CDC/ATSDR to submit the forms only to find out that the forms are outdated and new forms must be used.

The web portal data are the in-house data. Once administrative data are all in-house and processed, web portal data are requested through ATSDR's IT contractors. These data are typically ready shortly after the end of the calendar year. Data formatting does change from time to time, so recoding may have to be done. These data are only as complete as the patient inputs them.

In terms of combing all of the datasets, data are matched across all 4 datasets (e.g., VBA, VHA, CMS, and web portal). A rigorous matching process is used to de-duplicate any redundant patients. The matching criteria include the following:

- ❑ First name (e.g., John, Jack, Doe), Soundex
- ❑ Last name (e.g., Doe, John, Dough), Soundex
- ❑ SSN (at least last 5 digits)
- ❑ DOB (exact date as well as day and year)
- ❑ Gender

Matching is not always straightforward as names can be entered variably, last names can be misspelled, first and last names may be switched, et cetera. Therefore, Soundex matching is used. This is a phonetic algorithm that indexes names by sound as they would be pronounced in English. This will help in trying to match names that may be misspelled. The matched data are then merged so that they are counted only once in the calendar year of analysis. After these data are combined, they are formatted for the National Death Index (NDI). The NDI has a specific format in which the data must be sent. Possible duplicates can be sent at no additional charge to help improve the matching criteria. The NDI will look for matches in their database and send back any potential matches for the years requested. After the data are returned, they are secured, encrypted at the FTP site, and recoded and then reviewed to determine whether any of the matches have ALS as the cause of death (COD). The following table shows the Registry data complication over time:



National ALS Registry Data Compilation Over Time

Data Source	2016	2017	2018	2019
CMS	Annual Report Published 8/23/2021	Data received	Data received	Data not yet available
VHA		Data received	Data requested	Data requested
VBA		Data received	Data received	Data received
Web Porta		Data cleaned	Data cleaned	Data cleaned
NDI Process		Part 1 Complete	To be completed in mid-2022	To be completed in late 2022

The algorithm that is currently being used to identify definite ALS cases includes the following elements:

- ❑ Any 2 of the following: 1) an encounter coded for ALS (ICD-10 G12.21) in 1 or more years in the same source (VBA, VHA, or CMS); or 2) death certificate listing ALS as any cause of death or 3) prescription or Riluzole (in 2017 and beyond will include Edaravone) OR
- ❑ An encounter coded for ALS (ICD-10 G12.21) in ≥ 2 years for which at least 1 visit must be with a neurologist visit in the same source OR
- ❑ A person aged <65 years with an encounter coded for ALS (ICD-10 G12.21) in Medicare where at least one visit with a neurologist; OR
- ❑ An encounter coded for ALS (ICD-10 G12.21) in ≥ 1 year(s) for which at least one visit must be with a neurologist visit in the same source and an encounter coded for ALS in another source; OR
- ❑ An encounter coded for ALS (ICD-10 G12.21 or Veterans Benefits Administration 8017 codes) in three or more sources; OR
- ❑ An encounter coded for ALS (ICD-10 G12.21) in 1 year and five or more neurologist visits in the same source.

The current year's data are then compared to the previous dataset. Matching and de-duplication are performed again, the algorithm is run again, the NDI dataset is created again for definite and possible ALS cases, and the dataset returns from NDI and then is re-matched based on name and date of birth to the existing dataset. The algorithm is run one more time and definite ALS cases are finalized for the calendar year.

Recent findings from the Registry include the topics of vigorous physical activity (VPA) before an ALS diagnosis, female reproductive history and ALS, MADPH and National ALS Registry comparison, and the effects of the pandemic on ALS Death. A cross-sectional study published in January 2021[2] of 5,463 ALS patients with a VPA history and 956 ALS patients who never engaged in VPA was recently published. This study found that patients with VPA at least 3 times per week before age 35 were more likely to have an ALS diagnosis earlier compared to patients who did not ($p < 0.0001$). Controlling for year of birth, associations were found between those reporting VPA at age 15–24 and 25–34 and diagnosis of ALS earlier ($p = 0.0009$, $p = 0.0144$). Patients with ALS who had a history of VPA before age 35 were significantly more likely to be diagnosed with ALS before age 60 compared to patients with ALS who never engaged vigorously.

In terms of reproductive history, a cross-sectional study published in July 2021[3] collected and analyzed for 1,018 female ALS patients. A univariate analysis found that women were more likely to be diagnosed with ALS before age 60 if they were non-white ($p = 0.015$), had attended college ($p = 0.0012$), had a normal body mass index (BMI) at age 40 ($p < 0.0001$), completed menopause before age 50 ($p < 0.0001$), had never been pregnant ($p = 0.046$), or had limb onset ($p<0.0001$). A multivariate analysis found that those who completed menopause before age 50 were more likely to be diagnosed with ALS before age 60 (OR = 1.8, 95% CI: 1.4–2.3). The mean age of ALS diagnosis for women who completed menopause before age 50 was 58 years and 64 years for women who entered menopause after age 50 ($p < 0.0001$).

In draft of a study evaluating the proportion of ALS cases identified by the Massachusetts Department of Public Health (MADPH) to the National ALS Registry from 2011 to 2015 that includes 1,554 subjects from the National ALS Registry residing in Massachusetts and 1,042 in the MADPH Registry. Subjects were matched on first name, last name, month and year of birth, sex, and Soundex name matching. Those cases identified in the Massachusetts Registry that did not match in the National Registry were more likely to be under 65 years of age. Passive systems such as the MADPH and the National ALS Registry, it continues to be challenging to find all cases.

An analysis to assess the effects of the pandemic on ALS deaths is scheduled to begin in January 2022. This study will analyze death data from the NDI for the years 2016 – 2020, and will compare ALS deaths before the pandemic and during the first year of the pandemic (2020). The 2016 – 2019 data have been received and downloaded and the 2020 data are expected in December 2021.

Discussion Summary

A question was posed regarding what is learned by recording 16,000 as "prevalence" if it is known that this excludes a large number of patients, and whether it is productive to have the head of the National Institutes of Health (NIH) testify before Congress saying, "There are 16,000 patients living with ALS" if the true figure is known to be closer to 30,000.

[2] Jaime Raymond, Paul Mehta, Ted Larson, Pam Factor-Litvak, Bryn Davis & Kevin Horton (2021) History of vigorous leisure-time physical activity and early onset amyotrophic lateral sclerosis (ALS), data from the national ALS registry: 2010–2018, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, DOI: 10.1080/21678421.2021.1910308

[3] Raymond J, Mehta P, Larson T, Pioro EP, Horton DK. Reproductive History and Age of Onset for Women Diagnosed with Amyotrophic Lateral Sclerosis: Data from the National ALS Registry: 2010-2018. Neuroepidemiology. 2021 Jul 2:1-9. DOI: 10.1159/000516344

Dr. Mehta responded that it is important to distinguish that 16,000 is the number that has been estimated from ATSDR's case ascertainment capabilities. Regarding where NIH gets their cases counts and data, he could certainly understand why they would go to CDC to get that information as a sister agency. Regarding the 30,000 figure, there will be a much better estimate of the number of missing cases once they have the capture-recapture adjusted numbers reported. There will be lower, upper, and mid bounds. The premise is that with these demarcation points, there will be a better estimation of what the case counts are in the US. It is very difficult to capture all of the cases in the US because this disease is not reportable or notifiable to CDC. They do what they can with what they have and feel that their algorithm using CMS, VA, and Registry portal data is robust. By adding new data sources from the ALS Association, MDA, Les Turner Foundation, and others they certainly could have a much better estimation of case counts in the US.

Regarding a question posed regarding whether deaths are captured from the NDI data that do not include ALS on the death certificate that are found in CMS data, Ms. Raymond indicated that all of the NDI data are captured back into the database into the Registry dataset. As part of the algorithm with NDI, a variable was created that would code them as "No" for NDI death. That would be the same across CMS, VHA, VDA, and the web portal data.

Dr. Brooks mentioned that there is a COVID-19 ALS registry that can be found on clinicaltrials.gov that is collecting information on adverse events (AEs) from the COVID-19 vaccine, et cetera. Dr. Mehta indicated that ATSDR helped to recruit for this study through the University of Cincinnati.

Regarding a question about why the 2016 report was so delayed if the capture-recapture could not be included in the report, Dr. Mehta indicated that they do everything they can to obtain the data as soon as possible. It does CDC/ATSDR no good to have these data sitting in-house. They wanted to publish the 2016 report as soon as possible and anticipated capture-recapture getting published and released very quickly. However, additional data analyses had to be done and they wanted to ensure that they were complete, valid, and correct. Because of that, these data were not included in the 2016 report. They did not want to come into this meeting not having the 2016 report published. They decided to go with the *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* (*ALSFTD*) journal because they had a much faster time for publication and room to publish the report very quickly. The *Morbidity and Mortality Weekly Report* (*MMWR*) had delays due to COVID-19 with all-hands on deck and much of the print space relegated to COVID-19 findings. While they want to get data out as soon as possible, the 2017 data will probably be published in the 2022 timeframe. There has been discussion internally about potentially publishing 2017 and 2018 together in one report. The intent is to have capture-recapture results in the 2017 data in order to present the corrective factor of missing cases in the 2017 report.

Regarding a question about whether the new methods for case findings were the same as what was shared in 2020, for instance in terms of already working on the list of patient organizations, Dr. Mehta emphasized that ATSDR has been working with these organizations. They are the boots-on-the-ground. They see ALS patients and have clinics. CDC/ATSDR works with these groups to get information about the Registry out to inform and educate patients and caregivers. What CDC/ATSDR is doing differently is that they have asked these organizations for their data. There are approval factors on both ends for getting this patient information securely and it may be a while to obtain this. The consent forms also must be updated to ensure that these are feasible as well. A lot of these patients come from private pay and are receiving their care from outside of Medicare or the VA system, so they may not be captured. However, they could be

captured by one of the patient organizations. By obtaining data on these cases and including them in the Registry, case ascertainment methods could be improved.

Regarding a question about the timeline for approval of releasing ALS data at the state level, Dr. Mehta responded that the request is currently in OMB and awaiting their response. The state data may be used with the 2017 report so that case estimates will be included based on the CDC/ATSDR algorithm, capture-recapture, and the state counts.

Impact of COVID-19: How it has Transformed ALS Care

James Berry, MD
Director, Massachusetts General Hospital (MGH) ALS Clinic
Chief, Division of ALS and Motor Neuron Diseases

Dr. Berry summarized the COVID-19 pandemic's impact on changes in care and highlighted some research. The COVID-19 pandemic affected society and therefore PALS rather than primarily affecting PALS. While pre-pandemic 20% of people worked exclusively from home, during the pandemic 70% did. US school closures affected 55.1 million students in 124,000 schools. Nearly every state ordered or recommended that schools close in 2019-2020. These affect PALS just like they affect the rest of the population. This affects parents who have ALS, co-parents, grandparents who have children with ALS, et cetera. There was a major effect on people who relied on home healthcare. In June 2020, which was still early on in the pandemic, a survey was conducted among 94 Massachusetts home healthcare agencies. The survey found that 74% had aides who had COVID-19, were symptomatic, and were quarantined and 99% experienced a decrease in demand for home visits due to clients' concerns about infection, family members assuming care duties, and aides unavailable for work. This vicious circle led to a breakdown of home healthcare, which put a lot of stress on families.

MGH had a smartphone study[4] underway at the time that assessed 8-10 people who were using a GPS tracking program on their cell phones for this ALS study. This found that with this cohort, there was an increase in the amount of time spent at home. Already before the pandemic, people were spending 19.5 hours a day at home. Afterward, it was almost 24 hours a day. This compared to the general population who spent about 10 hours a day at home pre-pandemic, which increased to 14 hours a day. The pandemic clearly had a huge impact on PALS and their families.

While telemedicine was not new to the pandemic for PALS or anyone else, MGH and many others began working on video visit programs. At MGH, work began in 2011 on a video visit program for PALS at home with support from the ALS Association. They were able to expand the existing infrastructure for hospital-to-hospital communication. This originally used a very byzantine software program that was Health Insurance Portability and Accountability Act (HIPAA)-compliant. The practicalities were that PALS must first be seen in person to establish care. Then they had to agree to televisit, which usually supplanted clinic visits. Televisits included an observational exam, but generally were not multidisciplinary. While there were potential upsides to telemedicine for PALS related to travel/access and rapid communication and connectedness, potential downsides included possible disconnected feelings, providers' discomfort with the ability to make medical decisions, and uncertain cost-effectiveness. In terms of the cost-effectiveness of the TelePALS program, MGH used its patient base that drew from

[4] 2020, Beukenhorst

areas around the country to assess the cost to the patient for the televisit and to the institution to get a clearer understanding of the costs. A sensitivity analysis showed that this is cost-effective, even if just drawing from the local population. The adjusted patient cost for a televisit was $119 versus $1116 for an in-clinic visit and the adjusted institutional cost was $472 for a televisit compared to $799 for a clinic visit.[5]

COVID-19 caused an immediate and robust turn to telemedicine in clinics. In 2019, 11% of patients used telehealth. Now 76% are using or interested in using it and 57% of providers view telehealth more favorably now. Different specialties took up telemedicine differently. At least 70% of ALS clinics used telemedicine routinely during the pandemic. The more interventional the field, the less uptake of telemedicine. For instance, psychiatry had a huge uptake, neurology somewhere in the middle, and more uptake in general medicine and surgery though at the lower end.[6] ALS is a subset of neurological medicine and there is a fair amount of ongoing care that is not so much interventional but rather is relational, understanding symptoms, and being able to respond to those symptoms.

The telemedicine journey has just begun. In the 20th Century, care became centered at hospitals because new technology dictated centralization. For instance, imaging required people to present to a central location to receive care. In the 21st Century, care can now become decentralized because new technology permits remote connection and monitoring. One of the challenges right now is that pre-pandemic, there were restrictions on telemedicine across state lines. While those were lifted for the pandemic, pandemic-era freedoms from state-by-state regulations have been revoked. Though a couple of states have exceptions, practicing across state lines now requires a license for most states. Obtaining licenses in all states is impractical and probably still would not allow a practitioner to work in all states. Federal fixes are challenging because this fractured licensing is governed state-by-state. There are bills in Congress aimed at fixing this problem. This is a healthcare problem overall rather than an ALS problem per se, but because ALS is positioned to use telemedicine effectively, patient advocacy could help. The ALS Association is working on this.

There are aspects of ALS care that are not so amendable to telemedicine. For instance, electromyography (EMG) is an important part of the diagnostic process that must be done in person. Groups such as the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) felt deeply about this, who published[7] an approach to triaging EMGs during the pandemic into urgent, non-urgent, and possibly urgent as shown in this table:

Urgent	Non-Urgent	Possibly Urgent
- Clinical presentation is acute - Significant or rapidly evolving neurological deficits over days to weeks - EDX studies are believed to be necessary	- Clinical presentation is chronic or improving with mild sxs/signs - EDX studies are not required for dx or management - No harm in delaying	- Presentation not acute or severe, but progressive (wks-mos) - Delay in EDX could delay dx or rx or result in poorer outcomes.
- GBS, Botulism, MG	- CTS, polyneuropathy	- ALS, CIDP

[5] 2019, accepted for publication
[6] McKinsey and Company (https://www.mckinsey.com/industries/healthcare-systems-and-services/our-insights/telehealth-a-quarter-trillion-dollar-post-covid-19-reality)
[7] AANEM Quality and Patient Safety Committee of the AANEM , 2020

The Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS) sent out a survey to survey to 133 ALS Clinical/Clinical Research Centers,[8] of which 61 centers responded. The survey was conducted early in the pandemic over a 1-week period between April 21, 2020 to May 1, 2020. The aim was to understand limitations on clinical care and research at centers across the country and the variability of these restrictions across centers. Looking at new and returning clinical patients, a few things stood out. About two-thirds of sites were still offering in-person new patient visits. However, only about half were allowing patients to return to the institution. This was very spotty by geography, which continues to be seen. There were clear limitations in seeing people, which was a devastating blow to how patients are cared for. Video visits were replacing in-person visits, with about the same number offering video visits for in-state patients. The number of video visits increased across any state. At this point in the pandemic, a very small number were seeing new patients across state lines. Many centers used the older technology of telephone to stay in touch with their patients.

There also were limitations on evidence-based care options for PALS. At the top of the list is spirometry, which is very important in getting people bilevel positive airway pressure (BiPAP) machines and understanding where people are in their disease. Other limitations were identified as well. About 1/3 of sites in the NEALS study reported that they had challenges in scheduling appointments and performing feeding tube insertion, treatments were delayed, and some PALS chose not to have feeding tubes as they did not want to go to the hospital or risk getting COVID-19. Many institutional processes were changed. For instance, MGH moved completely to day surgery unless complications occurred. PALS generally preferred getting home sooner, so MGH incorporated that into the workflow even though it is not necessary. Some facilities moved to day surgery only in the beginning, but that was not the case uniformly. There also were changes to durable medical equipment (DME) insurance coverage requirements. It used to be that DME required face-to-face visits, but that was temporarily relaxed in order to get BiPAP machines and power chairs during COVID-19 without seeing them in the office. This begs the question regarding whether there is a path to long-term acceptance of this way of doing business, which is something to advocate for. At the same time practitioners are saying a person needs a power wheelchair, they also are saying they have to have an in-person meeting to do that, which does not make a lot of sense.

With all of these challenges come opportunities. Telemedicine availability is a major opportunity. Home-based spirometry is another opportunity that is gaining a foothold in clinical trials, which may also play a role in care. MCH has been experimenting with this in one of their house-call programs to leverage what they are doing in trials. Alternative measures are also being used such as counting out loud and vocalizing a sound in order to estimate home-based or clinic-based spirometry to get people the care that they need. Capitalizing on previous work showing that multi-disciplinary ALS care is possible via telemedicine is a major area that can be innovated upon. In fact, MCH worked with a company that was engaged in virtual reality physical therapy and received reimbursement from insurance. Some great feedback has been received from patients about this. Hence, there are new ways of doing business that are going to open up as a result of COVID-19.

[8] Andrews et al. 2020

An interesting trend observed in a paper[9] that was on the fringe of a lot of papers looked at predictions about the way that ALS will progress to focus on ALS care. This was in the setting of the pandemic, but it raises the idea that perhaps there are better ways of rationing the care that is given anyway. This paper looked at D50, which is a model describing ALS progression as a sigmoidal state transition of functional loss in terms of the estimated time in months it took for a patient to lose 50% function and whether that prediction could be used to ascertain which group patients were in. PALS were divided into low (D50 >30 months) or high (D50 < 30 months) and were categorized into at least 3 phases:

- Early semi-stable Phase I (0 rD50 < 0.25)
- Early progressive Phase II (0.25 rD50 < 0.5)
- Late progressive and late stable Phases III/IV (rD50 0.5)

This also raises the question regarding whether thought should be given to how patients are seen. For instance, many clinics schedule a 3-month follow-up appointment for almost all patients. However, this could be more sophisticated based on a lot of the work that has been done during the pandemic. There is a lot of interesting work that is likely to have a long-lasting effect on the way that PALS are cared for over time.

Also part of the NEALS survey was identification of the impact of the COVID-19 pandemic on ALS research. About 20% (1 in 5) centers halted all ALS clinical research. Only 20% centers allowed new research enrollments in person. Only 2 out of 5 centers allowed follow-up research visits in-person. While Institutional Review Boards (IRBs) and the Food and Drug Administration (FDA) were forgiving about protocol violations, the reality is that much research was simply halted. A huge number of observational studies were unfortunately halted, but have come back online due to the hard work of many centers and people advocating for PALS to be engaged in research. This has steered work toward distributing clinical trials in a much faster way. Prior work had been occurring, but was arduous and not mainstream. Rick Bedlack had been designing distributed trials, Zach Simmons had been validating at-home pulmonary function tests (PFTs) for many years, numerous groups had been working on mobile digital outcome measures, and IRBs had been considering remote consenting and e-consenting. These concepts are now at the fore of ALS trial design. There are massive networks in ALS, new companies, et cetera. A great deal of work is needed to catch up to the desire for these features now, and the community needs to band together to determine how to do this well so that there is not fracturing, and determine and leverage the key components.

Some of the work in digital biomarkers, remote collection of data, and patient report outcome measures can inform how studies are conducted moving forward. MGH has been working on the Symptom Monitoring for ALS in Real Time (SMART) real-time study using cell phones to collect passive data such as accelerometer, gyroscope, GPS, call and text logs (Android), WiFi, Bluetooth, and power status and active app data to collect baseline survey data through the Communitive Participation Item Bank, weekly survey data, and weekly recordings (e.g., speech sample and cough). A pilot study[10] found that smartphone self-entry and clinic-delivered Revised ALS Functional Rating Scale (ALSFRS-R) correlated highly at baseline (0.92), but that self-entry was slightly higher (2.4 points higher). This suggests that one maybe cannot go back and forth so easily between these. That study was repeated[11] in a clinic population only using clinic waiting room tablets to obtain self-entry ALSFRS-R, which was found to correlate well with

[9] Steinbach, JCM, 2020
[10] 2019, Berry, ACTN
[11] Chew 2021

standard ALSFRS-R. No single question or domain is responsible for mismatch. The slopes were not significantly different for clinic and self-entry ALSFRS-R.

Speech over time also has been assessed and it has been found that speech and articulation rates declined fastest in people with abnormal speech at baseline. There are correlations between variables that can be collected such as how much time people are spending at home, which correlates well with the ALSFRS-R self-entry scale. Interestingly, how much time people are spending at home is also correlated with their speaking rate. The Communitive Participation Item Bank is a survey in which people talk about communication in their life and how challenging it is.[12]

Digital biomarkers are beginning to be integrated into ALS care and research. Mobile digital biomarkers allow remote collection of data, including passive data nearly continuously and active data through surveys and speech recording data at regular intervals. In terms of research, this offers potentially more opportunities to collect more quantitative and more statistically powerful outcomes. In clinic, these data need to be organized and presented to patients and physicians in a way that makes it more actionable. In addition, more data need to be related to clinical "threshold" events to inform decision-making. That is, speech may be slowing, but when is it time to intervene on that and in what way? This is going to require new infrastructure for clinical care in order to integrate this into the clinic setting. Leading the pack are digital biomarkers for quantitative motor speech and vital capacity, but there will be others.

Dr. Berry emphasized that it has been a very difficult year for PALS and their families, particularly with regard to isolation and families being in crisis much of the year. The hope is to be able to leverage some of these opportunities.

Discussion Summary

Regarding a question about the effect of COVID-19 on delay of diagnosis and whether there might be effects on the eligibility for clinical trials in the next couple of years, Dr. Berry said that he did not have a quantitative number to say that it affected diagnosis delay in a certain way. That is a very interesting research question that he would have to thinking about more in terms of what methodology would be needed to get at that. As far as whether it will impact clinical trial eligibility, and this is purely subjective, getting new patients in has improved at this point and it feels like a lot of the excess delays have been worked through. There are so many trials underway in ALS right now and there is such a robust landscape, it is important to do a very good job of making sure that research and access to research become part of routine care for every PAL. One way to do better is to bring a focus to diversity, equity, and inclusion (DEI) in clinical trials. With a grant from an organization called Tambourine, MGH has observed that ALS trials have not been doing a good job of achieving DEI. If trials are not doing a good job of enrolling a wide distribution of people with ALS, then they are not doing a good job of promoting trials.

Dr. Siddique expressed gratitude to Dr. Berry for all of his effort during COVID-19. He emphasized that neurologists are among the few physicians who actually examine their patients hands-on. While this may not be easily measurable, many practitioners believe that there is an important aspect of healing in examining the patient in-person. One issue of virtual reality is that it is not clear how well it serves the purpose. The inability to go to a central location due to disabilities, getting organized, and having morning clinics are all difficulties for patients. These

[12] Connaghan, Interspeech, 2019

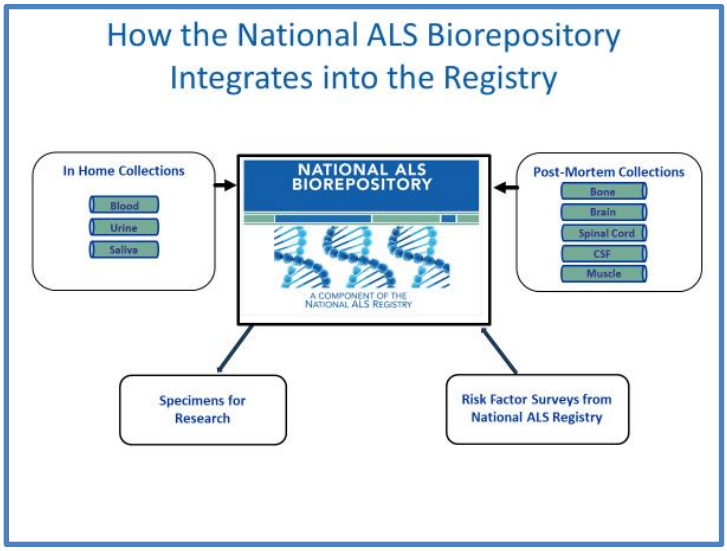
are not issues related to the disease per se in terms of examination of the patient or seeing the patient, but rather are technical or logistical difficulties. The second issue relates to the fact that this is not the last pandemic. He requested that Drs. Berry and Brooks convene people to consider how to prepare for an emergency or pandemic in terms of the care of ALS patients.

Dr. Berry agreed that in neurology, especially as a part of the diagnosis, the in-person exam is probably more important than any other specialty. In his opinion, it is very important to acknowledge that telemedicine in its best use has a role in caring for patients. In the pandemic, there was a much expanded role because it had to be. However, he thought they also reached the limits of what could be done via telemedicine. New patients in particular were very challenging to see by telemedicine. He had some telemedicine diagnostic dilemmas, but when he saw patients in clinics the next time, there was no dilemma at all in making a diagnosis within 30 seconds of a person walking in the room. However, he could not work it out over telemedicine. While it might be his shortcoming, a shortcoming of the technology, or maybe a combination of both—he thinks there is a shortcoming. The way he thinks of this is that it is not like the telephone was invented and crises stopped. The telephone is a very important piece of technology for delivering healthcare, but it does not supplant clinical visits. Telemedicine is likely to be the same way. It will be another arrow in the quiver that has a place, but it will have a place alongside clinic visits. This is likely to differ person-to-person, but they do need to work out as a community what constitutes a thoughtful way to do this in terms of best practices around telemedicine. As for the next pandemic, it is important to have a plan for when this happens again.

National ALS Biorepository Update

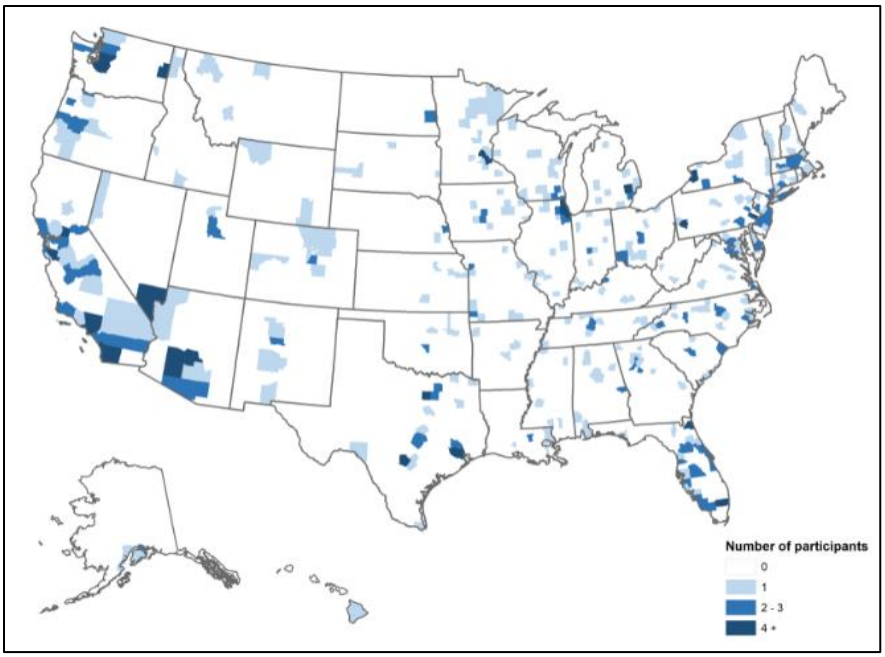
Laurie Wagner, MPH
National ALS Biorepository Coordinator
McKing Consulting Corporation

Ms. Wagner presented an update on the National ALS Biorepository, which is a component of the National ALS Registry, focusing primarily on the activities over the past year. As a reminder, this diagram illustrates how the National ALS Biorepository integrates into the National ALS Registry:



COVID-19 has had a direct impact on in-home collections, which were halted on March 17, 2020. For the safety of patients, existing appointments were cancelled and new appointments stopped being scheduled. During that time, new procedures were developed to complete blood draws by qualified home health workers already going to participants' homes and by staff members at already scheduled doctors' appointments. There was low participation as not many patients had healthcare workers coming to their homes and many doctors' appointments were cancelled or were held via telemedicine. In addition, COVID-19 safety procedures were developed for in-home collections. This plan added extra precautions for phlebotomists to enter participant homes safely. IRB and OMB approval were received to resume in-home collections in June 2021, and at this time in-home collections were resumed. However, there continues to be lower interest from Registry enrollees, possibly due to safety concerns.

Biorepository participation from October 1, 2020 – August 15, 2021 included consent for 6 in-home blood collections, 0 saliva only, and 2 postmortem. There were 5 in-home blood collections, 1 saliva only collection, and 2 postmortem collections. Among the 5 collections, 1 invovled a home healthcare worker who already was going to the home and was able to conduct the collection and 2 had samples collected at their doctors office where they already had scheduled appointments. When these situations arise, the Coordinators at the Biorepository speak with the individuals who are doing the collections to explain the process. All supplies are provided in the blood collection kit and they drop off or call for a pick up of the collection at FedEx the same proecedures as the in-home phlebotomists follow. In FY17-FY19, there were over 200 blood collections per year. From October 2019 through March 2020, over 100 blood samples had been collected. There were only a few more collections after that, for a total of 130 that fiscal year. FY21 has been impacted the most challenging so far. This map illustrates the historical geographic distribution of all participants through 2019:



This map also shows that participants from all parts of the US have the opportunity to provide samples.

Over 1400 participants have donated samples to the Biorepository, which has resulted in over 75,000 samples. The Biorespository sample inventory is shown in the following table:

Sample Type	# Aliquots	Aliquot Size	# Participants
DNA	22,870	2 µg	1,384
Hair	241	40 strands/vial	157
Nails	268	10 nails/vial	268
PBMC's	1,106	500,000 cells/vial	74
Plasma	9,130	.5 ml	1,152
RBC	3,856	1.0 ml	1,149
RNA	10,070	2 µg	1,157
Serum	7,172	.5 ml	1,144
Urine	10,046	1.8 ml	1,062
Urine (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.

Postmortem tissue and samples collected include brain and spinal cord (frozen and fixed), cerebrospinal fluid (CSF), bone (stored in formalin), muscle (stored in paraffin blocks), and skin for fibroblasts. To date, postmortem samples have been collected from 50 participants, 7 participants withdrew and did not donate, and 7 participants continue to be followed. The samples collected from all 50 participants include brain, spinal cord, CSF, bone, muscle, and skin. Human primary cells have been collected from 28 participants. The participants who withdrew, some simply joined other registries and others changed their mind about donating. Regarding the demographics of the postmortem collections through August 15, 2021, collections have been distributed fairly even between males and females.

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. Prior to submitting their applications, many researchers will contact the Biorepository and either Dr. Kaye or Ms. Wagner speak with them to provide guidance and ensure the samples being requested are available. With regard to the official 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 (initial review for completion, laboratory expert review, and scientific review through ATSDR's review committee). The researchers must have IRB approval from an accredited IRB to be approved for the request for samples. After approval from ATSDR, the researcher signs the Material Transfer Agreement (MTA) then pays the cost to pull and ship the samples. McKing selects the appropriate samples, and the laboratory or Boston University will pull and ships samples to the researcher.

This table shows research requests that have been approved and the types of samples that have been requested, some of which are from the Biorepository and some of which are from the Registry:

Group Conducting Analysis	Sample Types Requested
AbbVie	DNA, RNA, Plasma, Urine, CSF
CDC	Blood/Urine (Heavy Metals/POPs)
Center for Neurologic Study	Plasma, CSF
Cerevance, Inc.	Serum, brain, spinal cord
Columbia University	Brain tissue, whole blood, hair
Harvard Medical School	Peripheral Blood Mononuclear Cells (PBMCs)
Icahn School of Medicine Mount Sinai	Human primary cells, whole blood
NIH	DNA (Genotyping/WGS)
QuarAlis™	CSF, Plasma
University of California Los Angeles (UCLA)	Serum (Biomarkers)
University of Pittsburgh	Blood (POPs)
University of Utah	Human primary cells (targeting Ataxin)
University of Vancouver	Plasma

COVID-19 has had an impact on sample distribution. There has been limited opportunity to promote the Registry. For instance, it has not been possible to attend conferences other than a few online. There has been some difficulty in shipping the samples outside the US, which has been affected by customs limitations. The customs issues were worked out and the samples were shipped but shipping took longer than expected. The other issue that has impacted sample distribution is that the laboratories receiving samples have had limited staff working to receive shipments.

One direction for the future is that the National ALS Biorepository is partnering with the ALS Postmortem Tissue Core at Johns Hopkins University. This partnership will expand the number of postmortem collections and samples. Researchers will have access to samples from both Johns Hopkins and the National ALS Biorepository. There also are plans to evaluate the types of samples collected by the National ALS Biorepository and if necessary, changes will be made. In-home blood collections will continue. Due to the COVID-19 impact, the number of collections have been lowered for the next year. Everything else will remain in place.

CDC National ALS Registry – JHU ALS Postmortem Tissue Core Collaboration

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Director, JHU Tissue Repository

Dr. Ostrow observed that it felt like fate that JHU started a collaboration with the CDC during this pandemic that everyone is living in. He was on service at Johns Hopkins Hospital this week. Another physician-scientist graciously agreed to cover for him so that he could attend the Annual ALS meeting. He emphasized that being in a hospital right now is tough and that he is tired. Though he got less than 2 hours of sleep the previous night, he stressed that he was not complaining because it is a tired that he is proud of because it is a privilege and an honor to be someone's doctor. He is reminded of that every day, especially by his ALS patients. There have been many challenges during this pandemic in terms of diagnosing ALS patients. These patients are followed in the clinic and practitioners wish they had more to offer them for treatments. When one of his patients decides that they are going to donate to this research program, he is the one who is going to make sure that it gets into the hands of the right researchers so that every time this disease wins, they do everything they can to figure out what is going on so that eventually, they are the ones who are going to win. While it is an incredible honor to serve these patients, it also is an incredible responsibility. He expressed his hope that in the short presentation, he would convince everyone that this collaboration with the CDC offers a chance to do something really special. He expressed his gratitude for this opportunity and emphasized that he does not intend to let his patients down.

Everyone hears about different things that "cause" ALS and every week new papers come out. There are new basic science discoveries. Over time, it has been learned that there are many different cells involved in what occurs in ALS—not just the motor neurons. The following is a small and partial list of examples of "pathogenic" mechanisms implicated in ALS:

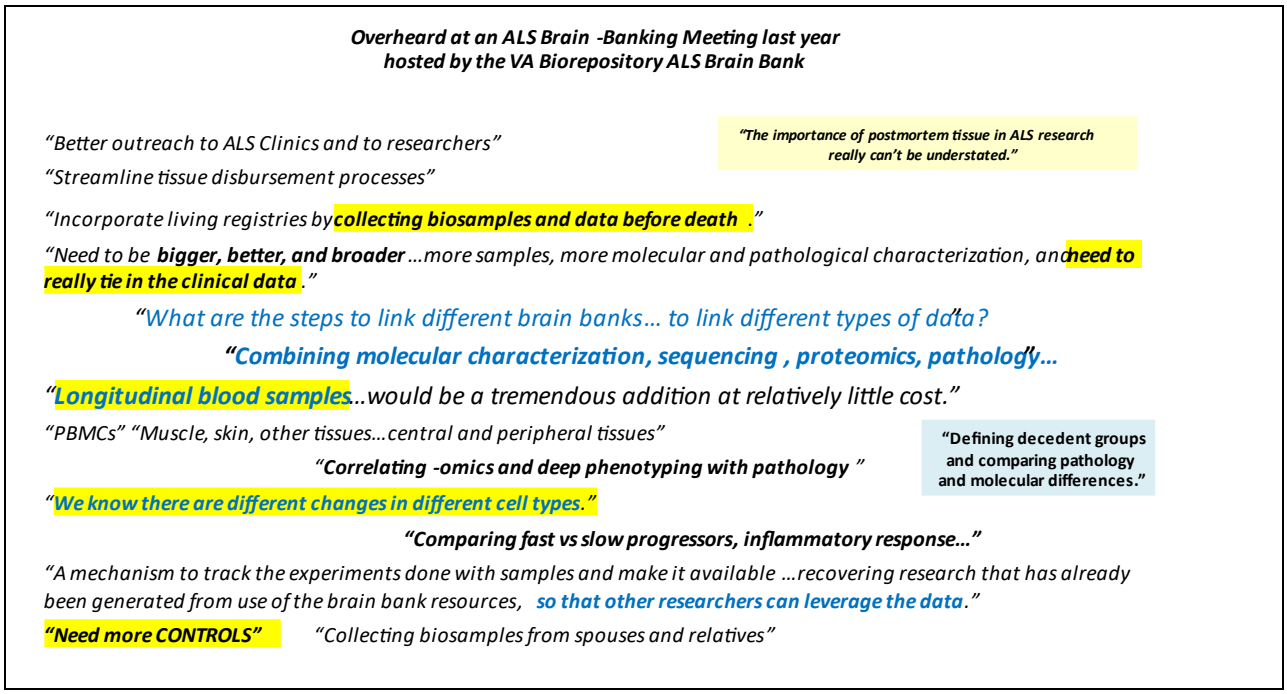
- ❑ Glutamate induced excitotoxicity
- ❑ Reactive gliosis and other astrocyte dysfunction
- ❑ Oxidative stress
- ❑ protein aggregation / misfolded proteins
- ❑ ER stress
- ❑ Mitochondrial dysfunction
- ❑ Activation of neuro-inflammation
- ❑ Impaired axonal transport
- ❑ Oligodendrocyte dysfunction
- ❑ Axonal degeneration
- ❑ Dysfunctional RNA processing
- ❑ Endogenous Retroviruses
- ❑ Abnormal Nucleocytoplasmic Transport
- ❑ TDP-43 mis-localization and loss of function
- ❑ Microglial activation
- ❑ Dysfunctional protein quality control
- ❑ Cortical hyperexcitability
- ❑ Environmental exposures

In terms of how to conduct this research and what it means when looking into cell types or a mouse or other animal that has an ALS mutation, it is all pretty simple in terms of the way any medical research is done. Diseased cells are compared with normal cells. Sometimes the difference is pretty obvious and sometimes it is not. Sometimes special technology, imaging, or something else is needed to see the difference discovered in a laboratory that is thought to be important and may matter in figuring out this disease. The truth is that it is not always known what is important to measure or whether there are treatments that work. The kinds of measurements made keep changing, but that is because it is important to meet the evolving needs of the research community.

About 90% of ALS is thought to be sporadic and it is not known what causes this. It is not a specific genetic mutation, or if it is, it has not yet been discovered. There likely are many distinct "causes" of ALS. In different patients, there may be different combinations of "causes." In most cases, the disease may be the product of multiple inter-related factors combined in different patients. Because of that, the right patients must be identified when developing a therapy. Many efforts are focused on identifying distinct patient subsets, such as with various integrated -omics approaches. This is somewhat of a mess because ALS is a fatal disease with a clinical diagnosis with variable presentations, rates of progression, and biological causes. Much has been learned about this disease and the science of it from laboratory models, but a lousy job has been done of translating this into trials. JHU is a tertiary referral center, so they have all sorts of weird stuff admitted in-patient and they often do not know what is wrong with the patient. However, because of something about their disease, there is an evidence base that tells them that perhaps a particular treatment will help the patient.

Despite promising pre-clinical data in laboratory assays and animal models, countless drug candidates have failed to translate into successful clinical trials. Therefore, consideration must be given to whether the animal models and cell cultures created by genetic manipulation are a good model for what happens in other ALS patients, and whether the right treatments are being tested in the right patients. This highlights the importance of validating new results with relevant patient-derived laboratory tools and patient-derived biosamples. There remains a substantial unmet need for high quality human postmortem tissues for ALS research, and the tissue has to have the right kind of data with it in order to know whether it is an apple, orange, or pomegranate; what species of pomegranate it is; and how long it was on the tree. Tissue is like apple pie and the ratio of the ingredients change as the disease progresses. Given that no laboratory model or assay can recapitulate the findings of every patient with ALS, it is important to validate findings with relevant patient-derived laboratory tools, including postmortem tissues, induced pluripotent stem cells (iPS) cells, and biofluids. There also is a need for rigorous and standardized clinical, epidemiological, and pathological data linked to the biosamples. It is also important to know that the diagnosis is correct. ALS is a clinical diagnosis. It is important to know that when comparing with controls that the controls do not have some other disease. Therefore, it is very important to have the rigorous pathology and other data that go with the samples.

In 2020, the VA Biorepository ALS Brain Bank hosted a meeting of all of the brain banks on ALS to discuss how to do this better and how to work better together. The VA team is comprised of the same neuropathologists who evaluate all of the CDC ALS Registry postmortem pathology. This graphic represents the notes that Dr. Ostrow took during that meeting about the kinds of things that were being said that illustrate that while the postmortem tissues are needed, the right data need to be included with them:



It is vital to find ways to work together and to collaborate to make samples and data interchangeable so that researchers in the research community can get what they need. There was a lot of discussion about different ways to compare different decedent groups and different pathologies. Ideally if something is discovered in a subset of tissues, perhaps there is something in the biofluids from those same patients that could be used to identify which patients are more likely to respond to a given therapy. In order to do that, matched biofluids, tissue, and clinical data are needed. Coming out of that meeting, the thought was that the plan should be to collect and analyze everything thought to be important to understand ALS from everyone and to:

- ❑ Recruit as many subjects and relevant controls as possible
- ❑ Find ways to combine efforts with other biobanks and data collection and analysis efforts to increase numbers, breadth of samples and data, and analytical capabilities
- ❑ Make all data, samples, and analyses broadly available
- ❑ Establish central platforms / "data hubs" to combine and analyze multimodal data, and to define and compare subsets of samples and patients
- ❑ Leverage the results, tools, and wisdom of the global ALS research community for everyone
- ❑ Educate and encourage participants in established longitudinal data and biosample collection efforts to consider postmortem tissue donation.

The JHU ALS Postmortem Tissue Core now has over 120 autopsies with a goal to provide high-quality, well-characterized postmortem tissues and data that specifically meet the needs of ALS researchers while maximizing the use of every case, ensuring responsible use of the tissues, and fostering collaboration and promote open science and the rapid sharing of data to accelerate ALS research. Standard operating procedures (SOPs) are in place for tissue dissection, processing, quality control (QC) analysis, clinical data elements, and neuropathological characterization that are specifically optimized for ALS research. Whole genome sequencing (WGS), and multiple CNS region RNA sequencing (RNA-Seq) are available for every autopsy, linked to bar-coded tissue/slide inventories, QC measures, and de-identified clinical, demographic, and neuropathological metadata. All policies are designed to

provide samples and data as quickly as possible, while ensuring responsible, open, and unbiased use of all Core resources. Researchers using samples and data retain full ownership of their ideas and results, without authorship/IP requirements.

The JHU ALS Postmortem Tissue Core collects frozen and fixed CNS tissues, liver, and several muscles from ALS/MND and non-neurologic control autopsies. In standard autopsies, things are dissected in a way that is not very useful. ALS researchers are interested in particular parts of the brain, parts of parts, or tiny pieces. The Core finds the parts that researchers need and dissects them initially into tiny pieces that are the exact size needed for research so that this does not have to be done later. The goal is to produce the maximum number of individual, optimally-sized tissue samples from each ALS-relevant region, while preserving the architecture of the tissue. This minimizes subsequent freeze-thaw and labor that otherwise is necessary when re-dissecting frozen slabs or larger tissue regions. They have a bar-coded inventory system that is maintained by NEUROBANK™ that is de-identified. When a researcher has a particular need, the Core's goal is to have the tissues ready to go and not have to do anything else. They know what researchers need because they periodically survey the research community to ask them about what assays they are using, sample sizes, QC variables, clinical data needed, et cetera in order to meet evolving needs.

In terms of genetics, an incredible genomics effort was spearheaded by Dr. Hemali Phatnani at the New York Genome Center (NYGC) and funded by the ALS Association, the Tow Foundation, and Target ALS. The genetic data are freely available, linked to the tissue samples, and de-identified metadata, with no embargo or IP concerns. Samples can be annotated by genomic criteria to help design sample sets testing specific hypotheses. WGS and RNA-seq raw data files in multiple formats can be requested via an online form and established data transfer workflow. C9orf72 and Ataxin2 repeat expansions are separately evaluated with ExpansionHunter on PCR-free DNA. This has been a game-changer in the way a lot of samples are used. While unfortunately this is coming to an end now, there are some options under consideration such as through some already established collaborations that the CDC/ATSDR Registry has in place.

The JHU ALS Postmortem Tissue Core says "yes" to every request and does its best to meet the needs of every researcher. Requests are evaluated based on feasibility rather than the science in terms of whether they can do the experiments and whether the result will be interpretable. There is a need to ensure that scarce and precious samples are not wasted and that experimental plans are optimized and staining protocols and tissue assays are validated. Experimental designs always should consider the next steps, such as identifying potential biomarkers for eventual clinical trials. The Core will work with researchers to optimize their experimental design. Existing data and analyses are leveraged to provide robust complimentary results, such as using genomics and neuropath data to plan "black/white" test sample sets. This is the ultimate donation. None of this would be possible without the generosity of incredible patients. If patients and families are donating their tissue, it is imperative to make sure that samples are being used responsibly by as many researchers as possible and not wasted.

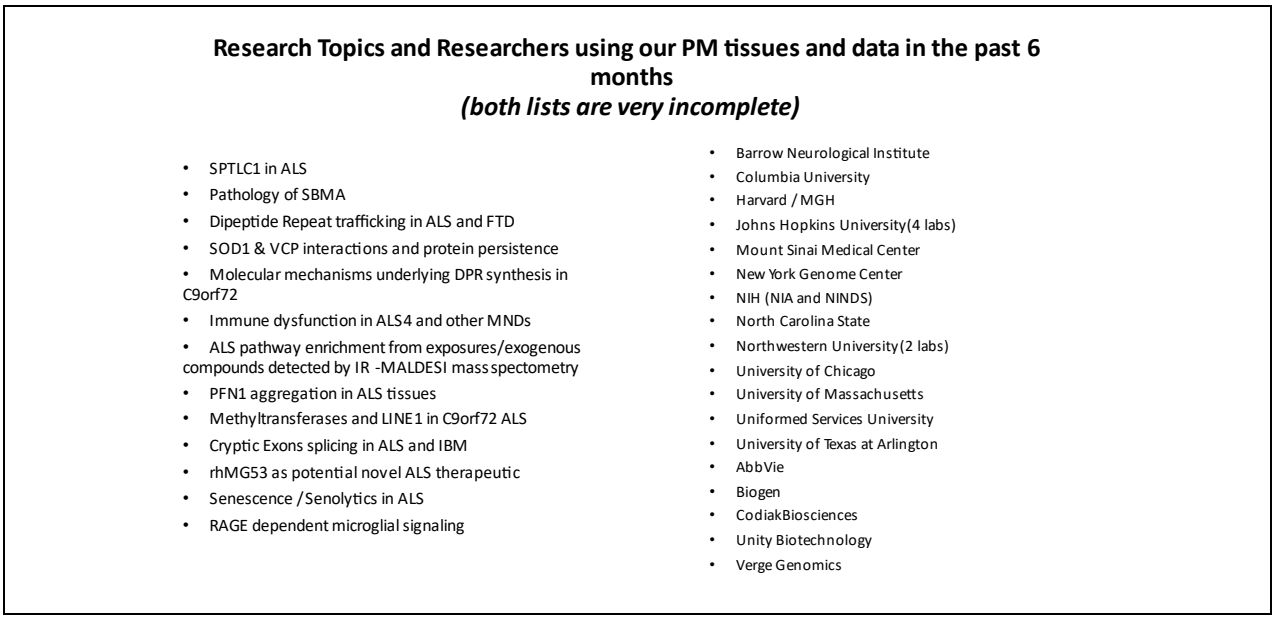
While the SOPs might be designed to meet the needs of researchers, as far as Dr. Ostrow is concerned, they work for patients and it is because of patients that they are able to do this. The Core spends a lot of time considering what it means to "validate" an experimental result using human tissue in terms of what types of measurements to make; how to relate those to a particular type of ALS; whether the questions can be used to design the optimal tests; how the postmortem results will affect what a researcher does next; whether a researcher thinks a mechanism is specific to a genetic subtype, gender, or other subgroups; how far iPSCs were

differentiated; and the nature of the samples used in the original experiment. Anatomical considerations involve conserving the scarcest resources, understanding that bulk tissue assays on spinal cord have lots of variability, thought about when it is appropriate to use thoracic instead of cervical or lumbosacral spinal cord, and considering whether to use primary motor cortex versus spinal cord. Decedent selection considerations involve consideration of what "controls" would provide the best comparison for the question being asked, pathological variability versus assay variability, and the meaning of "end stage" tissue.

In terms of clinical and genomic data considerations, clinical and demographic information are collected for autopsies to inform tissue requests and to correlate with genetics, neuropathology, and other analyses. It is important to consider when the clinical data were collected in relation to death. While postmortem tissues are not longitudinal, disease severity within the neuroaxis can vary dramatically in an individual decedent. WGS and RNA-Seq data can be used to identify relevant tissue samples and slides. Consideration must be given to whether specific subgroups display gene signatures enabling patient selection for clinical trials. Assay validation considerations are that very large numbers of targets are often identified in cell/omics-based analyses. Initial slide/sample requests are frequently calculated based on looking for large panels of targets in multiple CNS regions. The Core provides test sample/slide sets to help optimize staining. "Quantitative immunohistochemistry" remains challenging, especially in spinal cord. Frozen tissue-based assays or "bucket biology" on homogenates and batch effects must be considered. They also spend some time trying to determine ways to get results that are invalid, because this helps them to know how to design assays.

The point of all of this is that what they have learned over the past several years is that the part of this process that requires the most attention, time, and effort is not the collection component. While that is critical, selecting and dispersing the right samples and doing it in a way that maximizes their use and doing it quickly on a rolling basis so that researchers can get meaningful results is paramount. Rather than focusing primarily on sample procurement and analysis, most of the JHU ALS Postmortem Tissue Core's efforts are devoted to selecting and disbursing the optimal samples and data to meet each individual researcher's needs. All policies are designed to provide samples and data as quickly as possible, while ensuring responsible, open, and unbiased use of all Core resources.

The collaboration with the CDC/ATSDR National ALS Registry that is enabling them to do this now started just 6 months ago—during the pandemic when laboratories were shut down, some of which still are. Despite all of that, over 800 slides and 70 frozen tissue samples and the related data have been provided to 24 laboratories at 14 academic institutions and 6 industry laboratories in just the past 6 months. The demand has been quite remarkable. Slides and tissue samples are usually provided in several batches, as the projects progress and work together to optimize experiments. Letters of support (LOS) have been provided for grants and fellowship applications to the NIH (3 R01s, 1 early career/mentored award), a TEDCO Maryland Innovation Initiative (MII), Alzheimer's Drug Discovery Foundation (ADDF)-Harrington proposal, and several others. At least 5 manuscripts have been submitted or recently published, and a PhD thesis was just defended. Brief descriptions of all ongoing projects soon will be available online, along with links to published manuscripts and preprints using collaborative resources. The following reflects a sample of some of the research topics and institutions using the data in the past 6 months:



The Core started using Zoom before the pandemic because of the frequent interactions with the research teams using the samples. It has been amusing to watch the world go through this process of learning to use Zoom effectively in the interconnected world in which everyone now lives. Since this collaboration began, the teams from CDC, McKing, and the Core have been having Zoom calls and working together to try to find ways to harmonize what they are doing and best capitalize on their different resources. It is very invigorating and there is a potential to have the National ALS Registry that is collecting data that are then able to be correlated with biosamples during life with longitudinal data, with postmortem samples, et cetera. While this will evolve over time, there is some "low-hanging fruit" that can be leveraged right now to get to this. Future plans include harmonizing ALS pathology nomenclature and analysis; implementing a combined request form and workflow for both resources; surveying/assessing the evolving needs of the ALS research community; harmonizing GUID practices; accepting autopsies from other academic centers; collaborating with other mature ALS biosample and data collection efforts; and linking to biofluids and longitudinal clinical data, cell lines (iPS, others), and CDC ALS Registry Data.

In closing, Dr. Ostrow noted that one of the other roles he plays is serving as a volunteer chair of the Department of Defense (DoD) Congressionally Directed Medical Research Programs (CDMRP) ALS Research Program, which is compiling a database of all publicly available ALS biorepositories, data sets, and other research resources.[13] Again, he thanked ALS patients and emphasized the need for researchers to do better to beat this disease. None of this could be done without patient samples—the ultimate donation. He emphasized again that despite his lack of sleep, he was proud of being tired and proud of being ALS patients' doctor.

[13] https://cdmrp.army.mil/alsrp

Perceived Causes and Risks of Disease: An Analysis of Free-Text Responses by Individuals Enrolled in the National ALS Registry

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Ms. Jordan first acknowledged and expressed special gratitude to all of the PALS who have contributed to the risk factor surveys, without whose participation it would not be possible to analyze potential risk factors for ALS. During this session, she presented some preliminary findings from an exploratory analysis of the risk factor survey referred to as the Open-Ended Survey Module. The Open-Ended Survey Module is important because it is the first of its kind for ALS or for any national registry system for that matter. This particular survey module is the only nationwide scientific-driven forum for individuals with ALS to provide their responses in open-ended text format. This means that the respondents are not looking for a drop-down list of options to choose from or a select button style survey question. Instead, they are able to type in their personal narratives into a text box. It is important to acknowledge that individuals with ALS are the most knowledgeable for describing the ALS experience. They are interactive partners in their disease management, and they are experts at living with this illness and talking about possible risk factors of disease.

This module was developed and implemented because ATSDR learned that individuals with ALS desired a way to contribute directly to research by sharing their knowledge for risk, risk perceptions, personal stories, and detailed input about their disease. The module that Ms. Jordan analyzed contains two open-ended questions: Q1) Please enter your ideas or thoughts regarding risk factors that may have caused your ALS; and Q2) Please enter any ideas about factors that may cause ALS in general. Each questions offers a text box for respondents to type into. The free-text is limited to 1500 characters per question or about 300 words each. Prior to these analyses, the Open-Ended Survey Module response rate and respondent characteristics had not been examined and the quality and utility of these data were not known. A qualitative thematic analysis regarding perceptions of personal and general causes and risk factors for ALS on a dataset of this size had not been attempted.

The objective of this particular analysis was to: 1) characterize survey respondents and open-ended data quality; and 2) qualitatively describe perceived causes and risk factors for ALS among a cohort of open-ended survey respondents. This exploratory analysis looked at 2 years of data. Data were collected from January 1, 2014 to December 31, 2015. During that time period, 1548 surveys were submitted for analysis. In addition to the responses to those two open-ended questions, 10 additional variables were included in the analysis data set, including: Age, Sex, Race, US Census Region of Residence, Education Attainment, Military History, Smoked Per Day For 6+ Months, Drank Per Day For 6+ Months, Family History of ALS, and Family History of Other Neurological Diseases. As a reminder, only individuals who are self-enrolled in the Registry can complete any of the survey modules. The overall Registry protocol was approved by the CDC IRB and these analyses used de-identified data.

Descriptive statistics were used to characterize survey respondents compared to Registry self-enrollees and those identified in the administrative databases. Dichotomous Yes/No variables were created to determine the count and percentage of responses that:

- ❑ Were blank
- ❑ Contained line-listings versus substantive responsive or anecdotal 300-word stories
- ❑ Contained PHI
- ❑ Contained the concept "I Don't Know"
- ❑ Were superfluous
- ❑ Responses in Q2 that were continuations from Q1 that might have impacted the thematic analysis for the Q2 data

An a priori codebook was developed via a review of the scientific literature and the current risk factor survey modules. Codes and code groups were programmed into Atlas.ti. The final codebook contained 152 codes grouped into 34 code groups. Inter-coder reliability was assessed on 310 records. Agreement was 97.14% and the Cohen's kappa 0.83. All discrepancies and mismatched coding due to incomplete code definitions were resolved in the final data analysis dataset. Overall thematic analysis was performed in Atlas.ti. This table shows a comparison of the demographic characteristics of the open-ended survey respondents and Registry self-enrollees:

	Open-Ended Survey Respondents n=1548			**Self-Enrollees Only n=6154**			
	#	% (CI)	Valid % (CI)	#	% (CI)	Valid % (CI)	p-value
Age (in years)							<.001
18 – 39	45	2.9 (2.2. 3.9)	**3.0 (2.2, 4.0)**	347	5.6 (5.1, 6.2)	**6.5 (5.8, 7.2)**	
40 – 49	182	11.8 (10.2, 13.5)	**12.0 (10.5, 13.8)**	982	16.0 (15.1, 16.9)	**18.3 (17.3, 19.3)**	
50 – 59	459	29.7 (27.4, 32.0)	**30.4 (28.1, 32.7)**	1911	31.1 (29.9, 32.2)	**35.6 (34.3, 36.8)**	
60 – 69	493	31.9 (29.6, 34.2)	**32.6 (30.3, 35.0)**	1516	24.6 (23.6, 25.7)	**28.2 (27.0, 29.4)**	
70 – 79	270	17.5 (15.6, 19.4)	**17.9 (16.0, 19.9)**	488	7.9 (7.3, 8.6)	**9.1 (8.3, 9.9)**	
80 or older	63	4.1 (3.2, 5.2)	**4.2 (3.3, 5.3)**	131	2.1 (1.8, 2.5)	**2.4 (2.1, 2.9)**	
Unknown	36	2.3 (1.9, 3.2)	n/a	779	12.7 (11.9, 13.5)	n/a	
Sex							.026
Male	929	60.0 (57.6, 62.4)	**61.4 (59.0, 63.9)**	3588	58.3 (57.1, 59.5)	**58.3 (57.1, 59.5)**	
Female	583	37.7 (35.3, 40.1)	**38.6 (36.1, 41.0)**	2566	41.7 (40.5, 42.9)	**41.7 (40.5, 42.9)**	
Unknown	36	2.3 (1.7, 3.2)	n/a	n/a	n/a	n/a	
Race							.880
White	1422	91.9 (90.4, 93.1)	92.6 (91.2, 93.8)	3330	54.1 (52.9, 55.4)	92.8 (91.9, 93.6)	
Other	113	7.3 (6.1, 8.7)	7.4 (6.2, 8.8)	260	4.2 (3.8, 4.8)	7.2 (6.4, 8.1)	
Unknown	13	0.8 (0.5, 1.4)	n/a	2564	41.7 (40.4, 42.0)	n/a	
US Census Region							<.001
Northeast	201	13.0 (11.4, 14.8)	13.4 (11.7, 15.2)	921	15.0 (14.1, 15.9)	15.0 (14.1, 15.9)	
Midwest	460	29.7 (27.5, 32.0)	**30.6 (28.3, 32.9)**	1558	25.3 (24.3, 26.4)	**25.3 (24.3, 26.4)**	
South	500	32.3 (30.0, 34.7)	**33.2 (30.9, 35.6)**	1553	25.2 (24.2, 26.3)	**25.2 (24.2, 26.3)**	
West	335	21.6 (19.7, 23.8)	22.3 (20.2, 24.4)	1312	21.3 (20.3, 22.4)	21.3 (20.3, 22.4)	
Other	9	0.6 (0.0, 0.01)	**0.6 (0.3, 1.1)**	810	13.2 (12.3, 14.0)	**13.2 (12.3, 14.0)**	
Unknown	43	2.8 (2.1, 3.7)	n/a	n/a	n/a		

As a reminder, the Open-Ended Survey Module respondents are a subset of the self-enrollees. Of the self-enrollees, 25.1% (1547 of 6154) completed the Open-Ended Survey Module. There was a large amount of missing data for self-enrollees, with 41.7% (n=2,564) missing race and 12.7% (n=779) missing age. This made it somewhat difficult to compare and understand the subset of open-ended survey respondents in comparison to the overall population of self-enrollees. Survey respondents were older and more likely to be males compared to Registry self-enrollees.

This table shows the results of the analyses to better understand the quality and utility of the open-ended data for the question, "What do you think caused your ALS" (Q1) and "What do you think causes ALS in general" (Q2) for the period January 1, 2014-December 31, 2015:

	"Your ALS" (Q1) n=1548		**"ALS in General" (Q2) n=1548**		
	n	% (CI)	n	% (CI)	p-value
Contained Protected Health Information (PHI)					
Yes	10	0.6 *	0	0.0 *	*
No	1538	99.4 *	1548	100.0 *	
Blank Response					
Yes	149	9.6 (8.3, 11.2)	484	31.3 (29.0, 33.6)	<.001
No	1399	90.4 (88.8, 91.7)	1064	68.7 (66.4, 70.1)	
Exclusive "I Don't Know"[a]					
Yes	324	20.9 (19.0, 23.0)	446	28.8 (26.6, 31.1)	<.001
No	1224	79.1 (77.0, 81.0)	1102	71.2 (68.9, 73.4)	
Contained Superfluous Information[b]					
Yes	53	3.4 (2.6, 4.5)	46	3.0 (2.2, 3.9)	.475
No	1495	96.6 (95.6, 97.4)	1502	97.0 (96.1, 97.8)	
Continuation[c]					
Yes	n/a	n/a	78	5.0 (4.1, 6.3)	n/a
No	n/a	n/a	1470	95.0 (93.8, 95.9)	

	Your ALS" (Q1) n=1022[d]		**"ALS in General" (Q2) n=489[d]**		
	n	% (CI)	n	% (CI)	p-value
Type of Response					
Simple Itemized Listing	327	32.0 (29.2, 34.9)	350	71.6 (67.4, 75.4)	<.001
Substantive Stories	695	68.0 (65.1, 70.8)	139	28.4 (24.6, 32.6)	

*Not calculated
[a]Response included "I Don't Know" or some iteration of this concept
[b]Response contained information irrelevant to the question
[c]Response included information related to a thought continued from Q1 and did not answer Q2
[d]Excluded Blank, "I Don't Know," "Superfluous," "Continuations," and "You are Supposed to Tell Me (n=5)"

Interestingly and good news for ATSDR is that only 0.6% of responses to Q1 contained protected health information (PHI). Most of the time, it was someone stating their name. That information was redacted from the analyses and any write-ups of these data. There were no instances of PHI in the responses to Q2. Ms. Jordan knew that she wanted to be able to exclude blanks from the overall thematic analysis, so she coded Yes/No if there were blanks for Q1 and Q2. For Q1, about 10% of the submitted responses were blank. For Q2, upwards of one-third of the responses were blank. The demographic characteristics of those who left blank responses and those who did not were similar for Q1 and Q2. Some responses that included "I don't know" (IDK) or some iteration of that concept were coded twice. For instance, a response of "I don't know, maybe it was my work in the military" was coded twice—once for IDK and once for military. That response was retained in the analysis dataset because that is code for military. Anytime a response was exclusively IDK, it was coded "Yes." For Q1, about 21% of responses said IDK or some iteration of that concept. For Q2, that was close to 29%. Again, the demographic characteristics did not differ for those who responded IDK versus those who did not.

When coding these responses looking for any new codes that needed to be created, Ms. Jordan noted that there were some instances in which the respondent noted something that was certainly important to them, but did not really answer or address the question (e.g., superfluous). In an example from Q1, a respondent was telling what they used to do a year ago, *"…At this time last year I was running 20-25 miles a week, eating very healthy foods and was even skiing with my 6 and 8 year old boys. I have never smoked, consumed alcohol very responsibly and have been very healthy."* While this is important, it did not quite answer the question of "What do you think caused your ALS?" These were coded as superfluous and were not included in the thematic analysis for Q1. For continuation, another interesting phenomenon happened for about 6% of responses for Q2 for respondents who wanted to continue their stories. For example, a respondent from Q2 kept typing into Text Box 2 what their personal story was, *"(continued for #1) came down with various illnesses I believe due to weakened immune systems due to massive and repeated antibiotic treatments. I was also fearing a resistance to the erythromycin based upon some of my research…"* Again, this was very valid and very important. However, this response does not answer the question, "What do you think causes ALS in general?" Therefore, this part of the response was excluded from the analyses for Q2.

Exclusion of the Blanks, IDK, Superfluous left 1022 responses (66%) of the submitted surveys that could be analyzed for Q1. This was divided by itemized lists (N=327; 32%) and substantive (N=695; 68%). Exclusion of Blanks, IDK, Superfluous, and Continuation left 489 of the submitted surveys that could be analyzed for Q2. For Q2, there were 350 (71.6%) itemized listings and 130 (28.4%) substantive listings. For the 1022 responses to Q1, there were a total of 2382 coding instances using 126 codes. For 489 responses to Q2, there were a total of 938 coding instances using 146 codes. For Q1, 6 major themes emerged representing 64.4% (n=1533) of all coding instances. These 6 themes were: 1) Personal Health, 2) Occupational, 3) Military, 4) Physical Trauma, 5) Physical Activity and Exercise, and 6) Place of Residence. For Q2, 5 major themes emerged which represented 64.5% (613 of 951) of all coding instances. The following section provides a description of these 5 themes: 1) Personal Health, 2) Environmental, 3) Genetics, 4) Physical Trauma, and 5) Chemical (Not Work-Related). In the interest of time, Ms. Jordan did not do a deeper dive into all of the subcodes that were under some of these themes. Instead, she shared some of the quotes to illustrate some of the themes individuals with ALS are reporting:

Related to Personal Health

- "I believe that stress events play a factor in my diagnosis. Work (CFO for multiple small and fast growing companies) and the loss of both parents have resulted in extreme stress environments for me and how I handle those situations may be different than others who do not ultimately get ALS."
- "The first time I saw signs of ALS, was after surgery to fuse my neck. Immediately after surgery the left side of my face was drooping and my words were slurring."
- "I was treated for Lyme and it's been a downhill slide ever since."

Related to Occupation

- "I wonder if working at the World Trade Center site on 911 and for two months after that could be responsible for my contracting ALS."
- "I worked with various chemicals in the printing industry my whole life."
- "I was a plumber and worked in and around lead before pvc plastic pipe and fittings were introduced."

Related to Military

- "I am a military member and believe that this affiliation is responsible for my ALS. It may be due to my deployment to Iraq as the symptoms began 1-2 years after my return. It may also be related to the many immunizations that I have received over the years related to multiple overseas deployments."
- "In 2008 the VA listed ALS as a "service-connected" disability. The reason: Combat vets have twice the incidence of ALS (attributed to stress). I'm now on 100% VA disability. - - I would rather have my life back."
- "Serving in Vietnam with daily spraying of Agent Orange."

In conclusion, a small subset of Registry self-enrollees completed this module. Therefore, generalizing the results of the current analyses is cautioned. However, the collected data can certainly reveal useful information as described in the thematic analysis that can be used for future research endeavors. Item non-response was low for "Your ALS" (Q1) and higher for "ALS in General" (Q2). Some possible reasons for non-response include:

- Fatigue after completing Q1 resulting in not feeling compelled to answer Q2
- Could have "timed out" while typing answers and became frustrated
- Could have been more comfortable providing information about their personal risk factors, but unable or unwilling to extrapolate their personal perceived causes and risk factors to ALS in general
- May not have felt compelled to answer the second question to avoid redundancy as per conversational norms

Two-thirds of respondents reported factors related to personal health, occupation, military, physical trauma, physical activity and exercise, and place of residence as causes and risk factors for their ALS. Emergence of these 6 code groups is not surprising. Codes within each theme are present in the scientific literature and are included on the Risk Factor Survey at the Registry. Respondents rarely indicated "Interplay of Multiple Risk Factors" as the cause of their disease, but these were older data from 2014-2015. More recent literature does begin to point to epigenetics, with an eye toward a better understanding and untangling of the intersection of genetic predisposition and environmental exposures. It is certainly a possibility when looking at subsequent years of data that these sorts of things might emerge as a new sub-theme or theme in general. Novel, complex epidemiological studies are ongoing. Their findings could influence responses to the open-ended survey questions in the future.

In terms of study limitations, registry self-enrollment and survey module participation are voluntary. There is a percentage of individuals with ALS throughout the country who do not self-enroll in the Registry who are then ineligible to complete the survey modules, which can be a problem when trying to generalize these data out to the whole US population. A certain type of individuals with ALS may self-select into completing any and all of the survey modules. Some individuals with ALS may exhibit response fatigue, especially for this open-ended survey in which they are typing in or speaking their answers, which may limit or truncate their comments to the open-ended surveys questions.

In terms of recommendations and next steps based on this 2-year data analysis account, several new survey items have been developed that could be incorporated into the survey modules. Considering what responders said in their narratives and reviewing the surveys that are currently deployed, Ms. Jordan thought about what was missing from what people said and/or whether a number of responders made similar comments to consider what instrument items could be developed. Some examples include:

- ❑ Have you been told that you that you have a specific gene related to ALS? If yes, please describe.
- ❑ Did you play football or other contact sports in while in school (grade school, and/or high school and/or college)?
- ❑ Did you sustain a head injury due to playing football or another contact sport? This came up a lot but during the time period of the analysis, the survey did not have an item about head injuries from playing football.
- ❑ To your knowledge, were you exposed to Agent Orange during your military service? If yes, please describe.

A manuscript of the methods, data utility, and overall findings in is progress and should be submitted to a journal in the fall. Consideration is being given to expanded analyses with more years of data so that the analyses are more robust, allowing for additional quantitative analyses on these data in addition to the storytelling analyses. Consideration also is being given to performing more targeted analyses in order to do a deeper dive into themes. For example, this dataset had 10 additional variables. Perhaps a deeper dive can be made into what women say versus what men say or into those with a military history versus those who do not have military history.

Discussion Summary

Dr. Thakur asked what the next steps are other than collecting more data and what it would take for him to complete the Open-Ended Survey Module. For instance, he would only put down things that he found to be very unusual or that he thought already were linked to ALS to begin with. This module would not necessarily pick up on some new exposure, but even if it did, it could not be verified through this kind of methodology. For instance, someone might report using a certain type of antacid that they think might be related to their ALS. More surveys could be conducted with the people in the Registry to determine whether they used that antacid as well and perhaps without a control, it would be possible to determine whether there is some elevation in risk. However, the next step of experimental validation would be needed that could not be done on humans. He feels like there is a ceiling to this effort and wondered what the thoughts are on how to move out of the hypothesis generation and association and into studying causation.

Ms. Jordan agreed that there certainly are limitations to any type of survey research, cross-sectional studies, and qualitative research in general. They will discuss with ATSDR whether to analyze more years of data, do a deeper dive, and/or add additional contextual evidence to a quantitative survey that is being done to help investigators generate some hypotheses for conducting some other research.

Dr. Mehta added that ATSDR is always seeking to upgrade the surveys, whether it is potentially to remove one or add other surveys. Regarding causation, a case is slowly being built by ATSDR and others in terms of looking at different risk factors for potential causation. While everyone wants to build a case faster and sooner and get the results out, it is important to make sure that the results that are put out are accurate and validated.

To push on this more, Dr. Thakur recalled that Dr. Mehta gave an overview earlier in the day of some of the exposures that have been identified. One of the exposures was lead, which is known to be associated with numerous types of neurological problems. The idea that it may be associated with ALS is not surprising, but it is not clear how to translate that information into guidance for people who do not have a known risk for ALS or who carry a gene for ALS. He sees all of this great research being done, but it needs to keep moving toward patient intervention. How to do that is not obvious to him. When he sees rich work like Ms. Jordan just presented it makes him think even more about how these pieces can be put together faster.

Dr. Mehta agreed and emphasized that they are trying to solve that puzzle. Lead is a great example. Lead has been removed from gasoline, but lead is still present in older homes, paints, et cetera. While he wishes there were more data going back to previous years when lead was eliminated from gasoline to see whether the incidence of ALS was lower afterwards, those data do not exist. The premise is whether it is lead, mercury, or other sorts of metals and so forth, the case must be built to point at which guidance can be given. Plumbers are probably aware that if they work in a home where there are lead pipes, they need to take precautions. He is hoping to get to a point soon to ascertain which areas need more focus.

Having had these conversations numerous times, Dr. Goutman completely agreed that one goal is to figure out a threshold for action, what data are needed, and when to react. The systems must be in place to help with this. For instance, it is necessary to know how many people are developing ALS on a regular basis and where they are living. As much data as possible about their geographic location and occupational exposures would be extremely valuable for the efforts that have been mentioned to ensure that the sample is unbiased. Part of the challenge of the CDC/ATSDR Registry is that as fantastic a resource as it is, it still requires some voluntary initiative to go into the Registry to answer the surveys. The ability to obtain some unbiased information from everybody would be great, for which there are examples from other countries. It is interesting that the physical activity surveys are going to be removed from the Registry. However, there is a fascinating article from Sheffield on physical activity, polygenic risk, and whether those who carry C9 have an earlier age of onset than more physically active persons. Removing the physical activity survey may miss an opportunity to collect some very important data in the Registry. This comes down to what people agree is an actionable threshold, which differs between what someone might think who is looking at rigorous scientific evidence versus someone who wants to take action now. While the position on both sides is understandable, it is difficult to know what should be done before there is agreement on the actionable threshold.

Dr. Thakur pointed out that it is not just a matter of survey questions. He recalled that Dr. Goutman performed an interesting survey in which he was measuring metal exposure through teeth. The Registry does collect specimens and in some cases, those specimen data could be correlated with survey data. Speaking pragmatically, the level of evidence needed depends upon the intervention that the evidence would justify. If evidence suggests that people would need some type of surgical intervention, leave their homes, or make a dramatic change in their life, the level of evidence would need to be very high. If the level of the intervention required is relatively small, such as buying a water field or wearing a respirator when soldering a circuit board, a lower threshold of evidence might be needed and he would want to make that based on clinician-scientists who work with this every day who might say, "We don't know if this is going to work, but these are things that you can try that may have some benefit" and give a fair assessment of where the evidence is and what is required of people. That will have to evolve over time. It is the same kind of decision that clinicians make all of the time when thinking about dosage of a medication. The evidence is not perfect and everyone has to do their best. If the focus is on application to either managing or reducing risk rather than just on collecting and answering questions, it will be possible to get to the point of intervention much faster with everyone focused on the intervention component.

Dr. Goutman emphasized that it also is important to know whether they are "moving the needle." This is where registry efforts are important. He agrees that there are certain things just make sense. It is probably better not to be exposed to lead than it is to be exposed to lead, setting aside some of the survival studies based off of lead, but just in terms of a risk factor. This is where the Registry efforts pay off in terms of needing the accurate numbers. In Michigan, they are advocating at the state level to get those numbers. There is an actionable threshold in terms of the level of proof. He recalled when he and Dr. Thakur talked at a workshop a year ago, he referenced a podcast about the burden of proof needed to make actionable changes. They also need to know whether they are "moving the needle." He thinks in that framework, they could start making some suggestions that seem reasonable. However, they would want to know whether these suggestions are making a difference. It would be beneficial to know in real-time whether they are making a difference.

Dr. Thakur agreed that this is important to do, but that it also is very difficult to do that because exposures now do not lead to disease until decades later. In between, there is an aging population and hopefully much better case-finding, so there is going to be a lot of noise in the data. He would much rather be able to say that in the short-term, it looks like X has an effect on laboratory animals or in experimental conditions and therefore, the assumption can be made rather than waiting 15 years to get fuzzy signal through some population-wide measure. He did not think it would ever be possible to know in real-time whether something seems reasonable.

Assuming that ALS is a combination of some genetic predisposition and exposures, Dr. Stommel suggested that one reasonable approach would be machine learning (ML) to look at lifestyles and exposures. The biochemical pathways involved with various toxins are known, so it should be possible to look for patterns and ultimately for precision therapies that might affect several biochemical pathways.

Dr. Weisskopf agreed with Dr. Stommel and thought it would be very interesting to start looking at certain exposures and their relation to ALS, but also to look at some sort of biological markers of what is going on and what might be related to both the exposure and subsequent ALS. His suspicion is that a lot of these exposures may be tapping into some other biological pathways. Exploring common biological pathways or biological markers being affected might offer some

insight into a common mechanism on which to focus, rather than the exposure itself. If markers could be determined, they could be tracked.

Dr. Goutman added that there is dysregulated metabolism based on the fact that someone has ALS and then on top of that, moves those pathways into a more dysregulated state because of the exposure.

Dr. Factor-Litvak agreed with Drs. Goutman, Stommel, and Weisskopf. However, she emphasized that it would be very difficult to choose who to screen for disrupted metabolic pathways. Should people at higher risk for ALS be screened because they are in the "ALS family" so they may have other genetic markers, not familial ALS, which might predispose them to ALS? While the ML approach or other approaches are very important in terms of environmental-mixtures, careful thought must be given to how to apply them in general populations because ALS is still a relatively rare disease.

Dr. Siddique emphasized that the bottom line is that there is a knowledge gap in terms of sporadic ALS. As complex disorders have been dissected in psychology, neurology, and other complex diseases, it has become ominously detrimental that with genomic studies there is an issue of diminution of returns. That does not mean that there will not be an insight into the mechanism of disease, but geneticists are recognizing that there may be an issue of not only monogenic disease that was examined in the 1980s and 1990s, but also perhaps with omnigenic disease. That may be the case with many complex disorders and that is a very difficult task. A small study was conducted out of the Mayo Clinic looking at all of the counties in Minnesota, which did not find any difference in incidence of ALS in terms of exposures in specific areas or environments. The question regards whether there is omni-environmental exposure, which would be exceedingly difficult. Those who studied lead and conducted chelating studies for a very long time found occasional cases that looked like ALS who were treated and got well, just like some human immunodeficiency virus (HIV) cases. This is like déjà vu because they were not really a "smoking gun." He would say the same thing about genetics spreading ALS. If there was something that stood out like Mount Rainier, they would see it. He thinks they must think harder to determine whether other methodologies or approaches are needed to try to examine this intractable problem that has frustrated them all.

Dr. Mehta expressed hope that someday there would be a validated and accurate biomarker for ALS. An example would be myocardial infarction (MI) for which there is elevated troponin and is indicative of a heart attack.

In response to an inquiry posed regarding why in the area of artificial intelligence (AI) data were just now being analyzed 7 years later from 2014-2016, Dr. Mehta replied that AI and ML are not currently used. However, CDC/ATSDR is considering potentially using AI with the risk factor surveys in the future. CDC/ATSDR does not own the data. The data are owned by CMS and VA and CDC has robust user agreements with these agencies. The data from 2014-2015 were published previously and 2016 data were recently published. AI has not been used to assess incidence, prevalence, or mortality at this point.

Ms. Jordan added that the iteration of data that were assessed for the Open-Ended Survey Module was to perform a fact-finding mission to determine whether there was utility there. They could use AI using the code she generated to delve deeper into the data. Sometimes the first level of exploratory analyses must be done to ascertain what is possible. A good example of what AI would not pick up is when someone continues a response from Q1 to Q2. They have to

figure out how to educate the AI system on how to analyze these data. While this takes some time, perhaps the risk factor modules can use AI in the future.

Regarding a question about whether a comparison is made to the NDI only once a year and if that means that people who have died will receive notifications, Dr. Mehta indicated that if they find in the NDI that a patient has passed away, the patient is removed from the Registry so that further notifications are not sent to them. A comparison is made with the NDI 2 or more times per year. Currently, notifications go to over 10,000 patients who have consented. It is a very robust system and it certainly helps to enroll patients in clinical trials and so forth.

It was pointed out that it is known that socioeconomic and demographic groups are less likely to receive standard medical care and are less likely to show up in the administrative data. Therefore, it is not clear whether it is productive to report demographics if they are known to be heavily biased. Dr. Mehta responded that in his medical opinion as a physician, he likens this to sickle cell disease (SCD). SCD affects African Americans predominantly, but also affects Asians, Hispanics, and other groups. The data are showing that ALS affects whites more so than any other group, which is also being shown in other parts of the world. Based on the data from CMS and VA, the bulk of patients are white. There is a plan to tap into the Medicaid database, such as was done in the first reports. The Medicaid database has been updated through CMS, so the hope is to add Medicaid cases to future year that hopefully will add more diversity. First, CDC/ATSDR must gain access to that database through CMS.

Regarding a question about whether attending college really is thought to be a risk factor for ALS, Dr. Mehta replied that it is a variable to assess but he does not believe it is a risk factor in and of itself.

In response to a question about how many patients from Massachusetts data were captured in the Registry, Dr. Mehta indicated that the data are still being analyzed.

Regarding an inquiry about how many patients per year join the self-portal versus patients who are identified through VA, CMS, and NDI, Dr. Mehta indicated that 1200 to 1500 patients annually are registered in the self-portal. COVID-19 has impacted that, so it was down by about 20%. VA, CMS, and NDI would make up a much larger proportion of the patients coming in. In the most recently published report, there is a breakout of where patients came from. About 72% of patients came in through CMS, 20% came in from the portal, and the rest were VA.

In response to a question regarding how many surveys are completed each year in the Registry, Ms. Raymond indicated that over 600 demographic surveys had been completed for 2020 and the numbers dropped somewhat for each survey following the demographic survey. During non-COVID years, there were closer to 800 demographic surveys. There has been a decline of about 22% during the COVID-19 pandemic for the demographic survey to about 26% to 27% for the rest of the surveys in 2020.

Dr. Mehta emphasized that the surveys are voluntary. While they cannot make people take surveys, they do send out reminders.

Regarding a question about whether any of the presenters were aware of any initiatives to make ALS a federal reportable disease and if not, whether anyone had advice on how to start such an initiative, Dr. Mehta said that he could not speak to this being a federal employee. Reportable disease happens at the state level, typically through state legislatures.

Dr. Goutman added that in terms of their strategy, they have someone who is familiar with the laws of the State of Michigan and they had conversations with their state epidemiologist and physicians. He stressed that this probably varies from state-to-state.

Regarding a question about whether CDC/ATSDR has data on genetic on the tissue samples, the samples are genotyped and WGS is done. This is done by their colleague Dr. Bryan Traynor at the NIH. The samples for the pilot years and 2017 have been completed. Over 500 samples have been genotyped and Dr. Traynor's team is doing the WGS at this time. Once over 1000 patients are genotyped, the data will be published. What they are seeing at this point is that about 10% of the patients have familial ALS (FALS), so the 90/10 ratio is still holding in this population.

Regarding whether there are racial and ethnic demographics on the samples, Dr. Mehta indicated that a file is distributed with the samples to researchers that provides race, ethnicity, and other demographics as well.

In response to a question regarding what is being done to achieve some level of diversity in the Biorepository and whether the postmortem samples are also exclusively from white patients, Ms. Wagner indicated that race/ethnicity comes from the Registry. The Biorepository participants and samples are part of the Registry. The racial/ethnic breakdown is the same as for the Registry, which is predominantly white.

Dr. Mehta added that at this point, the proportion of patient samples coming into the Biorepository are largely white. About 50 postmortem samples have been collected. They do a pretty good job with geographical representation to ensure that they are not getting patients from just one location. There are patients from across the country. An effort is made to try to limit patients from a particular area if there are already patients or samples from that area to make sure that the samples are diverse.

Regarding a question about heavy metal exposures and whether biorepositories are collecting samples of bone and teeth since they are demonstrated to show long-term heavy metal exposure, Dr. Mehta indicated that childhood teeth certainly can have an accumulation of lead. The CDC Biorepository currently collects bone but not teeth. However, there have been discussions internally about collecting teeth. A group of subject matter experts (SMEs) from the Biorepository who were involved in the pilot phase will be reconvened to discuss this in the fall or winter who will provide more information and direction about what should be collected in the near future. Teeth could be added. Ms. Wagner indicated that that bone is collected from the spinal area.

Dr. Weisskopf explained that teeth would provide information about early childhood, while the bone would provide information about more recent years prior to excision of the bone. The spinal bone absolutely could be used to look for metals, certainly lead, though not every metal will accumulate in the bone. Metals can accumulate in all bone types, but it depends on how it will be analyzed. The surface of any bone is largely cortical bone. One approach looks only at the surface, so they are looking at the same type of thing that typically comes from tibia. Going deeper into the spinal process, all that will change is the exposure window being assessed with the approach.

Dr. Goutman added that some really nice teeth work has been done at Michigan by Dr. Claudia Figueroa-Romero, who also did some mouse work, and Dr. Manish Arora who is at Mount Sinai New York. In terms of human samples, they use a laser ablation technique. It is somewhat like rings on a tree in which they drill into the tooth and figure out up to about the early teens the exposure to metal over time. The advantage of teeth provide a sense of what the exposures were from early childhood to the early teen range.

Partner Updates

ALS Association

Neil Thakur, PhD
Chief Mission Officer
ALS Association

Dr. Thakur reviewed the priorities for the ALS Association and how those align with the priorities for the Registry, and discussed some of the efforts the ALS Association has been engaged in to support Registry recruitment and build on some of the ideas that Dr. Mehta mentioned earlier. The ALS Association is attempting to make ALS a livable disease, which means that they are interested in fundamentally transforming the experience of ALS in the short-term while continuing to find a cure. What that means is that people with ALS need to live longer and have access to treatments that work that are available to everyone. It is not just about living longer, but living better as well. Part of that is the autonomy and independence of people with ALS so that they get to live their lives the way they want, engage with the world as they want, and do whatever is most important to them whether that is being with their family, having a career, doing volunteer work, or having some sort of engagement with their community. It is also important to find ways to reduce the harms of ALS financially, physically, and emotionally for the person with ALS and their families as well.

In addition, it is important to find ways to reduce the harms of ALS in and of itself. For example, Dr. Mehta mentioned a paper that the ALS Association is working on with Ted Larson and some others about causes of death. If it turns out that many people with ALS are dying of pneumonia, there may be things that can be done to prevent or treat that pneumonia even if how to manage the ALS itself is not well-understood. Dealing with some of the consequences that also hurt people and shorten their lives, gains can still be made in the progress of fighting the disease. Another aspect of prevention is reducing the risks for people who might develop ALS or training people very early in the course of their illness to help prolong periods of functioning and slow progression, or maybe even prevent transition to a disease state where there is significant impairment.

In terms of how to get there, new treatments and cures are needed. This may mean that thought needs to be given to shifting the research portfolio being funded by the ALS Association and others to focus more on timely impact and clinical research. The treatments and care that exist must be optimized to ensure state-of-the-art care is being delivered, while continuously reassigning what the state-of-the-art is as more information is learned. Dr. Berry's presentation was an excellent example of how to keep learning and driving what is learned back into clinical care. As new treatments are identified, it is important to make sure those new treatments work in concert with existing treatments. Preventing or delaying harms associated with ALS is of major importance not only to identify potential risk factors, but also how to apply that knowledge to people so that it results in a better quality of life for them and for their families.

The ALS Association funds a lot of research across the ALS research enterprise, and is currently funding about 150 active projects and is continually bringing on new projects. The ALS research enterprise includes basic science, development of potential targets for ALS, identification of risks and causes of ALS—which is part of what the Registry is identifying, some of which might actually turn into targets for clinical intervention through the clinical pipeline of Phase I, II, and III research. Once an intervention gets into the market, clinic, and practice, another set of studies can be conducted in terms of managing (e.g., Phase IV Medication, Assistive Technology, Families and Caregivers, Access and Quality, Natural History). Between and outside of this, there are public health approaches that can be leveraged to work with the population as a whole to change the incidence of ALS and change what it is like to have the disease.[14]

As a reminder, the Registry is playing a huge role in many different aspects of the research enterprise in terms of creating connections and driving progress. The Registry work, including the risk factor surveys and the Biorepository, is facilitating work that is being done by people outside of the Registry. There are the grants of the Registry funds themselves and others in academic centers and the private sector who are using these data and specimens to drive their own work. On top of that, Registry participants are part of a pool for recruiting into other studies. In fact, the Registry supports most aspects of the ALS research pipeline.

In terms of how COVID-19 has impacted outreach and what measures have been taken, the ALS Association has had to switch to virtual events for most of its activities such as walks and the advocacy conference. The advocacy conference has been virtual for the second year in a row and walks and other events have been modified. In terms of service delivery, the ALS Association supports a network of about 90 multidisciplinary clinics around the country. Those services have been in flux with in-person versus virtual services at clinics. A lot of services have been carried out virtually over the past few months. While they have been switching back to in-person, they may switch back now that Delta is quite prevalent. There are a lot of opportunities for telemedicine and remote clinical trials. Those opportunities interfere with the ability to recruit people while they are in a waiting room for their visit at a clinic.

The ALS Association supports enrollment into the Registry through social media support in the way of Facebook posts and Registry retweets, enrollment support during in-person clinical visits when services staff mention the Registry and distribute literature, and through enrollment support during events through literature distribution and framing of the Registry at research events and through webinars. When Dr. Thakur does a webinar or research event, he usually talks about the Registry one way or another. The ALS Association recognizes the importance of the Registry in making ALS livable, driving the clinical research enterprise, and finding ways to prevent ALS and identify the risks of ALS for people who have ALS in their families. To share an example of all of this, the annual conference was switched in June 2021 to the National Virtual ALS Conference. Many people with ALS typically travel from all over the country to participate in this conference, where staff from the Registry have a booth where they talk about the Registry and sometimes collect specimens. While the conference had to be convened virtually, a special effort was made to talk about the Registry. There was a lot of discussion in several panels and sessions during that virtual conference about preventing ALS. The Registry had one of the virtual booths as well, though virtual booths have some limitations.

[14] https://www.als.org/research/research-we-fund

There is weekly Prevention Workshop with a goal to develop a framework for how identified risk factors can be turned into guidance for prevention of ALS. The Registry funded this workshop, which included experts supported by the Registry and working in this space and other government funders, including the National Institute of Environmental Health Sciences (NIEHS), DoD, NIH, VA, academic investigators, patients, patient organizations, et cetera. The topics discussed included toxin and injury risk factors, gene-environment-time interactions, and scientific and non-scientific policy approaches for ALS risk modification. This is exciting and builds off of the work that everyone who has volunteered to participate in the Registry has set the basis for.

Another opportunity that the ALS Association has is a survey called ALS FOCUS,[15] which is one of the surveys that they offer for everyone in the ALS community to understand what the ALS perspective is so that they can inject into service delivery, policy discussions, and research trial design. This is important because it is a way for the ALS Association to reach the entire ALS community in a way that they normally can only reach people who are receiving services from them directly. This survey platform uses the GUID system that the Registry has begun to develop as well, so as Dr. Mehta has been thinking about ways in which the ALS Association can contribute data more directly to the Registry, there is an opportunity to build on the ALS FOCUS platform as well. For instance, perhaps people could go on ALS FOCUS and see reminders of the status of all of the different survey modules they have completed or could complete to get that data integration between the Registry and ALS FOCUS going. Based on the GUID system, there is likely a way to do this that would protect everyone's privacy. They will work through this as Dr. Mehta receives more feedback from the OMB.

The ALS Association is in the process of a reorganization and will implement for the first time a unified data system for care and services across the entire country. One of the things they want to do is to work on GUIDs for people who are simply just receiving services and are not necessarily part of a research project. There are a lot of ethical issues and concerns to work through, but if that is possible it may even further simplify the de-identification that the Registry would have to do if the ALS Association becomes effectively a reporting entity to the Registry. This is something that they would love to do. Dr. Thakur is also very excited about working with the Registry to increase enrollment from under-represented groups. This problem was raised in conversations throughout the day and is a problem not only for the Registry, but also for the ALS community as a whole. It takes too long to diagnose people, the US health system is incredibly fragmented, and people of color and those who have lower economic resources have poor access to healthcare. Therefore, it is assumed that they are also less likely to be diagnosed as they should and that causes all sorts of access problems. The ALS Association would like to be much more aggressive in that space and the Registry wants to as well, so there is an opportunity for some important collaboration there. This also builds on some of the work that the ALS Association has been doing to reduce the time to diagnosis, with the kickoff soon of an outreach campaign to community neurologists who are not associated with multidisciplinary centers that the ALS Association and the Muscular Dystrophy Association (MDA) runs. This will offer a significant opportunity to pull more people into ALS clinics, get them diagnosed faster, get them treated sooner, and get them recruited into the Registry. Hopefully, this will result in much more representative data collection as well.

[15] https://www.als.org/research/als-focus

Muscular Dystrophy Association

Peyton Navarrete
Associate Director of Care Center Programs
Muscular Dystrophy Association

Ms. Navarrete presented on how the MDA uses the full scope of its work to improve health outcomes for individuals with ALS, their families, and the community. For 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. MDA's neuroMuscular ObserVational Research (MOVR) Data Hub™ is the first and only data hub that aggregates clinical, genetic, and patient-reported data for multiple NMDs to improve health outcomes and accelerate drug development. The MDA supports the largest network of multidisciplinary clinics providing care in more than 150 of the nation's top medical institutions.

Organizationally, the MDA serves as a convening platform across and the neuromuscular field bringing forth the intersection of research, care, support, and advocacy all 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 the MDA to support and promote breakthroughs in research across diseases. The MDA works across disease-specific boundaries because research breakthroughs in one disease can fuel the progress in others.

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 its inception, the MDA has attributed over $168 million to ALS research, including more than $18 million invested in just 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 PALS, their families, 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, MDA staff members, MDA's communication channels, community and educational events, and research and advocacy initiatives.

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

ALS Registry to ALS clinicians who then relay that information to PALS, caregivers, and families within their clinics.

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 visit interactions, focused call-out initiatives, outreach to newly diagnosed PALS, and sharing updates and information with MDA Care Center providers. The Navigating ALS Program was established earlier in the year to establish and maintain relationships with clients and families affected by ALS. These clients and families receive calls following their registration sharing pertinent information regarding MDA programming, education, opportunities for engagement, additional information about the ALS Registry, and external resources when needed. MDA's National Resource Specialists provide ALS Registry information to PALS, caregivers, and families contacting the MDS National Resource Hub for resources and information.

MDA is committed to equipping all of its staff with the knowledge and tools they need to ensure that 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 staff come on board, annual training, participation in any 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 supports progress is through its multiple channels where they directly connect with patients, providers, and research communities. This includes a combination of MDA's national and local level social media accounts, including information about the Registry on the main ALS landing page on the MDA website, and including an educational page in MDA's quarterly publication of its *Quest Magazine* publication.

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 to patient and clinician communities, incorporates educational and 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 when these are possible, 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 and continues to have a substantial impact on MDA's work. Although MDA has had to shift the way in which it delivers its mission, this has brought forth unique opportunities for MDA to reach and impact an 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. This page continues to evolve and is updated regularly. Many MDA Care Centers made the shift to telehealth amid the pandemic, which in turn has allowed many ALS patients to continue having

access to the quality care they need. Throughout this time, MDA Care Specialists have been virtually supporting MDA Care Centers' telehealth and in-person visits and continuing to share Registry information through their one-on-one interactions with PALS. Last year, MDA launched its Facebook Live Event series and has engaged medical experts to answer the questions of the community and the families that it serves. The series are all available for playback on MDA's COVID-19 landing page or MDA Facebook page.

The MDA also has successfully pivoted a number of its programs to virtual platforms, including the 2021 Annual Clinical & Scientific Conference; MDA Engage Educational Events; and a number of upcoming events, including Stream-a-Thon. Additionally, MDA 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 that therapeutic development and clinical trials are able to continue amid the pandemic. They also have joined with other patient organizations in urging Congress to protect patients through legislation. More information about these advocacy initiatives and the COVID-19 Community Survey on MDA's COVID-19 landing page at mda.org/covid19.

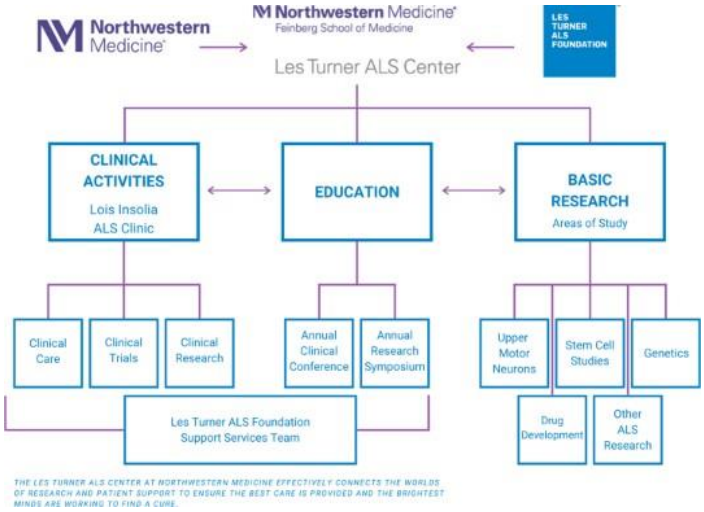
Les Turner ALS Foundation

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

Ms. Webb indicated that the Les Turner ALS Foundation is one of the longest standing independent organizations in the country serving individuals living with ALS. MDA was founded in the 1950s and Lest Turner ALS Foundation was one of two additional ALS non-profit groups. The Les Turner ALS Foundation began its journey working with individuals in the Chicagoland area. The Les Turner ALS Foundation offers a comprehensive approach to care, focuses on helping patients confidently navigate ALS, and provides research funding and support to study the treatment and prevention of ALS.

In 2020, the Les Turner ALS Foundation funded nearly $1.7 million to the Les Turner ALS Center at Northwestern Medicine, which continues to be at the forefront of ALS research and clinical care at the national and regional levels and funded 6 novel basic science pilot grants. Using a virtual platform, one-on-one personalized visits made to people and families living with ALS by the Individual Support Services Team were up by 40%. That represents very intense work that was done with patients to ensure that their needs were being met during COVID-19, so there was an increase in scope and intensity of services. PALS were able to have easier access to their doctors and providers at the Lois Insolia ALS Clinic at the Les Turner ALS Center at Northwestern Medicine, with nearly 1000 patient visits provided in 2020. It was very interesting to see some of the challenges that other clinics were encountering and various ways they were solving issues to best serve patients and to continue clinical trials. A dedicated COVID-19 webpage was launched that was dedicated to those impacted by ALS to provide information and resources. They worked very closely with pulmonologists who were helping the Support Service Coordinators to work with those who were hospitalized on their equipment. They also launched a COVID-19 emergency services grant that involved sending out checks of $250 to individuals who applied, which was a very successful program. Inspired by the need in the community, they initiated new bereavement support groups and a new online ALS Learning Series, where they host monthly webinars on such topics as ALS clinical trials and genetics and ALS.

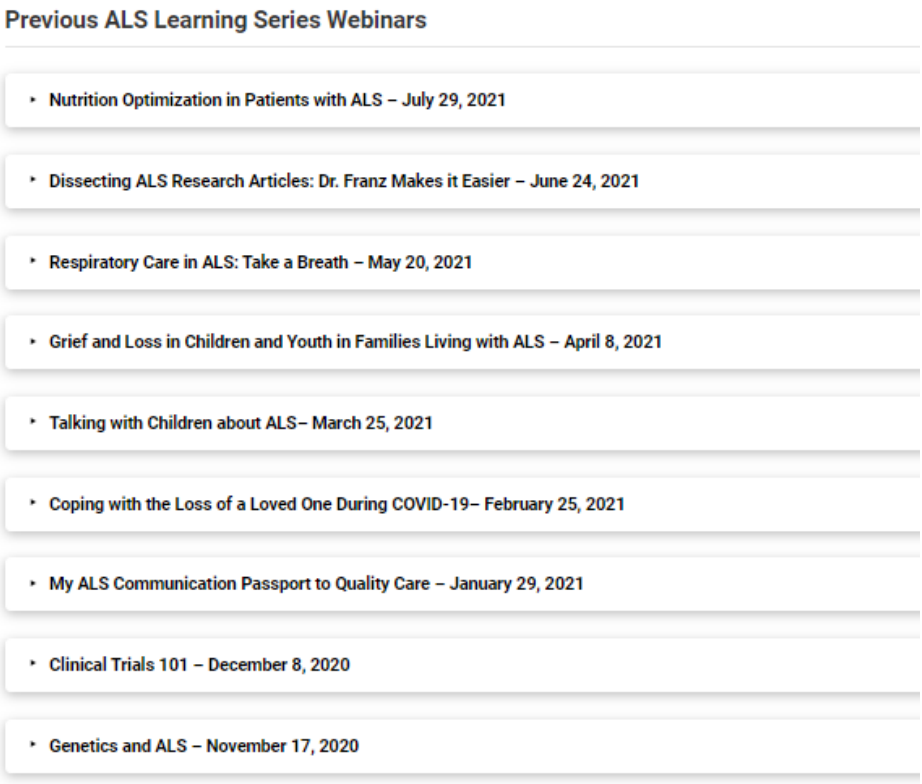
Support services for patients, families, and caregivers include care visits by ALS Support Services Coordinators, support group meetings, education materials and programs, access to medical equipment and communication devices, need-based grant programs and community resources, and in-service education for community care. Through the Lois Insolia ALS Clinic, the Les Turner ALS Center offers access to enrollment in clinical trials and dedicated clinical trial coordinators. They have Chicagoland's first and largest multidisciplinary ALS Clinic, with the highest number of neurologists and dedicated pulmonologists. The multidisciplinary care brings together an experienced team of neuromuscular specialists in one clinic to provide comprehensive support to improve quality of life and help expand life expectancy through collaboration with the patient, family members, and care providers. This graphic illustrates how all of the components work together:



The Les Turner ALS Foundation realized during COVID-19 that they needed to modify and expand its service delivery and education, so they launched the ALS Learning Series and changed how services are delivered. This did have a negative impact on the number of Registry discussions that they recorded by 17% in 2020 versus 2019. This was primarily because other needs surpassed this effort and the normal flow of how they talk to patients changed. They shifted from walking in with some ALS Registry materials and talking to people in the clinic and having a very prescribed way of doing things to addressing current and real issues to which people needed answers, because many people were very scared. There was an increase in the number of support groups and new ways were developed for engaging and talking about the Registry through various virtual programs.

The Les Turner Foundation hosted the first-ever 2021 Chicago Virtual NEALS ALS Clinical Research Learning Institute (CRLI), which was a great success. This was attended by 24 patients, caregivers, and surviving family members who joined for the annual two-day program. Now, all attendees are certified as ALS Research Ambassadors, which provides them the opportunity to influence and improve the ALS research process in the future. Ms. Webb emphasized that she left that training in awe of the amount of emergency, strength, and creativity that Research Ambassadors have and what they bring to the whole community.

The Les Turner ALS Foundation's online ALS Learning Series is aimed at empowering its ALS community through the latest information and insights. Educational webinars and interactive Q&A's covering a diverse array of topics, from telemedicine to respiratory care, are hosted monthly by the Foundation's Support Services team and clinicians from the Lois Insolia ALS Clinic at Northwestern Medicine. The ALS Learning Series also includes blog posts and articles on ALS research, clinical trials, and caregiver support. Some of the topics covered during the ALS Learning Series Webinars have included the following:



This program will continue, with more opportunities to be engaged in learning about different topics within the ALS community. This has been a very important way to engage with the local community, as well as increasingly more people outside the Les Turner ALS Foundation's traditional service area.

The MY ALS™ DECISION TOOL will soon be launched. This is an interactive tool to simplify complex medical decisions; gauge a patient's understanding of options to accept or decline treatment; clarify patient preferences and values related to their care; facilitate conversations between patients, families, and multidisciplinary care teams; and address health inequities by using best practices for health literacy. For instance, this tool can help people make decisions about whether they want to have a feeding tube or non-invasive ventilation. These are two very important interventions that are at the disposal for clinicians to use, but these are underutilized tools in terms of people not having an opportunity for people to learn more about respiratory and nutrition needs before they occur. This is a nice way for patients to engage that walks them through various options. This gets at the heart of starting to address inequities and best practices in terms of health literacy.

The Les Turner ALS Center at Northwestern Medicine will host the 11th Annual Les Turner Symposium on ALS during which Dr. Robert Brown will serve as the Keynote speaker. The annual symposium features presentations from leading ALS clinicians and researchers, including members of the Lois Insolia ALS Clinic at the Les Turner ALS Center at Northwestern Medicine.

The Les Turner ALS Foundation's National ALS Registry promotional efforts 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 and Twitter

The Les Turner ALS Foundation has a dedicated National ALS Registry Associate, Cara Gallagher, MA, LCPC, who works very closely with patients at clinic to help them with enrollment. People really like this, particularly because some families do not have access or understand technology. Enrollment in the Registry is time-consuming and sometimes the number of modules can be overwhelming. Some of the feedback Ms. Gallagher has collected over the years from patients is that they are hoping to make a difference, they would like to gain more information about new treatments, they are looking to participate in trial studies, and/or that the surveys made them think of their lifestyle choices and potential causes of disease. Biorepository feedback from PALS reflected that they felt that registration is easy, the paperwork requirements are manageable for caregivers, tissue donation provides a sense of personal contribution to future ALS research, and disappointment that post-mortem tissue donation is no longer available. Every time that the Les Turner ALS Foundation engages with industry, they inform them that the National ALS Registry is a tool for them to assist with future recruitment of patients into clinical trials and studies. In addition, they launched a landing page on the Les Turner ALS Foundation that lists clinical trials and studies.[16]

The Les Turner ALS Foundation's 20th Anniversary ALS Walk for Life will take place at Soldier Field, where the ALS Registry will be promoted. Plans are currently underway to ensure that the walk is safe. They know that families have been missing this wonderful opportunity to engage with each other, and this is a great place to talk about the ALS Registry.

In terms of key initiatives going forward, more emphasis will be placed on the "concierge approach" as they realize that the way to continue the conversation and increase engagement with families, they must be very deliberate with that. They saw the impact with COVID-19 and the need to continue to do that. The Les Turner ALS Foundation has a heavy focus with individuals on completion of surveys. They also continue to utilize the Les Turner ALS Foundation website as a "virtual tool" for families to learn more about the National ALS Registry. In addition, they look forward to collaborating with the Registry to improve case-ascertainment. They know the importance of the missing cases and taking a proactive approach. In closing, Ms.

[16] lesturnerals.org/clinical-trials-studies

Webb thanked all of the patients who have participated in the Registry, all of their caregivers for their tireless work, and all of the ALS researchers for participating.

Registry Communications & Outreach Initiatives

Francie Killebrew & Shona Wilson
Brunet-Garcia Advertising, Inc.

Ms. Killebrew indicated that Brunet-Garcia Advertising, Inc. has been contracted with ATSDR to work with the Registry for over 5 years to support all communications and outreach efforts to increase awareness of and enrollment in the Registry. At the beginning of each fiscal year, there is an assessment of all of the outreach efforts on which the Registry is working to ascertain what is working well and what could be adjusted, updated, and/or improved. Last year at this time, a considerable focus was on COVID-19. The objectives were to increase awareness and engagement in the Registry, focus on under-enrolled populations, increase the online presence, and coordinate with partner efforts.

In terms of highlights and accomplishments during July 2020 – July 2021, Brunet-Garcia researched impactful messaging and used it with consistent branding across resources. Messaging and branding includes testimonial quotes, social media, and digital tools. There has been confusion over the years regarding the various registries, so they tried to create a visual look and feel that people would recognize specifically as the National ALS Registry. The online presence includes virtual conferences, CDC/ATSDR feature articles, newsletters, and social media. With COVID-19, a virtual presence has been key.

Ms. Wilson reviewed the various tactics used over the past year for the online focus. Due to COVID-19's impact over the last year and previous year, a lot of in-person events had to shift to virtual platforms. One of the projects was working on collateral that fits on the small screen. The Registry itself had many events, but Brunet-Garcia specifically created content for these. Typically, 2 CDC/ATSDR feature articles are developed annually—one for National ALS Awareness Month in May and another in October for the anniversary of the Registry. Upcoming will be the 11th anniversary. These are featured on the CDC website, CDC social media, et cetera. This is a really great way to help disseminate information about ALS. An article titled, "Joining Together to Fight ALS" focused on different groups coming together in the fight against ALS in order to focus on everyone who is helping to contribute.

Anyone can subscribe for free to the "National ALS Registry Newsletter" though it is created specifically for PALS and researchers in mind. The newsletter includes news for patients and news for researchers. The newsletters are sent out a few times a year to share updates, new studies, patient spotlights, information about the Biorepository, et cetera. Specifically this past year, the look of the newsletter was revamped to align more closely to the new look and feel that was created for the Registry so that it is obvious that it is about the National ALS Registry and not one of the other organizations. Within the same look and feel of creating this identity for the Registry, Brunet-Garcia creates new social media every quarter that is shared with partners, across CDC social media, MDA, the ALS Association, and the Les Turner ALS Foundation. The social media focuses on different topic areas each quarter in order to be inclusive of everything that is going on within the ALS community.

An effort is made each quarter to assess the work through an evaluation of the metrics to ascertain which type of content performs best and to ask partners what type of content they would like to see. Using this input, new content is created every quarter. Once example of an observance on which Brunet-Garcia worked was the introduction of Lou Gehrig Day on June 2, which they knew would be a good way to gain a lot of reach and to reach a lot of people. They created different social media that they shared with partners, CDC, twitter, Instagram, et cetera in order to continue to address new observances as they arise.

Ms. Killebrew added that they leveraged Lou Gehrig observances in multiple ways over the past years, not just through social media. Matte articles represent another example, which the Registry has done over the years as a way to reach under-enrolled populations such as those in more rural areas. Matte articles largely go into print and traditional outlets. In addition, Brunet-Garcia has been working on some new infographics that are still in development. Infographics can be used in a variety of places, including in print materials. A folder is in development to hold print materials and that includes spaces where patients can keep track of their username and email, risk factor surveys, et cetera. What is printed on the folder will match the risk factor surveys that are available online.

Next steps are to finalize materials that are currently in development, focus on strategies that fit with changes related to the pandemic since there are less in-person opportunities, and create tools and resources that support partner efforts.

Recommendations from the 2020 Annual ALS Meeting

Reshma Punjani, MPH
Health Scientist Fellow
National ALS Registry

Ms. Punjani presented on the 2020 Annual ALS Meeting recommendations and the progress that has been made so far throughout the past year. The recommendations were divided into the categories of Communications/Outreach, Data and Reports, Surveys, and Miscellaneous.

In terms of Communications/Outreach, the first recommendation was to increase promotion/outreach efforts, including Facebook and other social media, to increase minority population representation in the Registry and Biorepository. The status of this recommendation is completed and also ongoing. Due to the pandemic and the associated challenges, ATSDR focused more on social medial outreach. They published a matte article in print media to honor Lou Gehrig. The Registry also worked with Major League Baseball (MLB) to promote the Registry via twitter. The second recommendation in this category was to represent minority groups with photos of ALS patients of all races and rotate and highlight photos on all documents, not just targeted outreach efforts. The action item to accomplish this was to add minority photos to the home page. This recommendation has been completed. The third recommendation in this category was to engage with VA researchers to discuss ALS-related Veteran affairs. To complete this ongoing recommendation, ATSDR is working with the VA more closely to discuss next steps to complete the recommendation.

The fourth recommendation in the Communications/Outreach category was to provide information/feedback to persons with ALS frequently. The two action items developed last year were to include this in newsletters that are sent out to patients, and to develop a dashboard thermometer indicating percent of completed surveys by patients. The status for this is that the first action item has been completed. ATSDR continues to send out newsletters to patients. Development of the thermometer is still underway and will be implemented when the survey is revamped. The fifth recommendation for this category was to use more appealing or eye-catching titles in the subject of emails that are sent out by the Registry. To accomplish this, there were 2 action items. The first was to simplify the email names to the National ALS Registry Message and the second was to simplify the contact email address from alssystemadmin@cdc.gov to als@cdc.gov. Both of these action items are completed and the email is ongoing. The sixth recommendation was to continue to inform physicians about the Registry so that they can share information with their patients. The action item was to work with clinic directors to educate them about the importance of the Registry. The Registry worked with their partners and ATSDR to educate not only the clinicians, but also the care service staff on the Registry so that they are able to pass that information on to patients with whom they work.

In the category of Data and Reports, there were 9 recommendations. The first recommendation was to provide annual reports in a timely manner. The two action items identified last year were to request approval from OMB for the release of limited data. ATSDR will continue to make efforts to release timely ALS prevalence reports. This recommendation is in progress and ongoing. As Dr. Mehta mentioned earlier, the OMB package has been submitted and if accepted will potentially allow the release of the state-level data. In addition, the 2016 data report was released the previous week and ATSDR is continuing to work on the 2017 data as well. The second recommendation in this category was to provide demographic data including race and ethnicity for the Registry and Biorepository. The action items in this category were to present data showing the percent in the Registry by race and ethnicity, and to continue to present demographic data breakdown in current and future manuscripts. The status of this recommendation is ongoing as ATSDR continues to publish using data from the Registry. The third recommendation was to characterize demographics for the Registry and Biorepository. This recommendation is also ongoing as ATSDR continues to provide the breakdown of the demographic data. The fourth recommendation was to use prevalence ranges instead of actual prevalence rates when presenting data. With this recommendation, the goal was to include ranges in the 2016 reports. However, this is ongoing and the plan is to include prevalence ranges in the 2017 data reports. The fifth recommendation in this category was to consider pre-releasing Registry data prior to publication reports. The action item was to share data with partners approximately 1-2 months prior to the release of the *MMWR* report. This was completed in that ATSDR was able to provide its partners with an update on the 2016 data report prior to release in the journal and also generated FAQs for the public for additional clarification on this report.

The sixth recommendation in the Data and Reports category was to use residency data along with geographic information system (GIS) data and the relationship to environmental exposures. The action item for this requires geospatial analysis and mapping of patient populations. This is an ongoing recommendation and will be continued next year as well. The seventh recommendation in this category was to have a more nuanced discussion on the limitations in publications. For this recommendation, the action item was to continue to include limitations. The status of this recommendation is completed. The eight recommendation dealt with limitations regarding the number of patients enrolled in the Registry in *MMWR* reports. This action item has been completed in that the Registry continues to include a statement in publications that there are missing cases. The ninth recommendation was to disseminate a

Progress Report on the recommendations at a 6-month mark and present the progress at the next annual meeting. The status of this recommendation is ongoing, although the Progress Report was not completed due to staff turnover. However, the plan is to provide continuous updates after this meeting.

For the category of Surveys, the first recommendation was to prioritize surveys so that the more important surveys are listed first. ATSDR was able to complete this recommendation as Survey 17 was moved up. With the new survey redesign, there will be categories that will make survey completion more user-friendly. The second recommendation was to engage persons with ALS who are not completing surveys. ATSDR was not able to engage persons with ALS directly due to OMG restrictions. However, they do continue to inform patients about the surveys through newsletters, emails, and partners. The third recommendation in this category was to analyze survey completeness to look for improvements (e.g., how many registrants are enrolled, how many surveys have been completed). The status of this recommendation is ongoing. Due to the pandemic, enrollment was impacted and therefore survey completeness was impacted as well. The fifth recommendation was to show survey completion. The action item for this recommendation was to display a thermometer on the home page to show how many surveys each patient has completed. This items is pending completion of the survey revamp, but will be included so that patients and their family members can see how many of the surveys they have completed. The fifth recommendation in this category was to compare the statistics for the under-enrolled states with the number identified through the administrative data. For this recommendation, ATSDR is continuing to provide information on under-enrolled states. The Registry sends out a monthly report on enrollment that is available to partners as well.

The first recommendation in the Miscellaneous category was to make ALS a reportable disease. However, this is not within ATSDR's mandate and is instead a state-level action. This is ongoing more from a support perspective. There are state-level efforts underway in Michigan, Vermont, New Hampshire, and Alabama. The second recommendation was to find a way to recruit from Medicaid. While this not within ATSDR's mandate, the ability to obtain and include the number of Medicaid cases in future reports is being evaluated. The third recommendation in this category was to have a webinar that steps partners and clinic staff through registration and a sample of surveys. The action items for this recommendation were to ask partners what the most frequent problems encountered by patients are with registering and taking risk factor surveys, and to develop a webinar to show how the Registry works. ATSDR continues to offer an annual webinar to the care services staff and partners. They also are looking into having this option available as a pre-recorded option on the website.

Discussion Summary

It was noted that the Environmental Protection Agency (EPA) databases for Superfund sites and the Toxics Release Inventory (TRI) Program are searchable. With that in mind, an inquiry was posed regarding why the CDC Registry is not searchable for ALS. Dr. Mehta responded that they are hoping to make some of the data available for search purposes, such as the state-level data. If OMB grants approval, the hope is to have a more useful platform that will allow users to search cases at the state-level and perhaps by region.

An inquiry was posed about why the Registry does not cross-populate with data from Superfund Sites and the TRI Program, especially for known toxins like volatile organic compounds (VOCs), benzine, hexane, and styrene. Dr. Goutman's thoughts were requested as his research creates associations with Superfund sites. Dr. Mehta indicated that Dr. Goutman had to step away from the meeting, but noted that some years ago the 2013 ALS cases were overlaid and their

distances were mapped to the clinics and found that patients typically live 50 miles or more from the closest ALS clinic across the US. There has been some discussion internally about superimposing where patients live with Superfund sites. This is a taxing process due to the need for GIS involvement.

Dr. Brooks asked whether the 20% decrease in the portal entry reported earlier in the day was observed in other CDC registries.

Dr. Mehta said that while they have not looked at other registries, they likely experienced some type of decrease if their outreach was limited. This is certainly something that they could check into.

Dr. Horton added that the World Trade Center (WTC) Health Registry is not a real-time registry like the ALS Registry. The WTC Health Registry collects data in waves from people either quarterly or twice a year. However, he has not seen any impact from COVID-19 on that or any other registry that they run. They also run a Tremolite Asbestos Registry, but that is specific to one small county in Montana so he did not know whether they would pick up any kind of COVID signal there. He agreed that it would be interested to see how COVID-19 has impacted other surveillance systems and registries.

Regarding the text analysis, Dr. Brooks asked what the overlap was between people answering Q1 and Q2 in the clinical survey and whether utilization of riluzole or whether people are married have been assessed and if there were any interesting demographic correlations between the type of information that went into the 4 major categories. He noted that several years ago in a meeting, an NIH group presented a word cloud evaluation of a clinical trial and looked at the word cloud versus the actual measurements in the clinical trial and found differences. He wondered if it would be possible to use something as simple as a word cloud to look at the ALS data.

Ms. Jordan indicated that the 10 additional variables that were pulled into that dataset did not include any variables from the clinical survey; however, a future analysis could include pulling some of that information from that risk factor survey and turning on filters to look at the open-ended questions to see if there is any correlation. They could do the same thing for marital status and other demographic characteristics. They did not delve any deeper than the 10 variables for this initial round of analyses. Use of a word cloud to analyze the data has been suggested previously, but has not been done at this point. It is interesting to depict qualitative data in different ways, so certainly they could build out a word cloud in this and future analyses.

A question was posed for the partners regarding how many unique people with ALS each organization served last year and how many of them were new patients. Dr. Thakur indicated that the ALS Association served about 20,000 people across the country. That is pretty close to a unique number, though there may be some overlap. They did make an effort to de-duplicate, but he did not know how many of those folks overlap with the Les Turner ALS Foundation or the MDA. Ms. Webb reported that the Les Turner ALS Foundation served around 350 individuals, 250 of whom receive more intensive case management. They typically have about 50 to 60 new patients each year. Ms. Navarrete reported that last year, the MDA served approximately 11,000 individuals with ALS. She did not have the number of new patients immediately available, but indicated that she would look it up and report back.

Dr. Brooks asked the partners to comment on whether they have any sense of what percentage of their case populations are military veterans.

Dr. Thakur said he could not give a comprehensive nationwide answer, but this is something that the ALS Association is building into their nationwide database. Ms. Navarrete added that the MDA has a similar scenario. This is a question they ask upon registration, but it is not a required field. It is something they would like to gather for all individuals registered with them in the future.

Ms. Webb indicated that while she did not have these data, it is a question that the Les Turner Foundation asks for screening purposes and to make sure that they are referring people to the right services with the VA.

Persons Living with ALS Perspectives on the Registry

Gwen Petersen
San Francisco, California

Ms. Petersen was diagnosed with ALS in 2018 at 32 years old. Since her diagnosis, she has participated in 35 research studies, 2 of which were with an experimental ALS therapy. Through her participation in research advocacy, she hopes to change the trajectory of ALS from terminal to treatable so that the next young woman diagnosed can go on living her life her way.

Hi there. Thanks so much, Tori. I've been up since 4:30 this morning for an early start on the West Coast. I've taken notes in spite of the lack of coffee early on. I do have a few comments. Of course, I make all of these comments and anyone on the call who is willing to jump in can. Unfortunately, I have to say I'm really underwhelmed by the output of the Registry. Throughout today, I really heard a lack of innovation really around the data, how we collect data, how we measure it. That was kind of a constant theme unfortunately. I did like Lyle's presentation and am so glad to have James Berry here. I'm confident that with those two on board, we'll continue to innovate or see more innovation. The numbers were quite startling to me. Only 1200 new patients register on the portal each year. From what I heard surveys are not really being completed. In 2019, 800 people completed Survey 1. In 2020 with the pandemic, that number dropped 20%. Then as you continue on with Survey 2, there's a 30% drop off after that. I heard that we've got some work to be done around the surveys. Also another comment/suggestion is that a lot of this information is given at clinic and these things sort of start at clinic. Have we considered signing patients up for the Registry at diagnosis? Have we also considered collecting samples right in ALS clinics? Certainly, it would be more cost-effective versus sending out a phlebotomist. Lyle had a great talk around the issue with duplication of efforts for patients. As a patient who has participated in blood draws, surveys, you name it—I've only heard about the obstacles we're up against such as studies having different study goals, it's been really hard to issue GUID. To Lyle's point, I'd love to continue conversations about what can be done. As a patient, duplication of effort is really frustrating. Also, lastly, I think we can do better on our diversity efforts and reporting on people of color who are diagnosed and living with the disease. I am a testament as a young woman diagnosed at 32 years old, no family history. I am part of a group of 35 other young women diagnosed in their 20s and 30s, so I think the data is more robust and this is no longer an old white man's disease. We certainly can do better on the diversity front. I'll pause there and if anyone has any questions or comments, I'm open.

John Robinson
Parrish, Florida

Mr. Robinson retired from the US Army in 2020 after 32 years of active service. He now sits on the Board of Trustees of the ALS Association as a person with ALS.

Thanks very much and I appreciate the opportunity to speak with everyone today because I believe in the Registry and I registered immediately upon diagnosis. I am proud to say that I filled out every survey that was available because I'm a good sharer, and also because one of my last positions in the Army was running the largest research and study program for the largest 4-Star Command in the Army and I have an appreciation for your mission. That said, having registered and having filled out every survey, I'll share a few thoughts from a patient's point of view and also somebody from the Association's point of view because I think you know we have worked tirelessly to ensure your continued funding. We are pleased that the recent HHS appropriations bill included good language and $10 million in funding. Now, of course, we wait for the Senate appropriations to do their part. But I'd like to focus a little bit on the language in that HHS bill and tell you what it means to me as a patient and as a researcher. The plan should consider ways to translate Registry findings to human applications. This is language in the bill that you'll recognize. It also speaks to timeliness and that the community can view as much Registry information as possible without, of course, compromising the privacy of the participants. That's language from the bill. I'd like to make a couple of comments on that. The first is that we want researchers to be able to leverage the information in the Registry more than they do today. What researchers have told me recently is that they will often rely on other datasets rather than the Registry, and that appears to be in part an issue of timeliness. On that score, there are a couple of things to say. I will simply use one data point to encapsulate it. The annual report's release simply must be more timely. The 2016 report that under normal circumstances should have been released in 2019 was in fact released one week ago. I'm afraid that 5 years is just too much. As a patient, 5 years is outside the window of my lifespan, so we've got to be more timely in that respect. But even if the 2016 report were to have been released on time, which would have been 2019 by your standards, I'm afraid that 3 years is simply too much yet again because the average lifespan is 2 to 5 years for an ALS patient as you know. So if it were possible to tighten up our reporting channel to release our annual report every 2 years instead of 3 and avoid further delays, I think that that would enhance researchers' faith in the data that is available. There is a comment about estimates of ALS prevalence in the HHS bill.

As I was introduced, I am a Veteran, and as I think you know, Veterans are disproportionately represented in the ALS population. I found when I filled out all of the surveys that it was informative to me to better understand that causations of my disease. Unfortunately, as you also heard, I've been in the Army for 32 years so it turns out that all of the causations that I could find in the surveys that I took in fact applied to me because after over 3 decades, you're exposed to virtually everything that it turns out are troublesome triggers for ALS patients: petroleums and lubricants, a brain injury, foreign environments, ammunition, and so forth. I'm afraid they all apply, so I'm not exactly the poster child for identifying which of these causations are applicable to me. However, on the point of prevalence, I would point out that the Registry may want to consider recent studies which indicate a greater prevalence in post-911 Veterans over Gulf War Veterans. Now again, that does not apply to me because I fought in the first Gulf War and then again in Iraq and Afghanistan in post-911 conflicts, so I've covered it all. But most Veterans who you'll encounter have not been quite that active and they can more easily be categorized as pre-Gulf War Veterans, or Gulf War Veterans, or post-911 Veterans. What the studies are telling us is that there is a greater prevalence in post-911 Veterans over even Gulf War Veterans. Having

faced the exposures in those theatres, I'm sure I can offer some ideas why and I'm happy to do so if you call on me at a future date.

Finally, I would make a point about the Biorepository. While I have contributed exhaustively to every survey, I have not participated in the Biorepository and you should understand why. In my dialogue with the Registry representatives, what I walked away with was an understanding that there was a possibility of compromise to PII in sharing with the Biorepository. Even if that likelihood is small, that was enough of a concern for me. My second impression having discussed the Biorepository with the CDC representatives was that the Biorepository activities have been farmed out to a subcontractor and were not handled directly by CDC personnel themselves. As a fellow government employee, I always have concerns if I know some activities have been farmed out to contractors. It doesn't mean necessarily they are less safe or handled less well, but I am aware of the activities that are not directly under a government umbrella. For those reasons, I opted not to participate in the Biorepository. But frankly, it is my preference to participate in the Biorepository, so I would appreciate if those concerns could be addressed—not here and now, thank you Paul—I would like to be respectful of my good friend Troy's time and give him a chance to talk, but perhaps afterward. I'll leave it at that, but I appreciate the opportunity to share. Thank you.

Troy Fields
Tampa, Florida

Mr. Fields is 57-years-old and is a husband, father of 4, and grandfather to 3 wonderful children. He was diagnosed with ALS in June 2018 and has served on the Board of Trustees of the ALS Association's Florida Chapter for the last 2.5 years, currently serving as its Treasurer.

Thanks everybody for the opportunity to address this group. As John mentioned, I've been involved in some of the advocacy efforts and we are very proud of what those efforts have contributed in terms of securing funding for the ALS Registry. The reason I do the advocacy work is because I believe in the benefits that it serves to the ALS community in general. In addition to what has been said before, I have different areas of concerns and improvements to address in terms of the Registry. I want to focus on a different side because it's probably where my background comes in working in a technology company 26 years prior to having to walk away because of my ALS diagnosis. I look at myself not just as a patient, but perhaps a consumer of the services. My interaction with the Registry has been interesting, I guess. The effort to get on board, capture the information, and go through that took a bit. Perhaps it's just because of where we were. We happened to have at the Advocacy Conference of the ALS Association where members of the Registry were there to sign up and enroll. It could have been another issue, but the process itself seemed somewhat cumbersome. As a consumer where I spend my time, especially when I have limited time given my diagnosis, I want to be much more selective of something that perhaps might be a little bit easier for me to navigate, easier to understand, and easier for me to understand what the return is on that time. Again, I support the Registry and understand how meaningful it is to contribute to better targets or trials and provide that kind of information, but also as a consumer, you need to understand that there's others, let's call them competitors to the Registry—other entities that also do similar tasks, on a much more limited basis perhaps, but that are doing their own research, and collecting data.

I found myself as that consumer to gravitate more toward those other entities, private entities, or in some cases my ALS clinic that happens to do their own research. It's a large research institution not just in the State of Florida, but nationally, so I participate in contributing to the Biorepository, contributing to their surveys, and providing that data because it's actually what's convenient for me, not just in terms of the user interface or how I interact with this technology, but because they make it so easy while I'm in clinic to just go ahead and take care of it rather than having to go elsewhere and do it multiple times because there's different entities or do part of the work in one place and part of the work someplace else. I will admit that following those first couple of months after my first interaction with the Registry, I pretty much started giving my attention elsewhere and have not really interacted much with the Registry probably in the last 2 years following those first initial months of actually going ahead and enrolling. I guess from my background, I tend to look at those elements in terms of the competition that's out there and how easy it is to interact and how easy it is for me to understand the benefit that I get. I know previous comments, you're right, ALS patients are highly motivated, but there are multiple options for us. I don't think it's about motivation. I think it's that we're motivated to other areas where we feel, or at least have the perception, that we're getting a greater return, greater information, and that it's clear to us where our time and effort is being spent. With that, being mindful of time, I'll stop for others who have questions or comments.

Discussion Summary

Dr. Siddique emphasized that this is a terrible thing for a person as young as Ms. Petersen to have. They have a registry of young women who have disease and have some interesting preliminary findings, but they need more young female patients to join. This is based upon the principle that extreme phenotype and what would be the most likely environmental or genetic cause. Based on the demographic data from the last 40 years, young women and women per se are generally more resistant than older men to the disease. They can add to this cohort, which represents more than 20 years of effort to find young women for this research and this extremely phenotype, which is very tragic. He will request that someone send her his email.

Ms. Petersen said she would love to connect with Dr. Siddique after the meeting. As a side note, she does a lot of work for recruitment into clinical trials. She is sure she could help in getting young women to simply sign up and enter demographic data at the very least for this registry. She is happy to devote some time to this on calls.

Dr. Mehta emphasized that they always appreciate comments whether they are good, bad, or ugly. Regarding Ms. Petersen's comments on innovation, he said that they are always looking for new strategies, ways to get cases, et cetera. It is not easy, given that ALS is a non-reportable, non-notifiable disease. They estimate with what they have using the best methodology possible, which is current looking at administrative databases and the online portal. They want to bring in new data sources, which is why they are working with the ALS Association, the MDA, and the Les Turner ALS Association. They feel that by looking at external groups, they potentially could add these cases into the Registry as unique cases and increase the number of cases they have. The biggest hang-up and criticism is the number of missing cases. ATSDR has always been forthcoming in terms of cases in every single talk that he and Dr. Horton have given and in all publications. They are not trying to hide the fact that they are missing cases. He also stressed that they do a lot more than just count ALS cases. They want to fund the research looking at the risk factors for ALS to understand who gets ALS and why they get ALS. In the government, there are many silos in terms of research. CDC looks at risk factors and etiologies, NIH looks at genetics and conducts basic science research, and the DoD looks at pre-clinical research. While they are siloed, they all work with one another to consider

innovations. The NIH does CDC's genotyping and WGS. The DoD has CDC's information on samples and the samples from JHU available for researchers for their Funding Opportunity Announcements (FOAs). The Registry is always trying to improve enrollment. They enrolled about 1500 people in 2019 and 1200 in 2020. This tends to fluctuate year-by-year. They wish they could enroll everybody, but there are some IRB constraints. For instance, they cannot make anybody join or coerce them to join. Therefore, ATSDR gives people information through their partner organizations to have them join. There has been internal discussion about performing sample collections in ALS clinics. During COVID-19, a collection was done at a doctor's office. The Biorepository team contacted a doctor's office who agreed to do the collection. One problem with collections in clinics is that they each have their own IRBs to which ATSDR has to apply to for approval to draw samples. While that can be a long process, ATSDR is very open to that. It would be a great opportunity to partner with MGH on the East Coast, Northwestern or the University of Chicago in the mid-West, San Francisco on the West Coast, a clinic in Texas, another in Florida, and one in Arizona to reach many areas to do the collections. ATSDR is always open to do this, but their resources are very limited. Most of what comes into ATSDR is allocated to external researchers. He welcomed the PALS to attend the second day to hear about some of the groundbreaking science that is being done to find out what causes this disease. The Registry is always transparent. Anyone can come to them with any question they have and it will be answered. Like the United Nations (UN) or Switzerland, they will work with anybody. Dr. Mehta thanked Ms. Petersen for joining and for her comments.

Dr. Ostrow thanked Ms. Petersen for the compliment. He stressed that ALS patients in general are the most motivated patients in the world. With that in mind, he wondered why they are not completing the surveys. They should think about the "low hanging fruit" and not try to fix everything all at once. Personally he keeps coming back to the idea of the GUID, because it is not "reinventing the wheel." It already exists. CDC/ATSDR are already collaborating with JHU. If the Registry was tasked with administering a global GUID for ALS, it would be extremely helpful for researchers and linking data. It also seems like the kind of thing that instantly would increase catchment, because if doctors and patients had to go to the CDC website to get their GUID, participate in trials, and enroll in registries, that would be a way to get them to the CDC Registry and get them to complete the surveys. This would be a low-cost effort that could be very helpful.

In terms of GUIDs, Ms. Petersen indicated that a coordinator at a busy center told her that in order to give every patient a GUID, the IRB would have to be updated and the coordinator would need to call every patient to ask for their consent to be issued a GUID, and she would then have to collect their date of birth and address over the phone. This sounded cumbersome and burdensome on the already overworked coordinator. She agreed with Dr. Ostrow that ALS patients will do anything as a rule. In terms of why they do not sign up for the Registry or complete the surveys, in her case she did not find out about the Registry at clinic. She had to do her own research to find the Registry and then from there, she completed the first couple of surveys. She completed the Environmental Causation Survey and shortly after that, she completed Dartmouth's Environmental Survey. Therefore, she thinks duplication of effort is a factor. Also, the return on investment (ROI) for patients may not be clear.

Dr. Mehta indicated that California, Texas, Florida, and New York are the 4 states where ATSDR wants to do much better, because they are the 4 largest and 4 most diverse states. The goal is to work with partner organizations to increase enrollment in those 4 states, which make up a large proportion of minority patients. Just by focusing on these 4 large states, they feel that they can do a lot to increase the catchment area. In terms of Ms. Petersen's suggestion about registering people at the time of diagnosis, ALS is an emotional diagnosis and they do not want

to overwhelm the patients all at once. They tell their partners to wait until the second or third visits to the clinic to give patients the information.

Dr. Mehta thanked Mr. Robinson for his 32 years of service. To address the Biorepository, the comment regarding the compromised PII was certainly concerning. He had never heard that previously and he has been there for 8 years as the PI, so for that he apologized. They certainly will communicate to their staff and partners that this is not the case. He assured everyone that ATSDR takes patient privacy and security to the utmost to the extent that they are one of the few groups within CDC that has one of the highest ratings of security because they collect so much PII from patients. Patient information is accessible only to a few individuals. Dr. Mehta has access, but he does not even go to the database. Only 2 or 3 people within their system actually go into the database itself. He apologized if someone said something incorrect to Mr. Robinson about potential data security or release of PII. That is not the case. All Biorepository data and samples are all de-identified. A unique ID is attached to the patient themselves, which has no information such as name, date of birth, et cetera. Only a range is given of birthdate, age, and date of diagnosis. Regarding the subcontractor, ATSDR relies upon other experts who can help them do the work. These are individuals who have direct oversight from ATSDR as federal employees. Dr. Mehta assured everyone that there is direct oversight from himself and Kevin Horton, the Branch Chief. Their contractors know they "run a tight ship" and work very well with them. In terms of Veterans and ALS, he completely concurred. Dr. Weisskopf has produced a lot of research in the area of Veterans with ALS, who have twice the risk of getting ALS compared to non-Veterans though the reason is not clear. Potentially it could be an exposure they experienced during their service. ATSDR funded a new grant last year in this area. In terms of timeliness, the 2016 prevalence report was very hard for ATSDR because they assumed certain things in terms of capture-recapture to get the report out and it just did not come to fruition. They waited for the capture-recapture data to be published so that they could cite the methodology. It is a cumbersome process unfortunately, but they need to be able to state that information has been vetted and validated. 2017 and 2018 data are in-house and he assured Mr. Robinson that they would do a much better job getting out the prevalence reports in a much timelier fashion. These data do not do ATSDR any good internally. They want to make sure they are out for the public to view and comment on. In terms of Mr. Fields' comment, Dr. Mehta said he certainly could understand his hesitancy and why he wants to go to the Florida clinic, which is a great clinic. It is important to keep in mind that the Registry works with all partners across the country for clinical trials and so forth. Since Mr. Fields is likely still receiving emails from the Registry about trials for which he may be eligible, Dr. Mehta welcomed him to take the opportunity consider some of those. He stressed that as he mentioned earlier, the are there to take the good, bad, and ugly comments.

Mr. Fields indicated that Florida has several multidisciplinary clinics. He did not think anyone would argue the validity of having good data across the board. The better the data, the better the sampling, the better the results. This is one of these reasons that they spend hours on the phone talking to members of Congress to ensure that funding is made available. In fairness, perhaps his first impression could change. Even national organizations that work with pre-clinical trial data, the structure of their surveys and the user interfaces are easier. It is easier for him to use and navigate so that less of his time is spent to provide the information because it is organized in a way that is more efficient from a time standpoint, or because interactions happen while he already is dedicating time during a clinic visit. For him, that convenience is hard to ignore. He perceives on the other side the output or benefit he might get out of it. He can understand it and see how it is relevant to him in a much more direct way. He is a consumer and it is no different from other decisions make as consumers—not because there is no value in the other options, but because from a time investment and return back to him as an individual is

a lot clearer for him to understand. Perhaps this relates to explaining the value to the person who is interacting with the Registry in a way that is much clearer and feels more relevant. He can get clinical data listings from a lot of other places to see what other trials might be available. Perhaps there is an opportunity to encapsulate the message as to what exactly the benefit is that will be gained from the Registry that will not be achieved elsewhere and how that becomes much more relevant to the consumer as the means of selecting the Registry as their method of participating, entering the data, and driving through the output on the other end that comes as a result of that participation.

Dr. Mehta reminded everyone that ATSDR is seeking to revamp the existing 18 Registry surveys, which will be broken into various categories by demographics, occupation, et cetera. The goal is to make them much more user-friendly and more responsive. He certainly respects someone's decision to give their valuable data to others.

Mr. Fields expressed appreciation for Dr. Mehta remembering him from the prevention workshop.

Dr. Horton added that in a perfect world, they would not need administrative data. In a perfect world, people would go to the Registry website and enroll and they would have complete data. Since the world is not perfect, they know that they will never be able to get 100% completeness from the web portal alone. They are trying by working with the partners who can be the mouthpieces for promoting the Registry to their constituents. Given that the world is not perfect, they do have to rely on other sources of data. They would publish annual reports if possible, but they move as quickly as they receive the data from CMS and the VA. As Ms. Raymond mentioned earlier in the day, it takes a while to get these data because there is a lag on the other end. They can only move as quickly as the data are provided. Once the data are in-house, they still have to be cleaned that requires going through a series of steps. He emphasized that they are not trying to make excuses, but are trying to educate people on why it takes so long to receive the data, prepare it, analyze it, and eventually publish it. Over the next 6 months or a year, another report will be published. As mentioned earlier, there is discussion about combing 2017 and 2018 data into one report. While this has not yet been decided, progress is being made. Even though CMS is CDC/ATSDR's sister agency, that does not mean anything. To them, ATSDR is just another group. Procedures are in place to obtain data as quickly as possible, but they are reliant on other groups to get the data. If they could deploy a CDC team out to collect biospecimens in all 50 states they would, but they are a small group with about 10 to 15 people total working on the Registry and the Biorepository. Therefore, they do not have the bandwidth or capacity to go out to collect samples themselves. They have to rely on other experts such as the phlebotomists and nurses who go out to collect the samples. Otherwise, there would be no feasible ways for ATSDR to undertake this Biorepository. The concern is legitimate, but they have to rely on other groups to help them get the data and the specimens. It is all a collaborative effort, and CDC/ATSDR cannot do this alone.

Dr. Ostrow said he was interested in the responses as far as impressions for why more people are not completing the surveys and entering the data. Ms. Petersen made the point that perhaps people really do not know about it and that is just about messaging and making them aware, which is easy. However, all three of the PALS suggested that there are other similar efforts and a question of the time spent being worth it when the output is not perhaps as useful or perceived as a benefit. In some ways, that is a self-fulfilling prophecy because if the data are not being entered, that in some ways is hindering having good data to get out. If there is something about the forms that is particularly tedious, perhaps there are easy fixes to help with that. Thinking about Dr. Horton pointing out that we do not live in a perfect world, there are some countries

that would be the "perfect world" like Sweden where there is universal healthcare, and government mandated public health registries that link everybody. It made him consider a couple of things, such as whether the forms that those sorts of efforts use are different, easier, similar, et cetera. In addition, it is critically important to have the best data possible to get good estimates of incidence and prevalence. In terms of having a wealth of data about ALS and figuring things out about the disease, he wondered whether it would be possible to compare the CDC Registry to some of the countries that have much more robust catchment to ascertain whether the answers are different. Also, people have asked what can be done during an ALS clinic visit. The ALS clinic visit is a long day and there is a lot to get done, people are there a long time, and the clinic staff see a lot of patients. At some point, that becomes an issue, especially if there is a local similar effort or some other big data collection, screening for clinical trials, and PT, OT, and pulmonary. He wrings his hands somewhat about trying to do more during the clinic visits, but it certainly is something to try.

Mr. Robinson said he would like to apologize if Dr. Ostrow got the impression from his comments that he was not fully participating. He completed 100% of the surveys and quite frankly would have filled out more because he is an inquisitive person and he appreciates the hard work that goes into the research. He has heard from others that surveys may be cumbersome, but he has not spoken to anyone who said it was too hard, too long, and they had to stop. He would simply offer himself and invited anyone to call on him anytime to assist if he can be of any help that area. He has some experience in this area, he is a PALS, and he is associated with the ALS Association.

Mr. Fields said that to be completely transparent, he participates with the ALS Therapy Development Institute (ALS TDI) group for example. It is short and easy to go through to update changes in his therapy and his functional review survey. That is an output that he uses, so there is direct and relevant connection to him as an individual. It is an easy, straightforward process where he can see the relevance directly. It is a lot narrower in terms of the value that perhaps that exercise might have, but to him in terms of relevancy, it is right there. He immediately sees his score, he is updating it, and he understands their mission more clearly. It is not that it is not worthwhile, but the general public in support groups are wondering what it is they are going to get beyond a listing of clinical trials in which they might be eligible to participate. As a tangible, relevant output, that might have value. But he can get that elsewhere as well. There are different sources of that information, including his local clinic that by definition has to do some research. He drives 3.5 hours from Tampa to Jacksonville to the Mayo Clinic. It is a long day, but the research team then takes over at that point and he will stay another hour because he is already in Jacksonville for them to draw blood and whatever else they might need to do. He is there in person and they explain very clearly the purpose and benefit behind what they hope to get out of the data. He may not have that opportunity to hear that directly in terms of all of the wonderful things that the ATSDR Registry is doing, because he is not there. While he did not have specific recommendations, it was the experience.

Dr. Ostrow noted that he did hear a recommendation, which was clear and succinct messaging. It sounded like that would make a huge difference and it is easy.

Ms. Petersen added that it is not the "sexiest" interface complete with graphs, tracking one's progression, and all of that.

Ms. Webb shared with the group that she has been revising some educational materials and has had a lot of reviews with various patients, particularly ALS Research Ambassadors who have been very helpful in reviewing materials and pointed out some key and obvious things that she missed when she was revising. They gave her some very rich feedback on the design. While she did not know where ATSDR was with the mock-up phase for the surveys and with the recommendations, some of the ALS Research Ambassadors also have reviewed other things as well. This has been of tremendous benefit due to their collective knowledge of sharing what works. Something they are seeing with all of the innovations and focuses is making it relevant. Looking at all of the work the Registry is doing, the Les Turner ALS Foundation's team works very hard on completion with patients and is constantly asking whether they have completed the surveys. ATSDR is putting stylistic things in place and changing the structure as Ms. Raymond highlighted in her talk.

Dr. Mehta indicated that the surveys are still in development and he has seen part of the interface itself. Because they are still in development, there is still room for improvement.

Ms. Webb suggesting that involving this other group and having some of their input could be beneficial—not just people who are involved in the Registry and have intimate experience and knowledge. For example, something might not translate to somebody because they are so used to hearing it. Now would be a great time for them to share the mark-ups for input from patients and ambassadors.

Regarding Dr. Ostrow's question from earlier about comparing with other registries throughout the world, Dr. Horton pointed out that there are a number of European ALS registries. However, no one does what ATSDR does. No one deploys surveys like this. They do not offer online risk factor surveys. Given that ATSDR is the only one doing this, it is another great opportunity for PALS to contribute data to the Registry by completing these surveys. Unfortunately, they have heard criticism both ways. Some people say that the surveys are too long and that they do not have time to complete them, while others say that the surveys are not asking enough questions and more surveys are needed. However, ATSDR is restrained by the OMB and cannot ask 40 different surveys. There is an upper time limit that they cannot exceed, which is 90 minutes cumulative if one were to answer all of the survey at once. They can retire a survey or two, create a new survey, and get new data into the Registry. He expressed appreciation to Mr. Fields for taking the time to look around to see what other data repositories there are, but he also would request that he take a look at the purpose for each one of these. ALS TDI is a great group that focuses on precision medicine. PALS are able to contribute data and get information on precision medicine. The ATSDR Registry's purpose is not the ALS TDI's purpose. The ATSDR Registry's purpose is to examine the epidemiology of ALS around the US in terms of incidence, prevalence, mortality, and risk factors. The website contains the ALS Registry ACT that shows all of the things that Congress tasked them to do, which all involves epidemiology and risk factors. That is why they are not able to necessarily put up slick interfaces that some of the private groups have because they have not been tasked to do that. That is not to say that they could not do it down the road, but he wanted to be sure that people are clear that each platform has different purposes.

Ms. Petersen said that putting purpose aside, she still thinks they can look at others best practices and share those. She thought that was Dr. Ostrow's point, not specifically in terms of surveys. If double the amount of PALS are registered with Sweden's registry, what are they doing well?

Dr. Horton responded that he totally agreed and that they are not above or below stealing, begging, borrowing best practices from any group. If something works for another group and ATSDR can implement it in the Registry, they will. However, most of these European countries are all universal single payer countries and their healthcare systems are not fragmented like the US healthcare system. Healthcare in the US is so fragmented that it does not make it easy to get cases from different places, specifically in terms of private payer. In a perfect world, ATSDR would be getting data from all of the private payers. However, they are not going to share their data. That is why ATSDR is using administrative databases. As Dr. Mehta mentioned, they are going to try to conduct a pilot with an HMO or PPO to see if there is a possibility of getting their data. If so, that method can be used with other HMOs and PPOs. They have to start somewhere. They also are constrained by 509 compliance, which means that they have to make sure that their website is not too bright, not flickering, has an 8th grade level of text, et cetera. If they did not have all of these constraints, they would make this like the Vegas Strip and would light it up, include blinking buttons, arrows pointing here and there, and so forth. However, they cannot do that.

Dr. Siddique noted that since 1984, he has been trying to find ways of collecting information and specimens and it has been wonderful that the Biorepository came along. One has to differentiate between information that is put out by websites and the actual value of things that are being done. Sometimes in this world whether there is a lot of information, flashy websites, and so forth, it is difficult for many people to differentiate what is real and what is fluff. While he did not mean to indict anybody, he just wanted to point out that this sometimes can be difficult, especially if somebody has a disease diagnosis that is terrible and they want quick answers. Because of the nature of the world today, there is a lot to choose from and that becomes a difficult problem sometimes. There has to be some sort of endorsement, which there is from researchers across the country, about the work that ATSDR is doing. He was not saying that it cannot be improved or that they should not listen to patients—that was the reason they were there. At the same time, efforts must be made to ensure that this is truly a national repository and reporting system. All who can, should go to their Senators and ask them that this be mandatory reporting. Afterall, there are many pressure groups who have done that in other areas of health. More force and effort needs to put behind this so that ALS becomes a reportable disease entity, making ATSDR's work much easier and much more productive.

Mr. Robinson reminded everyone that the system does work. It has only been a day or two since he received his last automated message that said something along the lines of, "Because you registered with the Registry, we're making you aware of the following trial and/or study that is being conducted in location X. For further information . . ." They should take pride in the fact that the system is working. As a user, even when he receives a notification like this, regardless of whether he happens to know about it or not, in the back of his mind there is a switch that clicks to say that the system continues to work, he is remembered, and information is flowing. They should take comfort in that.

Dr. Mehta indicated that this year has been very active, with one application submitted every single month. For whatever reason, the researchers are coming to ATSDR for their efforts in clinical trials and epidemiological studies. They want to make sure that they have communication with patients so that they can inform them about upcoming studies.

Update from Actively Funded Registry Grants

Pre-Disease Biomarkers of POPs, Immune System, and ALS

Marc Weisskopf, PhD, ScD
Professor of Epidemiology
Harvard University

Dr. Weisskopf presented information on a study focused on pre-disease biomarkers of POPs, the immune system, and ALS. There are a number of POPs that are persistent in the environment and the body, hence the name. They are very long-lasting over many years. Examples include the following:

- ❑ Dieldrin
  - Insecticide widely used on corn and cotton
  - Banned in the US in 1974

- ❑ Heptachlor (epoxide is breakdown product)
  - Insect control in homes, buildings, and on food crops
  - Mostly banned in US in 1988
  - Can now only be used for fire ant control in underground power transformers

- ❑ Hexachlorobenzene (HCB)
  - Fungicide to protect the seeds of onions and sorghum, wheat, and other grains
  - Used to make fireworks, ammunition, and synthetic rubber
  - No current commercial uses, but they persist in the environment

- ❑ Polychlorinated Biphenyls (PCBs)
  - Electrical equipment
  - Thermal insulation
  - Paper products
  - Caulking
  - Largely banned or restricted but persist

- ❑ Polybrominated Diphenyl Ethers (PBDEs)
  - Flame retardants used in many products:
    - Synthetic textiles
    - Furniture
    - Electronics
  - Some still produced, as well as other similar compounds with possibly similar biological action

The issue with POPs is that they persist both in the environment and body. Once they get in the body, they are very lipophilic. The have known neurotoxic effects and effects on the immune system. There are several epidemiology studies that have implicated POPs to some degree in ALS. Essentially, all of those studies have relied on exposure assessments of how much someone was exposed to these compounds on surrogate measures (e.g., occupation, questionnaire of past use). At least one study, by Dr. Goutman, suggested getting a biomarker after disease onset for getting a much more accurate assessment of POPs exposure in a person. The limitation is that it is a marker after disease onset. Since the sample was collected

post-disease, this opens the chance that the disease itself has in some way affected that measurement. While this complicates the interpretation, interesting associations have been found with this. No studies have assessed POPs in blood prior to disease onset, which is temporally what they would want if they think it is related to the onset of the disease. That is probably because it is a hard study to conduct, but that is what they are setting out to try to do in this study.

In terms of immune dysregulation and ALS, multiple ALS genetic mutations enhance neuroinflammation (e.g., SOD1, TARDBP, OPTN, C9orf72). Transgenic models with such mutations show ALS-like features and inflammation; iinvolvement of microglia, peripheral T lymphocytes and monocytes; and increases in TNF-α and receptor pre-symptomatically and with severity. Neuroinflammation is a common pathological feature in ALS with activated CNS microglia and astroglia, proinflammatory peripheral lymphocytes, and macrophages. There has not been an assessment of inflammasome in humans prior to disease onset, so a lot of what is seen is post-disease. Again, it is unclear whether this is a reaction to the disease when assessing someone who already has ALS. The other complication is that inflammation in certain settings is good and what is desired initially, although it can become toxic after too long. The question regards exactly what role this is playing. This is part of the basis of the work that Dr. Weisskopf and colleagues are going to be doing.

Another issue with inflammation is that many typical markers in the periphery are quite variable and can change quickly. They decided to take a slightly different approach to assessing the inflammasome than may be typical in terms of measuring these types of cytokines and the like in peripheral blood. That is to take advantage of the somewhat newer understanding of extracellular vesicles (EVs). Basically, it is understood now that pretty much every cell in the body essentially will slough off from the cell little bits of plasma membrane that form a little ball that then gets sent around systematically and reach far and wide in the body. It is thought to some degree that some of this may actually be some form of signaling from one cell to another. If not, at the very least, these are little capsules coming from the parent cell that in the process of splitting off from the parent cell wind up containing elements of that parent cell. Things that are in the plasma membrane of the parent cell also can be trapped in the membrane of the EVs, which is quite useful because those markers can to some degree be used as an indicator of what parent cell a particular EV came from. One thing that can be done is to try to enrich for EVs that came from immune cells using markers like CD4, CD34, HLA-G, and others like that. Assessing those EVs specifically can give a window into the state of the parent cells, which is hugely advantageous for an epidemiologist who often cannot get source tissue in an otherwise healthy individual. The other thing is that there has been some exploration of EVs coming from the immune system cells and it has been found that there is an age-related decrease in these immune-related EVs that has been referred to as "inflammaging." They also carry mitochondria form the cells they came from, the health of which can be assessed to ascertain what the parent cell mitochondria status might have been like.

Overall for this work the hypotheses are that: 1) POPs exposure prior to disease onset increases risk of ALS and shortens survival with ALS; 2) immune and mitochondrial changes, as revealed through Evs, prior to disease onset predict ALS risk and shorter survival with ALS; and 3) POPs exposure may affect the immune system and mitochondrial functioning identified by EV-related effects, and that these effects may be meditating the effect of POPs on ALS risk and survival. The tricky part is that getting pre-disease samples cannot be done in a case-control setting, so they are working with some cohorts in Denmark and Finland that established cohorts more for cardiovascular disease (CVD) and cancer research, but these cohorts recruited many thousands of people and collected blood samples at baseline. They include:

- ❑ Danish Diet, Cancer, and Health study cohort (Danish EPIC) with 57,053 subjects 50-64 years of age recruited from 1993-1997 from Copenhagen & Aarhus who were free of cancer
- ❑ Finnish Mobile Clinic Health Examination Survey (FMC) with 62,440 subjects 15+ years of age recruited throughout Finland from 1966-1972, not all of whom provided samples
- ❑ Finnish Mobile Clinic follow-up survey (FMCF) that collect additional samples from 1973-1976
- ❑ Mini-Finland Health Survey (MFS) with 7,217 adults 30+ years of age recruited in from 1978-1980

This table provides the age and sex distribution in each cohort at baseline when the blood samples were collected, with a total of about 120,000 people:

	FMC (1968-1972)		FMCF (1973-1976)		MFS (1978-1980)		Danish EPIC (1993-1997)	
Age	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
20-29	4925	3957	2161	1991	0	0	0	0
30-39	4544	3299	2012	1826	899	957	0	0
40-49	4051	3420	2175	1806	837	789	0	0
50-59	2835	2666	1683	1779	723	862	20577	23879
60-69	1836	2104	1276	1416	516	675	6514	7534
70-79	578	859	444	647	269	476	0	0
Total	**18769**	**16305**	**9751**	**9465**	**3311**	**3864**	**27091**	**31413**

What makes this very advantageous is that both Denmark and Finland have registers that track all hospital activity, so people can be identified in these cohorts who developed ALS later through linking with these registries. They have identified 80 cases with serum identified in Finland and 144 in Denmark through 2013. Approximately 260-270 ALS cases total are expected to be identified through 2019. Then the investigators can randomly select 2 controls per case out of the original cohorts matching on variables such as age, sex, cohort, and for Finland, municipality. That random selections offers a huge advantage in terms of not worrying about who happens to participate in the study.

In terms of the methods, typical statistical analysis methods will be utilized. Conditional logistic regression will be used for ALS incidence; Cox proportional hazards for ALS survival; and linear regression framework (POPs-EVs), case-control framework (EVs-ALS), and Cox framework (EVs-ALS Survival) for EV characteristics. The EV characteristics bring up a lot of issues pertaining to mixtures, so the investigators are working with the statisticians at Harvard to handle the setting of having multiple exposures, many potential outcomes, and predictors of ALS. Plus, a variety of variables can be adjusted for based on the original cohort data that included surveys of different aspects of people's lives (e.g., age, sex, smoking, education, BMI, occupation, serum cholesterol, et cetera.

There are some issues that the investigators will be able to explore. With regard to timing of blood collection, there is a lot that can be unpacked. There will be a range of timing of blood collection such that they will be able to explore the relevance of timing with respect to disease onset and age at time of collection to assess whether any of that is relevant for any associations. They also will be able to examine differences by country and multiple exposures using high-level statistical approaches. Preliminary organochlorine pesticides include HCB, β-HCH, p,p'-DDT, p,p'-DDE, and Dieldrin. Preliminary PCBs include 118, 138, 153, and 180. There was a steady increase in concentrations PBDEs in Sweden from the early 1970s through the 1990s. The sum of PBDEs in breast milk went from 0.07 ng/g lipids in 1972 to 4.02 in 1997. Similar trends occurred in Norway and Germany. PBDE concentrations in Europe generally lower than US, but this depends on timing.

There have been not only COVID-related slowdowns for this study, but also the European Union (EU) has become much stricter about their data. Different EU countries are handling that differently. They seem to have managed most of the hurdles with Finland and are on the brink of getting those samples and data, although Dr. Weisskopf just heard that there was another recent EU regulation that might be slowing things down slightly. Denmark is much more concerned, particularly the Danish Cancer Society, so they are really struggling with them to try to deal with the legal issues of getting samples out of Denmark. That has been a major headache for Dr. Weisskopf over the past year that they are still trying resolve.

Serological Profiling of the Human Virome and ALS Risk in a Military Population

Albert Ascherio, MD, DrPH
Professor of Epidemiology
Harvard University

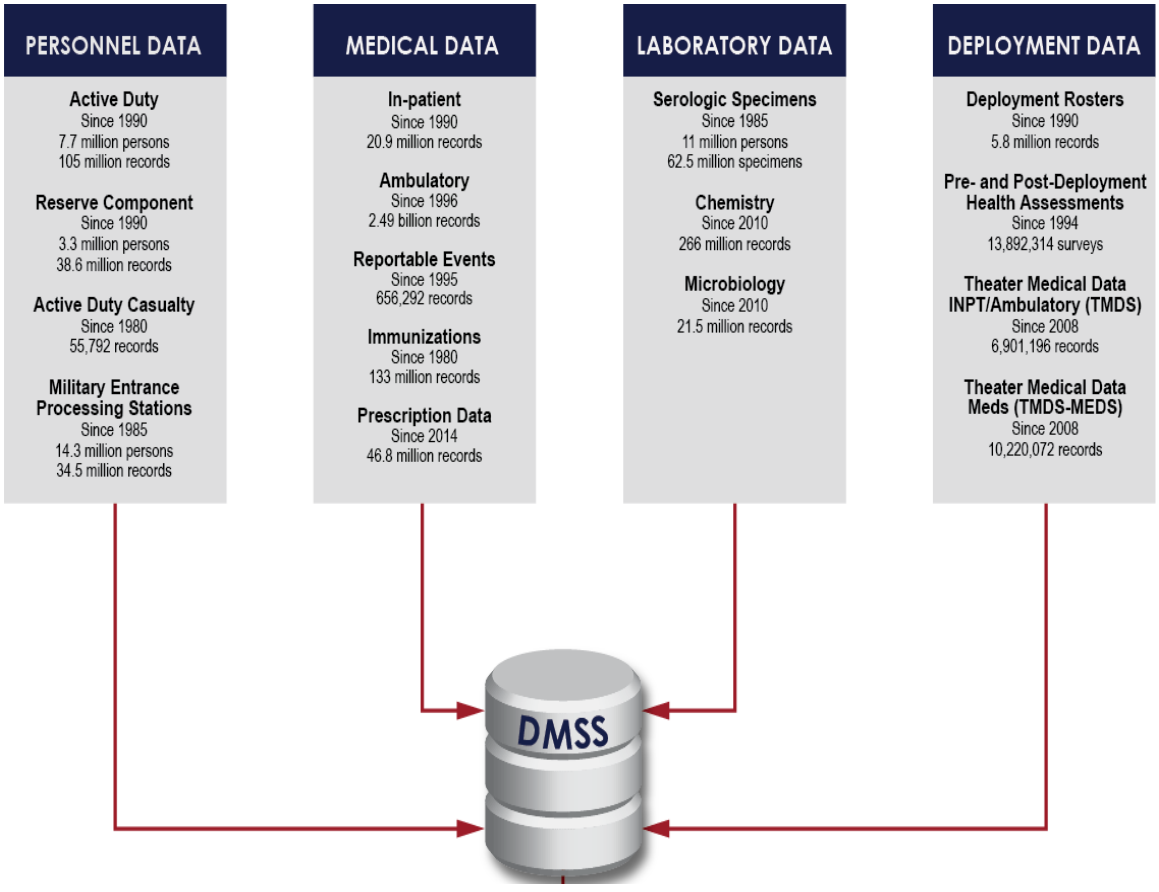
Dr. Ascherio presenting on serological profiling of the human virome and ALS risk in a military population. He noted that like Dr. Weisskopf, he is trying to identify pre-disease biomarkers. Following the same philosophy here, serum samples collected years before the person developed ALS will be examined. It is like a window to the past to look at factors that are most relevant for disease etiology. The thought is that ALS does not have many characteristics of an infectious disease. They are not thinking that the role of viruses is a trigger of acute infection that causes ALS, but rather that the level of inflammation that can create disease after several years and may be important in ALS pathogenesis.

The specific aims of this study are to: 1) assess whether enteroviruses associated with AFM (e.g., coxsackievirus B3, enterovirus A71 and enterovirus D68) contribute to predicting ALS risk; neurotropic herpesviruses (e.g., herpes simplex virus 1 and varicella zoster virus) contribute to predicting ALS risk; viral infection profile (virome) at baseline or its changes during the follow-up are associated with ALS risk; or incident viral infections are associated with increases in serum levels of neurofilament light chain (NfL); and 2) assess potential confounding by traumatic brain injury (TBI), deployment history, smoking, body mass index (BMI), diabetes, and/or family history of ALS.

This will be done relying on the DoD Serum Repository (DoDSR) that has over 50 million serum samples collected from a population of several million young men and women who served on Active Duty in the US Army, Navy, and Air Force. The unique feature of the DoDSR is that it contains repeated blood samples collected over the years. A breakdown by person-years of follow-up by branch and age strata from 1990-2019 is shown in the following table:

Age, Years	Army, n	Navy, n	Marine Corps, n	Air Force, n	Total, n
<26	6,975,170	5,105,019	3,650,605	4,271,397	20,002,192
26-30	3,229,407	2,349,052	860,244	2,396,353	8,835,057
31-35	2,350,524	1,671,655	495,586	1,690,929	6,208,693
36-40	1,790,823	1,335,919	327,744	1,486,190	4,940,675
>40	1,414,566	1,036,089	208,997	1,207,817	3,867,469
Total	15,760,490	11,497,734	5,543,176	11,052,686	43,854,086

The following diagram provides an overview of the data available in the Defense Medical Surveillance System (DMSS):[17]



[17] (Figure retrieved from: https://health.mil/Military-Health-Topics/Combat-Support/Armed-Forces-Health-Surveillance-Branch/Data-Management-and-Technical-Support/Defense-Medical-Surveillance-System on February 20, 2020)

There are a few challenges in this work. An Active Duty member is suspected to have developed ALS and has a fitness for duty medical examination through the Physical Disability Agency (PDA). Medical records are retrieved from individuals with Veteran Affairs Schedule for Rating Disabilities (VASRD) code 8017 (ALS) from PDA evaluations. Confirmation of ALS is made according to the revised El Escorial criteria by two independent reviews of the medical records, and confirmed ALS cases are included in the study. Based on this, the following table reflects the projected number of ALS cases by branch and age from 1990 to 2019:

Age, Years	Army, n	Navy, n	Marines, n	Air Force, n	Total, n
<26	14.2	8.9	6.4	7.7	37.3
26-30	10.3	6.4	2.3	6.9	25.9
31-35	6.6	4.0	1.3	4.0	15.9
36-40	10.1	6.4	1.7	7.1	25.3
>40	30.5	18.9	4.0	22.5	75.9
Total	71.7	44.6	15.6	48.2	180.2

For each ALS case, 2 controls will be selected using risk-set sampling and matching on time of blood draw. While this research team has experienced some issues with the process, they have received IRB approval and anticipate soon being able to review the medical records for the ALS cases.

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 provided an update on their CDC-funded research to identify and characterize potential environmental risk factors for ALS using ATSDR ALS Registry cases and a control population. The University of Pittsburgh was funded at the end of 2017 and was making pretty good headway until COVID-19 wreaked havoc on this project because they were using a national population-based sample of controls, which involved travel throughout the country to collect samples and complete surveys. The surveys were not as difficult, but having a stranger knock on the door to collect a blood sample for this study in the midst of COVID-19 was a challenge. Therefore, Dr. Talbott was extremely happy to report that they collected their last blood specimen on June 1st and received their last set samples back from the laboratory in July, so they are well-poised to complete the analysis.

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: 1) evaluate self-reported environmental/occupational exposure to metals, pesticides, and solvents as independent risk factors for ALS; and examine exposure to ambient air pollution (fine particulate matter [$PM_{2.5}$] and ozone) (2002-2015) and air toxics; 2) measure exposures to pesticides in samples with a battery of tests using blood concentrations of persistent environmental pollutants (pesticides) 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.

ALS case data was provided by CDC. This includes ALS Registry survey data (Demographic, Employment, Military History, Smoking, Residential History, Occupational Exposures, Home Pesticide Exposures, Hobbies) for PALS in the Biorepository Pilot (n=80) and the National Biorepository (n=200). From the ALS Biorepository, results were provided from analyses of blood specimens for organic pesticides (n=280) and genetic material were provided for further deoxyribonucleic acid (DNA) testing of cases of ALS (PITT). Controls (matched on birth year, gender, and county) were identified by Pitt researchers using databases from a sample vendor, Marketing Systems Group (MSG). Samples were drawn every 2 months from landlines and controls were interviewed using a similar survey to cases. Blood specimens were obtained and analyzed for pesticides in same laboratory as the cases. Of the 268 controls, 96% completed surveys and there are complete surveys and blood specimens for organic pesticides for 243 (87%) controls. This table provides some of the descriptive characteristics of the matched ALS cases and controls:

Characteristic	Cases (n=267)	Controls (n=267)
Male (n/%)	168 (62.9)	168 (62.9)
Age at the First Survey (mean/SD)	62.7 (9.5)	67.0 (9.0)
White race (or part white)	264 (98.9)	263 (98.9)
Education (n/%)		
Less than high school	4 (1.5)	2 (0.8)
High school diploma/GED	31 (11.6)	31 (11.6)
Some college, technical/trade school diploma	50 (18.7)	52 (19.5)
College graduate or higher	167 (62.6)	178 (66.7)
Other	15 (5.6)	4 (1.5)
Member of Armed Forces (n/%)	54 (20.2)	62 (23.2)
Deployment	16 (29.6)	16 (26.2)
Smoking status (n/%)		
Never smoker	153 (57.3)	174 (65.2)
Ever smoker (≥1 cigarettes/day for 6+ months)	114 (42.7)	93 (34.8)

While the controls were age matched by year of birth, there was a time lag between when the cases were enrolled and the controls actually were seen. Therefore, age of blood will have to be adjusted for. In addition, the investigators are beginning to look at the occupational groupings for the cases and controls for the longest jobs each held. There was a list on the PALS survey of 27 different occupational groups or sectors, so the investigators are in the process of grouping them to arrive at a general occupational grouping. They classified self-reported longest Industry work by the North American Industry Classification System (NAICS) Supersector for ALS Cases (n=267) and Controls (n=268). While they will have to examine this in a more

refined way, there are general groupings of goods-producing, service-providing, and transportation. Other data points that the investigators have are self-reported occupational and at-home exposures and lifetime prevalence of hobbies by case status. Many people have had pesticides and herbicides in and around the house, so it will be very important to correlate this as best they can with the toxicology data from the serum samples.

In terms of progress to date on the the first aim related to exposure to ambient air pollution $PM_{2.5}$ and ozone, daily estimates of ambient $PM_{2.5}$ and ozone (2002-2015) at each census tract centroid were downloaded from EPA https://www.epa.gov/hesc/rsig-related-downloadable-data-files. Average annual pollutant estimates of $PM_{2.5}$ and ozone were calculated for each Census tract using a Bayesian space-time downscale model. Air pollutant estimates for each ZCTA (zip code) were assigned using two methods: 1) calculating the nearest distance census tract centroid to each ZCTA centroid (SAS); and 2) determining the Census tract which contains the ZCTA centroid (ArcGIS). Air pollutant estimates were linked to each case/control by zip code at residence of blood draw. The next step will be to analyze the estimated exposure to ambient $PM_{2.5}$ and ozone for cases compared to controls, with adjustment for potential confounders and consideration of temporality by assigning exposures of 1, 2, and 3 years prior to the diagnosis for the cases based on the residential history. The exposure for controls will be assigned for the same exposure interval as their matched case.

Also for Aim 1, US EPA National Air Toxics Assessment (NATA) data for 2011 and 2014 were used in order to assign exposure levels based on residence at the 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 (e.g., point, nonpoint, on-road, and nonroad source groups) and monitored data, reports, models, et cetera. NATA data have been applied as an exposure estimate in research settings. Quartiles for NATA also will be modeled. Cut points for quartiles are decided by the distribution among controls. The years 2011 and 2014 were selected because this was when the Registry just got started and people were enrolling in the Registry, but they do have data going back to 2002.

In terms of the progress for Aim 2, CDC provided serum pesticide results for 280 cases. The laboratory analyses were conducted in SGS AXYS laboratories in British Columbia. Following recruitment, survey, and consent of controls, PITT scheduled an in-home blood draw by ExamOne. ExamOne did an excellent job. Blood samples were overnighted to Dr. Chris Donnelly's laboratory and forwarded in batches to SGS AXYS laboratory for 243 controls. Dr. Donnelly a Neuroscientist in the University of Pittsburgh Department of Neurobiology. This work was completed in May 2021. All final laboratory results were obtained by July 16, 2021. The investigators are currently in the process of evaluating and analyzing the results.

Regarding progress for Aim 3, laboratory analyses are being conducted by Dr. Donnelly. These analyses will be measuring the length of the C9ORF72 repeat expansion (N=45) in cases who tested positive provided by CDC. Also, being considered will be newly identified genetic polymorphisms for FALS in those individuals who reported a family history of ALS or Alzheimer's disease to the Registry and who were not positive for one of the genes tested for on the Neurochip. There are 8 newly identified polymorphisms. There is evidence of mosaicism in blood samples tested thus far. Additional DNA has been obtained for each sample because sample 4ugs are needed to repeat findings. This is now a standard amount of starting genetic material and will increase confidence in the findings.

Additional sequencing was done on 21 FALS cases. The genes that were tested included KIF5A (2018), NEK1 (2016), GLT8D1(2019), ARPP21 (2019), C21orf2 (2016), CCNF (2016), TIA1 (2018), and ANXA11 (2017). No mutations were noted in the familial samples. Whole exome sequencing (WES) was performed on the 21 FALS samples and run through Single Nucleotide Polymorphisms (SNPs) and Insertion/Deletion (InDels) variant calling data analysis pipelines. All target genes in each sample were screened for SNP and InDel mutations. Sample 20 tested positive for the NEK1 R261H mutation, 4 of the 21 samples have the rs35104895 INDEL in KIF5A, and 13 of the 21 samples have the R230C SNP in ANXA11. Both genes are already implicated in ALS, but the specific mutations are potentially novel. They will examine this further.

Over the next few months, work will be done to format and collate all of this very important information. Manuscripts in preparation or planned include the following: 1) Environmental and occupational risk factors associated with ALS: Results of Case Control Study; 2) Exposure to ambient concentrations of air pollutants and air toxics and risk of ALS; 3) The association between persistent organic pollutants in blood and ALS: Results of Case Control Study; and 4) Length of the C9ORF72 repeat expansion and newly identified mutations in ALS. A manuscript already has been published that focuses on the recruitment of population-based controls for ALS cases from the National ALS Registry.[18] In addition, there are 2 accepted abstracts[19] and 2 presented abstracts.[20]

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

Diane B. Re, PhD
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Dr. Re expressed her gratitude for the opportunity to present updates on their CDC/ATSDR funded research project. She reminded everyone that during the previous year's meeting, she described their effort with the group of Neil Schneider and Matt Harms at Columbia to develop novel mouse models of metal-gene and pesticide-gene interactions in ALS. The aims of their project are to assess: 1) measure ALS patient exposure to non-persistent organic pesticides in hair; 2) investigate CNS-derived EVs as metal exposure and ALS progression biomarkers; and 3) examine concordant transcriptional signatures/GxE ALS mouse models. It is important to uncover the signaling trigger by specific exposure and to identify early molecular markers predictive of ALS pathogenesis.

[18] Bear TM, Malek AM, Foulds A, Rager J, DePerrior SE, Vena JE, Larson TC, Mehta PD, Horton DK & Talbott EO. (2021) Recruitment of population-based controls for ALS cases from the National ALS Registry, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 22:5-6, 395-400, DOI: 10.1080/21678421.2021.1887262

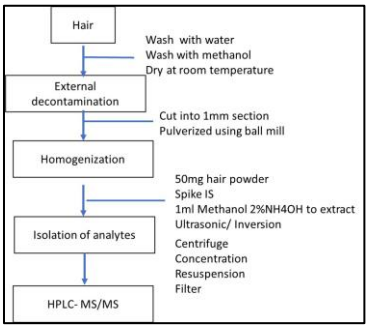
[19] Wu F, Malek AM, Rager JR, Arena VC, Buchanich JV, Vena JE, Sharma RK, Bear TM, Foulds A, Talbott EO. Long-term Effects of Air Pollution and Amyotrophic Lateral Sclerosis Risk. American College of Epidemiology (ACE) annual meeting (virtual). September 2021. (poster presentation); and Wu, Fan, Malek, Angela M, Rager, Judith R, Arena, Vincent C, Buchanich, Jeanine V, Vena, John E, Sharma, Ravi K, Bear, Todd M, Foulds, Abigail, Talbott, Evelyn O. The Relation of Exposure to Ambient Air Toxics and ALS using the EPA National Air Toxics Assessment Database: A Case-Control Study of ALS involving the National ALS Registry. International Symposium on ALS/MND virtual meeting. December 2021. (poster presentation)

[20] 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); and 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 particular, they are interested in organophosphates (OPs) and they are using hair and blood samples from the same ALS patients enrolled in the ALS Registry and Biorepository. This work is focused on non-persistent pesticides, given that occupational exposure to OPs is proposed to be linked with higher risk of ALS in farmers, Gulf War Veterans, and soccer players.[21] Few epidemiologic studies measured individual exposure all on persistent organic pollutants.[22] The choice of studying persistent neurotoxicants is obviously supported by the rationale of increased odds of environmental exposure and internal detection, but chronic or repeated exposure to non- or at least less-persistent neurotoxicants like OPs could also have a critical role in triggering ALS. Therefore, they decided to address this gap. The question regards how to reliably capture a patient's exposure.

They were inspired by a case report showing that OPs in addition to non-persistent pesticides could be detected in the hair of an ALS patient at diagnosis at least 5 months after symptom onset and at least 3 months after diagnosis.[23] They thought that hair, a biospecimen which has been investigated in only very few studies in ALS, could be of particular interest to assess OP exposure in patients. They obtained hair samples from the US National Biorepository from 180 ALS patients at 2 different time points 6 months apart in which they are measuring for non-persistent OP (dialkylphosphates) and pyrethroid (PT) metabolites (cyclopropane-carboxylic acids) by LC/MS/MS. At the start of the project, they were asked to add control hair samples in the analyses, for which they collaborated with Dartmouth-Hitchcock Medical Center that provided 83 hair samples. The 83 hair samples (age/sex matched non-neurological patients) will be tested for the same OP and PT metabolites by LC/MS/MS.

The exposure window that can be captured with the ALS Registry hair samples is mid-late life, post-diagnosis, and the 2 biospecimens that were collected 6 months apart. Each 1.25 cm (1/2 inch) of hair retraces 1 month of exposure. Of the samples, 66% capture exposure to pesticides over 1-3 months and 94% retrace less than 6 months. Thus, the two longitudinal samples have negligeable overlap. As for the Kavanouras 2011 case report, it can be assumed that the first specimen collected may represent better the pre-disease regular exposure of the subject to pesticides. The research objectives were to: 1) improve previous methods of extraction to measure OP/PT metabolites in hair (recovery rate very low and need of at least 100mg of hair); ALS registry hair samples ranged between 2 and 80 mg (median 45 mg); and 2) determine whether OP/PT metabolite levels and profiles are different between control and ALS patients. Dr. Beizhan Yan from the Lamont-Doherty Earth Observatory (LDEO) and his technician developed the following hair extraction procedure:



[21] Merwin et al., Archiv. Tox. 2017
[22] Su et al. JAMA Neurol 2016; Vinceti et al. Env. Res. 2017
[23] Kanavouras et al. Toxicol Appl Pharmacol 2011

The key point of that method development is that the major issue was the deprotonation of OPs, which formed a strong association with hair, leading to the low recovery rate. Raising pH solved the recovery rate issue. Limitations of other methods were addressed (e.g., use of only one internal standard, low relative recoveries, no data of extraction efficiency, labor intensive with derivatization for GC-MS, needed extra purification step). The remaining limitation that Dr. Yan is trying to address are that pyrethroid and TCP signals are suppressed, so new methods are being developed for PT and TCP metabolites.

In terms of preliminary results, 399 hair samples have been analyzed. DETP and Total DAP were significantly different in t1 ALS hair as compared to controls. In addition, DEP and DMTP were also close to significance at t1, but only DETP remained significant when comparing Controls to the 2 ALS time points. There are a number of ongoing and remaining analyses. The first is assessment of whether OP/PT metabolite levels different between control and ALS patients. The investigators are now running generalized estimating equation (GEE) for repeated measures and exploring if ALS status affects the efficiency of detoxification for these pesticide exposures (reduced % of detection in some groups). Second is examination of whether OP metabolite levels are associated with ALS severity using linear mixed-models and generalized additive mixed models (GAMMs). Third is the assessment of whether OP metabolite levels are associated with disease duration using linear mixed-models. Fourth is assessing exposure to mixture of OP using Bayesian Kernel Machine Regression (BKMR).

The preliminary conclusions with regard to Aim 1 are that OP metabolites measured in ALS patients' hair, especially at t1, appears promising to gain information on past and recent exposures. Overall, measured OP metabolite levels are comparable to those reported in population biomonitoring in Europe and urban areas.[24] However, they are much lower than those reported in the 2011 ALS case report. This suggests that exposure to OPs was exceptionally high for this specific patient. However, the maximum levels that were measured in some subjects were not that far off, so they will closely study this sub-group of patients.

Turning to Aim 2, to investigate CNS-derived EVs as metal exposure and ALS progression biomarkers, ALS research is hampered by lack of biomarkers of CNS toxicant exposure. Metal exposure has been linked to ALS etiology and progression, but the pathogenic role of metals remains unclear, mostly because peripheral measures rarely reflect CNS metal load. Of course, unfortunately, it is not possible to easily access the brain directly, and there are no accurate and non-invasive biomarkers of actual central nervous system, or CNS, metal burden. Only a few of the previous studies investigating the environmental origin of ALS have assessed individual biomarkers of exposure (mostly to persistent pollutants). So far, progress in this field is hampered by the lack of specific biomarkers for monitoring both environmental exposure to neurotoxicants, such as metals, and disease progression. EVs provide a novel opportunity to address these urgent research gaps.

EVs are nano-sized membrane-bound vesicles released by virtually all cell types into the extracellular space. They are often referred to as exosomes, microvesicles, or apoptotic bodies depending on their mechanism of release or size. They have been found in nearly all biofluids tested including plasma, urine, breast milk, semen, and saliva. They play roles in regulation of gene expression, activation of signaling, and distribution of catalytic activity. EVs also operate as "trash bags," allowing cells to eliminate unwanted materials. It is their role as a cellular disposal system on which this aim focuses. EVs play local and also long-distance roles. They can cross the blood-brain barrier (BBB), enter the bloodstream, and be detected in the

[24] Peng et al. 2021

periphery. As reported by several groups, EVs that originated from the brain can be isolated from peripheral blood because of their expression of different membrane surface markers of their cell type of origin, such as L1CAM for neurons and glial glutamate aspartate transporter (GLAST) for astrocytes. In terms of what the link is between EVs and metals, Cisplatin-resistant tumors extrude Pt metal via increased EV release. EVs contain many proteins involved in metal metabolism (e.g., EVpedia, Exocarta, and vesiclepedia). Perhaps CNS cells also use EV production as a mechanism of metal homeostasis.

For this study, primary astrocytes were cultured and treated with 2.5µM of either As or Mn (or vehicle – saline) for 3 or 7 days. The investigators first confirmed isolated EVs by transmission electron microscopy showing the presence of rounded vesicles ~50nm in diameter and by Western Blot showing that the EV prep was enriched in the EV markers CD9 and Flotillin-1, but not in calnexin, an endoplasmic reticulum protein not expected to be enriched in EVs. Then they assessed EV release over time. From Day 3 to Day 7, they saw an increase in EV release in astrocytes exposed to vehicle, and As (assessed by Flotillin-1 levels) (less clear here for Mn). Furthermore, they measured metals in these EVs by ICP-MS, and found that the levels of both Mn and As in treated astrocyte EVs increased over time, whereas these metals were not detected in control cells. Mn is an essential metal, so they do not release it right away until day 7 when it is too high vs As excreted right away because there is no biological reason. This pilot supported the hypothesis that CNS cells can extrude excess metals via the release of EVs.

The pilot study included 7 National ALS Registry patients for whom samples were obtained of whole blood, cortex, spinal cord. CNS EVs of neuronal (L1CAM) and astrocytic origin (GLAST) were isolated via direct immunoprecipitation (IP) method modified from Shi et al., Acta Neuropathol, 2014. Metals (e.g., As, Cu, Fe, Mn, Pb and Se) were measured by ICP-MS. At first an attempt was made to characterize GLAST and L1CAM EVs by 2-step and direct IP methods. However, it was found that direct IP was more efficient to enrich in astro and neuro markers. They also found that the L1CAM reagent more variable, less efficient, and not as specific for neurons as previously reported. Importantly, CD81 was unchanged in ALS and was confirmed as the best normalization factor for EV isolation efficiency. The final data, which will need to be confirmed with a much higher number of patients, are suggesting that GLAST-EV Mn levels may better predict spinal Mn levels than total blood Mn levels. However, it is not as clear for cortex Mn levels, which are fully predictive by both blood or GLAST EVs. GLAST-EV Cu Levels may be a better predictor of final cortex Cu levels than total blood Cu Levels.

To investigate CNS-derived EVs as ALS progression biomarkers, they are now studying 57 ALS patients at 2 timepoints 6 months apart for levels of Al, Cd, Cu, Fe, Hg, Mn, and Pb in GLAST-EV IP from blood measured by IPC-MS. Preliminary linear models indicated no association between change in metals and change in ALSFRS scores. Accurate metal detection was impeded due to high background, so samples have been re-run in optimized, metal-free conditions to improve metal detection.

Ongoing and remaining analyses for Aim 2 are to: 1) determine whether GLAST EV metal levels and profiles are different between control and ALS patients (ongoing); 2) evaluate whether GLAST EV metal levels associate with disease duration (to be started soon); 3) evaluate whether GLAST EV metal levels associate with disease progression (ongoing); and 4) assess exposure to mixture of metals (to be started soon).

In conclusion, use of CNS-EV metals and CNS-EV-miRNA as biomarkers of metal exposure will, for the first time, provide CNS-specific relevant information of exposure. Metals have been consistently linked to several neurological disorders, from neurodevelopment to late degeneration, and the findings from this study can revolutionize CNS metal exposure assessment.

Discussion Summary

In terms of methodology, Dr. Dave asked Dr. Weisskopf whether they are spinning samples down, getting the EV fraction, and then measuring concentration. He also asked whether they are able to see enough in the fractions. His sense has been that the fractions are so small compared to overall fractions that it may not be possible to see anything of relevance.

Dr. Weisskopf responded that they basically spinning it down to isolate EVs of certain sizes, but then flow cytometry can be used with markers for the surface markers to pick out ones with particular immune-related surface markers. In terms of the size of fractions, they have based this on published methods essentially doing the same thing in terms of looking at EVs of those cell types.

Dr. Feldman asked whether Dr. Weisskopf's team is looking at microvesicles, exosomes, the smallest or largest microvesicles, and from which blood cells and whether the theory pertains to where the cargo is going. She found this piece to be very interesting, but could not follow the science on it. Concerning the Scandinavian population, which she found fairly interesting, she asked what is known about their known exposures compared to the US which is agricultural and industrial and has all of the EPA data.

Dr. Weisskopf said he did not recall the exact size of the exosomes versus the EVs off the top of his head, but one of those is a subset of the other. In terms of the hypothesis behind where they think the cargo is going, release of these EVs seems to be an active process. It seems likely that there may be two types, active formation of these EVs that certainly strikes one as being related possibly to some kind of signaling mechanism. Exactly what that is remains unclear. A second possibility is probably also occurring, which is that this is not active and is kind of a "garbage dump" of the cell. At this stage, he is not necessarily caring whether it is an active signaling process or just a dumping out of the cell, because what he is trying to do is use it as an indicator of the state of the parent immune cells. It is not known at this point what the signaling corpus of these EVs is. This is a very interesting newer area of biology that it may well be doing something or allowing other parts of the body do understand the state of different organ systems, but for the purposes of this study he is more interested in what it is telling him about the cell that it came from rather than something more downstream. They have done some sampling of the Finnish and Danish populations for their levels of these POPs.

Dr. Brooks asked whether the VirSCAN gives antibody titer to poliovirus types 1, 2, and 3. Some of the older work with respect to ALS and polio is important in this respect. Earlier NIH studies looked at this as well, but there is now a huge cohort that is being immunized with polio vaccine, so it would be very interesting to know what their response to poliovirus immunization is prior to their developing the ALS.

Dr. Ascherio indicated that the VirSCAN combines DNA microarray synthesis and bacteriophage display to create a uniform, synthetic representation of peptide epitopes in the human virome. In terms of discriminating the specificity of the various downstream work, he could not answer at this point.

Dr. Ostrow noted that there has been a lot of discussion about the selective vulnerability of ALS, particularly when discussing toxic or environmental exposures in terms of what is making it cause a MND. Often the handwaving is about these being cells that are metabolically active or somehow more sensitive mitochondrial or metabolic issues, but this is somewhat known not to be true because if that was the case, then most diabetic neuropathies would be predominately motor or other metabolic or toxic issues. It is known for example that in the case of mitochondrial disorders or other metabolic cytopathies that they specifically affect the eye muscles preferentially. However, the eye muscles are spared in ALS. There is evidence that some of the OPs are acetylcholinesterase inhibitors and interfere with neuromuscular transmission. In his patients with myasthenia gravis (MG), it is their eye muscles that are preferentially involved. Given that ALS this is the part of the motor neuron system that is spared, he wondered whether anyone had any thoughts about how these toxic metabolic mitochondrial exposures are causing this disease.

Dr. Weisskopf replied that this is a bit of the "Holy Grail." The question regarding why ALS is the manifestation of exposures is very difficult to answer. His suspicion is that these exposures may be related to other neurologic diseases as well, and that perhaps these kinds of exposures are acting on some genetic background. These same questions exist in terms of Parkinson's and Alzheimer's diseases.

Dr. Feldman suggested that it has something to do with the anatomy of the peripheral nervous system. They have a lot of data in which they compared mitochondrial trafficking in sensory neurons versus motor neurons. Motor neurons are much more susceptible to toxins, while sensory neurons are much more susceptible to metabolic impairments such as glucose. It is very interesting how far the axon has to travel from the motor neuron to the neuromuscular junction. Pesticides and OPs for example could have a double-dip both at the neuromuscular junction and at the motor neuron. Therefore, she thinks anatomy plays a role.

Dr. Andrew added that if they could find models that accommodate these specialty issues and are not just a genetic factor that is affecting every cell in the body, that could get them closer to finding something that can prevent progression.

Dr. Stommel pointed out that there are inherent differences in the neuromuscular junction and the motor neurons versus other large neurons. The innovation of the types of muscle fibers that go out to the motor muscles versus skeletal muscles and limbs is quite different. He thinks acetylcholinesterase inhibitors are very important and there is a lot of literature to suggest that the neuromuscular junction is where ALS starts.

From Dr. Talbott's presentation, Dr. Nelson thought it was a very interesting finding that the R230C polymorphism of the gene that has been implicated in sarcoidosis. It triggered a memory for her that there has been interest in and observation in sarcoidosis and possible confusion of sarcoidosis and ALS clinically. She requested more information about the sarcoidosis potential link there.

Dr. Talbott said that she talked about this with Dr. Donnelly and it is fascinating, but he did not know what to make of it either. There were 21 people who reported a family history of ALS with either their mother or father. Thinking about people with a FALS history who also mentioned Alzheimer's, she wondered if perhaps this might be more of a function of the Alzheimer's history. She would be interested in hearing what people think about a possible co-occurrence with sarcoidosis.

Dr. Feldman has been seeing ALS patients and she has not noticed an association. Michigan has a fairly high incidence of sarcoidosis, but she was not aware of this association. It is not something that she has been aware of clinically or that has caught her attention clinically.

Dr. Brooks added there is a huge literature on sarcoidosis and ALS in the French and English literature. He has seen several cases of sarcoid and ALS and rituximab slows down the ALS, but they have no idea what is actually occurring. They have tried to convince companies to look at subgroups of these patients internationally. The answer is that it can occur, but what it means is another question.

Dr. Factor-Litvak pointed out that while OPs are not very persistent, repeated exposure can be considered to have long-term effects. In studies of children exposed to these pollutants, there are sex differences particularly in causation and behavior. More importantly for this discussion, there is an emerging literature that there are sex differences in motor function from either prenatal or early postnatal exposure to these compounds. She expressed interest in how the various studies are going to address the sex differences, particularly given that ALS in most cases occur in men and whether there will be sufficient power to assess this [she was fading in and out, so not certain this is entirely correct/complete].

Dr. Talbott said that she is very intrigues by male/female differences and that with only 280 cases, of which 60% are male, this is not a large sample size. Across the board, she thinks that women have different exposure patterns over their lifetime. She did not think the 18 Registry surveys have a lot of information about early life as far as childbearing history, but she agreed that this is very important. They do plan to look at the differences in men and women in their case-control study in terms of the pesticide levels.

Dr. Mehta indicated that this is included in the survey for reproductive history, but it is not expansive.

Dr. Feldman indicated that she and her colleagues recently published a paper on sex differences and the immune system in ALS, on which she is the senior author and Dr. Benjamin Murdock is the lead author and Dr. Stephen Goutman is a co-author. This is a great question and she thinks it is very important to factor in these differences.

Dr. Weisskopf indicated that they have these data, but obviously the power goes down. However, they certainly can explore it.

To briefly address what Drs. Brooks and Nelson said with regard to sarcoidosis, Dr. Siddique commented that ALS mimics are seen all of the time. The issue of selective vulnerability was addressed even older studies, including one from the Mayo Clinic. They recently published a paper with a new model for CHCHD10 showing profound pathology of the nervous system, but also the mice died of heart disease and heart failure. There is an issue of heart involvement in ALS. Perhaps there is a layer cake effect and a certain vulnerability, but the question remains regarding why people get muscle disease and ALS or other disease and ALS.

Additional Talks Presented but Not Included in This Summary

The agenda included the following talks and related discussion that were not recorded or documented in the meeting summary, given that the research was in various stages and was not ready for public presentation. Questions regarding these talks should be directed to CDC/ATSDR:

- ❑ **Update from Pharma** (Antoinette Harrison, PharmD Medical Science Director, Medical Affairs Mitsubishi Tanabe Pharma American)
- ❑ **Pesticides Applied to Crops and Amyotrophic Lateral Sclerosis Risk in the US** (Angeline S. Andrew, PhD, Associate Professor of Neurology, Geisel School of Medicine, Dartmouth College)
- ❑ **Metabolomic Signatures Linking ALS to POPs Exposures** (Stephen Goutman, MD, MS, Associate Director, ALS Center of Excellence Associate Professor of Neurology University of Michigan)
- ❑ **A Novel Innate Immunity Risk Factor for ALS** (Teepu Siddique, MD, PhD; Professor of Neurology, Cell and Developmental Biology and Pathology; Feinberg School of Medicine, Northwestern University)
- ❑ **ALS Risk in Latin Americans: A Population-Based Case-Control Comparative Study with Three European Population-Based Cohorts** (Orla Hardiman, MD; Professor of Neurology Trinity College – Dublin, Ireland)
- ❑ **Capture-Recapture Update** (Lorene Nelson, PhD; Professor, Stanford University)

Wrap-Up, Adjourn

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

Dr. Mehta indicated that ATSDR staff had been jotting down the comments for both days to capture suggestions and recommendations. He noted that the Registry is now 11 years old, so ATSDR wants to be able to make the changes that are within the bounds in which they can operate in order to make it a much better and more mature Registry. Everyone's input is very important to them and they do listen to comments, suggestions, recommendations, et cetera. He emphasized that the Registry belongs to the patients and ATSDR is the caretaker of it. He expressed gratitude to the patients who attended the meeting and shared their viewpoints. Whether they were good, bad, or ugly, the ATSDR staff are there to listen to all of the comments and certainly appreciate that. He also expressed gratitude to ATSDR's partners for their participation and support, stressing that they are the "boots-on-the-ground" who see and know the patients needs and provide care services to them. Dr. Mehta also thanked all of the researchers and institutions ATSDR funds for their participation, presentations, and great research they are doing. ATSDR is proud to have researchers as a part of the Registry and will be adding 2 more grantees in the Fall. He thanked the Registry and contract staff for their

support, along with Dr. Horton for his leadership, listening to the Registry staff, and being open to their views and ideas.

While he recognized that this Zoom format offered a very good opportunity to see and hear one another, Dr. Mehta expressed his hope that they could all be together in person for the 2022 meeting.

Discussion Points

The following final suggestions were made/emphasized:

- Rather than just seeking causes, true public health success in the past has involved looking at deficiencies such as with folic acid. With that in mind, perhaps consideration could be given to studying deficiencies.

- PALS expressed their hope that patients, caregivers, providers, and partners would reach out to their local and state representatives to educate them on the importance of why ALS should be reportable.

- The ALS community does not feel as connected to the Registry as it should, so efforts must be enhanced to better promote the Registry and to demonstrate to PALS the value it has for them such that they will be motivated to complete the surveys. This seems to be largely a function of the need for better marketing, particularly with regard to getting the point across that the Registry is not just about counting cases, but also it is critical for ascertaining risk. It will not be possible to better understand risk if they do not do a better job of helping patients understand why their personal risk factors and completing the risk factor surveys are so important.