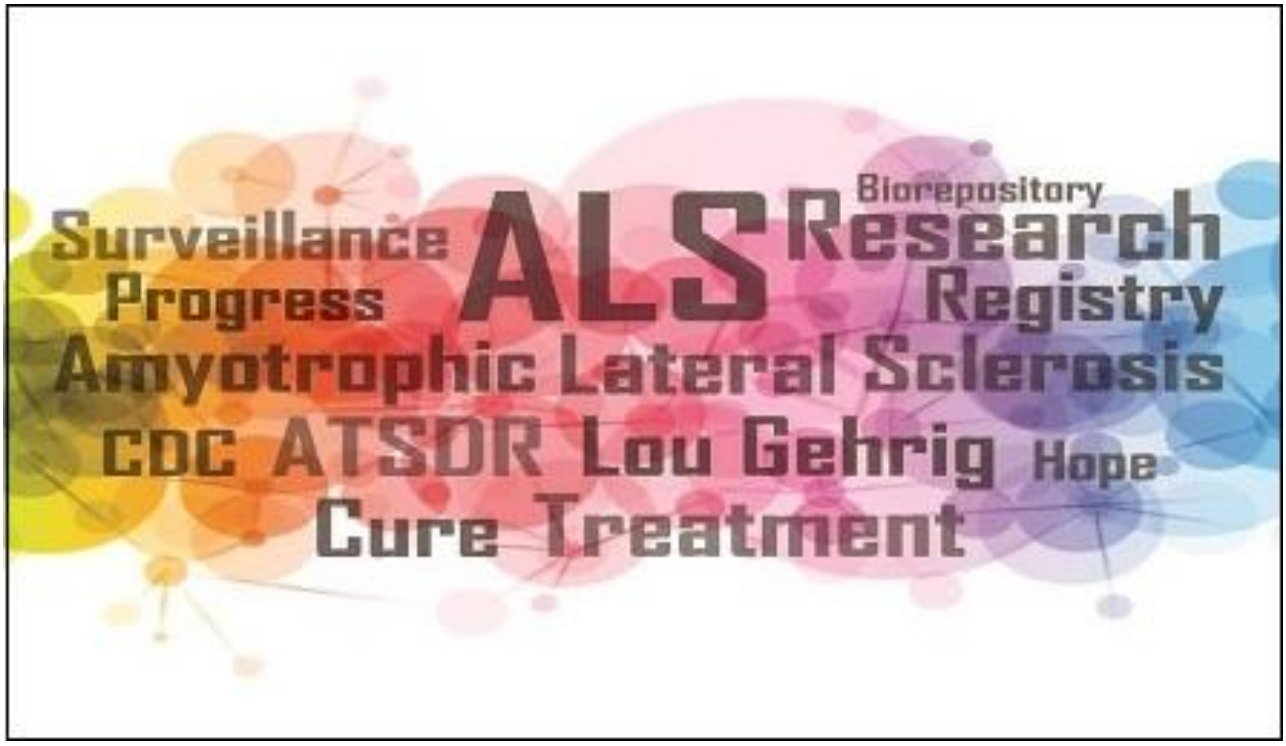
Department of Health and Human Services
Centers for Disease Control and Prevention
Agency for Toxic Substances and Disease Registry

National Amyotrophic Lateral Sclerosis (ALS) Registry Annual Research Symposium and Meeting



August 29-30, 2023
Summary Report

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Acronyms Used in this Document

Acronym	Expansion
ACS	American Cancer Society
ADI	Area Deprivation Index
ADS	Associate Director of Science
AFHSD	Armed Forces Health Surveillance Division
AFM	Acute Flaccid Myelitis
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 Dementia*
AM; A. muciniphila	*Akkermansia Muciniphila*
AOD	Aerosol Optical Depth
ASOs	Antisense Oligonucleotides
ATSDR	Agency for Toxic Substances and Disease Registry
BBB	Blood-Brain Barrier
BMAA	β-Methylamino-L-alanine
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CDMRP	Congressionally Directed Medical Research Programs
CDW	Corporate Data Warehouse
CMS	Centers for Medicare & Medicaid Services
CNS	Central Nervous System
COBRA	Consolidated Omnibus Budget Reconciliation Act
COD	Cause of Death
CPS	Cancer Prevention Study
CReATe Consortium	Clinical Research in ALS and Related Disorders for Therapeutic Development Consortium
CSF	Cerebrospinal Fluid
CT	Computerized Tomography
CVD	Cardiovascular Disease
Danish EPIC	Danish European Prospective Investigation into Cancer and Nutrition
DaVINCI	Department of Defense VA Infrastructure for Clinical Intelligence
DDT	Dichlorodiphenyltrichloroethane
DEERS	Defense Enrollment Eligibility Reporting System
DEI	Diversity, Equity, and Inclusion
DMDC	Defense Manpower Data Center
DMSS	Defense Medical Surveillance System
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DoDSR	DoD Serum Repository
DPH	Department of Public Health
DUA	Data Use Agreement
EBV	Epstein-Barr Virus
EMG	Electromyography
EMR	Electronic Medical Records
EPA	Environmental Protection Agency
ERS	Environmental Risk Score
ET	Eastern Time
EU	European Union

EV-D68	Enterovirus D68
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
GIS	Geographic Information System
GUID	Globally Unique Identifier
HBCUs	Historically Black Colleges and Universities
HHS	(Department of) Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRS	Health Retirement Study
HSV	Herpes Simplex Virus
ICD	International Classification of Diseases
IRB	Institutional Review Board
ISMMS	Icahn School of Medicine at Mount Sinai
jALS	Juvenile ALS
JEM	Job Exposure Matrix
JHU	Johns Hopkins University
KMR	Kernel Machine Regression
LAENALS	Latin American Epidemiology Network of ALS
MA ALS Registry	State of Massachusetts Department of Health ALS Registry
MD	Muscular Dystrophy
MDA	Muscular Dystrophy Association
ME	Maine
MFH	Mini-Finland Health Survey
miRNA	Micro Ribonucleic Acid
ML	Machine Learning
MLB	Major League Baseball
MMWR	*Morbidity and Mortality Weekly Report*
MND	Motor Neuron Disease
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MTA	Material Transfer Agreement
MUNIX	Motor Unit Number Index
NCEH	National Center for Environmental Health
NDI	National Death Index
NEALS	Northeast Amyotrophic Lateral Sclerosis Consortium
NFL	National Football League
NfL	Neurofilament Light Chain
NHANES	National Health and Nutrition Examination Survey
NHS	National Honor Society
NIH	National Institutes of Health
NIV	Non-Invasive Ventilation
NLMS	National Longitudinal Mortality Study
NMD	Neuromuscular Disease
NOFO	Notice of Funding Opportunity
NPS	National Park Service
OC	Organochlorine
OGS	Office of Grants Services
OMB	Office of Management and Budget
OR	Odds Ratio

ORNL	Oak Ridge National Laboratory
PA	Physician Assistant
PALS	Persons with Amyotrophic Lateral Sclerosis
Pb	Lead
PBDEs	Polybrominated Diphenyl Ethers
PBMCs	Peripheral Blood Mononuclear Cells
PCBs	Polychlorinated Biphenyls
PDA	Physical Disability Agency
PDC	Parkinson's Dementia Complex
PHI	Protected Health Information
PI	Principal Investigator
PII	Personally Identifiable Information
PIN	Personal Identification Number
POC	Point of Contact
POP	Persistent Organic Pollutant
PSA	Public Service Announcement
PUMAs	Public Use Microdata Areas
QOL	Quality of Life
RCRA	Resource Conservation and Recovery Act
RFA	Request for Funding
RN	Registered Nurse
RNA	Ribonucleic Acid
RNM	Research Notification Mechanism
RSEI	Risk-Screening Environmental Indicators
sALS	Sporadic ALS
SDOH	Social Determinants of Health
SES	Socioeconomic Status
SOD1	Superoxide Dismutase 1
SOPs	Standard Operating Procedures
TAR	Transactive Responsive
TBI	Traumatic Brain Injury
TDP-43	Transactive Responsive Deoxyribonucleic Acid (DNA)-Binding Protein 43
TRI	Toxic Release Inventory
TRI	Toxics Release Inventory
UK	United Kingdom
URM	Under-Represented Minority
US	United States
USGS	US Geological Surveys
VA	(United States Department of) Veterans Affairs
VASRD	Veteran Affairs Schedule for Rating Disabilities
VBA	Veterans Benefits Administration
VCU	Virginia Commonwealth University
VHA	Veteran Health Administration
VT	Vermont

Centers for Disease Control and Prevention (CDC)
Agency for Toxic Substances and Disease Registry (ATSDR)
2023 National Amyotrophic Lateral Sclerosis (ALS)
Annual Research Symposium and Meeting

Minutes of the Meeting
August 29-30, 2023

Welcome

Tori Bahe
Associate
Ross Strategic

Ms. Bahe called to order the first day of the 2023 National ALS Registry Annual Research Symposium and Meeting at 8:30 AM Eastern Time (ET) and welcomed and thanked everyone for attending.

Opening Remarks

Aaron Bernstein, MD, MPH
Director, National Center for Environmental Health/Agency for Toxic Substances and Disease Registry

Dr. Bernstein extended his personal welcome and thanked everyone for attending the 2023 National ALS Registry Annual Research Symposium and Meeting. He offered specific thanks to Andrea Pauls Backman, former Chief Executive Officer (CEO) of the Les Turner ALS Foundation in Chicago and someone who truly understands ALS, for moderating this year's meeting. As the relatively newly minted Director of NCEH/ATSDR, Dr. Berstein indicated that he was a native of the Northern suburbs of Chicago and attended Medical School at the University of Chicago. In some ways, he felt like being and having Andrea Pauls Backman moderate brought him right home. As a pediatrician by training and though ALS is not a common condition in children, in his work over many decades he has come to appreciate the importance of the ALS Registry and everyone's vital engagement in it. The ALS Registry is a groundbreaking effort to enable scientists from around the world to unravel the mystery of ALS. Everyone's engagement in the Registry is irreplaceable in terms of providing the insights and knowledge that will advance knowledge. Over the next couple of days, the meeting would be live-streamed and fully available to the public so that everyone could hear from ATSDR's grantees present their research work on the possible causes and risk factors for ALS and new initiatives that ATSDR has taken on over the past year. These included ATSDR's monthly listening sessions with Registry stakeholders, a new set of biosamples from the Guam population, and new ALS Biorepository clinical trials and epidemiologic studies that ATSDR has helped recruit for. There also would be opportunities to ask questions of ATSDR's ALS Team regarding ALS Registry activities. Dr. Bernstein stressed that he could not emphasize enough that the success of the ALS Registry depends on collaboration among all ALS stakeholders, including people with ALS, their caregivers, medical providers, researchers, support groups, and others. Everyone's feedback is invaluable to ATSDR, and stakeholders are an important part of the ATSDR team.

Bringing everyone together in a setting such as this annual meeting gives ATSDR insight and helps to shape the Registry in a way that makes it the best it can be for years to come. He invited everyone to convey their thoughts and comments throughout the meeting and beyond.

Andrea Pauls Backman, MBA
Moderator, Annual Research Symposium and Meeting
Founder, ALS Strategy Consulting, LLC

Ms. Pauls Backman said she was happy to know about Dr. Bernstein's Chicago connections and grateful for his leadership at ATSDR. She welcomed everyone to the 14th Annual Research Symposium and Meeting of the National ALS Registry. In terms of background, she indicated that she was a former caregiver to her mother, who lived with ALS, and a former board member of both the International Alliance of ALS/MND Association and the ALS Association and the CEO of the Les Turner ALS Foundation. She has spent the last decade advancing clinical care, clinical research, basic science research, and education in ALS, with the goal of bringing various advocacy groups together for the betterment of the community. Over this time, she has been fortunate enough to have worked with nearly every private and public ALS group in the country and several internationally. She also is involved in many ALS initiatives aligning interests to find solutions, not silos, to benefit people with ALS. In full disclosure, she indicated that she was moderating this meeting over the next 2 days as a subcontractor. She said she was pleased to welcome many new attendees to this meeting, as well as many recurring attendees. She was told that there were over 200 registrants, which is a record for this meeting. The entire 2-day meeting was being fully live-streamed and open to all, including all of the research presentations using data from the Registry.

Ms. Pauls Backman emphasized that the National ALS Registry is run by ATSDR, a sister agency to the Centers for Disease Control and Prevention (CDC), but it really belongs to the ALS community and could succeed only with participation from the ALS community. For those new to the Registry, she briefly explained that the Registry estimates and publishes the prevalence rate of ALS in the US (e.g., meaning the number of people living with ALS at any one time); estimates the incidence rate of ALS (e.g., the number of people diagnosed with ALS each year); collects data on environmental exposure from people with ALS; collects biorepository samples and data that can assist researchers in finding potential biomarkers of ALS; provides continuing education of ALS providers; funds research designed to determine environmental causes of ALS; and offers a research notification tool to allow clinical trial sponsors and researchers a mechanism through which to recruit for their trials and studies.

Ms. Pauls Backman concluded that this is the 9th ALS Registry meeting she has attended, and every year she has been more impressed with how the Registry has matured the epidemiological ALS research it funds that is not supported by any other public funder, and the involvement of people with lived experience who have improved the Registry and make it a more useful tool for research. She reviewed the agenda, explained how the Question & Answer (Q&A) component would work, and pointed out that while the meeting would not be recorded for public purposes due to concerns with obtaining consent, a meeting transcript would be made available.

National ALS Registry Research Update

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

Dr. Mehta provided an update regarding the Registry. He explained that there was a concerted effort in the early 2000s by people with ALS and the ALS Association to establish a registry specifically for ALS. The National ALS Registry was enacted by Public Law 110-373 that was signed by Congress in October 2008. The 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 (e.g., the who, what, and why).

The Act did not make ALS notifiable to CDC in the United States (US). In terms of what this means, diseases are categorized as "reportable" or "notifiable." Reportable diseases are mandatorily reported to jurisdictions by individuals in the health care community, including providers, facilities, and laboratories.[1] Each state determines which diseases/conditions must be reported. For example, ALS is reportable in the state of Massachusetts (MA), Vermont (VT), and Maine (ME), but not to the Registry. Notifiable diseases are reported to the CDC on a voluntary basis by each jurisdiction by health departments. Case records are reported in a de-identified format and include limited information about the patient and the case. Currently, 120 diseases and/or conditions are monitored by CDC. Given that ALS is not reportable or notifiable to CDC, the Registry had to establish novel case-finding methods.

Inclusion of cases in the National ALS Registry is a 2-pronged effort. Currently, Registry cases come from national administrative databases, including the Centers for Medicare & Medicaid Services (CMS), Veterans Affairs (VA) through the Veterans Health Administration (VHA), and Veterans Benefits Administration (VBA). An algorithm is applied that assesses International Classification of Diseases (ICD)-10 codes for prescriptions for riluzole and edaravone and from there, ATSDR determines whether it is a case or not. ATSDR has robust data sharing agreements with CMS, VHA, and VBA and works with these partner groups to ensure that they can obtain personally identifiable information (PII). "Non-Registry Eligible" cases include "Undetermined ALS" or "Not ALS" and "Registry Eligible" cases are identified as "Confirmed ALS" or "Likely ALS." Follow-up is conducted on the those identified as "Non-Registry Eligible" to determine whether anything has changed, such as the addition of a prescription for ALS or a diagnostic code for ALS. Cases are deduplicated. These individuals can move to the "Registry-Eligible" group at that point. Cases also are identified through CDC.gov/als, which is the National ALS Registry Web Portal where patients enter through the Registry and answer a series of questions voluntarily to be added to the Registry. From the portal side, patients can take risk factor surveys, acquire information about clinical trials and epidemiological studies, join the National ALS Biorepository, and be assigned a Global Unique Identifier (GUID) that allows patients to be tracked anonymously and cross-identified with other groups that use GUIDs. Currently, there are 18 risk factor surveys that asked questions about where a patient lived and

[1] NNDSS, CDC.gov

worked, whether they were in the military, if they smoke, et cetera. These are the benchmarks for assessing potential etiologies and risk factors for ALS.

There are numerous ALS research initiatives underway at the federal level, such as the following:

CDC/ATSDR
- ❑ Epidemiology of ALS at the state and national level – public health impact
- ❑ Identification of risk factors and etiologies for ALS (e.g., environmental exposures, heavy metals, et cetera)
- ❑ Identification of biomarkers via the Biorepository

National Institutes of Health (NIH):
- ❑ Basic sciences biomedical research
- ❑ Looking at effective approaches to halt cell death
- ❑ Slow disease progression
- ❑ Identify gene mutations and cellular defects
- ❑ Develop biomarkers
- ❑ Assess how ALS changes over time (e.g., symptoms)

Department of Defense (DoD) Congressionally Directed Medical Research Program (CDMRP):
- ❑ Pre-clinical development of therapeutic agents
- ❑ Steps required before Food and Drug Administration (FDA) approval of a new drug
- ❑ Stability, toxicology, pharmacokinetics, efficacy in cell and animal models

The prevalence of ALS in the US for calendar year 2018 was accepted by the journal *Amyotrophic Lateral Sclerosis and Frontotemporal Dementia (ALSFTD)* and was published on August 21, 2023.[2] The initial findings are that there are approximately 30,000 persons with ALS in the US. Case ascertainment has improved from 44% to 27% missing; that is, the Registry's revised algorithm is identifying more cases than previously. In terms of the results for 2018, the National ALS Registry found 21,665 persons meeting the case definition (i.e., having "confirmed" or "likely" ALS) for a prevalence of 6.6 per 100,000 persons. These cases were found by applying the updated algorithm to "undetermined" cases identified by the administrative databases and the web portal. Persons 18–50 years of age had the lowest estimated prevalence (1.1 confirmed or likely cases per 100,000 population) and persons older than 65 years had the highest (21.4 per 100,000 population). The prevalence of ALS among males (8.1 cases per 100,000 population) was higher than among females (5.2 per 100,000 population). The prevalence among Whites (6.1 per 100,000 population) was twice that among Blacks (2.8 per 100,000 population) and prevalence rate of those reporting race other than white or black was observed at 4.5 per 100,000 population. This is consistent with the previous capture-recapture (CRC) methodology estimates of ALS prevalence in the US of about 29,824 cases per year. Table 1 below depicts the number and percentage of ALS prevalence in the cases (N = 21,665) and estimated prevalence by age group, sex, and race:

[2] Paul Mehta, Jaime Raymond, Yuzi Zhang, Reshma Punjani, Moon Han, Theodore Larson, Oleg Muravov, Robert H. Lyles & D. Kevin Horton (2023) Prevalence of amyotrophic lateral sclerosis in the United States, 2018, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 24:7-8, 702-708, DOI: 10.1080/21678421.2023.2245858

Table 1: Number and percentage of amyotrophic lateral sclerosis (ALS) cases (N = 21,665) and estimated prevalence, by age group, sex, and race—National ALS Registry, United States, 2018

		Observed		Adjusted[c] cases			
Characteristics	Population[a]	No. observed cases (%)	Prevalence[b]	Reported % Missing	Missing Cell Estimate	No. total cases adjusted	Adjusted Prevalence[b]
Total	326,838,199	21,665	6.6 (6.5, 6.7)	27.4	8,159	29,824	9.1 (8.7, 9.6)
Sex							
Male	160,960,513	13,091 (60.4)	8.1 (8.0, 8.2)	22.2	3,730	16,821	10.5 (10.0, 10.9)
Female	165,877,686	8,554 (39.5)	5.2 (5.1, 5.3)	41.0	5,952	14,506	8.7 (7.8, 9.6)
Unknown		10 (0.1)					
Race							
White	254,064,310	15,396 (71.0)	6.1 (6.0, 6.2)	31.2	6,978	22,374	8.8 (8.3, 9.3)
Black	46,347,333	1,315 (6.1)	2.8 (2.7, 2.9)	31.4	603	1,918	4.1 (3.6, 4.8)
Other races	26,426,556	1,186 (5.5)	4.5 (4.4, 4.6)	34.1	615	1,801	6.8 (5.3, 8.3)
Unknown		3,768 (17.4)					
Age Groups (years)							
≤50	215,427,905	2,289 (10.5)	1.1 (1.2, 1.3)	56.8	3,015	5,304	2.5 (1.4, 3.5)
51-65	62,720,226	5,803 (26.8)	9.3 (9.2, 9.4)	48.1	5,388	11,191	17.8 (15.6, 20.1)
≥66	48,690,068	10,396 (48.0)	21.4 (21.3, 21.5)	29.8	4,407	14,803	30.4 (29.1, 31.7)
Unknown		3,177 (14.7)					

[a] Population estimates for 2018 are bridged-race Vintage 2020 postcensal estimates of the July 1 resident population. These estimates are prepared by the Census Bureau in collaboration with National Centers for Health Statistics.

[b] Cases per 100,000 US population.

Figure 1 below reflects the observed number of amyotrophic lateral sclerosis (ALS) prevalent cases, estimated under-counted, and total number of ALS prevalent cases by demographic characteristics for 2018:

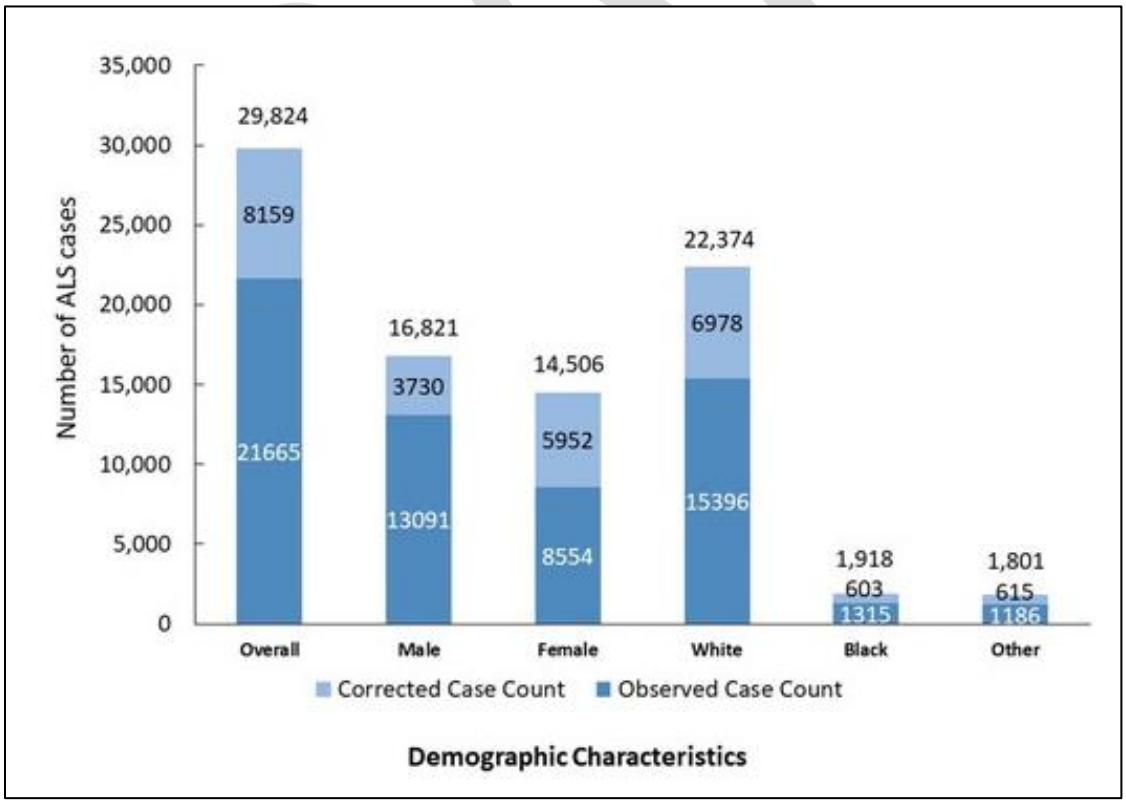
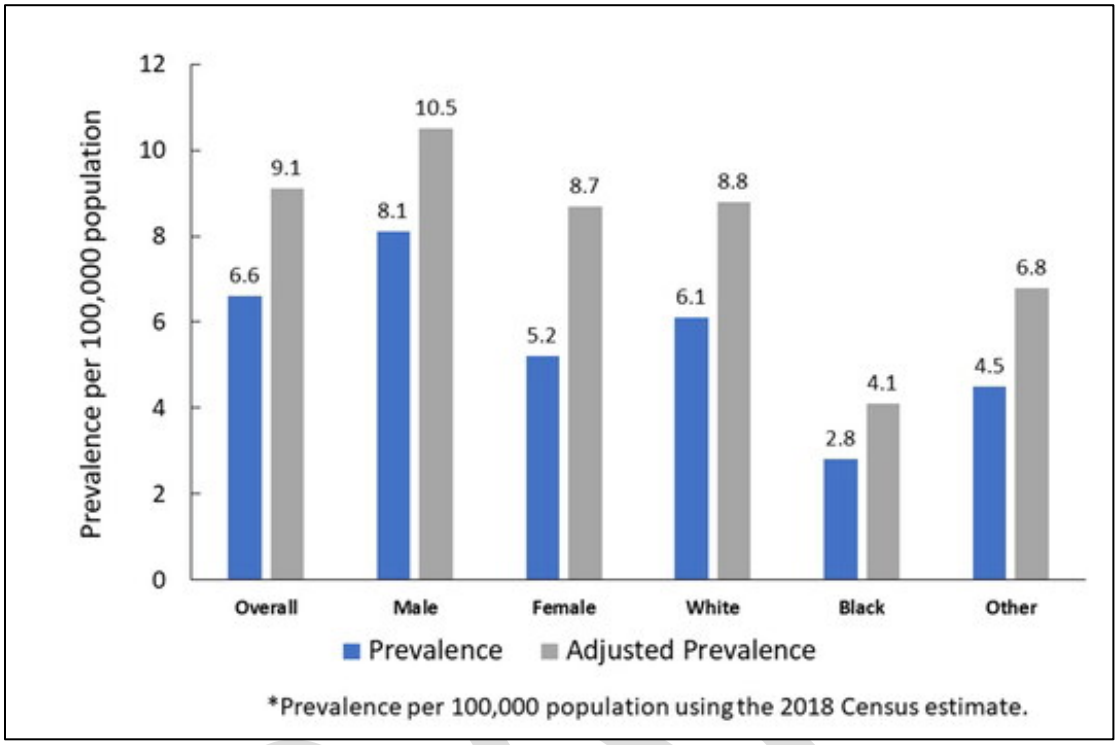


Figure 2 below shows the estimated prevalence and adjusted prevalence per 100,000 population of ALS by sex, race, and overall for 2018:



The first time incidence of ALS in the US was measured for the entire country from 2014–2016 was published in 2022. Evaluation of the 2017 dataset is in progress. This is the first time capture-recapture will be employed for incidence to estimate the number of missing cases. The publication timeline is anticipated to be between Fall 2023 and Winter 2024. It is known that the incidence reported in 2022 was slightly low, so the hope is to adjust that to be more accurate.

Dr. Mehta shared and reviewed a table summarizing data sources for prevalence, incidence, and mortality in terms of the status of upcoming reports, explaining that data were in various stages of being requested, cleaned, received, and cleared. He emphasized that while the goal is to publish data as soon as possible, it also is important to understand that ATSDR is receiving data from a variety of sources (e.g., CMS, VHA, VBA). In addition, the National Death Index (NDI) is utilized to determine whether any cases are deceased. It is important to do a thorough job and ensure that the information to be disseminated to the public is accurate, but this process takes time.

To update the research notification mechanism, this system has now been used by 73 organizations for their clinical trials, including numerous pharmaceutical companies. Some examples include the Atlas Study led by Michael Benatar, MD from Biogen, Inc. that will evaluate whether starting tofersen early (e.g., before clinical signs or symptoms that indicate that onset of ALS) will delay the appearance of signs or symptoms of ALS. The ALSpire Study by Dr. Sheena Chew, MD at Biogen, Inc. will evaluate whether BIIB1005 can reduce transactive responsive (TAR) DNA-binding protein 43 (TDP-43) clusters by reducing levels of ataxin-2. Dr. Terry Heiman-Patterson from Temple University is conducting an ALS Outcomes and Cost study that is evaluating the morbidity, quality of life, access/utilization, and cost for persons with ALS and caregivers.

To update the National ALS Biorepository that was launched in 2017, a total of 15 applications were received for review and approval from October 1, 2023 through July 31, 2023. This does not include requests reviewed and approved for funding by funded collaborator Temple University. Areas of interest include identification of ALS biomarkers to determine ALS subtypes, susceptibility, early onset identification (e.g., microRNA), progression, and validation of assays. Requested sample types include plasma, serum, urine, whole blood, DNA, RNA, and precentral motor cortex. It is important to note that the COVID-19 pandemic limited outreach and enrollment, which also impacted the Biorepository. It is critically important to get samples out to researchers, especially in terms of biomarkers since there is not currently a true blood test or other definitive test for ALS diagnosis.

In terms of some of the publications in 2022-2023, Larson et al.[3] evaluated 24,328 death certificates from 2022–2014. This study found that the most frequent causes of death (CODs) co-occurring with ALS were respiratory failure (n=6503; 25.3%), cardiovascular disease (CVD) (m=6077; 12.6%), pneumonia (n=1345; 5.2%), and pneumonitis (n=856; 3.3%). Regarding the conclusions, this study provides information about the natural history of ALS. With knowledge that some causes of death may be preventable, healthcare providers (HCP) may be able to optimize patient care and possibly postpone mortality and reduce mortality. For instance, practitioners should address CVD and other comorbidities in addition to a person's ALS itself.

Raymond et al.[4] compared ALS patient characteristics from the National ALS Registry and the MA Registry. There were 1042 ALS patients in the MA Registry and 642 patients (61.6%) matched in the National ALS Registry. Among these matched patients, 522 (81.2%) came from Medicare, which is expected since a higher portion of cases come from Medicare by itself. A total of 400 patients in the MA Registry were not matched to the National ALS Registry, which demonstrates that cases are still being missed. This study concluded that ALS's non-notifiable condition status at the national level continues to pose a challenge in identifying ALS patients.

Zizzi et al.[5] examined the symptoms and issues that have the greatest impact on persons with ALS. Recruitment assistance was received for this study from the National ALS Registry's research notification tool. This study found that the inability to engage in activities, fatigue, and problems with hands or fingers, mobility, and social situations had the greatest overall effect on people's lives. The study concluded that persons with ALS experience a variety of symptoms that impact their lives and that addressing the most prevalent and important symptoms provide potential targets for improvement in future therapeutic interventions. Notably, use of the Registry's recruitment tool was very beneficial in terms of augmenting the number of cases and data points included in the study.

[3] Larson, T.C., Goutman, S.A., Davis, B., Bove, F.J., Thakur, N. and Mehta, P. (2023), Causes of death among United States decedents with ALS: An eye toward delaying mortality. Ann Clin Transl Neurol, 10: 757-764. https://doi.org/10.1002/acn3.51762

[4] Raymond J, Punjani R, Larson T, Berry JD, Horton DK, Mehta P. Comparing Amyotrophic lateral sclerosis (ALS) patient characteristics from the National ALS Registry and the Massachusetts ALS Registry, data through 2015. Amyotroph Lateral Scler Frontotemporal Degener. 2023 Aug 4:1-8. doi: 10.1080/21678421.2023.2239301. Epub ahead of print. PMID: 37539949.

[5] Christine Zizzi, Jamison Seabury, Spencer Rosero, Danae Alexandrou, Ellen Wagner, Jennifer S. Weinstein, Anika Varma, Nuran Dilek, John Heatwole, Joanne Wuu, James Caress, Richard Bedlack, Volkan Granit, Jeffrey M. Statland, Paul Mehta, Michael Benatar, and Chad Heatwole; Patient reported impact of symptoms in amyotrophic lateral sclerosis (PRISM-ALS): a national, cross-sectional study; https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(22)00497-7/fulltext.

Bannick et al.[6] examined micro ribonucleic acid (miRNA) biomarkers for ALS from extracted extracellular vesicles in blood. This study used samples from the National ALS Biorepository. In this study, extracellular vesicles were extracted and isolated using immunoaffinity purification. The study found a repeatable measure of miRNA that differed statistically in ALS patient samples compared to control samples.

Benatar et al.[7] discussed prevention strategies for ALS in a study that included screening persons with ALS with familiar gene carriers of superoxide dismutase 1 (SOD1). In this study, preventive treatment with tofersen, an SOD1 antisense oligonucleotide, was compared with placebo when neurofilament light chain (NfL) levels rose above a pre-defined threshold. This study concluded that stopping neuronal loss before it manifests can prevent ALS. This study was sponsored by the National ALS Registry to assess genetic therapeutics and genetic counseling.

In addition to these publications, there are a number of pending publications as well. A study on the COVID-19 pandemic's impact on ALS deaths has been submitted to the journal *Annals of Neurology* for review. Led by Jaime Raymond, MPH, this study compares calendar years 2020 prior to vaccines to 2019 to assess whether the pandemic increased motor neuron disease (MND) or other deaths in 2020 compared to 2019. This study identified a slight increase in ALS deaths from 2019 to 2020. Data from 2021 have been received and are currently being analyzed. These data show that not only did the COVID-19 pandemic affect the world, but also that it affected vulnerable populations such as persons with ALS.

The Registry is currently collaborating with Pat Dolan, persons with ALS, and Earl Sarow who are expert geographers, as well as Clare Durrett from Team Gleason and Danielle Boyce from Johns Hopkins University (JHU). This study is utilizing geographic information systems (GIS) to evaluate the geographic distribution of ALS in the US. Areas being analyzed in the study include access to care, representation of minorities, and distribution of ALS cases. Access to care is extremely important to understand because it is known that care can be limited in different parts of the country and can impact patient outcomes. For example, some persons with ALS have to travel long distances for care.

The Registry is collaborating with Dr. Kelly Gwathmey, a neurologist from Virginia Commonwealth University (VCU), to compare minority populations in Virginia versus the Registry. Areas of focus in this study include evaluation of diagnostic delay in African Americans and phenotypic onset. A poster will be presented on this during the October 2023 Northeast ALS Consortium (NEALS) meeting. The Registry also is collaborating with ALS researchers in Canada in a study comparing patient populations of both countries that will assess age of onset and disease demographics. The Registry is in discussions with collaborators in Sweden to conduct a similar project to look at similarities and differences in different countries.

[6] Banack SA, Dunlop RA, Stommel EW, Mehta P, Cox PA. miRNA extracted from extracellular vesicles is a robust biomarker of amyotrophic lateral sclerosis. J Neurol Sci. 2022 Nov 15;442:120396. doi: 10.1016/j.jns.2022.120396. Epub 2022 Aug 30. PMID: 36081303.

[7] Benatar M, Goutman SA, Staats KA, et al. Benatar M, et al. J Neurol Neurosurg Psychiatry 2023;0:1–4. doi:10.1136/jnnp-2022-330473 3.

The Registry is evaluating juvenile ALS (jALS) cases among persons 18 to less than 25 years of age in the Registry. This collaboration with Edward Kasarskis, MD, PhD from the University of Kentucky is anticipated to be published in Fall 2023 or Winter 2024. The study includes 2024 individuals with jALS, which is extremely rare and tends to be linked to a specific gene. The Registry does not capture anyone below the age of 18 years because the Institutional Review Board (IRB) does not allow it.

Another project on which the Registry is currently working involves the evaluation of an area of interest in Montgomery, Alabama where approximately 9 ALS cases have been reported to the state health department. A physician in Montgomery contacted the state health department about a possible hotspot. The state epidemiologist contacted the Registry about potentially investigating the particular neighborhood located near a golf course with the 9 cases of ALS. In terms of the hierarchy in public health, a state must request a CDC Epi-Aid, which is an investigation by CDC's disease detectives. This type of study would involve evaluation of the cases' medical histories and collection of blood samples for analyses. The hope is that the state will make a formal request for an Epi-Aid, given that this would be the first time the Registry would be conducting a study in conjunction with CDC partners and the Epi-Aid office.

The Registry also is collaborating with a Major League Baseball (MLB) player, Sam Hilliard, who is an outfielder for the Atlanta Braves. His father was a physician who passed away from ALS. This project involves a public service announcement (PSA) to raise awareness about the Registry and ALS. The Registry created a PSA in 2022 with Brad Dusek, a former National Football League (NFL) player with ALS, that is available on the website. This allows the Registry to work with individuals.

The ALS Continuing Education Module has been updated. Training will provide an overview of ALS epidemiology, including clinical applications, diagnosis, treatment, and management. The audience for this module includes Physicians, Registered Nurses (RNs), Epidemiologists, Laboratorians, Physician Assistants (PAs), and Program Managers. The training is free of charge and is 1.5 contact hours. New Registry folders and pens are available for partners to give to people at the chapter and clinic levels. The folder contains an agronomical pen for persons with ALS and all of the materials available, including the Quick Start Guide, information on the risk factor surveys, the trial notification system for clinical trials, and information about the Biorepository. The agronomical pens were made in consultation with the ALS Association, Muscular Dystrophy Association (MDA), and the Les Turner ALS Foundation. These pens are ergonomically correct and can help those with ALS write.

As a reminder, the Office of Management and Budget (OMB) approves all federal data collection activities for the US federal government to ensure that data collection is not a burden to the public. The OMB request that was submitted about 1.5 years ago was approved in May 2023. It covers adding new data sources, such as partner organizations and MA, VT, and ME in order to add their cases into the Registry; updating surveys from 18 to 5 named categories; and releasing state data on incidence and prevalence. The 18 surveys will be organized into 5 main categories to make them easier to navigate. The previous surveys were not named to avoid creating bias, but with 5 main categories such as demographics and occupation, people with ALS can see the categories and take the surveys at their leisure. The release of state-level data will be novel and will increase the number of cases in the Registry. Data from 2010–2018 are currently being analyzed. The state data will include incidence and prevalence, but not the capture-recapture correction factor, so these will be actual cases that have been reported to the Registry. The plan is to include this information on the website, including a visual representation

of the US so people can click on their own states to see what is occurring in their own backyards.

Regarding public engagement, listening sessions were launched in Summer 2022 with patients and caregivers that concluded in January 2023. Led by Dr. Danielle Boyce, the purpose of these sessions was to provide input about where the Registry could make improvements. These listening sessions allowed for an open dialogue between the Registry and stakeholders. Future sessions are being planned that will include a new group of persons with ALS and caregivers. The following table summarizes the outcomes and actions taken from the listening sessions and the last annual meeting:

Category	Task	Status	Notes
Clinical Trial Notification	Remove deceased patients with ALS from the Registry (administrative databases).	Ongoing	Since the lasts annual meeting, approximately 4600 decedent records were removed from the Registry (administrative databases), largely through our NDI search. We also sent a notice to unsubscribe through email, which has led to 698 PALS being removed. Update: We are in the process of adding an unsubscribe function to the new email template.
Clinical Trial Notification	Clearly communicate to participants that not all trials use the notification system.	Complete	The website has been updated to include: "Please note, not all clinical trials are listed. To find the latest clinical trials, please visit ClinicalTrials.gov."
Dashboard	Remove references to "mean case rates."	Complete	This has been completed on the Dashboard.
Dashboard	Remove "bound" references.	Complete	This has been completed on the Dashboard.
Dashboard	Provide press materials so that ALS data are represented correctly by journalists.	Upcoming	ATSDR intends to have materials (e.g., fact sheets, infographics) out to the public when new reports are released. The Registry will continue to do outreach to Partners and researchers upon the release of new reports. A document for the Press/Pubic is in development.
Collaboration	Having both days of the National ALS Registry Meeting open to all	Continuous	This year ATSDR ensured both days of the annual meeting were open to all. We plan to do the same for the upcoming 2023 Annual Meeting and beyond.
Collaboration	Having a dedicated session at our annual meeting devoted to stakeholder concerns	Continuous	The 2022 Annual Meeting included a productive Stakeholder Committee session. Future stakeholder sessions are to be determined at this time.
Timeliness	Publish and maintain the expected timing of the 2018 report.	In Progress	Update: The 2018 Prevalence Report has been drafted and has been submitted to the journal ALS/FTD.
Timeliness	Define strategies to expedite 2019, 2020 reports to meet the three-year lag.	In Progress	ATSDR processes data as quickly as it is received from VA and CMS; however, we can't control the speed at which we receive the data. While we request the data annually, there are multiple steps to process the data externally and internally. Currently updating our SOPs to have a quicker turnaround time, where possible. ATSDR plans to create a page to display how we receive out data, what is available, and the process itself.
Participation	Incorporate an unsubscribe function for recruitment emails	Ongoing	ATSDR sent an email to all PALS/CALS asking if they wish to unsubscribe. So far, we have received hundreds of responses asking to unsubscribe. We are working on adding this function to all future emails. This is scheduled to be implemented by July/August.

Participation	Analyze and report on data to understand barriers to enrollment. Do patients only complete surveys when they first enroll? Which surveys cause them to stop? How might we motivate them to come back and complete additional surveys?	In Progress	ATSDR is proposing a survey redesign to reduce the time burden on the patients. This redesign will streamline 18 surveys into 5 comprehensive surveys. We currently send reminders for the disease progression survey at the following intervals: disease progression is 3 months, 6 months, 9 months, and 12 months for the first year; then 6 months thereafter. Update: the survey redesign has been approved by OMB and we are currently in the process of IRB approval and implementation.
Participation	Survey PLWALS to understand barriers and possible incentives to enroll.	Collaborative Effort	Update: ATSDR is collaborating with Partners (ALS Association) to develop an incentive pilot project. The project is in early development states and will require OMB/IRB approval. The goal is to provide incentives for those who enroll and complete all risk factor surveys.
Participation	Improve feedback to partners regarding enrollments and survey completions.	Continuous	The Registry Dashboard has information on the cumulative number of surveys completed. We are unable to release the exact number of monthly enrollments due to OMB restrictions. ATSDR provides monthly enrollment reports to Partners regarding state performance. Update: We were recently approved by OMB for releasing state level data and plan on publishing on state level prevalence/incidence in the next year.
Participation and Outreach	Improve outreach and participation by working with various ALS projects and teams	Continuous	ATSDR is working with Pat Dolan and Earl Sarow, retired geographers, to conduct a GIS analysis on Registry data such as residential history and proximity to environmentally impacted sites.
Participation and Outreach	Incorporate data sources from external agencies	Continuous	ATSDR aims to achieve more complete ALS case ascertainment by adding new data sources (totaling less than 9), including state ALS registries and non-profit ALS organizations. This request was recently approved by OMB.
Future Engagement	Meeting diverse stakeholders multiple times throughout the year versus just at the annual meeting	Continuous/Collaborative Effort	ATSDR is committed to regularly meeting with diverse stakeholder groups (e.g., PALS, caregivers, healthcare providers, support groups) to address all ongoing recommendations and progress.
Patient Outreach	Increase outreach and awareness of the Registry to patients and caregivers	Continuous	ATSDR has increased participation through multiple engagement initiatives: • Upcoming NEALS patient ambassador and Everything ALS calls • Invitation to Brooke/Her ALS Story to participate in the Annual Meeting • Packard Center and increased outreach
Outreach and Enrollment	Improve enrollment and survey completion	Continuous	Update: In efforts to increase Registry outreach and enrollment, the Registry team has increased their presence at ALS conferences, symposiums, and outreach events. We also have collaborated with the ALS Association to reach those living with ALS and their families through virtual presentations.

Regarding funding, the Registry has funded 24 research projects to date. A total of 3 new grants were funded in Fall 2022 and the hope is to fund 1 to 3 new grants in 2023 depending upon the availability of funds. In Fall 2022, the University of Missouri was funded to use machine learning (ML) to develop a method of identifying new ALS risk factors. The University of Michigan was funded to study the mechanisms by which the gut microbiome and the immune system impact disease progression. Harvard College was funded to study the association between military exposure and ALS in veterans using newly linked large databases. The new Notice of Funding Opportunity (NOFO) was released on August 1, 2023 on grants.gov and closes on December 19, 2023. It is open to domestic and international institutions. Option A covers established research and Option B covers novel topics.

Regarding overall National ALS Registry funding, $8.2 million of the $10 million total appropriated to ATSDR was allocated to the Registry for Fiscal Year 2022 (FY22). Of the $10 million, $1.8 million was allocated to ATSDR for overhead. The majority of funding (63%) was allocated to research funding. About 10% was allocated to personnel, 14% to outreach and education, 9% to information technology (IT) support, 3% to communications, and less than 1% to miscellaneous activities.

In closing, Dr. Mehta emphasized that the Registry does much more than just count ALS cases. The Registry has considerable impact in a variety of other areas. For instance, there is the National ALS Biorepository. The Registry includes assessment of the 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 over 100,000 completed surveys in the Registry, with data published on these for review. These surveys allow persons with ALS to tell their story and discuss their potential exposures throughout their lifetimes. 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 and is always open to partnering with others as well. 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, persistent organic pollutant (POPs), genetics, and others. In addition, the Registry provides updated national epidemiological estimates of ALS cases in the US using novel methodologies.

Discussion Highlights

Ms. Pauls Backman read some of the questions aloud during each discussion period. Questions that were posted during the registration process and raised during the meeting are included in the attachment sections for Days 1 and 2 at the end of this document.

Nitesh Sanghai observed that the overall prevalence and incidence of ALS cases is more in Whites compared to Blacks and asked whether there were any thoughts on this.

Dr. Mehta responded that based on the available data, ALS impacts Whites and especially males more than any other group. However, the reason for this remains a mystery.

Dr. Stephen Finger asked how it is that each demographic group is estimated to be missing over 30% of cases but the overall rate is 27% and how much confidence there is in the 27% figure.

Ms. Raymond responded that ATSDR feels confident regarding the 27% figure. The race data have 17.2% missing race, which makes the percent missing slightly more unstable and gives a higher percentage. The overall missing rate of 27% is a more accurate number because it includes all of the ALS cases the Registry has.

Peter Ambühl from Switzerland asked how ATSDR avoids double data using different databases.

Ms. Raymond responded that ATSDR has an extensive deduplication process that is done within each dataset as well as between the datasets. This is done each time the data are updated to ensure ALS cases are not being counted more than once.

Regarding clinical trial notification, Ms. M.C. Collet observed that the Registry's list of interventional trials continues to be <10% of recruiting interventional trials for ALS. She did not think people depending on notification realize that. She suggested pulling all ALS recruiting trials from ClinicalTrials.gov and featuring one each week, just cycling through them. This is public information on ClinicalTrials.gov. Or a link could be sent to people quarterly of recruiting interventional trials on ClinicalTrials.gov and a link for observational trials.

Dr. Horton responded that the clinical trial research notification tool is currently used to help researchers recruit Registry-enrolled PALS into active trials and studies. ATSDR does not control what types of studies that researchers want them to recruit for (e.g., interventional trials).

Nitesh Sanghai pointed out that respiratory failure is known to be linked with ALS pathology and wondered how cardiovascular comorbidity could be linked with ALS and if it was a new signal that should not be missed.

Dr. Mehta responded that while he was not sure whether it was a new signal, it is seen on death certificates as a potential COD. Outside of multi-disciplinary clinics, some patients may be receiving care from a local neurologist who is focusing on just ALS and not looking for and managing other areas of concern such as cholesterol levels, CVD, and so forth. The takeaway message is that not only is respiratory failure one of the CODs in ALS, but also it is important to ensure that providers are considering heart disease, other cardiovascular events, and other conditions and not just having a single focus on ALS alone. This will help to increase patient survival.

Maithili Deshpande asked whether there were any thoughts on the use of ICD-10 code G12.21 to identify ALS patients in various claims databases and whether the use of the code would leave out a lot of patients.

Dr. Mehta confirmed that they do use ICD-10 code G12.21 for all of the claims and NDI data.

Ms. Raymond added that this is the way the algorithm always has been, even when ICD-9 was being used. In particular in the NDI data, she looks for 12.29 and also compares it with the other data they have from CMS to determine whether a 12.29 might be a possible ALS case. For instance, she looks for a riluzole prescription. For the most part, they use 12.21.

Ms. Pauls Backman suggested that this might be a good point of education in some of the continuing education work that is being done.

Antoinette Harrison asked whether substances from the Anniston site in Alabama could be contaminating the aquifer.

Dr. Mehta responded that he was not sure they could make the assumption at this time about the substances in Anniston contaminating the aquifer without having the details of the Epi-Aid.

Meifang Li, Dartmouth College, requested Antoinette Harrison's email in order to send a map of the numerous Superfund Sites located in Anniston.

Noting that over half of Blacks in Massachusetts were missed, Dr. Finger asked whether ATSDR thinks they are underestimating missing cases in the prevalence estimates.

Ms. Raymond responded that in Massachusetts, there was a larger percentage of Black patients (62%) in the Registry than Massachusetts had (31%). Most of the Registry patients came from the Medicare data received.

Diane Hoey asked whether any helpful, interesting trends or changes have been seen in the data over the years the Registry has existed.

Dr. Mehta replied that the question of interesting trends or change was broad. Initially, there was under-ascertainment in terms of prevalence. Based on the use of the capture-recapture methodology, ATSDR is now comfortable saying that there are approximately 30,000 persons with ALS in the US. That by itself is probably the biggest trend for which they have adjusted since the original datasets were published in 2014. If new therapeutics coming online are efficacious, that would increase prevalence because the number of individuals with ALS would be living longer. In terms of incidence, it was not clear whether they would see an increase in the number of cases with the capture-recapture adjustments from 2018 and beyond.

In response to a question about how one could volunteer for research studies that may help future patients, Ms. Pauls Backman pointed out that people have always been encouraged to register to complete the surveys. These are now being nicely amalgamated into a shorter number of surveys, which she thinks is great.

Dr. Mehta added that joining the Registry by itself helps in the fight against ALS. Taking the risk factor surveys and joining the National ALS Registry Biorepository also are beneficial. The National ALS Registry is one of the largest research programs available in the US, and they certainly would like anyone and everyone with ALS who is interested to join. That alone will help to learn more about this disease and improve case ascertainment. In addition, people with ALS should speak to their neurologist or other providers about whether they know of any clinical trials for which patients may be eligible. There also is information on the NEALS website about research and activities in which patients may be eligible to participate.

Research from National ALS Biorepository: Guam Samples

Lyle Ostrow, MD, PhD
Lewis Katz School of Medicine
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Temple University

Dr. Ostrow began by pointing out that the collaboration between the CDC National ALS Registry and the ALS Postmortem Tissue Core started in 2012 when he was at JHU. Originally, this was a multi-center effort that was funded by the Target ALS Foundation and other organizations. In 2021, JHU separated from the multi-centered effort and partnered with the CDC. Over the past year, the ALS Postmortem Tissue Core was transitioned from JHU to Temple University. During this session, he provided an update on the activities of the Temple University ALS Postmortem Tissue Core and an exciting new resource for ALS researchers.

In terms of why the ALS National Repository and the ALS Postmortem Tissue Core matter and why tissues and samples are needed from people who died from ALS, researchers study the biology of ALS and look for new treatments by using laboratory models (e.g., cell cultures, mice, flies, et cetera). In order to translate laboratory discoveries into successful clinical trials, it is necessary to know whether changes seen in the laboratory experiments also are happening in the bodies of people living with ALS. It is also important to understand whether certain laboratory discoveries may be relevant only to some people living with ALS in order to identify who is most likely to benefit from a new therapy. Tissues in the body are like apple pie in that there are other ingredients (e.g., other kinds of cells). As a disease progresses the ratio of apples to other ingredients changes as some cells die or other cells are rooted. If studying a disease mechanism, does it matter whether one studies the apples still on the tree that perhaps are still doing well or the ones that fell on the ground that perhaps had some trouble? This is how researchers figure things out.

There are many different "flavors" of ALS, including different cells in the bodies of different people who have this disease. If developing a therapy, it is necessary to know which therapy might work best for which people who have the disease. Tissue, blood, spinal fluid, and other samples are needed to be able to determine whether the same changes are occurring in people who have ALS. It also is important to have rigorous data associated with samples to help understand how various measurements relate to clinical disease.

The goal of the ALS Postmortem Tissue Core is to provide high-quality, well-characterized post-mortem tissue for academic and industry ALS researchers throughout the world in the best way possible. First and foremost, this means making sure that sample donations are respected. It is amazing for someone who has ALS or their family to decide to donate their tissues to this research. It is critical to use these samples responsibly and in the best way possible. This is done by maximizing the use of every autopsy, ensuring responsible use of the tissues, accelerating ALS research, fostering collaboration, and promoting open science and the rapid sharing of data. These have been the "marching orders" since this started and that has not changed. It makes Dr. Ostrow feel good when he hears talks from just about anywhere now, given that they have worked with most large laboratories at some point.

There is a standardized system in place to optimize the needs of researchers to ensure that the right tissues and data are being provided. When somebody donates their brain, it is cut into tiny centimeter pieces that are from the exact regions researchers want. Great care and time are taken to ensure that there are proper quality measures, fixed blocks tissues and slides, a system of nomenclature, et cetera to ensure that the right data are being captured. They have a bar-coded inventory system that is maintained by NEUROBANK™ that is de-identified. Doing it this way means that they can say "yes" to everybody. Every time an autopsy is received, they are generating thousands of samples from it such that a given person's autopsy can be used in hundreds of research projects. The tissues and slides are linked to de-identified clinical, demographic, and neuropathological metadata, and to the pathology (e.g., the characteristic findings of ALS seen when the tissues are examined under the microscope). All policies are designed to provide samples and data as quickly as possible, while ensuring responsible, open, and unbiased use of all Core resources. There are very detailed meetings with all of the researchers who are using these tissues to ensure that the best possible samples and data are being provided for every experiment, that samples are being used in a way that they are not being wasted, and that the experiments are going to get results. This is all possible because of these unbelievable donations.

They have handouts that they use to go through the considerations when trying to translate something from a laboratory experience to the tissues in terms of the endpoints and how the Core can help make the data meaningful. There is a lot of discussion about measuring things in blood or spinal fluid. If the tissue is apple pie, the blood and spinal fluid are like the ice cream on top that is running down on the plate. Consideration must be given to what can be measured in that and how it reflects what is going on.

The transition to Temple University and continued collaboration with the CDC has enabled the ALS Postmortem Tissue Core to expand greatly and improve these resources for ALS researchers. Temple has provided a remarkable space in which to assemble a freezer farm with top-of-the-line freezers and online management. Kathyn Gallo and Kathleen Wilsbach are the Coordinators for this program. They manage everything to do with this work, including opening a refrigerator or freezer in the middle of the night when needed. The Core has recently incorporated over 30 additional ALS autopsies collected by Dr. Terry Heiman-Patterson over many years, who co-founded the ALS Hope Foundation. This offered a "dry run" for using standard operating procedures (SOPs) and methods to ingest data and resources from other efforts, harmonizing ALS pathology nomenclature and clinical data elements, and addressing regulatory considerations for sharing samples and data. This took a long time, given that Dr. Heiman-Patterson's samples were stored and catalogued differently. They took pictures of everything to ensure that they had a record, identified the anatomy and how it related to the Core's anatomy, ensured that the different inventory sheets were reconciled, et cetera. The Dr. Robert Sinnott ALS Research Laboratory at Temple University provided a lot of the resources needed for doing this work. Refining SOPs and regulatory practices will allow the Core to accept autopsies from other academic centers.

Each month, the ALS Hope Foundation's monthly newsletter features a different ALS Postmortem Core research project made possible with support from CDC, Temple University, and the Hope Foundation. Dr. Ostrow encouraged everyone to look up and perhaps sign up for the newsletter. These projects would not be possible without the tissues donated by people who have ALS and their families.

Dr. Ostrow reported on a new collection of resources that are related to ALS and Parkinsonism Dementia Complex (ALS-PDC or Lytico-Bodig), which refers to the striking combined increased incidence of ALS and PDC among the Chamorros on the island of Guam that was first recognized in the 1940s and 1950s. ALS, parkinsonism, and dementia occurred frequently in the same individuals and families. The rates of ALS were 50 to 100 times higher than they were in the general population. In a given family for instance, one person would get ALS, one person would get PDS, and one person would get both. Some family members did not seem to manifest it at all. During the latter half of the 20th Century, the incidence of Lytico-Bodig decreased steadily—the reasons for which remain unclear. The National Institutes of Health (NIH) conducted a study that ran for many decades to try to determine the cause. Some of the hypotheses about what was occurring were that perhaps changes to diet and cultural practices may have reduced toxic environmental exposures to β-Methylamino-L-alanine (BMAA), a non-proteinogenic amino acid produced by cyanobacteria, or exposures to something else in the environment in this isolated population who may have had increased genetic susceptibility. ALS-PDC or Lytico-Bodig in this setting offered a remarkable opportunity to study the intersection of environment and genetics which might relate to MND and the factors influencing the overlapping clinical syndromes and pathologies of parkinsonism, dementia, and ALS. A similar spectrum of ALS, dementia, and parkinsonism is now recognized in some genetic forms of ALS-FTD in some families.

The NIH had a center on Guam that collected blood, spinal fluid, tissues, and clinical data from people who suffered with these disorders and from their family members who did not. These samples and data were curated for many years by Dr. Ralph Garruto. About 2 years ago, Dr. Garruto reached out to the National ALS Registry to let them know he was retiring and wanted to make sure that this resource was made available for use by researchers. Dr. Mehta and his team reached out to Dr. Ostrow, which is how the Core got involved. They engaged in many detailed calls with Dr. Garruto and the whole team. One issue that made them nervous about incorporating this collection was that nothing was digitized. Everything was paper records in large filing cabinets that were stored in different ways and with different types of coding. However, they decided to figure out how to make it work because it is so important. At first, they thought there were just autopsy samples but learned in their discussions with Dr. Garruto that he also had cerebrospinal fluid (CSF) samples and records. The Guam ALS-PDC autopsy collection turned out to include frozen and fixed autopsy tissue from 400-500 people who died from ALS and/or PDC and many of their family members that were collected by the NIH center on Guam over many decades, along with their corresponding clinical and autopsy records. This collection also included CSF samples collected during life, including multiple longitudinal samples collected during disease progression.

Dr. Ostrow reminded everyone that he shared responses from a survey about unmet needs during last year's meeting show that the greatest unmet need is for non-neurological controls. One of the most exciting things about this collection curated by Dr. Garruto is that it includes longitudinal tissues and biofluids from the unaffected family members of the people who suffered from these diseases, which is going to provide elegant controls to compare to diseased tissues. In that same survey, people also said they wanted blood and spinal fluid samples from people as the disease progresses to match to postmortem tissue from the same people in order to try to correlate that with samples that can be measured during life. This Guam resource is exactly what researchers have been searching for, so it is very exciting.

Given that ingesting the Guam samples was going to be more complicated than anticipated, the decision was made to try to identify some priority projects to begin with instead of waiting until they got through all of the records in order to quickly distill important and simple data and share samples with researchers. Importantly, this also included many quality control considerations because the Core wanted to make sure that they knew what tissues could be used for and their condition. Specifically, they wanted to make sure that they could identify a clear list of autopsy tissues that had matched spinal fluid and blood, because those were going to be precious samples that they want to make sure are being used in ways that are the most meaningful to the most researchers. The samples and data for these projects are being identified and set aside while the Core is performing the initial re-organization and re-labeling of the collection.

Two trucks showed up with very well-cared-for samples that have been stored at −80° that were transferred into the Temple laboratory. They worked overnight for a couple of nights just moving everything in, including the samples, file cabinets, boxes of records, et cetera. Dr. Garruto provided some wonderful spreadsheets he created with basic labeling keys, but interestingly enough, the labeling keys were not correlated with each other, and they changed over the years. Nevertheless, they were tremendously helpful. The paper files include clinical records, codes, surveys and questionnaires filled out over many years by the NIH center for various purposes, pathology, raw data and analyses from innumerable experiments performed on the samples, published manuscripts, inventory files, old note cards, old triple pieces of paper, logs of serum, typed out neuropathology reports, various sorts of epidemiology reports, and much more. Even though it is easy to get overwhelmed, this is a remarkable collection. In terms of the clinical records, a lot of the people have the same surnames. This makes it difficult to generate unique identifiers for them. A remarkable variety of studies were conducted on these tissues over the years. Frozen tissues arrived in frozen boxes, which were immediately transferred into the Temple freezers. The boxes have numbers that have nothing to do with what is inside the boxes and do not relate to what is inside each box. Often a box has tissue from a dozen different decedents. The ultimate goal is to ingest and link the data to the samples over time in an information management system in order to be able to provide relevant information and publish papers on whatever research has been done already (e.g., heavy metals, twins, Australian virus antibody, and many more). It will be a labor of love to go through these and reorganize them in a way that is sensible for people to use and then it all will be put into the bar-coded system.

Fixed tissues are in a massive number of jars of fixative formula. These also are labeled differently with different codes. Originally there was an odor, so they had to figure out which ones were leaking before transferring them. They are now all in cabinets in order with at least inventory numbers. The next step with these is to prioritize which ones to embed in paraffin blocks according to the established standard regions. There is a variety of different tissues (e.g., formalin fixed brains, spinal cords, nerves, muscle, bone, et cetera). There are controls and longitudinal collections that are all coded differently than the tissues. All of this coding must be reconciled. There are boxes upon boxes of stained and unstained slides with different labeling systems on the different boxes and slides themselves. All of these need to be compared to the inventory files, logged into the PM Core Inventory, and linked to the tissue samples, biofluids, and other data. Once all of this is organized and ingested, there is huge demand to use the collection. Many researchers are talking to the ALS Postmortem Tissue Core about that and are planning experiments. That is why they are trying to prioritize the "low-hanging fruit" so that they can get these samples out to people right away.

Dr. Ostrow emphasized that while all of this is a lot of work, it is incredibly fascinating. The ALS Postmortem Tissue Core is unbelievably grateful to the CDC for its ongoing support so that they can continue to help accelerate ALS, for being a real collaborative partner in all of these projects, and for figuring out how best to help. They also are extremely grateful to Temple University for providing resources and space for this transition, and for Kathyn Gallo and Kathleen Wilsbach. Critically, none of this would be possible at all without the people who have this disease and their families who have donated tissue, blood, and spinal fluid. Research projects around the world that are using these resources already.

Discussion Highlights

Ms. Pauls Backman read some of the questions aloud during each discussion period. Questions that were posted during the registration process and raised during the meeting are included in the attachment sections for Days 1 and 2 at the end of this document.

Ms. Pauls Backman gave Dr. Ostrow and his team a lot of credit for going through all of the boxes and file cabinets to complete this amazing work.

Dr. Benjamin Brooks asked whether these samples are from the original NIH ALS station (Chen) or from the Canadian studies (Strong) and subsequent Mayo studies (Kurland).

Dr. Ostrow replied that he is learning about all of this he goes, but these are all from the original NIH Center. In fact, there was a lot of regulatory paperwork that the CDC helped with in terms of getting NIH's permission for Dr. Garruto to share these and to make absolutely sure that the transfers on these tissues would allow them to be shared openly and broadly with researchers in academia and industry who are conducting ALS research. There was quite a bit of back and forth, for which they are grateful. While these samples are from the NIH Center on Guam, there are other collections of these tissues and blood that were from the same center that are elsewhere. The Core is in the process of meeting with the researchers in that community, with the only goal to do whatever possible to make these available to researchers, whomever they may be. When he first heard about this, his first thought was that he could not believe they were not being used. There are longitudinal biofluids linked to tissues and it is ridiculous that they are not being used. Now he understands that it was because of the way they were collected and stored, which is why they are going through right now to reorganize and do what is necessary to make this a resource that is easily accessible by researchers.

Ms. Pauls Backman said she was well aware of there being many ALS biorepositories in many places that have been held either by individual PIs or held at different academic institutions. That always has been an issue for the ALS community and is one of the biggest challenges there is in the ALS community. She asked Dr. Ostrow to share his thoughts on this and how those biorepositories can be harmonized and some of the obstacles in that harmonization.

Dr. Ostrow said this is something he has been passionate about for a decade. When they started this effort, it was a federated model with many different centers, each of which adopted the same SOPs, uniform language, material transfer agreements, consents, et cetera. This is a lot of work that is very hard to do. The costs are different, the pieces are different, and the way the various academic centers perform autopsies and the way they interact between the biology departments and neurology departments differ. There is an established roadmap to be able to ingest autopsies from anywhere. There are efforts with other diseases that do this really well. For example, Alzheimer's disease has been able to accept tissues and data from centers anywhere that want to participate as long as they are able to conform to the harmonized

methods. He has spent a lot of time over the years studying the methods and processes. The survey that he presented during last year's meeting asked about local repositories and whether groups would be interested in contributing tissues and data. There is a way to make it work, but it takes a certain amount of funding. Autopsies are expensive. The cost for Temple for an autopsy in terms of procuring the tissues during the dissection, getting the neuropathology, getting the genetics, and everything that has to be done to analyze the tissues is about $5,000 per new autopsy. While the goal is to make sure that each autopsy is used by hundreds of different researchers, the costs are not trivial. Until the autopsy is done, it is not even clear whether the diagnosis was correct. There is a roadmap and the Core is engaged in discussions with the CDC, Temple, and other repositories. He emphasized that people who want to donate their tissues should donate to whatever their local bank is, because it is important that the autopsy is done quickly when somebody dies. There is such a need for tissues that wherever tissue is donated is going to be used.

Ms. Pauls Backman emphasized that not only are tissues needed from people living with ALS, but also tissues are needed from controls.

Dr. Ostrow pointed out that a critical issue is the unique identifier. After someone dies, they are not considered a human subject for the Health Insurance Portability and Accountability Act (HIPAA). Personal health information (PHI) is still considered PHI forever and needs to be protected. However, the rules governing tissues and data collected after death are different than the ones that apply during life. Linking studies during life to studies after death and linking studies to each other requires GUIDs because ideally, if somebody is in a clinical trial that collects blood and spinal fluid in Mississippi, who goes to another clinical trial in Baltimore, and then they die and have an autopsy in Michigan, it would be ideal to have those samples be linked in a regulatory and compliant way. It also is important for people to be broadly consented. If someone is in a study and the consent language says their samples can be used only for that ALS study, they cannot be used for anything else. This is a much bigger deal for controls because if they were consented for a different disease, it is sometimes hard to share. Adopting broad consent language is very important.

Dr. Finger recalled that in the past, over 97% of biorepository patients were White and asked what the current rate is and what the rate is in the tissue bank.

Dr. Mehta indicated that the portal is currently 94.5% White, so it has become slightly more diverse. Lack of diversity is a common issue in clinical trials in terms of who participates in clinical trials. Participation can favor a higher socioeconomic status (SES) and so forth. This is true with other disease groups and is not specific to ALS. Obviously, they have to do better to make sure that there is a much more diverse make-up through the Registry. The National ALS Registry works with partners to look at targeted geographical areas like Texas, California, and New York that have more diverse populations.

Dr. Ostrow indicated that Temple also is aware that they must do a better job of reaching underserved populations. Everything Temple University does is about reaching underserved, underrepresented populations in clinical care and medical research. For instance, Dr. Heiman-Patterson stood at a booth in the rain at a Hispanic community festival doing outreach to try to encourage people to participate in research and in autopsies. While autopsies are expensive, it also is important to overcome some cultural barriers. Some underserved populations do not want to get autopsies, but this is something everyone can work on. He stressed that he is personally invigorated by the emphasis on diversity at Temple in terms of finding ways to reach out to other communities. One of the things that happened because of the pandemic was that

telemedicine became much more common. There are many efforts in ALS to determine ways to reach people in their homes. While autopsies cannot be done in someone's home, education can be provided remotely about the importance of tissue donation.

Enhancing Collaboration Between the CDC ALS Registry and NEALS

Layne Oliff, PharmD
NEALS Research Ambassador
Patient Advisor to the NEALS Executive Committee

Dr. Oliff indicated that he was invited as an advisor to be on the NEALS Executive Committee several months ago and is working with them to get the CDC National ALS Registry more incorporated into NEALS. Before reporting on that, he first shared a photograph of his wonderful family and indicated that he is a pharmacist by training, has PharmD and MBA degrees, and has worked in the healthcare industry for over 30 years. His most recent endeavor was as a business owner of a healthcare communications company, so he understands healthcare and likes to say that he "knows just enough to be dangerous enough to understand the system." Regarding his ALS, he identifies himself as a "Unicorn." He has had symptoms since 2012, but fortunately was not really impacted until 2019. He continued hiking, trail running, cycling, swimming, et cetera. He was initially diagnosed with PLS in 2017, which was changed to ALS in 2020. The physician at the head of the team who cares for him is Dr. Matthew Harms at Columbia University. Dr. Oliff has been a participant in the CDC ALS Registry since 2020 when he received the ALS diagnosis, so he receives periodic emails from the CDC about upcoming clinical trials that are ongoing.

One of Dr. Oliff's missions is collaboration. There are over 70 ALS organizations in the US alone and he tries to get these organizations to work together. All of these organizations are good, but they would be better if they collaborated with each other and worked together—that includes the CDC ALS Registry and NEALS. This is a potentially synergistic combination. CDC and NEALS can help each other move forward in terms of ALS research, treatments, and eventually possibly a cure for ALS. NEALS' mission is to rapidly translate scientific advances into clinical research and new treatments for people with ALS and MND. NEALS has over 147 member sites worldwide. The NEALS Scientific Advisory Board (SAB) provides a forum for investigators and industry to discuss ongoing work and vet new ideas for drugs, technologies, and trials. The NEALS Coordinating Center provides strong infrastructure facilities for rapid institution and support of trials sponsored by industry, foundations, and federal granting agencies. The NEALS Biorepository has extensive clinical data and biofluid samples available to researchers to further the understanding of ALS and to develop disease biomarkers. NEALS does help the CDC National ALS Registry. For instance, there was a webinar in 2017 about the Registry. As Dr. Mehta mentioned, there is going to be an updated presentation in early 2024 for NEALS to talk about what the Registry is and how to move forward.

There is a Registry page on the NEALS website, so there is discussion back and forth between the Registry and NEALS. NEALS members are assisting in key projects, such as research notifications, the Biorepository, and surveillance projects. There is some overlap between NEALS and the Registry. In terms of where synergistic collaborations could take place, NEALS can help to increase awareness and education about the importance of the Registry in the ALS community and assist in improving registration and enrollment of people diagnosed with ALS. In addition, NEALS can improve engagement of the ALS multidisciplinary teams as a facilitator to increase enrollment in the Registry. It is very influential when a physician, nurse, or nurse

practitioner tells a patient with ALS that they need to register in the CDC National ALS Registry. This can be very powerful and motivating. NEALS can enhance the role of the Registry as a funder of epidemiologic research. The 2018 data were just recently published, but everyone wants 2019, 2020, 2021, and 2022 data. While it is understood that the CDC is restricted in many ways, NEALS could help to expedite the availability and scope of more current/recent Registry data that are available to clinicians and researchers. More collaboration is essential and needed.

Recognizing that Michale J. Fox has Parkinson's rather than ALS, Dr. Oliff included a photo and quote from Michael J. Fox stating, "This message is so simple, yet it gets forgotten. The people living with the condition are the experts" and emphasized how critical it is to involve people living with ALS in the process. Upcoming meetings are planned with Dr. Mehta to discuss how NEALS and the ALS community could make the data even more valuable than they are today.

Discussion Highlights

Ms. Pauls Backman read some of the questions aloud during each discussion period. Questions that were posted during the registration process and raised during the meeting are included in the attachment sections for Days 1 and 2 at the end of this document.

Ms. Pauls Backman summarized a couple of interesting items that Dr. Oliff raised that she thought were important. She agreed that there are more possible collaborations that could occur between NEALS and the Registry. Self-registration by people living with ALS has always been somewhat challenging despite great work by all of the partners. It is important to remember that about 20% of the data coming into the Registry is through self-enrollment. All of the environmental survey information is from self-enrollment, so to the extent that NEALS has influence over clinicians and clinical trials, it would be wonderful to see more promotion of registration through the clinician network. There also is an opportunity for NEALS to encourage clinical researchers and trial sponsors to use the research notification tool, because that tool is only as good as the number of clinical trial sponsors that are going to use it.

Dr. Brooks asked, as a pharmacist, whether Dr. Oliff would support having a specific designation of ALS drugs for the US Formulary and if he thought it would allow for better and more rapid coverage of treatment for patients who have such an advanced disease.

Dr. Oliff said he thought it would be beneficial, but that it was a question of whether it actually would happen. He has talked to some insurers that cover ALS drugs and they would appreciate knowing if a drug is indicated for ALS because it is a fatal disease. The problem is that insurers do not separate fatal from non-fatal diseases. They use the same process to review all therapies. Going in the direction designated by other fatal diseases is important and there have been discussions with insurance companies about doing this.

Lynn Brielmaier pointed out that payers are using inclusion and exclusion data from the clinical trials with respect to denying coverage. This leaves people who are living with ALS >24 months post-diagnosis out in the cold.

Dr. Oliff said he is aware that this is happening. When the claims are resubmitted multiple times, therapies eventually are approved most of the time. However, it takes a lot of time, effort, and human resources to keep submitting claims. Over the next several months, people are going to have to select their Medicare health plan coverage for next year. They need to look at what is

and is not included in the formulary and choose accordingly. He has had ALS for a long time and has had no problem getting coverage approved, but his co-pay is very high.

The Role of the National ALS Registry in Funding Research

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

Dr. Mehta indicated that next on the agenda would be to hear updates on some of the National ALS-funded research. Funding research is a very important part of figuring out the unknowns of ALS, especially potential risk factors and etiologies. The institutions that have been funded are engaged in cutting edge work. As mentioned earlier, the National ALS Registry is currently funding 24 institutions and are hoping to fund additional research this year. The research that the National ALS Registry funds offers a way to partner with academia and access their expertise in exposures, risk factors, and so forth.

National ALS Registry Funded Research Presentations: Part 1

Interactions Between the Microbiome, Metabolome, and Immune System as Underlying Mechanisms of ALS Pathogenesis

Benjamin Murdock, PhD
Research Assistant Professor
University of Michigan at Ann Arbor

Dr. Murdock presented an update on research the University of Michigan is conducting with funding from the National ALS Registry that is examining the microbiome in terms of its interaction with metabolism and the immune system as underlying mechanisms of ALS pathogenesis in order to use these both as biomarkers and ultimately as therapeutic targets. He explained that the microbiome is basically the collection of all the bacteria, local environments, and metabolites and everything that goes with those across the body. For the purpose of this talk when he used the term "microbiome," he meant the gut microbiome (e.g., bacteria and associated systems and environments in the gut) in terms of how that affects disease. During this presentation, Dr. Murdock provided background on the gut-brain axis, discussed the microbiome in ALS mouse models, and described the CDC ALS Registry project with human ALS patients.

The gut brain-axis is very complicated. While there are a lot of data and a lot of publications, Dr. Murdock provided a brief and simple overview and background in the interest of time to help people understand how the microbiome can impact the rest of the body, particularly central nervous system (CNS) diseases and neurodegeneration. It has been known for a while that the microbiome can affect other systems, although this is still a relatively young field that only in the last 20 years has become a major focus of research. In that time, a lot has been learned about the microbiome and how it affects different systems and different diseases. Under homeostasis and healthy conditions, the microbiome plays a central role in maintaining these systems and proper functions. For instance, the microbiome is entirely responsible for breaking down fibrous

materials and those produce short-chain fatty acids. These fatty acids not only maintain the integrity of the gut to prevent leaky gut, but also have anti-inflammatory effects. They are important for a number of other mechanisms, including fighting disease. The microbiome produces metabolites that can have a number of effects locally and on the nervous system. A lot of the early studies were done locally in the gut or areas around the gut, but it is now known that these systems are incredibly important for local homeostasis and the CNS as well. For instance, short-chain fatty acids such as butyrate, which is one of the major ones, are incredibly important for maintaining the integrity of the blood-brain barrier (BBB). They have anti-inflammatory effects in microglias, so they prevent neuroinflammation. While still somewhat controversial, it is known that neurotransmitters are created by the microbiome. At least a couple of studies have found that these can penetrate the BBB and have an effect on the CNS.

Having dysbiosis and dysregulation of the microbiome can have a severe effect on other systems, including the CNS. Dysbiosis often results in a leaky gut, which means the tight junctions of the epithelium in the gut are less pronounced. Metabolites and even bacterial products, such as endotoxins, can leak out into the periphery and into the blood, and there can be altered metabolites and different neurotransmitters. Losing short-chain fatty acid can affect BBB activity, as well microglial function. This has been observed in diseases such as inflammatory bowel disease (IBD), Crohn's disease, and neurodegenerative diseases. As Alzheimer's progresses, for instance, there is a significant correlation between amyloid beta deposition and an increase in inflammatory and microbiota. In contrast, there is a correlation with a decrease in anti-inflammatory microbiota. Similar factors have been seen with Parkinson's, with decreased neuroprotective molecules and dysregulated signaling. That correlates with increased bacterial populations of some sort or drops in others, increased toxic metabolites, altered protein metabolism, and decreases in short-chain fatty acids because bacteria are being lost in these diseases that are responsible for making short-chain fatty acids. Often there is an increase in pro-inflammatory bacterial components. These provide a proof of concept that changes in the microbiome and alterations in dysregulation can have an effect on neurodegenerative diseases, so this is one of the issues of interest in ALS.

Turning to the microbiome in mice, Dr. Murdock shared information from some of the more interesting studies conducted to provide proof of concept regarding why it is possible to jump from a project like that to human studies. ALS is known to have multifactorial causes, with the exception of familial ALS for which there is a known gene that is dysregulated, knocked out, or expanded. For the majority of sporadic ALS, multiple factors contribute to disease progression (e.g., genetic predisposition, immune system, exposures, et cetera). The goal is to determine potential associations and mechanisms and identify therapeutic targets and biomarkers that can be used in the future. A paper that was published a number of years ago in *Nature* speculated that a keystone species of bacteria, *Akkermansia muciniphila (AM; A. muciniphila)*, decreases over time and in many cases falls to a level below the limit of detectability. *A. muciniphila* has been shown to have a lot of anti-inflammatory and protective effects. When *A. muciniphila* was reintroduced into the microbiome of ALS mice, disease progression was delayed, grip strength did not decrease at the same rate, and there was a significant increase in survival. This suggests that manipulation of the microbiome can have a profound effect on disease course.

The ALS Epigenome-Inflammasome-Microbiome Mouse Study[8] did something somewhat similar in parallel. Rather than looking at one particular bacteria, this study examined the microbiome kinetically in order to look over time to determine whether the disease changed and in what order. In addition to physical phenotyping, the study assessed the microbiome over the course of the entire disease. There were regular immune phenotype intervals of time points so that these data could be linked. To validate this study and bolster the previous study that was done in *Nature*, this study assessed various bacterial species. One of the main bacterial species that was dysregulated in these mice was *A. muciniphila.* The mice were assessed to determine whether the microbiome was dysregulated in ALS in terms of whether sharp changes could be seen over the course of disease and when those changes occur. Looking at Alpha diversity, the diversity within the wild-type and SOD1 groups in terms of exactly how rich and varied the bacterial populations are, the ALS mice had enhanced richness and variability in their bacterial populations early on. As disease progressed, that evened out. At the very end stages of disease, that variability and diversity collapsed. That likely indicates that far fewer or far different bacterial species in ALS mice impacts disease progression, which is consistent with what is seen in humans.

Dr. Murdock noted that his primary focus since joining this research group has been studying the immune system in ALS. The immune system is complex in ALS and is not just good or bad. Getting rid of the immune system can actually make disease worse, but the immune system can be both protective and destructive. Certain pathways and certain cell types can slow the disease course while others accelerate it. The idea is to find out what cells and what pathways are causing disease acceleration and contributing to disease, as well as what is happening upstream and whether that can be changed without using a lot of drugs in ways that are more natural or easier. The microbiome is very easy to manipulate.

Some initial periphery and spinal cord phenotyping was done on these mice and some differences were seen in the periphery. Strikingly, over the course of disease, particularly in late-stage disease where the collapse of diversity was seen in the microbial populations, there were sharp increases in inflammation—particularly in the CNS. Activation markers and microglia were very up-regulated as well, suggesting that immune differences occur simultaneously or after changes in the microbiome. Putting this together and mapping it out on a timeline showed that dysbiosis of the microbiome occurs almost at the start of disease. The loss of diversity and very sharp change in the microbiome in ALS mice that occurs at later stages of disease occurs concurrently with the very sharp immune changes. This provided the impetus to look at some of these markers in ALS in human patients. In the final analysis, the immune metrics were correlated with microbial metrics looking at the top 20 bacterial populations in these mice at the end-stage of disease with a number of immune metrics. There were significant and strong associations between particular bacterial populations and CNS and immune functions, suggesting that the microbiome is playing a role. To summarize, specific bacterial populations can alter ALS survival. Changes in the gut microbial environment happen early, at least in mouse models, and occur upstream of motor dysfunction and immune dysregulation. Correlation analysis confirmed that there is some sort of relationship between the microbiome and the immune system.

[8] Figueroa-Romero et al. Dis Model Mech, 2019 Nov 15;13(2):dmm041947. doi:10.1242/dmm.041947.

This work is now being taken into the Human CDC Project that Dr. Murdock is working on for the National ALS Registry. The purpose of this project is to try to establish some of these links in human patients and drill down into the underlying networks to identify specific pathways or markers that can be used as biomarkers and therapeutic targets. The project as designed has 3 major aims that essentially piggyback onto the existing infrastructure, which is one of the strengths of the study and is probably one of the reasons it was funded. Rather than duplicating efforts, the study is using an existing R01 pipeline, attaching the microbiome to the initial datasets. Dr. Murdock noted that earlier in the day, they learned that the manuscript for some of the data he would be showing was accepted for publication. They have been collecting microbiome data and samples since at least 2016. The data accepted for publication were based on an older dataset to give everyone an idea of what they are working with. They have a number of cases and controls, as well as multiple beginnings of longitudinal data upon which the investigators plan to build.

Consistent with what was seen in mice, using a number of different statistical metrics to look at the Alpha diversity, ALS patients have reduced diversity in the fecal matter in the colon compared to healthy controls. They do not see the same stark differences, which is likely because the variability is much higher in human patients who live in a much different set of environments from one another than mice, which share the same cage and food. While the variability is going to be much higher in the microbial populations in ALS patients and controls in general, significant differences are seen. In addition, the study is also assessing the total levels of microbes that produce short-chain fatty acids, particularly butyrate-producing microbes. Butyrate is a very protective anti-inflammatory metabolite that is reduced in ALS patients as well.

As first pass, an analysis was performed using metabolic data that were generated from the parallel study combined with the microbiome data to determine whether there are patterns in terms of changes in ALS patients to prove that this is happening as a biological target. The microbiome and metabolism were combined to try to identify different metabolic pathways that were dysregulated. By and large the most dysregulated series of pathways are lipid metabolisms. It already is known from diabetic neuropathy and Alzheimer's studies that lipids can have an incredibly profound effect on the health, functioning, et cetera of neurons. In parallel, other pathways were seen beyond just lipids, such as sphingolipid metabolism and xenobiotic degradation in upregulated ALS and autophagy, infectious disease response, and protein metabolisms in downregulated ALS. Generating a profile based on a patients' metabolism and microbiome and then performing a principal component analysis (PCA) shows just how similar the 2 groups of patients are. While there is some overlap, they are very distinct in terms of patterns that show that these are dysregulated in the ALS group compared to controls.

In terms of the conclusions thus far in the human studies, the microbiome is dysregulated in ALS patients with fewer anti-inflammatory bacteria. The metabolome is dysregulated in ALS patients in terms of lipid metabolism in particular and in multiple additional pathways. ALS patients are very distinct in terms of their microbial-metabolic composition compared to controls. Moving forward, the study will assess this in a lot more detail to focus on specific microbial populations and species. The data presented have been collected slowly over the last couple of years. The plan with the CDC National ALS Registry grant is to expand the study to make it stronger and more informative. Part of that involves simply adding more patient samples. There are some longitudinal samples for analyses, but the goal is to add a lot more. In the past, changes in the immune system have been tracked to determine whether these changes can be associated with disease progression. For instance, if a sharp increase is seen in neutrophil,

more disease progression is seen in the Revised ALS Functional Rating Scale (ALSFRS-R). The plan is to do the same thing with some of these bacterial populations to determine whether someone losing a particular bacterial population is associated with more rapid disease progression. There are tons of published data and manuscripts showing that the immune system is linked to the microbiome. As part of the existing R01 and the pipeline that has been set up, there are now over 120 immune markers that are being examined using flow cytometry. There also is gene expression and cell pellets, and the observations the study has with the microbiomes will be linked to all of these metrics to see how they are related. For instance, if K-cells are thought to be associated with disease progression, are specific bacterial populations associated with more active or more aggressive in K cells and can that be changed somehow using therapeutics? There is a robust series of clinical metrics. Dr. Stephen Goutman, who runs the clinic, has done an incredible job of phenotyping these patients and collecting robust clinical data. These clinical data can be married to the microbiome, immune system, and metabolism data to identify ways dysregulation occurs. The number of participants are shown in this table:

	Overall	2023
Consented	927	228
Collected	461	96
Baseline	307	83
Longitudinal	154	12

Over 20% of the nearly 1000 overall patients were added in the last 8 months. Nearly 100 additional samples have been collected since the start of the year. These Baseline and longitudinal numbers will increase more rapidly. Efforts are being made to recruit control patients. These are not patients who are randomly selected from the internet, Facebook, and websites. Instead, the goal is to add controls who are relatives of patients who often have similar genetics, live in similar environmental conditions, and make much more robust controls. Emerging and future directions for this study will focus on answering the following questions:

- ❑ How do the immune system, metabolome, and microbiome operate together in ALS? How are they related? How are they associated with the metrics?
- ❑ Are altered gut-brain systems in ALS causative to disease progression?
- ❑ Are there any other microbiome other microbial interactions that have been shown in terms of genetics, environmental exposure, hormones, et cetera?
- ❑ Can we leverage the microbiome to modify the ALS disease course to ultimately buy patients more time? The nice thing about the microbiome is that it is very easy to modify, it is very cheap, and it is very accessible. That can be done at almost any clinic around the world. It requires antibiotics in a pill or antibiotics in a colonoscopy.

Discussion Highlights

Ms. Pauls Backman read some of the questions aloud during each discussion period. Questions that were posted during the registration process and raised during the meeting are included in the attachment sections for Days 1 and 2 at the end of this document.

Dr. Brooks asked whether the gut microbiome results are related to the amount of stool produced.

Dr. Murdock said that the amount of stool produced is not necessarily as relevant as relative abundance. Within a gram of fecal matter, relative abundance is done within that particular unit.

That being said, the composition of the microbiome is highly variable based on food intake, time of day, sex, age, and other factors. In terms of actual output, people are basically sent home with a piece of sterile toilet paper. After cleaning themselves following a bowl movement, they put the toilet paper in a package and send it back.

Emily vonScheven asked whether any longitudinal analyses have been performed to identify changes with medications, diet, or disease progression.

Dr. Murdock responded that this is on the "To Do List." One problem they are having now, and one of the reasons they wanted to conduct this study, is because the data are under-powered, especially the longitudinal data. They want to increase the power of baseline and longitudinal study components. For the longitudinal study of the immune system, they got by with about 25 to 30 patients because it was possible to see significant differences within that small sample size. Given the variability of the microbiome, they wanted to add many more longitudinal samples. He fears doing this next year because the first couple of years of this study were basically sample collection. However, the goal is to try to get as many samples as possible. In about Year 3, the plan is to run all of the samples at once to produce batch variation.

In terms of comparator groups, Emily vonScheven asked whether they have compared to other disease groups and how the controls were matched and Sarah Parvanta asked whether the controls in the human study are household controls.

Dr. Murdock indicated that the matching of the controls is done mostly through covariates, at least for the initial analysis. Basically, when their statisticians created these models, they would adjust for age, sex, and that sort of thing. That is really one of the reasons they want to include some at-risk patients for controls, family members, because that cuts through a lot of those problems, especially in terms of environmental exposure, diet, and things like that. Obviously, if there is a caretaker of a family member who is the brother of someone who has ALS who is his sister, he is not going to be able to match them exactly by age or by sex. But they do try to match by environmental factors. About 40% of the participants are ALS patients, about 45% are general controls (e.g., not environmental controls, but someone randomly off of the internet who volunteered for the study). About 20% of the controls are at-risk patients (e.g., household controls of people who share similar characteristics or environments). Going forward, they are going to have to figure out when it is appropriate to use general controls and when to focus on at-risk controls. A lot of power is lost by using just the at-risk controls because they can only be matched with people who have ALS. Regardless, they have controls and that is something they want to assess going forward.

Nitesh Sanghai asked whether these pathologies (i.e., decrease in microbiome) are a result of an aggressive SOD1 mutation as the studies are in G93A mice models, or if they can think in an opposite manner about whether the microbiome decrease leads to SOD1 aggregation and how confident Dr. Murdock is in the risk factors involved.

Dr. Murdock said that in terms of confidence in the risk factors, it is complicated. In terms of the SOD1 mice, it has been seen in other mouse models. The fact that they see similar patterns in their human patients validates what is being seen in SOD1 mouse models. Anytime there are SOD1 mouse models, there are going to be caveats because it only reflects a small fraction. Regarding whether a microbiome decrease leads to SOD1 aggregation, he said he did not know off of the top of his head. There are always questions about what is causative, correlative, upstream, and downstream. It is not known for sure whether this contributes to SOD1 aggregation. As with a lot of these systems, he always says that it is not necessarily A to B to C.

For instance, there are changes in the microbiome, that affects the metabolome, that affects the immune system, and that in turn affects the microbiome. They are conducting some of these studies to figure out what is causative, correlative, upstream, and downstream.

Nitesh Sanghai asked what microbiome they looked into in ALS mice models and whether the same microbiome is found in humans. That is, are they comparing apples-to-apples?

Dr. Murdock indicated that they have not done that study yet. It is not comparing apples-to-apples because there is a mouse model versus a human patient model. The main difference is that the mice are in a very controlled environment and the humans are not in a controlled environment. One of the reasons he showed the mouse data was more of a proof of concept to show that they do see associations and think that they are contributing to disease progression. Down the line, it is possible that they could compare the mouse microbiome to the human microbiome. But again, mice are going to have a different microbiome in control and healthy mice than they are in control and healthy patients. There are going to be some caveats with the analyses, but just because they are not directly comparable does not necessarily mean they are not important. One of the reasons they submitted this study to the CDC is because based on these observations, they want to assess whether similar patterns are seen in humans as are seen in mice. So far, they have. They have not assessed whether there are the same bacterial populations yet. His opinion is that there probably are not and there probably will be some significant differences. However, that does not mean it is not happening in human patients—it just might be with different bacterial populations.

Nitesh Sanghai asked Dr. Murdock to explain how the pathologies in the ALS models affect mostly the brain axis rather than spinal cord axis, or if they are both correlated.

Dr. Murdock said his guess is that they are correlated. One of the problems is that a lot of the research that has been conducted previously on the gut-brain axis has been focused on the brain and not the spinal cord in Alzheimer's, Parkinson's, and other diseases. Not a lot of work has been done to assess the spinal cord yet. Therefore, he did not want to make a lot of generalizations because there is not a lot of information. His guess is that similar patterns affect the brain and the spinal cord. The field itself is incredibly young. The microbiome field itself is barely 20 years old. It is a really good question and great observation, but it is still in its infancy and he did not immediately know whether anyone had ever compared the brain to the spinal cord to determine whether those changes are comparable.

Jonathan Guest asked whether Dr. Murdock would suggest that people with ALS use probiotics to promote lipids.

Dr. Murdock said when he gets this question and immunology questions, he prefaces his response by saying that he is not a clinician and is not legally allowed to give medical advice, but he could not see any way that using probiotics to try to get more short-chain fatty acids could hurt. He would like to assess this further before people start "pulling the trigger" on that sort of treatment.

Lynn Brielmaier asked how to start getting natural history studies to include and analyze fecal samples.

Dr. Weisskopf said that while he did not have a definitive answer, he thought they could start collecting these samples, for example, in large cohorts. The Nurses' Health Study is doing a lot

of collection of fecal samples. Samples are needed and they can then follow those people. Some studies are trying to do that, but it is a lot of work and takes some time.

Dr. Murdock added that especially for longitudinal samples, they have found that there is a large drop-off after the first sample. Getting longitudinal samples is particularly difficult, because it turns out that when someone has a motor impairment, collecting fecal samples is not a lot of fun for caregivers or anyone else.

Linking Long-Term Air Pollution Exposure with Inflammation, ALS Risk, and Disease Progression

Stephen Goutman, MD
Associate Professor of Neurology
University of Michigan at Ann Arbor

Dr. Goutman reported on linking long-term air pollution exposure with inflammation, ALS risk, and disease progression. Noting that his group at the University of Michigan is interested in environmental risk factors and ALS, he pointed out that the Midwest has some of the highest rates of ALS in the country so one of their interests has been to understand why the Midwest is unique. This group is interested in the idea of the exposome and the cumulative effects of environmental exposures and the corresponding biological responses across the lifespan. The exposome is challenging because it involves everything. It is very complicated to capture all of the various types of exposures throughout one's lifetime because it involves every exposure from the fetal timeframe throughout adulthood. This is not easy to do retrospectively or prospectively. It requires developing models to look at various exposures concurrently and using all of the data that are available to estimate someone's lifelong exposure.

While his group is interested in a host of other exposures, during this session Dr. Goutman discussed the role that air pollution may play in ALS progression. In order to dissect exposures, the layers must be peeled away like an onion to understand the totality of exposures. As shown by the gene-time-environment hypothesis, there is a genetic susceptibility or genetic load for somebody to develop a disease (e.g., ALS, cancer, diabetes, et cetera). In addition to genetic susceptibility, cellular damage occurs as people age. On top of that, individuals may have some sufficient level of exposure to toxicants and pollutants that pushes over a threshold to become the self-perpetuating disease process. Somebody who stops having exposures may prevent disease, but somebody who continues to have exposures may decline down to the risk of having ALS.

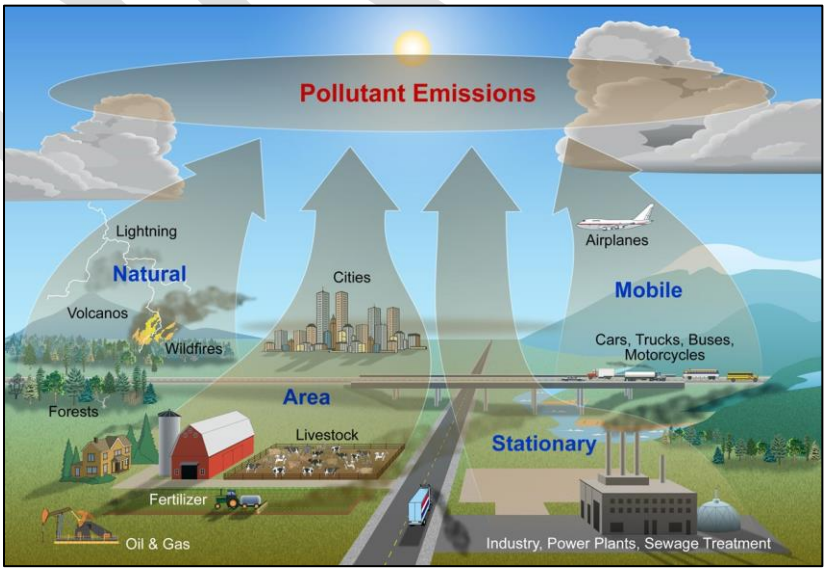
Air pollution has been of great interest for a number of neurodegenerative diseases. Lung inflammation is linked to asthma and other respiratory diseases, and more recently particulate matter and air pollution exposures have been linked to neurodegenerative disease. There is a small but building literature on ALS suggesting that perhaps people who have higher air pollution exposures have shorter times to hospitalizations. Superimposing the rates of Parkinson's disease on a map of particulate matter levels in the US illustrates that there is a high rate of Parkinson's in places where there are high levels of air pollution exposure. Dr. Goutman drew attention to Dr. Sara Adar's recent publication in *JAMA Internal Medicine*[9] Dr. Adar and her group were interested in seeing the different types of air pollution exposures. This

[9] Zhang B, Weuve J, Langa KM, D'Souza J, Szpiro A, Faul J, Mendes de Leon C, Gao J, Kaufman JD, Sheppard L, Lee J, Kobayashi LC, Hirth R, Adar SD. Comparison of Particulate Air Pollution From Different Emission Sources and Incident Dementia in the US. JAMA Intern Med. 2023 Oct 1;183(10):1080-1089. doi: 10.1001/jamainternmed.2023.3300. PMID: 37578757; PMCID: PMC10425875.

study illustrates that air pollution does not come from one source. Instead, it is a multifaceted type of exposure that includes agricultural, road traffic, energy production, wildfire, and other exposures. Dr. Adar and her team looked at the Health Retirement Study (HRS) of about 28,000 who have been recruited over many years and found that total sources of particulate matter were related to incident dementia. In particular, sources from the agricultural sector and wildfires influence this risk of dementia across several modeling systems that they used looking at a particular matter alone or combining other sources. This is strong evidence in multiple neurodegenerative diseases that air pollution matters and may play a role in the rate or risk of a disease.

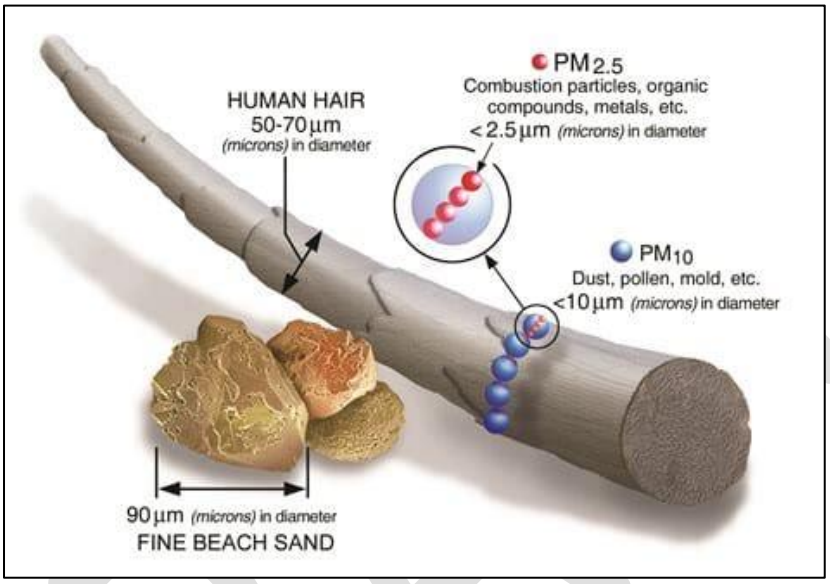
Dr. Goutman's group is currently looking at a number of air pollutants in their cohort, which is comprised of individuals recruited from the University of Michigan's Panger ALS Clinic. Controls are recruited from multiple collection sites throughout Michigan in order to have a geographically dispersed sample. At the beginning of COVID, there was an inability to recruit controls because many researchers had to pause their studies. Recruitment now has increased. They are effectively recruiting people by understanding what areas of Michigan they want to target. They have targeted individuals with random address mailing, though that aligned with the beginning of COVID. They also have had success using Internet recruiting resources, such as Facebook, in order to target populations of individuals who are interested in volunteering as controls. Controls are now recruited throughout the state. Because they are interested in understanding shared environmental risk factors with family members of individuals with ALS, they created an "At-Risk" category that is comprised of family members who share some genetics due to being a blood relative. Non-family household members are included in a separate category in order to understand the difference between people who are completely separate from participants with ALS versus people who share family history.

Dr. Goutman shared this graphic from the National Park Service (NPS)[10] to illustrate air pollution pathways from mobile sources (cars, buses, planes, trucks, and trains), stationary sources (power plants, oil refineries, industrial facilities, and factories), area sources (agricultural areas, cities, and wood burning fireplaces), and natural sources (wind-blown dust, wildfires, and volcanoes):



[10] https://www.nps.gov/subjects/air/sources.htm

To highlight a few of these sources of air pollutants, $PM_{2.5}$ comes from gasoline, oil, diesel fuel, or wood combustion. Ozone is formed via atmospheric chemical reactions of volatile organic compounds (VOCs) and nitrogen oxides. Black carbon comes from diesel engines, stoves, wood burning, and forest fire combustion. Sulfate is formed from burning coal, oil, or diesel. NO2 comes from automobile exhaust, power plants, and machinery emissions. This graphic from the Environmental Protection Agency (EPA)[11] helps to put the size of $PM_{2.5}$ into perspective:



Ozone is a process of an atmospheric chemical reaction when sources of oxides of nitrogen and VOCs are combined with heat and sunlight in the atmosphere.

Dr. Goutman's group is using measures of particular matter from NASA satellites that circle the earth. This satellite system continuously circles the globe and takes estimates of what is happening at a kilometer, diameter, and even smaller in some cases and is able to constantly read what is occurring on the ground. These satellites are able to use Aerosol Optical Depth (AOD), which is able to really understand how much light can really be transmitted through these vertical columns above the earth. Using this information, model systems can be created to estimate how much air pollution is occurring over the globe or in the US at any given time. The ability to have discrete intervals helps to understand over the course of a couple weeks what somebody's air pollution exposure is. The addresses of individuals can then be utilized to calculate each participant's $PM_{2.5}$. over a time period to assess disease risk and progression. It is not that easy to get an address history, so people are asked to go back in time to provide their addresses. This is not difficult for those who have lived in the same house lifelong, but it is much more difficult for those who have had many addresses. An incorrect address or misspelling can put someone in the wrong spot on the globe. While this takes a lot of effort, it strengthens their research as they have been able to line up over 80% of addresses.

[11] https://www.epa.gov/pm-pollution/particulate-matter-pm-basics

The focus of this group's study is on linking long-term air pollution exposure with inflammation, ALS risk, and disease progression. The hypothesis is that air pollution can interact with the immune system, triggering an inflammatory response. These 2 factors combined can alter one's risk of getting ALS, ALS risk survival, and the progression rate. Dr. Goutman shared information about their cohort during this presentation, which is not included in this summary report because these data were unpublished, not peer-reviewed, and being analyzed at the time of this meeting and he requested that they not be photographed, shared, or posted on social media as they were still considered confidential.

Discussion Highlights

Ms. Pauls Backman read some of the questions aloud during each discussion period. Questions that were posted during the registration process and raised during the meeting are included in the attachment sections for Days 1 and 2 at the end of this document.

Dr. Stommel noted that it seemed like $PM_{2.5}$ was reduced on the map in the Northern areas of the Continental US (CONUS), but he wondered whether this accounted for the use of wood stoves in cold relatively unpolluted areas.

Dr. Goutman thought this was a good question but indicated that he did not know off-hand, and Ms. Pauls Backman suggested that it would be a good topic for future research.

Emily vonScheven asked how they control for other geographically-associated predictors of health and medical care, including access to care, income, other resources, and other social determinants of health (SDOH).

Dr. Goutman replied that this is one of the untapped areas across the ALS sphere of research. There are health disparities, and a better job needs to be done of understanding and capturing these in ALS studies. It is important to better understand how SDOH impacts risk and progression of ALS. In their models, they use markers of SES as a covariate. For example, they use the Area Deprivation Index (ADI), which is a marker of SES. Consideration also is given to urban versus rural areas and how that may impact the models. He stressed that the ALS research community needs to do a better job of ensuring that diverse populations are incorporated into ALS research versus just adjusting for somebody's SES.

Regarding a question about whether this study is looking at where people have worked in addition to residential locations and a question from Brian Kaplan about whether the models consider indoor air, Dr. Goutman indicated that this model is not considering indoor air. They have separately looked at occupational risks. He acknowledged that the question of indoor air is an important one that related to a point he raised earlier that one is not exposed in a vacuum or silo to just one type of pollutant. People spend time in their homes and at work and engage in hobbies, physical activities, sports, et cetera. They had a paper published about a year ago that looked at self-reported occupational exposure histories and settings and how that risk was related to ALS. One thing this study showed was that exposure to combustion diesel exhaust was related to one's risk of ALS. A number of studies across the globe have shown that, so this is a well-known risk. All of these factors are increasing, so researchers need to be thinking about combined models to capture and understand occupational, residential, and other risks and how to factor the totality of these exposures together. Everybody's help is needed. Longitudinal studies are needed. Individuals need to participate and share their data. When a segment of the population is missing, that is a confounder of bias for the data. More needs to be

done to capture the diversity of people with ALS and the diversity of healthy participants. The more people involved, the better the research.

Military Exposures and ALS in a Large Veteran Population

Marc Weisskopf, PhD, ScD
Harvard University

Dr. Weisskopf presented an update on a recently funded project focused on military service and ALS in a large veteran population. This association first came to prominence in the early 2000s with a couple of papers following the Gulf War. Horner et al.[12] assessed deployed versus non-deployed Gulf War veterans. Haley et al.[13] compared observed and expected incidence of ALS in Gulf War veterans diagnosed before 45 years of age. Both studies noted about a 2-fold increased risk of ALS among the deployed veterans, which generated a lot of interest. There was some concern about the way the studies were conducted, finding cases, and the design. Dr. Weisskopf worked with Dr. Ascherio through a collaboration he had with the American Cancer Society (ACS) to study this question in a much more general military population[14] soon after these studies and also found an increased risk of ALS among those who served in the military. This study was conducted in the Cancer Prevention Study (CPS) cohort of the ACS. The CPS included interviews with 1 million people in 1992, half of whom were men. Drs. Weisskopf and Ascherio focused on the half a million males in that cohort and found a roughly 60% increased relative risk of ALS among those who had ever served in the military. There was some variation across the branches of service, but not dramatically. Of great importance is that this population did not have anybody from the Gulf War, which suggested that perhaps there seems to be something more general about military service that seems to be increasing the risk of ALS. Dr. Weisskopf has followed this up in some other cohorts as well that showed similar results.

He followed this up in some other studies as well. In the National Longitudinal Mortality Study (NLMS)[15] of a sample representative of the US population, he found an increased risk of ALS mortality, though the results were not quite as strong. He also does a variety or work with the Danish Registry,[16] which basically includes the entire Danish population. Military service means something very different in other countries in Denmark compared to the US. The way they could assess military service through the Denmark Registry was different from questionnaires in which people report whether they served. By looking at occupational history of being in the military in Denmark, they found an increased risk of ALS in military personnel in this cohort. A review[17] from a few years ago specifically of studies that had non-veteran controls showed increased risk of ALS in military personnel. Among all of the factors researchers tend to study with regard to ALS, the finding that military personnel seem to have an increased risk of ALS for some reason is one of the more consistent findings. There also is a nice review by Beard and Kamel in 2015 that goes through this and a few more of the studies.[18] It has still remained elusive as to what it

[12] Occurrence of amyotrophic lateral sclerosis among Gulf War veterans R.D. Horner, K.G. Kamins, J.R. Feussner, S.C. Grambow, J. Hoff-Lindquist, Y. Harati, H. Mitsumoto, R. Pascuzzi, P.S. Spencer, R. Tim, D. Howard, T.C. Smith, M.A.K. Ryan, C.J. Coffman, E.J. Kasarskis Neurology Sep 2003, 61 (6) 742-749; DOI: 10.1212/01.WNL.0000069922.32557.CA

[13] Excess incidence of ALS in young Gulf War veterans; Robert W. Haley; Neurology; Sep 2003, 61 (6) 750-756; DOI: 10.1212/WNL.61.6.750

[14] Weisskopf et al. Prospective study of military service and mortality from ALS. Neurology 2005; 64: 32-7.

[15] Weisskopf et al in 2005, Epidemiology, 2015

[16] Seals et al., Epidemiology, 2016

[17] Tai et al., J. Clin. Neuro., 2017

[18] Beard JD, Engel LS, Richardson DB, Gammon MD, Baird C, Umbach DM, et al. (2017) Military service, deployments, and exposures in relation to amyotrophic lateral sclerosis survival. PLoS ONE 12(10): e0185751. https://doi.org/10.1371/journal.pone.0185751.

is about military service that seems to be affording this increased risk of ALS that is relatively routinely seen. Some of these studies, including the one with Dr. Ascherio in the ACS cohort, could look at a few aspects of military service (e.g., branch, deployed, not deployed) and that is more or less what people have been able to look at because of the lack of more detailed data about military history. That is starting to change, which could help to dig deeper into the military experience and what may be increasing risk.

A relatively recent study of a military population combined VA and DoD data. Because VA data has mostly older people and often ALS is identified in VA hospitals and other places, it has been difficult to bring VA data together with DoD data to get more detailed information. This study did this to the extent possible to study military service and ALS on the West Coast. Among 226 cases identified in VHA between 2000-2015, 139 were identified as definite. In a piecemeal way, this study was able to pull in some DoD information and in a more detailed way. For instance, did they have a traumatic brain injury during their experience in the military? What job did they have in the military? What contaminants are common for particular jobs? They developed a Job Exposure Matrix (JEM) to determine ALS prevalence per 100,000 people for each type of major occupation. Comparing the different types of jobs, pilots and crew members of planes like Bombardiers were at significantly higher risk of ALS. They also found that HCP and scientists were at higher risk for ALS. This begins to address the question of what the underlying factors may be that are leading to these risks. Notably, the branch of the military that seems to differ in various studies are the Marines. For whatever reason, the Marines seem to be at lower risk. Dr. Weisskopf pointed out that he raised this to make clear that military service is definitely not going to be monolithic. It involves many different exposures, some of which may be protective and some that are not. Trying to dissect this is going to be an interesting area of research.

This is exactly the kind of study that Dr. Weisskopf's team wanted to do, but on a larger scale. They are now trying to take advantage of a new venture by the VA and DoD to try to facilitate this combining of data across the 2 agencies. The VA and DoD created the Department of Defense VA Infrastructure for Clinical Intelligence (DaVINCI). The creation of this infrastructure has been quite some time in the making. It was authorized in 2013, but has only been up and running for a few years. DaVINCI includes data from both VA and DoD to create one place to link and harmonize the data for individuals. Very few people take advantage of this system yet, which is good and bad, since Dr. Weisskopf's team will be guinea pigs. Still, they want to take advantage of this project across the 2 systems. ALS cases will be identified from within the VA data, but now new military-type data will be incorporated such that more accurate information will be available on traumatic brain injury (TBI) and blast injury for example. Datasets will be included such as the Defense Enrollment Eligibility Reporting System (DEERS) that that includes eligibility, enrollment, demographics, service, et cetera and the Defense Manpower Data Center (DMDC) that includes deployment-related information. There also are death files, pharmacy data, medical procedure data, demographics, et cetera). There are in-theater and stateside medical data. Some of the data go back to about 2000, but that varies by data source.

The key variables of interest to Dr. Weisskopf's team include the following:

- ❑ Military service history
  - Branch, jobs, deployments
  - Can be captured earlier than 2000
- ❑ Military health data
  - Traumatic injuries, pharmaceuticals, procedures, et cetera
  - In-theater and stateside
- ❑ VA health data
- ❑ Demographics, lifestyle data
  - Age, sex, race, ethnicity, smoking, education, body mass index (BMI)
- ❑ Death data

A method for identifying cases must be defined. Many researchers have examined VA data for ALS, so there are existing methodologies for case ascertainment. This reflects ATSDR's approach:

Definite
- ICD-9 335.2 or 335.20, ICD-10 G12.21 in 1 year AND
- Prescription for riluzole or edaravone, or relyvrio

Probable
- 2+ ICD-9 335.2 or 335.20, ICD-10 G12.2, G12.21 in 1 year OR
- 2+ prescriptions for riluzole or edaravone, or relyvrio

Possible
- Any ICD-9 335.2 or 335.20, 335.9, ICD-10 G12.2, G12.21 OR
- Any prescriptions for riluzole or edaravone, or relyvrio

Not ALS
- None of the ICD odes, no ALS meds, no VBA 8017 code

Controls will be matched on some factors, and it will be important to ensure that the controls do not have ALS. They are still debating the veterans benefit action that came out of the early studies on ALS in the military such that any military personnel who have ALS have presumptive benefits, which is the VBA 8017 code. There is some question about whether to use that because of needing to make an application and there are issues around that code in terms of who does and does not get it. They probably will use this as a rule-out but may not use it as an identifier. As best they can, they will define the onset of ALS from the first instance of any one of these variables and that they be in the data source for at least 1 year to enrich for incident cases versus those who have had ALS for some time. The controls will not have ALS. For computational reasons, there will be 10 controls per case to make this more manageable. The current discussion is to match on sex, being alive without ALS at the age of the ALS case, same VA station, and in DaVINCI or not.

This is the general context within which Dr. Weisskopf's team is starting out. The specific aims are to: 1) examine the association between military job (MOS) and ALS risk, with the ability to explore individual jobs and JEM; 2) examine the association between deployment and ALS risk factor (e.g., ever, location, et cetera); 3) examine the association between history of injury in the

military and ALS risk (e.g., head, other, et cetera); and 4) examine the association between statin use and AS risk (e.g., statin use as a modifier of other exposures).

They are working with some folks in one of the DoD research branches who collect information about different jobs and pollutants people are exposed to on those jobs and are speaking with them about creating JEMs across different jobs. There are ways to cross-talk that from civilian jobs, but they are also hoping to take advantage of actual military data on exposures in different jobs. The rationale behind assessing statins is because they wanted to have a potential avenue toward whether there could be interventions that might be helpful to those who have some past experience that puts them at higher risk. A relatively recent study review[19] about statins and ALS suggested that that may be protective for ALS, so they certainly want to explore that question within this very large database. Of course, statins reduce cholesterol and Co-enzyme Q_{10} and they are antioxidants, modulate the immune system, and are anti-inflammatory—including neuro-inflammation. Because of some of these properties, perhaps there are intervention possibilities that would protect against something in particular military jobs.

It has taken quite a lot of time to get through all of the paperwork, IRBs, and so forth to get access to the data, but they finally got access to some of the data in the last few weeks. Dr. Weisskopf noted that these are preliminary data that will be further explored, but he wanted to highlight the large numbers they will have. With a very broad ALS classification (e.g., ICD-9 335 or ICD-10 G12.2) almost 40,000 cases have been identified. With specific ALS ICD-9 codes (335.20 and ICD-10 G12.21), over 26,000 cases have been identified. The vast majority are male and there is racial and racial and ethnic distribution. While the cohort is predominantly White, almost 10% are Black or African Americans. Because the numbers are so large, there also are some numbers of other races and ethnicities. Race and ethnicity are still unknown for about 30%, but it is anticipated that this can be filled in with other records.

Discussion Highlights

Ms. Pauls Backman read some of the questions aloud during each discussion period. Questions that were posted during the registration process and raised during the meeting are included in the attachment sections for Days 1 and 2 at the end of this document.

Dr. Felman said she assumed this database contains the participants from the Million Veteran Program (MVP) studies, noting that individuals in this study have consented to genetic studies. She asked whether Dr. Weisskopf and his team have access to these data, which would allow them to investigate a genetic link to exposure risk.

Dr. Weisskopf responded that they are not exactly clear at this point who is in the DaVINCI database that has both VA and DoD data. Persons in the MVP studies should be including in at least the VA data. His colleagues at the VA will be much more knowledgeable about how they could access the MVP data or link to studies they are conducting. It would be extremely interesting to assess the genetics on their own and then layered on to determine whether genetics are related to exposures and whether genetics modify effects.

Dr. Finger noted that the Sagiaju paper found vast demographic differences between cases identified as "definite" and those classified as "possible," indicating that disadvantaged patients are missed when multiple visits are required to qualify as "ALS." He suggested being careful with these definitions.

[19] Chang, et al., Medicine, 2021

Dr. Weisskopf agreed that this was excellent point and acknowledged that it certainly is one of the concerns. There is trade-off between being as precise as possible versus capturing people who should not be captured. They want to be absolutely certain they know what they are talking about in this group, but also recognize that may not be representative. They do have the ability to expand out to the more possible range or play with the definitions somewhat to make sure. He thinks they will do some exploring of this to make sure that they are not missing under-represented populations. One of the advantages of this database is that it is so huge, they will still have numbers that even if those groups are relatively small and still will have the possibility of making some difference for them.

Tyler Gaetano requested further information about Camp Lejeune toxic water victims and possible connections to ALS.

Dr. Weisskopf said there are ways to look at that. Once they dig into the data, he will have a much better sense of what actually is doable and what is in there. He believes there will be information on where people did their basic training stateside, so they could either target very specific camps like Camp Lejeune know that those exposures were occurring, or they could look more broadly to determine whether there was any geographic distribution where military personnel were located for long periods of time.

M. C. Collet asked what the results have been from the studies of military outside the US and whether there has been any consensus on ALS in other countries' military members.

Dr. Weisskopf responded that there are the findings of his team from Denmark. There was a study out of France that more or less pitched that they did not see an association. That is one of the few that did not, but there are issues around that study. For example, the ALS cases were only being found in the actual military data, so that that restricted it to an extremely young population. People get ALS much older when they no longer are in the military. There were some subgroups in that study for whom there was an increased risk, but it is difficult to interpret that study. Since he had not thought about this for a while, he cautioned that he may be missing some studies. He thought perhaps Fang Fang's study in Sweden was looking at this and may already have been published.

Dr. Mehta added that Fang Fang's analysis would include military veterans.

Regarding Dr. Weisskopf's comments on statins, Jonathan Guest asked if he is looking at creatine kinase (CK) as a factor. He has been told that a high CK level is a reason not to use statins.

Dr. Weisskopf said that while he has not been considering this, it certainly is something that could be considered as a contraindication.

Pre-Disease Biomarkers of Persistent Organic Pollutants (POPs), Immune System, and Amyotrophic Lateral Sclerosis (ALS)

Marc Weisskopf, PhD, ScD
Professor of Epidemiology
Harvard University

Dr. Weisskopf presented an update on a somewhat older project that was only slightly more advanced due to some issue they had been having. The primary purpose of this study is to examine pre-disease biomarkers of POPs and ALS. He pointed out that POPs can be organochlorine (OC) pesticides, polychlorinated biphenyls (PCBs), polybrominated diphenylethers (PBDEs), and other compounds. They are organic in nature and persist in the body and the environment. These compounds are of interest in ALS for a variety of reasons, such as having known neurotoxic and immunotoxic effects. Because of the chlorine component, they are highly persistent in the environment and the body. The canonical of these would be dichlorodiphenyltrichloroethane (DDT) that was written about by Rachel Carson in the historic book *Silent Spring*.

A variety of studies have suggested that higher exposure to pesticides may be related to higher risk of ALS. A meta-analysis by Kamel et all in 2013[20] summarized many studies and found overall an increased risk of ALS with exposure to pesticides. Andrew et al in 2021[21] did some interesting work looking at US Geological Surveys (USGS) of pesticide use in different parts of the US in a broad analysis. They clearly found heavy weighting toward significant increased risk, suggesting some kind of signal between the use of pesticides and ALS. Drs. Stephen Goutman[22] and Eva Feldman published a paper with their cohort in a Michigan case-control study looking at blood samples taken from ALS cases and controls to measure a series of OC pesticides, PCBs, and PBDEs. This study found some signals suggesting increased risk of ALS with some of these compounds. There was another study out of Italy with just 38 cases and controls that also tried to look at this, but it was quite small and there was not anything terribly consistent in this study. These are the only studies that have tied to biomarkers of exposure to these compounds. One problem with these studies is that the cases already have ALS, so the concern is that perhaps something about the ALS biology or behavior of the person affects one's exposure or metabolites within the body, there could be differences that are related to the ALS. That can complicate the interpretation of the results.

Dr. Weisskopf and colleagues decided to explore similar questions but wanted to find out whether they could identify indicators prior to ALS onset in terms of the pesticide profile and how that related by collecting blood samples prior to the onset of ALS. To do that, they collaborated with groups in Finland and Denmark and took advantage of existing cohorts that were set up many years ago for cancer and cardiovascular disease (CVD). These studies enrolled thousands of people and collected blood samples at the time of enrollment. These samples were stored and were made available for use. Dr. Weisskopf and colleagues proposed to identify ALS cases in 3 cohorts in Finland and 1 cohort in Denmark. The prospective cohort studies in Finland with serum samples included the 1966-1972 Finnish Mobile Clinic Health Examination Survey (FMC), 1973-1977 follow-up FMC (FMCF), and the 1978-1980 Mini-Finland Health Survey (MFH) for a total of 56,862 people. The Denmark cohort came from the Danish

[20] Kamel et al.,Neurotoxicology 2013
[21] Andrew et al., Neurotoxicology 2021
[22] Su et al., JAMA Neurology 2016

European Prospective Investigation into Cancer and Nutrition (Danish EPIC) with a total of 57,053 people.

An advantage of the national health care system that tracks everyone's medical involvement in Finland and Denmark is that it is possible to identify the people in these cohorts who developed ALS later through linkages with the national registries there. Another advantage is blood samples were collected and stored at the time of enrollment, which made it possible to identify who has ALS in these cohorts, randomly match a couple of controls to each case, and then pull those samples specifically to analyze them for a suite of pesticides before ALS onset. They expected to identify approximately 250 ALS cases total would be expected from these combined cohorts. This study was funded around the beginning of the COVID-19 pandemic, which created some problems. This also coincided with changes in European laws regarding data security, which introduced many wrenches. Those wrenches have been more easily overcome in Finland than in Denmark. Each country in Europe interprets these rules somewhat differently in each institution.

The Danish Cancer Society who they are collaborating with had particular problems with how to handle this and Dr. Weisskopf and colleagues have only recently received approval to receive the Danish data and samples. One of the workarounds was that samples could not be sent to the US to analyze. Therefore, they have to identify laboratories in Europe. Suffice it to say, they do not yet have samples from Denmark because of all of this. Given that they were able to get over the hurdles much faster in Finland, Dr. Weisskopf focused on sharing information from the Finnish samples. Because these studies focus on a variety of data, it is possible to analyze a number of variables including the following:

POPS:
- ❑ Organochlorine pesticides (DDT, DDE, HCB, HCH, trans-nonachlor)
- ❑ PCB congeners (118, 138, 153, 180, 105, 118, 156, 157, 167, 189)
- ❑ PBDE congeners (47, 99, 100, 153, 154)

Covariates:
- ❑ Age
- ❑ Sex
- ❑ Smoking
- ❑ Education
- ❑ Body mass index (BMI)
- ❑ Occupation

In terms of the proposed study aims, Specific Aims 1 focuses on ALS risk and is a nested case-control study using conditional logistic regression that includes the cohorts of cases and controls matched 1:2 on age, sex, freeze thaw cycles (municipality). Aim 2 is focused on ALS survival using all available cases. Using a Cox proportional hazards analysis, cases are followed to time of death or end of follow-up time to determine whether their exposures identified in the blood samples predict a different survival rate. The focus of Specific Aim 3 is to assess immune status in relation to extracellular vesicles (EVs) that are indicative of biological processes going on. These are nano-scale particles secreted by all cells in the body that are present in peripheral blood and carry cargo from the parent cell, including proteins, micro ribonucleic acid (miRNA), and surface markers. EVs are becoming increasingly interesting to study for a variety of reasons, one of which is that they can come from a neuron, from an immune cell, can wind up in circulation, and can be identified from blood samples.

The EVs are different sizes, are released in different ways, may mean different things; are involved in signaling between cells at a very long distance; and/or may be jettisoning things from cells. Ultimately, they offer a way in peripheral blood to potentially assay things happening with the parent cells. All sorts of things can be found in these cells such as small RNAs and miRNA that relate to signaling function or proteins and enzymes. Because some of the proteins or enzymes are actually in the membrane, they are identifiable from the outside. That raises the interesting possibility that based on the things in someone's membranes, the cell type they come from can be identified because certain proteins only come from certain cells. The small RNAs that can play epigenetic roles may be able to tell something about certain genes that are being upregulated or at least influenced in some way under different conditions. The idea with Aim 3 is to try to identify whether exposures to POPs are related to the profile of the EVs in general, the profile of the ones thought to be coming from the immune cells, and whether the EV profile is related to subsequent risk of developing ALS. This potentially could provide some indication of biological processes that might account for an association or simply may serve as fingerprints or signals that are like a multi-dimensional machine learning (ML) approach. Do they predict who might develop ALS over time? While they are excited about this approach, they are now having to focus on it more in the Danish sample.

One of the key elements of the study is ability to assess mixtures in terms of multiple pollutants at a time and their possible synergy/antagonism and multiple EVs and characteristics. The methods utilized for this are dimension reduction (PCS, SEM) and kernel machine regression (KMR)-non-parametric that allows for non-linearity and interactions. Rajarshi Mukherjee, who is an expert in mixtures analyses of dimension reduction and KMR in the Harvard University Biostatistics Department, is working with Dr. Weisskopf and colleagues to assess interactions, synergies, patterns, et cetera. This will allow for assessment of EVs as possible mediators with a "meet in the middle" approach: POPs→ EVs, EVs→ALS, commonalities. Several findings could come out of this, one of which is that higher pesticide exposure may be related to ALS or the pesticide exposures are related to the EV profile. Another is that the EV profile may predict high risk of ALS, which would be very interesting for many reasons, not the least of which is having a biomarker in the near future of who may be more likely to develop ALS. Part of the analysis approach would be to assess whether any signals seen would suggest that the effect on risk of ALS is acting through these effects on the EVs.

The analyses have begun on the Finnish cohort, so there are some preliminary results for that cohort. At the time of this presentation, there were 97 cases and 194 controls. Notably in terms of some of the baseline characteristics upon entering the cohort, the ALS cases tended to be married more often than the controls and much more smoking among the cases, with only 10% identifying as having never smoked. In terms of preliminary data from the Finland Cohort on the analysis of POPs, in general with most of these compounds, there are much higher levels than would be seen currently in the US based on the 90th percentile from National Health and Nutrition Examination Survey (NHANES) from 2003-2004. That makes sense in terms of when these samples were collected, with some as far back as 1970 and 1980s before some of these compounds were banned. The levels of PBDEs in the Finland cohort are extremely low. PCB 153 is one of the most commonly found and it is used to compare across cohorts, which is definitely much higher in the Finnish cohort. Given that the findings are preliminary, have not yet been peer-reviewed or published, and Dr. Weisskopf requested that they not be shared, they are not included in this summary report.

Discussion Highlights

Ms. Pauls Backman read some of the questions aloud during each discussion period. Questions that were posted during the registration process and raised during the meeting are included in the attachment sections for Days 1 and 2 at the end of this document.

Sheri Strahl asked if Dr. Weisskopf could speak more about the potential impact of agriculture and related exposures on ALS.

Dr. Weisskopf pointed out that one of the issues is that agriculture involves a lot of pesticide use in different places and on different crops, and different animals are going to be eating various things. Absolutely one of the concerns is that some of that is affecting the risk of ALS. One of the things about using biomarkers is the ability to see at the level of the root regardless of where it came from. The papers he referenced from Kamel and Andrews used actual pesticide application data in the US, which gets at that more directly. Dr. Weisskopf and colleagues want to look further to examine whether pesticide use in agricultural settings is creating exposures that could be changing the risk of ALS.

Dr. Kaplan asked whether algal blooms have been considered as a pollution source.

Dr. Weisskopf responded that algal blooms are not the typical toxicant pollutant in the sense of something man-made that somehow gets into the environment, but absolutely as an exposure that exposure that is potentially toxic it could be related to ALS. Drs. Walter Bradley and Elijah Stommel and others have been assessing this. Certain types of algal blooms definitely put out compounds that are neurotoxic. There is very interesting work about exposure to that and high risk of ALS. Again, it boils down to exposure assessment and how well it can be determined whether someone was exposed to one of those harmful algal blooms. To some extent this has to do with how close someone is to the water bodies in which algal blooms occur. It would be great to identify biomarkers of exposure for this. Dr. Stammel's lung scans show cyanobacteria, so maybe lung scans can be used to determine how much someone is exposed to cyanobacteria.

Ms. Pauls Backman said she had seen presentations previously with respect to the aerosolization of cyanobacteria and how that can be captured.

Dr. Weisskopf added that cyanobacteria in the desert sands has been raised as one possibility of the increased risk of ALS among Gulf War veterans.

Dr. Stommel added that it is difficult to quantify cyanobacteria in the lungs as cyanobacteria are ubiquitous. Exposure can come from air conditioning systems, being near a lake, being out on a boat for a day. There probably are acute, chronic, and synergistic effects. There could be a risk if someone is exposed to an algal bloom 10 to 20 years ago, but that is not well-known at this point. They have definitely seen clusters of ALS around water bodies that have algal blooms that look statistically significant.

End of Day Wrap Up/Q&A

Andrea Pauls Backman, MBA
Moderator, Annual Research Symposium and Meeting
Founder, ALS Strategy Consulting, LLC

At the end of the day, Ms. Pauls Backman read some of the more general questions aloud. The questions and comments that were posted during the registration process and raised during the meeting are included in the attachment sections for Days 1 and 2 at the end of this document.

Discussion Highlights

Since there seem to be fewer anti-inflammatory bacteria in ALS patients, Morgan Quinn wondered whether focusing on consuming foods that decrease inflammation in the gut would be beneficial.

Dr. Murdock responded that it is too early to say for certain, but this is why they are looking at some of these data now. As he mentioned earlier, he would not "pull the trigger" on any particular treatment at this point.

Lynn Brielmaier asked what is known about why the vagus nerve is not affected like upper am lower motor neurons.

Dr. Mehta responded that the vagus nerve does appear to be impacted in bulbar onset of ALS and shared the following link: https://pubmed.ncbi.nlm.nih.gov/33167079/. In general the vagus nerve is linked to gastro conditions such as gastroesophageal reflux disease (GERD) and others.

Dr. Stommel added that it is well-documented in ALS that autonomic dysfunction is a big deal. There are ultrasound studies of the vagus nerve showing atrophy in the nerve in ALS.

Considering the multifactorial nature of ALS, Nitesh Sanghai asked whether there is a need for cocktail treatment, and whether a new drug discovery area is needed in terms of incorporating multiple molecules in a single capsule in the future.

Dr. Mehta agreed that a cocktail treatment regimen should also be investigated. This has proven successful in human immunodeficiency virus (HIV) care. As for drug discoveries, these need to be further investigated for safety and efficacy.

Dr. Stommel indicated that there are at least 2 dozen Mendelian forms of ALS with different mechanisms of action. There will need to be precision medicine to design a cocktail for individuals. He does not think any 2 ALS patients are going to have exactly the same needs unless they have a very well-defined genetic form of disease. Antisense oligonucleotides (ASOs) treatments may be helpful in some cases. Even in those cases, there are other things going on that need to be dealt with. ASO treatments are not a cure and, based on his experience, likely will require other interventions.

Peter Ambühl would like to establish a national registry for ALS and would like to know more about the international connection of the different registries existing worldwide and whether there is a template for setting up a registry and a data interface to exchange data with other countries, or if a project already exists at the International ALS Association.

Ms. Pauls Backman indicated that until recently, she was on the Board of the International ALS Association and is not aware of a current project that has been published at this point, though there may be additional work that has been happening there. She suggested that this question should go to the International Alliance at als-mnd.org

Dr. Mehta added that he certainly would welcome this particular individual to reach out to other countries in Europe who actually have established registers as they are called. Sweden, Scotland, the UK, Ireland, and parts of Italy are great examples with robust ALS "registers" as they call them. ATSDR has provided technical assistance (TA) regarding information about registries. In countries in South America, they helped to establish the Latin American Epidemiology Network for ALS (LAENALS) through Dr. Orla Hardiman at Trinity College. In general, they would be happy to discuss how to establish a system with Switzerland in terms of the National ALS Registry and encouraged them to reach out to their counterparts in other countries as well about establishing a registry.

A similar inquiry came in from India that ALS Care and Support is a group of patients and caregivers in India that has been established since 2008. They estimate that around 75,000 to 100,000 patients are in India and they would like to create the National Registry of India for ALS and would like to know how the CDC National Registry might be able to help.

Dr. Mehta indicated that they recently were approached by a group from India. There is an Indo US Bridging RARE Summit 2023 where CDC/ATSDR will be presenting information about what they do at the ALS National Registry. Every country is unique and resources also are important. He is sure there is a very large under-count of ALS cases in large countries, such as India.

Peter Ambühl inquired as to how much funding would be needed to set up a national registry.

Dr. Mehta replied that this is a complex question that is probably unique to each country. The National ALS Registry is fortunate to receive tax support through the public, which is very beneficial in terms of funding and conducting research. Each country would have to have a discussion with its own policymakers, non-profits, et cetera to find out whether they have an interest in supporting a registry.

Regarding a question about whether the Registry accounts for second homes noting that they have a second home in Cape Cod where 3 people on the same street have had ALS in the last 4 years, Dr. Mehta indicated that the questions ask for lifetime residential history. He thought that would be where a second home likely would be captured, but he did not think the questionnaire asks a specific question about a second home.

Ms. Raymond confirmed that the questionnaire asks only about primary homes, but not specifically about second homes. People who spend a significant amount of time in a second home might list it as one of their primary residences.

From the latest prevalence report, Dr. Finger expressed concern that the estimate of only missing 27% of cases overestimates the ability to identify cases and is in conflict with other findings. In Massachusetts, 38% of cases were missed. Roughly 40% of patients use private insurance and would not be picked up by the new algorithm.

Ms. Raymond responded that for the Massachusetts study, the Registry matched on just over 61%. Massachusetts had cases that the Registry did not have, and the Registry had cases that Massachusetts did not have. The cases that Massachusetts did not have were typically an older population. The ones that Massachusetts had that the Registry did not have typically were a younger population. It is not possible to compare apples-to-apples with the Massachusetts registry because of the way the National ALS Registry receives claims data and Massachusetts is receiving medical records. Also, their case definitions are not quite the same. The National ALS Registry is missing private insurance, but they are able to obtain this is patients register through the web portal.

Dr. Mehta added that regarding the 27% missing, the reduction from 44% to 27% is an improvement. Absolutely, they want to reduce that number more in the future. However, challenges remain, such as ALS not being a notifiable disease. There also are persons who are receiving their care from private payers who may never convert to CMS and may not be picked up. The National ALS Registry works with partner organizations to raise awareness about the Registry and the importance of joining, but that will be a continuous effort. He is not sure that a 100% capture rate is possible for any disease, even for reportable and notifiable diseases. COVID-19 is an example for which cases are missed all of the time. The Registry does the best it can with what they have and certainly strives to improve its case count. Hopefully, that has been demonstrated by the reports that are published showing a decrease in missing cases from 44%, to 27%, to 10%, and so forth. They want to improve.

Dr. Finger thought his question was misinterpreted and clarified that he did not believe the data supported the 27% estimate, which is much less than other specifications. It was not clear to him that they could be confident in the range from the latest paper if the 2 other estimates using complete demographic data fall outside of the range. The specification using the demographic data showed 35%, which is more reasonable considering the number of people who are on private insurance. He asked what the estimates were from the other specifications in that paper that were not selected and emphasized that the 27% underestimated the true prevalence of the disease.

Dr. Mehta indicated that they could certainly go back to make sure that everything was done correctly. They worked with Emory University for the calculations. There also was 30% which was missing for Whites and African Americans as well.

Regarding a question from Dr. Stommel about whether anyone has reached out to the reportable registry in Vermont since it started, which could be a good precedent for future reportable state registries, Dr. Mehta indicated that he testified before the Vermont Legislature. He pointed out that Dr. Stommel has been the driving force behind the registry in New England and could speak to how Dartmouth is working with the state legislature and health department to help make that happen. The National ALS Registry recently received OMB approval to add new data sources, that is a conversation they now can have with Vermont about having them included in the Registry, especially if it is easy to do in conjunction with the National ALS Registry.

Dr. Stommel emphasized that Dr. Mehta was very helpful in getting the State of Vermont to set up a reportable registry. Unfortunately, it is a tiny state. The hope is that there is some precedent of setting up a relationship between a reportable state registry like Vermont, Massachusetts, or Maine, so that when larger states like Michigan, California, or Texas come along, the same relationship can be used and the same data can be shared. This will make collection much more valuable. He assumed other states in the future would want to have reportable registries.

Dr. Mehta added that they have heard from other states that are interested in having their own registry. He believes Michigan is working on an initiative as well. He will be happy to have discussions going forward now that they have OMB approval.

Francois Gand asked Dr. Mehta whether they have looked at how ALSFRS-R score is being affected by quality of life (QOL) and if they would you be interested in learning how Brain-based Communication from non-communicative ALS patients can affect the ALSFRS-R score.

Dr. Mehta responded that they have not looked at how ALSFRS-R score is being affected by QOL, but only because they do not have QOL data that may be accessible at the clinic level. They certainly could work with organizations to look at QOL data at a much more granular level. The score they have is longitudinal, so they do not compare it. They look at this regarding survivability and progression, but do not mix it in with QOL. It definitely would be interesting to see how Brain-based Communication from non-communicative ALS patients potentially can affect the ALSFRS-R score.

Dr. Goutman added that some of this pertains to thinking about other scales that may better capture these types of qualities and characteristics as they learn the limitations of the ALSFRS-R.

Lauren Webb asked whether Dr. Goutman could talk more about his team's role in environmental health policy and how they share their impressive work to create change.

Dr. Goutman indicated that this is a challenge, which they have talked about at length in the past with different working groups in terms of the types of evidence needed on the science end to support public policy. Scientists and researchers want to make sure that they are generating the best body of data they can in order to inform public policy. At the same time, they also recognize that studies of environmental risk factors, research advances much slower just because of the complexity and the need to study large numbers of individuals. Consideration has to be given to the findings on the research side and the best time for that to intersect with public policy. Partnerships are needed for this with the organizations that are involved like the ALS Association and the MDA, which have public policy wings.

Regarding an inquiry about getting good information since there is much questionable, false, and misleading information on the web and whether there is a way to provide some sort of official authentication certificate to indicate sites that are legitimate and approved in some way, Ms. Pauls Backman said that the partner organizations that work with the Registry on each of their websites have information regarding resources that have been vetted and are reliable. Those include the ALS Association, Les Turner ALS Foundation, and MDA. She would start there.

Some questions were raised about how individuals are supposed to know which clinical trials and medications they might qualify for. Ms. Pauls Backman recognized that it is always hard to know when looking at descriptions of clinical trials which ones an individual might quality for. What has been recommended generally over the years is for individuals to first speak with their own doctors, who know them better than anyone else and should be aware of all of the clinical trials. That said, not everyone has the same access to their doctors. There are a couple of published sites, including clinicaltrials.gov. While this is the best resource, it can be a confusing website to navigate. There also is the https://iamals.org/ website and a program called ALS Signal at https://iamals.org/get-help/als-signal-clinical-research-dashboard/.

Dr. Goutman agreed that it can be frustrating to try to align oneself with a clinical trial. Some of the trials have participant navigators. The exciting thing about ALS right now is that a ton of drugs are being studied. But trying to fit those into the same system has limitations in terms of available staff and available physicians. The ALS community needs to get more people interested in caring for individuals with ALS and participating in clinical trials from a researcher perspective and clinical coordinator perspective, and then build the infrastructure. There clearly are people who are thinking about building the infrastructure to expand accessibility to clinical trials.

A participant noted that they could not remember whether Relyvrio or Radicava claims that life may be extended by a couple of months, but wondered whether that meant QOL life would be improved or just that people would live longer.

Dr. Goutman responded that he did not know off the top of his head whether QOL data have been published.

Dr. Stommel added that QOL near the end of life with ALS is not great. If life is being extended, it would be better to extend life in the middle of one's disease versus the end.

Ms. Pauls Backman did not recall any of the studies presented on those drugs looking at where patients were in their stage of disease, but they did look at survival.

Lynn Brielmaier indicated that the Motor Unit Number Index (MUNIX) adds objective muscle electrophysiology to ALSFRS-R.

Dr. Brooks asked whether there are any CDC studies looking at US distribution of ALS and enterovirus D68 (EV-D68).

Dr. Mehta said he was not aware of any studies within the Registry looking at EV-D68 and ALS. While there could be CDC studies looking EV-D68 excluding ALS, he was not aware of any at this time.

Dr. Pauls Backman noted that based on her count, the National ALS Registry team had answered over 100 questions that came in either prior to registration or during the course of this meeting for the first day. She thanked everyone for their interactiveness, openness, and transparency in terms of asking and answering questions. That goes a long way toward the work the Registry is doing. She reviewed the agenda for the next day and officially adjourned the meeting.

The National ALS Registry Annual Research Symposium and Meeting stood in recess until 8:30 AM ET on August 30, 2023.

Personal Experience Perspective

Brooke Eby
Personal Experience Perspective

Brooke said she thought it sounded very unrelatable when she talks about her first 29 years, because in hindsight they were picture perfect. She grew up in Maryland with 2 older siblings, had a great group of friends since kindergarten, who are still her closest group of friends. She went to Lehigh University (LU), where she studied business information systems and quipped that she probably had a little too much fun. Following college, she moved to New York where she started working for a software company. After that, she got to travel to San Francisco and live there for a few years to continue working in technology. During her first 29 years, she traveled extensively, dated a lot, and made many friends. She has a very good family and her first 29 years were like a movie, which is why she thought it was not the most relatable sounding ALS journey. She emphasized that while the first 29 years versus the following 5 years that she has lived with ALS are pretty stark, the first 29 years built her to be able to handle the last 5 years. The first 29 years were like training camp for having ALS. Once she was diagnosed, she needed everything else to be stable in order to process the diagnosis very quickly. The more someone has control, the faster they can maybe not accept the diagnosis, but perhaps manage it, which is what she would say she is doing. Having such a great group of friends and a very supportive family was important in the midst of the disarray of first getting the diagnosis. She also had a very supportive employer, so all of the building blocks were in place to be able to manage the diagnosis as positively as she could.

In terms of her diagnosis journey, the process was a long one for her. When she was turning 29, she was moving from San Francisco back to New York. She started noticing what she thought was calf tightness when walking her dog. Because her calf felt tight and she was thinking about what professional athletes do, she kept rolling it out. However, it was not getting any better. New York is a place where it is not possible to walk slowly without being plummeted over, and she noticed very quickly that she was not keeping up with the crowd of New York. She was not really concerned at the time and just thought her leg was tired. Something was going on, but she did not think it was super serious. Some of her colleagues commented that she was limping and walking differently from before. Her sister is a doctor, who she asked to run a "living room" test. Her sister made her walk forward, but her left heel would not stay up as she was walking. It kept slapping onto the ground, which her sister identified as "foot drop" and thought she had a pinched nerve. That kicked off a 4-year diagnosis process beginning with a general practitioner, followed by an orthopedic surgeon. Over the course of that 4 years, she thought she must have gone to every type of doctor during hundreds of appointments and hundreds, if not thousands, of tests. This included magnetic resonance imaging (MRIs), computerized tomography (CT) scans, and laboratory work. Then 2 years into it in 2020, she finally got an electromyography (EMG) from a neurologist. At this point, she has probably had 10 EMGs and they never get more comfortable. During the first one, they saw denervation in her left foot, but every other limb looked okay. This was not enough for it to be considered a progressive MND like ALS. The doctor who did the first EMG suggested that she might have something like Lou Gehrig's disease and immediately sent her for genetic testing. To the uneducated patient, only 10% of ALS cases are genetic, so getting back a negative test was not a clear "yes" or "no" indication of having ALS. When that came back clear, her family cheered like they were at a football game because they thought they were in the clear.

At that point, she put ALS out of her head and continued to think that this was a one in a billion case of a left foot that did not want to cooperate. As she continued living her life in New York City, her calf continued to get skinnier and her foot continued to feel weaker. It was not until the beginning of 2022 that she started losing her balance and noticed that her right foot was slapping down the way her left foot had She went back to a neurologist, and her family thought she was crazy because they thought everything had been ruled out. She had another EMG, probably her ninth at that point, and the neurologist officially saw that her right foot had been affected also. Both were showing signs of denervation, and both of her calves were atrophying. The neurologist sent her to an ALS clinic because they had the best expertise to make diagnoses and he did not want to get it wrong. In March 2022, she was officially diagnosed with ALS after 4 years of pretending like nothing was serious until faced with the fact that this was ALS and then having to figure out how to move forward from there. She had attended the diagnosis appointment alone because by that time, she was so fatigued from so many appointments and was more desensitized each time, so she told her family not to join her because the doctor would just do and say what they had every time. At the point of diagnosis, she wished she had brought someone along because she knew driving home was going to be a sticky situation.

She said what she found to be most comforting in the months after diagnosis were M&Ms. She did not think there was a healthy way to process the diagnosis. She was in shock the first couple of months and just went through the process of survival—getting up, walking the dog, eating M&Ms, brushing her teeth, getting back in bed, watching television, reading books. She had a short list of requirements for herself at first. She was trying to escape in her mind. She read tons of books after her diagnosis. She would start a book and then Google "ALS" and then quickly close out the search window and go back to her book. She was just trying to stay sane in the first couple of months. She spent a lot of time lying in bed, watching television, and reading books until she was forced out of her house to go to her best friend's wedding to serve as a bridesmaid. While it would have been fair for her to cancel, this was one of her closest friends from college and she wanted to be there for her big day. When last everyone from college saw her, she was fit, cute, and fun. By the time of the wedding, she had been eating M&Ms constantly for 2 months and showed up in a too tight dress and using a walker. It was clear that something was going on with her. Another of her friends was invited and drove and along the way, Brooke asked her to turn around and go home because it hit her how embarrassing it was going to be. Her friend encouraged her to go anyway and make a fun day and story out of it. Her friends rallied around her on the dance floor, the bride used her walker for limbo, and she gave people rides all over the dance floor.

It was fun and it reminded her of herself before the diagnosis, which she had not felt in the past couple of months. It made her realize that she could still be herself despite all of the physical changes and mental burden that she was experiencing. It was not entirely a gift because she did catch COVID from that wedding, but she still began feverishly typing up all of the funny things that had happened to her since her diagnosis, and she realized that she should share her story on a broader scale. If she was able to dance with a walker in front of a hundred strangers at this wedding, perhaps she could share it on a bigger scale. That is when she met Sunny and was introduced to "Her ALS Story" girls. She was in her head a lot when she first met those girls and was not ready to share. Even at the wedding, she did not tell people it was ALS. She just brushed off the questions and told people her foot was hurt. Then she met Sunny who was holding the ALS Filmfest that she holds every year. On one of the calls, Sunny told her that if she was not comfortable sharing her own story to share Sunny's. Booke said she still gets goosebumps whenever she repeats that because Sunny has put her whole ego aside and is fully charging toward this mission of sharing her story in the hope of helping the ALS

community. Sunny is not thinking of herself in sharing her story. She is thinking of the whole ALS community. After that, Brooke thought, "Game on. I'm going to download TikTok and see what happens" and laughed that she has been over-sharing ever since.

Specific to ensuring that people are aware of the National ALS Registry and its benefits, Brooke said that when she went to her first clinic, they handed her a thick orientation packet filled with information related to ALS. When she got home, she put the packet aside for a while and decided to deal with it later. It seemed like way too much for her mental capacity at the time, which was overflowing. At that point, she did not think that she had even accepted that she had ALS. She was still convinced there was some White Knight going to come in and say, "You don't actually have this. You could take this antibiotic and then you'll be cured." She was still in the denial phase when she received this packet from her clinic. She did not actually look in the packet until months later. When she finally opened it, one of the pieces of information was about the Registry, which she signed up for and received a packet in the mail after that. That was her only experience with the National ALS Registry until she was invited to speak and met people from the CDC who explained the goal of the Registry in terms of understanding the prevalence, the incidence of ALS, trying to find potential hotspots, looking for general themes, et cetera. As someone who works in technology, she understood that having more data is better. In terms of ways to make sure people are aware of the Registry and its benefits, she would ask the CDC team what they need. They are getting funded every year to build up this Registry and in the ALS world, every dollar counts. This is such an under-funded and devastating disease, she does not want one penny to go in the wrong direction or go to waste. Spreading awareness and getting the word out outside of the insular ALS community. It is sometimes difficult to break out of that, but social media is helping with that in terms of getting people outside of the ALS community interested in ALS. She would like to know where she can have the most impact. Is it sharing information about the Registry and getting more people to register? Will that make the 5-year backlog of data analysis worse? She works for Salesforce and has a slew of data scientists who are eager for pro bono projects. Perhaps they could get them involved to help with the backlog. CDC needs to share a problem statement with her and Sunny so they can use their strengths and networks to tackle some of the problems. From a patient standpoint, the Registry has not held a lot of meaning for her yet. She would love to help make the Registry a universally valued tool for the ALS community versus another bullet on the list of every other resource.

Sunny Brous, Med
Personal Experience Perspective

Ms. Brous shared that she is 36 years old and lives in Hico, Texas. She was diagnosed in 2015 right before her 28th birthday and has been rocking the ALS world for the last 8 years. She grew up in Hico, which is a small town where everyone has to do everything or there are not enough people to do anything. She was a multi-sport athlete, cheerleader, drum major, and National Honor Society (NHS) President. She then went to Tarleton State University. Even though it was tough, she had more free time in one day than she did in 4 years of high school. She remembered calling her mom to say she did not know what to do with herself and that she was not going to graduate as fast as she could. Instead, she was going to take her time, graduate on her own schedule, enjoy it, and not be in a rush. She graduated 4 years later with 2 extra credits, so that plan did not work out. She then looked for every reason not to go to graduate school. She applied for some ridiculous jobs, and nobody wanted to hire her. So, she went to Texas State University. She thought she knew everything about life, college, and balance. But when she got to a college campus with a river running through it, all of that went out the window. She got her Master of Education and a really good tan in her time there. Then she got her first

"big girl" job as the Assistant Director of Student Housing at Weatherford College, which she would not wish on her worst enemy. She had 270 roommates and their mothers, and they lived in very close quarters almost every day of the year. From there, she went to work for a non-profit called Junior Achievement where she ran large fundraising events and learned that she is really good at asking people for money and really enjoys it. Parlaying that skill into a career went really well until ALS turned up and her company was very gracious.

Regarding her diagnosis journey, she said it was much the same as Brooke's except that hers began in her left hand. She was playing softball and noticed that she could not close her glove. It was enough of an issue that she realized that for safety, she should not play softball if she could not close her glove, so she made excuses not to continue playing. That was in April 2015, and she never actually saw a doctor until December 2015 when she threw her back out. Pain motivates. That spoke to her fear that it could be serious because she was in major pain by that time. That appointment kicked off an MRI to rule out a mass and a lot of bloodwork, including an autoimmune panel. She went to a spine specialist, a pain management specialist, and an orthopedist. During that time, she had lapsing insurance because she changed jobs. She was on COBRA (Consolidated Omnibus Budget Reconciliation Act) while she waited for her new insurance. Appointments are booked 4 to 6 weeks out the higher up the specialty wrung, so it became gruesome to make these appointments, fit them into her work schedule and life, and not give too much energy to them, because that is zapping and horrifying. She was diagnosed in January 2015. The way things worked out that day, she was by herself. It was an appointment just like all the other appointments. She just knew she was going to go in and the doctor was going to say what it was not, what she thought it was, and who to go to next. She got dressed for work, went in expecting a referral, and expected to go on with normal life. When the doctor told her she had ALS, all normal life ceased to exist in that moment. One thing she thought was cool, recognizing that not everyone has this experience—especially during their diagnosis appointment, was that the doctor was very clear and concise explaining that in terms of possible, probable, definite that Sunny was in the probable category. The doctor asked her whether she wanted a second opinion, which she did. The doctor referred her to the University of Texas Southwestern in Dallas. The doctor also asked if she would like to know about clinical trials and connected her with the Clinical Coordinator to start researching these opportunities. In addition, the doctor asked if she wanted to start taking the only FDA-approved drug at the time, which was riluzole. She asked the doctor why anyone would turn that down. The doctor said it is expensive and some people choose to use the money they would have invested in the drug to go on one last hurrah or have one last family gathering. Sunny opted to take riluzole and has been on it since that time. While it was not a positive appointment, the doctor handled could not have handled it any better.

Laughing, she said that what she found to be most comforting in the months after diagnosis was tequila. She said that thankfully, she is a millennial and can find comfort in the online community. Being diagnosed 6 months after the Ice Bucket Challenge was a blessing because ALS was now in everyone's periphery. Whether they read deeply about the disease or not, at least they had heard of it. That helped as far as talking to people. She did not have to explain something that was absolutely foreign. It was a global phenomenon that raised hundreds of millions of dollars. That opened the door to in-person support groups. At her ALS clinic, they met in an infusion suite, so it was just like a workgroup where they could get to know each other. When COVID happened, making the transition to meeting online was easy because of being a millennial. She always has found comfort in groups and community, so when she is talking to people about their diagnosis, whether it is new or they have known for years, she tells them to lean into this community. There are groups on Facebook. There are online support groups. There is "Her ALS Story." There are some face-to-face groups that still meet locally.

She tells people that this community will love them, and that this disease only impacts the best people. For so long, this diagnosis was very isolating. People were diagnosed and told to go home, get their affairs in order, and die. Now, people are seeing that others with ALS are living a long time and doing something with the time they have left rather than staying home alone and wallowing in it. People would not know that if they were not connected. Getting into these communities helps people shoulder the burden of this disease and learn from each other.

Specific to ensuring that people are aware of the National ALS Registry and its benefits, when she and Brooke schedule their first call to talk about this ALS meeting, she thought she knew about the Registry, but it turned out that she knew about the Biorepository and not the actual Registry. She then set out to make sure she was registered and was a part of the National ALS Registry. She said that to be completely honest, she got through the registration page and remembered why she had never completed the whole process—because it is not user-friendly, and she got frustrated. Her takeaway would be that this registry is not like registries for other diseases for which everything is reported automatically. The National ALS Registry is generated from different sources of information and sometimes is self-reported from patients. There needs to be a stronger focus on making the Registry user-friendly across different technologies. For example, in "Her ALS Story" some people use Voice Notes or Eye-Gaze and some people type. They place a lot of emphasis and time on making sure everyone is accommodated and a part of the conversation at their own comfort level. That is important for the National ALS Registry as well, knowing that this population most likely utilizes different forms of technology to participate.

Discussion Highlights

Ms. Pauls Backman read some of the questions aloud during each discussion period. Questions that were posted during the registration process and raised during the meeting are included in the attachment sections for Days 1 and 2 at the end of this document.

Dr. Mehta thanked Brooke and Sunny for their perspectives, emphasizing that posting their videos and sharing their life stories means a lot to many people and has a major impact on them. Clearly more needs to be done in terms of having a quicker time to diagnosis, having more money for research, and so forth. As he always has said, "This is your registry. We are here for you, and we want to make it better." He said they would love to have Brooke and Sunny be part of the public engagement session in 2024 where they can give their perspective to discuss what the Registry team is doing and how they are making improvements. While they are a small team, they do a lot with what they have. They appreciate input on the "good, the bad, and the ugly" in terms of where improvements can be made. They are always trying to make the Registry more user-friendly, and they understand that there are sometimes constraints, some of which may be more internal than external in terms of making sure that things are compliant. He would like to have an app for the Registry that is much more user-friendly and can be used on a tablet, mobile phone, and other technology. For instance, the passwords were expiring every 6 months, so they worked with the IT department at CDC to offer an option to have the password expire at 6 months, 1 year, or never. They do take notes, discuss input they receive, and try to act on it to make the Registry better.

Brooke Eby pointed out that it is an interesting business model, because the doctors are really the salespeople for the Registry in this situation. Every ALS clinic should be bringing up the Registry in the first clinic and at every 3-month appointment thereafter. The ALS Association has someone attend each of the clinics to tell people about the value of the association. Perhaps that could be used as a model, but right now it is just hoping that a doctor will remember to bring up the Registry. Putting the information in a packet of 100 other things did

not highlight the Registry's value to the ALS community. Filling that funnel needs to be fixed because not all doctors enable patients on what the Registry could do.

Dr. Mehta recognized that ALS by itself is an overwhelming disease and the last thing they want is for people to be overwhelmed by the Registry. They work with partner organizations like the ALS Association, the MDA, and the Les Turner Foundation and provide them with materials to share with patients about the Registry. People with ALS, like Brooke and Sunny, have tremendous power and "boots on the ground" to share information about the Registry, explain how it works, and let people know that it is a way to be counted and join the fight against ALS.

Lynn Brielmaier asked Brooke & Sunny as former athletes how many cumulative TBI events they thought they might have had in their lives.

Sunny said she remembered hitting her head playing sports, but never had any thoughts that she definitely had been concussed. She was in a car accident in her senior year and may have had whiplash, but nothing for which she was ever treated.

Brook said she did not identify as a super athlete the way Sunny does, but she did not recall any head injuries or brain trauma—at least none that were serious enough for her to remember. She has an autoimmune condition, ulcerative colitis, which is similar to Crohn's disease in which the body attacks the digestive system. That was diagnosed in 2012 and was mostly under control until about 2017 when she had a bad flare-up for which she took high-dose steroids for a year, which was 10.5 months longer than anyone should be on high-dose steroids. Just as she started weaning off of that was when her calves started feeling tight and she began limping. She does not necessarily think her ALS is related to a head injury, but 100% fully believes that her autoimmune condition triggered something. Maybe it was the condition, the flare-up, the steroids, but it definitely triggered some sort of domino effect in her body to start the ALS symptoms.

Michelle Schmitz asked whether the information provided within the packet about the registry was a single line within the paperwork or a stand-alone brochure.

Brooke recalled that there was a standalone brochure that included everything needed to fill out information and mail it back.

Lauren Webb asked Brooke and Sunny to talk more about what "user-friendly" means to the ALS community. It would be helpful to create a document that uses "technical specifications and requirements" to provide the Registry with actionable steps to go through approval processes. The approval process takes time and phases would be helpful.

Brooke indicated that there are accessibility consultants who are paid to answer that question. Coming from the technology world, the general theme for her is less clicks, less confusion. Accessibility consultants can and should be hired to determine how someone with Eye Gaze would go through the Registry or how a caregiver could do this on behalf of someone living with ALS. She thought this should be hired out rather than posing it to her and Sunny, though Sunny might have a better response.

Sunny agreed that the registration process needs to be tested on different platforms. "Her ALS Story" has some very technology-savvy people who can modify the quizzes and polls that they put out, but they are doing this blindly. There are better qualified people for this.

Aditi Narayan Minkoff suggested that in addition to the 2024 public engagement sessions, building an ongoing feedback mechanism would be great to continue to learn from the community. That way, updates can be timelier and more responsive to the community's needs.

Ms. Pauls Backman said she thought that was an excellent comment and something that the staff at the National ALS Registry would take to heart. She thanked Brooke and Sunny for their honestly and openness, which was very meaningful and impactful.

Breaking News

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

Dr. Mehta reported that the Registry funded 2 new institutions that they are happy to bring into the Registry family:

- ❑ ALS Therapy Development Institute
- ❑ University of Michigan

He recognized both of these groups as being powerhouses in terms of ALS research, noting that the University of Michigan already is doing some work with the Registry. While he did not have the exact information at the point due to the firewall between them and the Office of Grants Services (OGS). CDC follows the NIH model in terms of the peer review process. These institutions will be awarded new 3-year R01 grants beginning in FY2024.

National ALS Registry Funded Research Presentations: Part 2

Identifying and Evaluating Potential Risk Factors for ALS in Sweden

Fang Fang, PhD
Professor of Epidemiology
Karolinksa Institute (Sweden)

Dr. Fang described some of the ALS research work being done in Sweden by the Institute for Environmental Medicine at the Karolinska Institutet (KI). KI is located in Stockholm and was founded in 1810. It is Sweden's single largest center of medical academic research, offers the widest range of medical courses and programs in Sweden, and received the Nobel Prize in Physiology or Medicine. In terms of why the research is being conducted in Sweden, she explained that Sweden is one of the Nordic countries together with Iceland, Norway, Finland, and Denmark. Sweden provides a unique opportunity for research and care of ALS as a good complement to all of the other efforts that are ongoing in North America, Latin America, and Asia. The population size of Sweden is currently about 10 million, with 90% of the population being Caucasian. The capital city of Sweden, Stockholm, currently has a population size of about 2.2 million. The life expectancy is quite high in Sweden at about 81 years of age for men and 85 years of age for woman. Given that this population is quite old, neurodegenerative diseases, including ALS and MND, are increasingly important as healthcare and public health problems. Like many other European countries, Sweden has a universal health care system.

Sweden's healthcare system is nationally regulated and locally administrated and is funded primarily by general taxation. This means that every member of society is entitled to free-of-charge medical care.

Everyone in Sweden has a personal identification number (PIN) that is used broadly in all aspects of life by authorities, healthcare sectors, schools, universities, banks, insurance companies, et cetera. This specific number makes research relatively easy and less expensive. There are some unique research possibilities in Sweden, including 4 main components. The first is the national public authority registers that include information on population and socioeconomics, health, and population-based surveys that are conducted by the government regularly. The second opportunity is disease quality registries. Physicians in the country have initiated a lot of disease-specific quality registries over the last decades. Currently, there are more than 100 of these. These disease quality registers are partly or completely funded by the government and have a primary purpose to develop and ensure quality of care for patients who have different diseases. The third unique research opportunity in Sweden is research-generated data. These are maintained databases in research institutions and universities. Biobanks represent the fourth research opportunity. These biobanks often have decades of history and from research-oriented activities and healthcare. In addition to various types of biospecimens, these biobanks contain data related to test results, clinical diagnoses, and self-report reporting through questionnaires.

Regarding the burden of ALS in Sweden, Dr. Fang described a paper that she published 15 years ago that looked at the burden of ALS from 1991—2005 using the Swedish patient registry[23] to calculate age and sex standardized incidence rates. This study was based on ICD codes, especially IDC-10, including ALS and MND in general. During the period from 1991—2005, there was steadily increasing incidence from just below 2.5 per 100,000 to about 3.0 per 100,000. Males had a slightly higher incidence rate of ALS compared to females. The peak age for ALS diagnosis was between 70—79 years of age for men and women. A new analysis was performed using data from 2002—2020 using a similar approach with the ICD-10 codes.[24] Again, there seemed to be an increasing trend for both men and women. However, some turbulence was noted around 2018—2019. While the reason is not known, it seems like this is an increasing general trend of ALS in the population even after standardization by age.

KI and the Karolinska University Hospital strive for multidisciplinary research and care for ALS. In terms of research, they have researchers dedicated to both pre-clinical and clinical research. Pre-clinical research focuses on cell lines, animal models, and population studies. Clinical research focuses on treatment patterns, patient outcomes, health economics, et cetera. Currently, there are more than 10 clinical trials actively recruiting patients in Stockholm in Karolinska University Hospital. At the major university hospitals and a few large regional hospitals in Sweden, there are specific ALS Care Teams. These are expert teams comprised of occupational therapists, curators, physiotherapists, psychologists, speech therapists, doctors, and nurses. There also is the ALS Center Karolinska that takes care of all ALS patients in Stockholm.

[23] Fang F, et al. JAMA Neurology. 2009.
[24] Sennfält S, et al. unpublished data

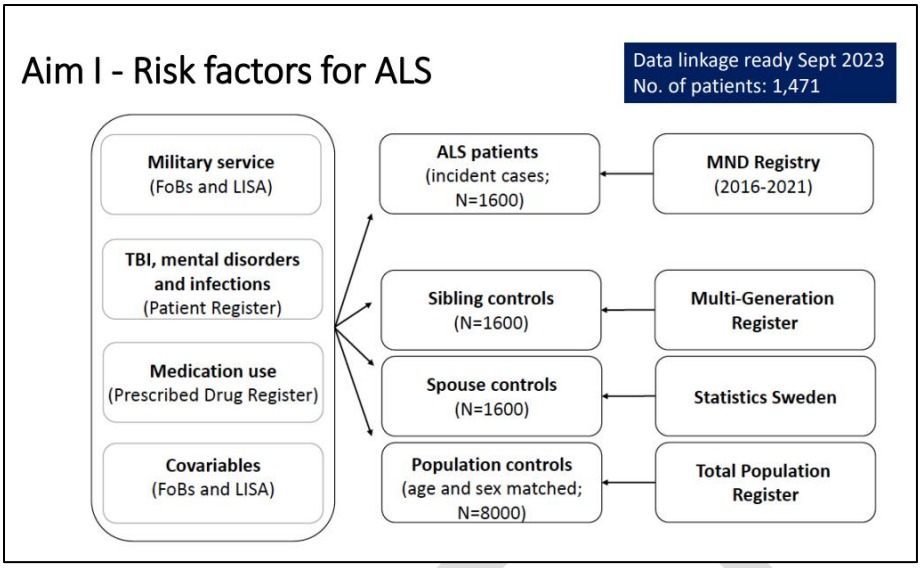
To briefly introduce the KI's research program that was funded by the CDC and the US National ALS Registry in 2022 to identify and evaluate potential risk factors for ALS, this program has 3 aims, which are to: 1) identify potential risk factors in the Swedish ALS population, with a focus on multiple risk factors individually and in combination with regard to disease risk, disease prognosis, and phenotypic variations; 2) evaluate how these risk factors function in terms of determining the risk for ALS, including effect modifications and genetics, chemicals, and gut microbiome; and 3) incorporate the results of the first 2 aims and stratify patients using a novel patient stratification method based on outcomes and exposure history to correspond those matrix to one's exposure history to different risk factors. The long-term goal of this program is to improve the understanding of the disease etiology for ALS in a population in a Nordic country and to gain knowledge on potential preventive and therapeutic targets for this disease.

For Aim 1, the investigators ambitiously plan to study the following risk factors that have been proposed as being potentially relevant for ALS:

- ❑ Military service, TBI, mental disorders, and infections
- ❑ Risk and prognosis of ALS
- ❑ Swedish population and health registers
- ❑ Swedish MND Quality Registry
- ❑ ALS patients vs. sibling controls, spouse controls, and population controls

The Swedish MND Quality Registry will be used to try to identify information on risk, prognosis, and phenotypic characteristics of ALS. The Swedish MND Quality Registry was viewed on top of the Swedish Neuro Registries in 2015 and has improved information on newly diagnosed ALS and MND patients in Sweden from 2015 onward. Currently, this included information on over 80% of all MND patients in Sweden. From 2017 onward, it has included almost 100% of MND patients. Information in this registry includes clinical characteristics, including patient-reported outcomes on cognition, depression, anxiety, quality of life, pain, et cetera. The information in this registry is updated by patients and their caregivers through a patient reporting portal and by the Care Team for ALS patients. The MND Quality Registry is funded by the Swedish government and essentially all clinics in Sweden that are diagnosing and caring for ALS patients are participating in this registry. That is perhaps why they have higher coverage than a few other registries for ALS. This registry is being used in different ways in order to improve research and care. A specific utility of this registry is that it can be used for patient identification in terms of trials. All newly diagnosed patients are in this registry, so once there is a trial available, patient characteristics can be quickly matched to identify potential candidates for trials. Hopefully, this can be of use to other registries of a similar type elsewhere.

For Aim 1, multiple control groups are being used. Controls include blood relative sibling controls who are ALS-free (N=1600), spouse controls (N=1600), and population controls who are not related to the ALS patients but who are age- and sex-matched (N=8000). Contrasting ALS patients with 3 different types of controls can take care of some of the methodological considerations that sometimes arise when ALS patients are controls to make sure that they are not different in terms of age, sex, lifestyle, other shared family factors, or genetics. This diagram shows the data for risk factors, controls, and data registers that will be linked them for Aim 1 for 2016–2022:



This diagram indicates that 1600 newly diagnosed ALS patients will be identified according to the MND Registry between 2016-2021, but now this can be done through 2022. These patients will then be linked to 1600 sibling controls through the Multi-Generation Register, which includes information on familiar links for everyone who was born in Sweden from 1932 onward. Then 1600 spousal controls will be identified by Statistics Sweden. From the Total Population Register, 5 controls will be identified for the 1600 ALS patients who are matched on age and sex for a total of approximately 8000 population controls. Once the patients, siblings, spouses, and controls are identified, they will be linked to the population and health registries mentioned to identify information on potential risk factors, as well as other co-variables that are of relevance in the studies on risk factors for ALS. For instance, in terms of military service, occupational history has been identified for all of the patients and controls. In terms of TBI, mental disorders, and infections, information has been identified from the Swedish Patient Registry that has been collecting information on hospital discharge from 1964 onward on inpatient care and outpatient care from 2001 forward. To understand how medication use can interact with potential risk factors in modulating the risk and prognosis of ALS, information will come from the Prescribed Drug Register. The Prescribed Drug Register has been collecting nationwide information on all prescribed medications in Sweden since 2005. In addition to these main sources of information, sociodemographic factors will be obtained from the population surveys concerning SES, education, household income, and so on.

The idea is to understand whether the presence of these risk factors will differ between ALS patients, siblings, spouses, and controls and whether the comparison between ALS cases and controls will differ across different control groups. Secondly, the analyses will try to determine whether these risk factors modulate the prognosis of ALS after diagnosis in terms of risk of disease progression and death. Progression will be measured by the ALSFRS-R. Individual risk factors and risk factor combinations will be assessed to determine whether any combination of factors result in a larger risk modulation in terms of being diagnosed with ALS or in terms of surviving the disease after diagnosis. The difficulty in getting data from Finland and Denmark to the US was mentioned the previous day, but it also can be difficult to get the data within the country and has slightly delayed the linking of these data. Data have now been received from the MND Register and Sweden will be delivering data to the investigators very soon. A total of 1471 cases of ALS have been identified for whom they are confident of data completeness and

diagnostics. These data will be analyzed intensively over the next year, so Dr. Fang hopes to have interesting new results to report.

Aim 2 seeks to assess gene-by-environment and environment-by-environment interactions in terms of modulating the prognosis of ALS. The goal for this aim is to characterize interactions between TBI, mental disorders, and infections. For genetic modifiers, the focus will be on genetic susceptibility to ALS, chemical exposures, and gut microbiome. The ALSrisc Project will be used for this aim, which is a population-based case-control study of ALS in Stockholm. ALSrisc has been recruiting newly diagnosed ALS patients from the entire Stockholm area from 2016 onwards, as well as the sibling and spouse controls of these patients, from the Stockholm population size of 2.2 million. Approximately 50 to 80 cases of ALS are diagnosed every year there. A total of 360 patients and 220 controls are anticipated to be included in this aim. From the cases, details clinical information will be collected from medical records and the MND Quality Registry. Clinical data and CSF have been collected from the patients. Several final samples will be collected from patients and controls, including blood, fecal, hair, and nail samples and risk factors have been collected from self-reported data using a questionnaire regarding ALS research from a large consortium in Europe. Based on these biospecimens, biomarker data have been collected, including clinical chemistry, genotypes, C90rf72, proximity extension assays, fluorescence-activated cell sorting, and shotgun metagenomics. Hair samples are sent to the Icahn School of Medicine at Mount Sinai (ISMMS) for measurement of approximately 10,000 chemicals using a specific technology developed by the team there to quantify the dynamic exposure map of chemicals using hair samples. To summarize, for the 360 ALS patients and 220 controls, there will be information on disease phenotypes, including clinical characteristics and follow-up data. For patients and controls, there will be information on risk factors (self-reported and register-based), genotypes and C9orf72, gut microbiome metagenomics (fecal), and approximately 10,000 chemicals (hair-based).

To briefly introduce some of the analysis of ALS risk, an analysis by Dr. Charilaos Chourpiliadis who is a member of the team, assessed several risk factors (e.g., BMI, smoking, head injury, diabetes mellitus, dyslipidaemia, & hypertension), effect modifiers (e.g., sex and C9orf72), and outcomes (e.g., risk of ALS, risk of death after ALS diagnosis, and ALSFRS-R decline after ALS diagnosis). This analysis included 280 incident ALS cases diagnosed between March 2016–September 2022 in Stockholm and 207 sibling and spouse controls. Risk factor data came from Euro-MOTOR questionnaires and C9orf72 was determined by Columbia Genetics at Columbia University Hospital. In this analysis, fairly few cases and controls have been exposed to these risk factors. The sample is representative of the ALS population in Stockholm. The median level of diagnosis is about 13 months. Unconditional and conditional means that the analysis is conditioned on whether the cases and controls from the same family. Higher BMI was associated with a lower risk of ALS, which validates what has been seen in other studies or ALS patients have lower BMIs than controls. Nothing was found about smoking or head injury. However, diabetes seemed to be protective against ALS and ALS patients are more likely to have dyslipidemia compared to controls. There was not a very clear difference between cases and controls in terms of C9 mutation. Looking at differences by sex, there was some difference for hypertension. There has not been much reported on this, so this finding will have to be further validated. Cases and controls reported BMI for every decade prior to diagnoses. BMI has been increasing over time among cases and controls, but not as rapidly for ALS cases compared to controls. Looking at BMI more than 25 years before diagnosis, a very clear inverse association can be seen between BMI and ALS for both men and women. Looking at mortality after ALS diagnosis by risk factors, nothing appeared to be statistically significant apart from the fact that hypertension seemed to be associated with a higher risk of death after ALS, especially among C9 patients. About 10% of patients in this analysis have C9, which is as expected in the

Nordic population. Looking at ALSFRS-R score after ALS diagnosis, dyslipidemia and hypertension both seem to be protective against a fast decline on the functional scale. This has been reported in some studies, but not all in the previous literature.

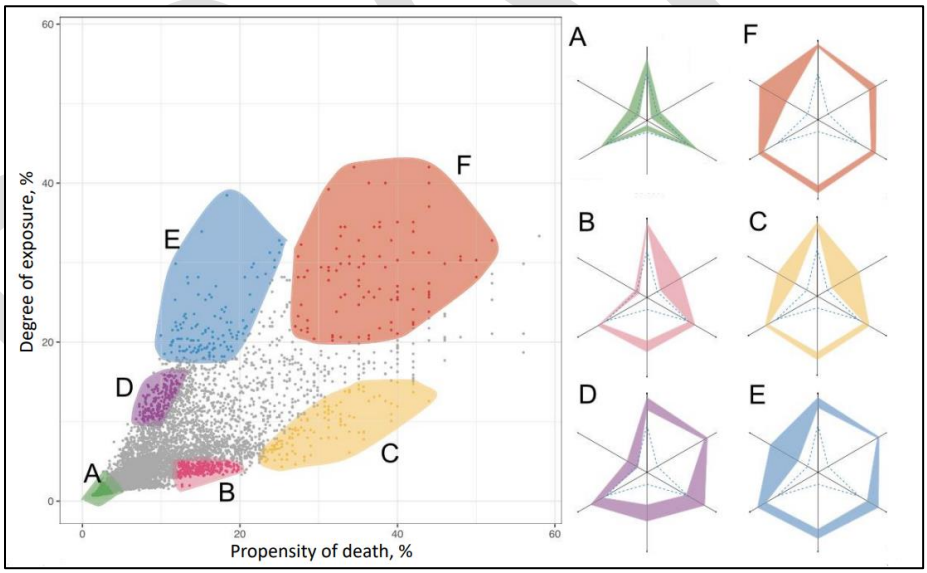
Using the findings from Aims 1 and 2, Aim 3 (clinical application) will focus on developing a stratification method of ALS patients based on the exposome, genetic susceptibility, and clinical measures. This aim will include 360 ALS patients from the ALSrisk cohort with complete follow-up data. A variety of information has been collected across these patients. These variables will be classified into the 3 categories:

1. Exposure Variables: TBI, neuroinflammation, and infections; chemical exposome (hair); and gut microbiome (feces)

2. Outcome Variables: Survival (data/cause of death); self-reported quality of life (QoL) from ECAS, HAD, EQ5D, and LISAT-11

3. Indicator Variables: Clinical characteristics and chemistry; genotypes; C9orf72 (number of expansions; neurofilament light (CSF); neuroimaging (bran MRI); and immune responses (T-cells, et cetera)

Then ideally, these patients can be mapped with the Y axis being the degree of exposure and the X axis being the outcome variables, with the hope of identifying specific clusters or patients according to degree of exposure to potentially harmful risk factors and propensity of death as illustrated by this graphic:



While these 3 aims may not make the best or most unique contributions, what Sweden has to offer is at least slightly unique in terms of helping to improve the understanding of ALS and in finding potential preventive and treatment strategies for patients and people at high risk.

Discussion Highlights

Ms. Pauls Backman read some of the questions aloud during each discussion period. Questions that were posted during the registration process and raised during the meeting are included in the attachment sections for Days 1 and 2 at the end of this document.

Observing that the estimated peak incidence age for ALS continues to increase, Bjorn Oskarsson asked whether Dr. Fang and colleagues believe that they will see an even later peak with their detailed methodology.

Dr. Fang responded that with the register-based approach, they always see a peak of 70–79 years of age, which is seen in other European countries as well (e.g., Germany). However, in the case-control study, they still see a mean age of diagnosis of 65 years. This is partially because the most vulnerable patients do not participate in a research project like the ALS Risk Study. Their study has a good response rate of about 85%, but they lose about 15% of patients who are too vulnerable to participate. While she did not know if she could trust the 70–79 years of age completely, in a population like Sweden where the life expectancy is about 80 for both men and women, further increasing age is not likely to be seen in the near future.

Regarding a question from Lynn Brielmaier regarding whether higher BMI is also associated with slower progression, Dr. Fang replied that this does not seem to be the case unfortunately. Other studies have not seen strong signals for this either. Type 2 diabetes has been repeatedly shown to be protective against ALS onset. However, people with diabetes do not necessarily have a longer survival or slower disease progression than other people. Therefore, it is difficult to be definitive at this point. Slower weight loss after diagnosis is protective against mortality, but BMI per se is not.

Antoinette Harrison noted that Dr. Fang used the acronym FoB in one of her earlier studies and she wondered what that meant. Dr. Fang indicated that this was the Swedish National Household Census, which is population-based survey.

Dr. Benjamin Brooks asked whether anyone is collecting data on those patients who are diagnosed as not having ALS.

Dr. Fang indicated that the NMD Registry collects every patient who has been suspected of having ALS. The diagnostic work is always ongoing for a longer time than it should have been, so they are updating all of the diagnoses regularly. Some patients' diagnoses become an MND rather than ALS, while some patients migrate from an MND diagnoses to an ALS diagnoses.

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

Kjetil Bjornevik, MD, PhD
Co-Investigator
Assistant Professor
Harvard University

Dr. Bjornevik indicated that he would be providing an update on this project on behalf of Dr. Ascherio who was prevented from presenting. In terms of background, there is a growing interest in the role that infections may play in the development and progression of chronic diseases, including neurological disorders. The group at Harvard has been interested in the role of Epstein–Barr virus (EBV) in multiple sclerosis (MS) and other herpes viruses, such as the

herpes simplex virus (HSV), which has been linked to Alzheimer's disease. One reason for this is the ability that certain viruses and bacteria have to infect cells in the nervous system. EBV infects B-cells and resides there for the life of the host after primary infection. HSV is known to infect and establish a latent infection in neurons. Because of these neurotropic properties, viruses and bacteria also can play a role in the development of ALS. Studying infections may seem trivial, but it can be quite challenging. Traditional research often has been limited by relying on data collected post-onset, such as in post-mortem tissue. These samples often have been collected years after the potential triggering viral infection. Therefore, the samples could have been affected by behavioral changes or the disease pathology itself, making the results from these studies quite difficult to interpret. The role of infections in ALS development also could theoretically be studied by obtaining a detailed infection history and evaluating it in association with ALS risk. This can be challenging because it may be difficult to recall infections and because many viruses can cause mild, non-specific symptoms that may go unnoticed.

For this reason, this study used a different approach of conducting a longitudinal seroepidemiological study that involved analyzing repeated blood samples from a large population when men and women who were followed until some developed ALS. This was possible because the study is based on a very unique resource, the Department of Defense Serum Repository (DoDSR). This biorepository contains more than 60 million frozen archived serum samples collected approximately every 2 years from over 11 million active-duty members across all military services. Drs. Ascherio and Bjornevik have previously conducted several studies on MS for which they used samples from the biorepository, including recent work on EBV. They are now very excited to extend this work to ALS. By documenting the occurrence of ALS in this population and analyzing the archived samples of ALS cases and matched controls for antibodies, they aim to provide a rigorous and unbiased assessment of the relationship between past and recent viral infections and the risk of ALS.

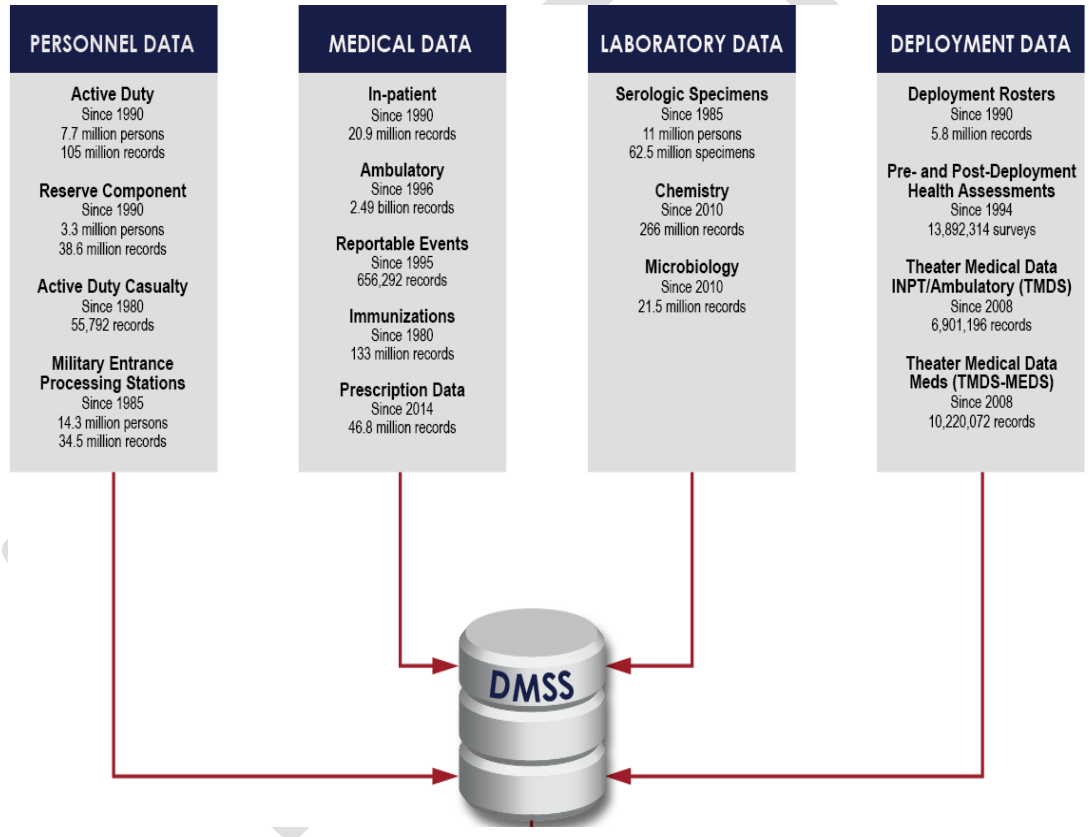
The specific aims of this study are to: 1) assess whether enteroviruses (EVs) associated with acute flaccid myelitis (AFM) (e.g., coxsackievirus B3, EV-A71 and EV-D68) contribute to predicting ALS risk; 2) assess whether past or recent neurotropic herpesviruses (e.g., herpes simplex virus 1 and varicella zoster virus) contribute to predicting ALS risk; and explore whether the viral infection profile (virome) at baseline or its changes during the follow-up are associated with ALS risk; 3) assess whether incident viral infections are associated with increases in serum levels of neurofilament light chain (NfL), a marker of neuroaxonal injury, and serum NfL or changes in serum NfL contribute to predicting ALS risk; and 4) determine whether there is potential confounding by TBI, deployment history, smoking, body mass index (BMI), diabetes, and/or family history of ALS. This table shows the estimated number of person-years in the study:

Table: Person-years of follow-up by branch and age-strata from 1990 to 2019.

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

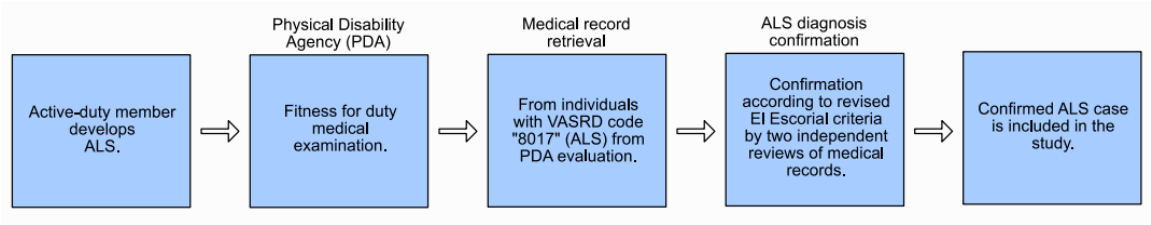
Because of the very large study population of active-duty members, there is a very large number of persons years of over 43 million, making it a very large population. Because of the age distribution of active-duty military personnel, the person-years of follow-up is geared toward a younger age group than in the general population. Most of the person-years of follow-up are in the age group of individuals <26 years of age. This makes the study population also suitable for study on a disease like ALS that in general occurs later in life than, for example, MS. Because of the large size of the population, a fair number of the persons in the study population developing ALS overlap with individuals developing ALS in their 40s, 50s, and 60s.

In addition to the blood samples, it will be possible to collect covariate data that are important for the analyses. The following diagram provides an overview of the data available in the Defense Medical Surveillance System (DMSS):[25]



[25] (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)

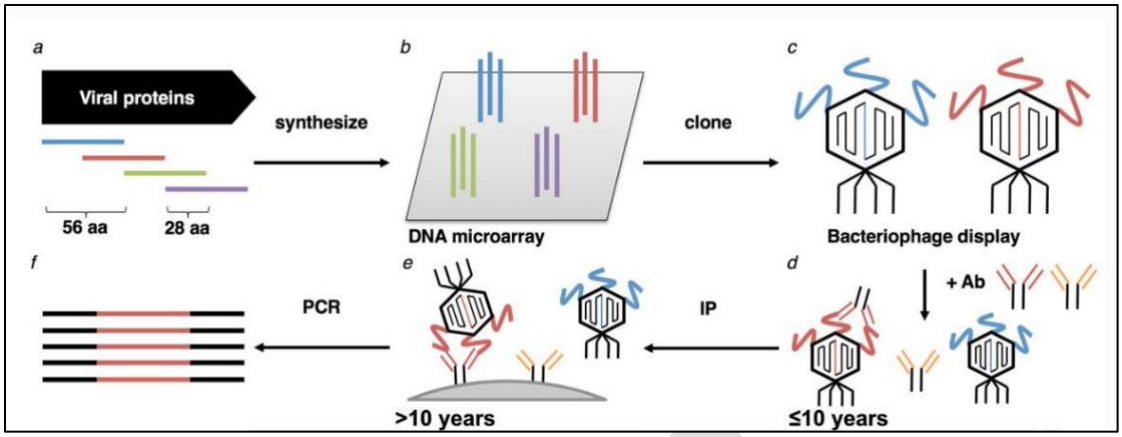
This is the flowchart that is used to confirm ALS cases:



When an active-duty member develops ALS, they go through a rigorous fitness for duty medical examination through the Physical Disability Agency (PDA). If the diagnosis is confirmed, the individual will be released for medical reasons from active duty. The investigators will retrieve medical records for individuals who have a Veteran Affairs Schedule for Rating Disabilities (VASRD) code "8017 (ALS)" from the PDA evaluation. The ALS diagnosis will be confirmed according to revised El Escorial criteria by 2 independent reviews of the medical records. Confirmed ALS cases will be included in the study. There are several key elements that makes this a very compelling and rigorous approach to study infections and study risk factors in general.

A rigorous approach also is taken in terms of how controls are selected, risk-set sampling and matching on time of blood draw, which is critical for validity and risk of bias in the analyses. By using a risk-set sampling approach, it will be possible to select controls who were at risk of developing ALS when the case developed ALS. By using this approach, it will be possible to obtain unbiased estimates of a study conducted in the whole population of 11 million individuals, making this a very methodologically rigorous and strong approach. Using this procedure, it will be possible to virtually eliminate the probability of selection bias. All procedures and samples will be handled identically for the cases and controls because the laboratory is blinded in all stages of the investigation, which will help to eliminate the risk of measurement bias in the study. In addition, it will be possible to closely match on the time of blood sample collection because of the large pool of potential controls. There will be 2 controls selected per each ALS case, and for each sample it is possible to match most of the cases within 30 days of sample collection and within 90 days of collection for almost everyone. This makes it possible to eliminate the influence of possible seasonal variation in antibody levels, for example. This has been very important in previous investigations on Vitamin D and MS risk for which there is a marked seasonal variation. Since they are conducting agnostic screening of a large number of viruses, it is good to be able to account for possible seasonal variation.

A novel technique, VirScan™ (PhIP-Seq), also is being used to profile all of the virus infections in the study population. This technology was developed by Stephen J. Elledge from Harvard Medical School, who is a collaborator on this project. If the traditional approach was used to measure antibody levels for single infections or single viruses, it would have been limited to a very small number of viruses, because the antibody test for each virus would have required a fair amount of volume, but there was only a limited volume of serum for each participant. They developed a library of bacteriophages, which are viruses that infect bacteria that display a short specific sequence from viral proteins. When serum or plasma is added to this library, antibodies from viruses will bind to the bacteriophages that display the corresponding viral peptide. When the mixture is washed out, bacteriophages are found, antibodies remain, and DNA can be sequenced for the remaining bacteriophages to find which peptides in the person' serum contain antibodies against specific viruses. This graphic illustrates this serological profiling using VirScan:



With this technique, as little as 10 µg/L can be used to measure antibody levels against hundreds of viruses and bacteria, making it a powerful approach for a more agnostic screening of a large number of infections. The serological profiling of the human virome and ALS risk in a military population study will use a library that contains over 400 species and strains and bacterial proteins. Several landmark papers in recent years have used this technology to characterize the antibody response to hundreds of viral species in various medical conditions, including neurological diseases. This is the approach that the Harvard team used in their previous investigation on the Epstein-Barr Virus (EBV).

In terms of the status of the serological profiling of the human virome and ALS risk in a military population study, the COVID-19 pandemic has delayed the project and it has taken longer time than expected to execute agreements the military PDAs. Data Use Agreements (DUAs) needed to obtain medical records were signed with the Army PDA in October 2022 and Air Force PDA in March 2023, but are still on hold with the Navy. A total of 55 electronic medical records (EMRs) with VARSD 8017 (ALS) were pulled and reviewed in June 2023. Of these, 34 ALS diagnoses, 5 primary lateral sclerosis (PLS) diagnoses, and 1 progressive muscular atrophy (PMA) diagnosis were confirmed. Regarding the demographics of the confirmed ALS cases, the age at onset ranges from 23–54 years, there are 33 males and 1 female, 27 cases had limb onset and 7 had bulbar onset, 2 have a family history of ALS, and 2 genetic mutations have been identified (e.g., 1 C9orf72, 1 SOD1). Notably, approximately a third of the confirmed ALS cases were diagnosed in their 20s, a third in their 30s, and the remaining in their 40s or 50s.

Because of the delay in the project due to COVID-19 and because it has taken longer to identify, confirm, and obtain serum samples from these cases, about a year ago, the Harvard team started a project to extend its work to the VA. They established a collaboration with a VA investigator, Christine Fournier (Emory and Atlanta VA Center) to include ALS cases diagnosed after retirement from the military. Through Dr. Fournier, they have submitted a research protocol to the VA that has been now approved. As part of this protocol, the plan is to include veterans satisfying the following criteria in the virology study:

- ❑ Died between January 1, 1995 and December 31, 2022
- ❑ Retired from active military duty after January 1, 1993
- ❑ Received a diagnosis of ALS at anytime
- ❑ A request for the identification of ALS cases is being submitted to the VA national Corporate Data Warehouse (CDW)

Regarding the study procedures, the list of eligible ALS cases will be transmitted by the VA directly to the Armed Forces Health Surveillance Division (AFHSD). Other steps of the investigation will be identical to those developed for active-duty military personnel. This extension project has been approved by the VA and it has been submitted for approval to the DoD. It is expected that several hundred eligible cases will be identified in the CDW. Additional funding will need to be obtained for the inclusion of these cases and matched controls in the study.

Discussion Highlights

Ms. Pauls Backman read some of the questions aloud during each discussion period. Questions that were posted during the registration process and raised during the meeting are included in the attachment sections for Days 1 and 2 at the end of this document.

Dr. Brooks asked whether Drs. Ascherio, Bjornevik, and their team have a detailed history of previous immunizations at time of entry to military and, if so, whether there is a relationship to the results.

Dr. Bjornevik replied that as far as he knowns, they will be able to obtain immunization history after they join the military. However, there may not be a detailed history of immunization prior to that.

Regarding a question from Juliet Pierce whether these data indicate a particular branch of service with a higher incidence of ALS, Dr. Bjornevik said that they have not looked into this in their study, but that Dr. Weisskopf might be able to respond. Dr. Weisskopf added that they are going to look at this within their data. When working with the military population, there is a different age distribution of cases. If the other VA cases are added in, it still will be limited to people who got ALS while in the military, so it is a slightly different population. The wider question to the military as a whole probably would be slightly better answered in the larger VA databases that will have access to data that are not restricted to people who were diagnosed during their military service. They still miss people because there are some who will not go to the VA for their care. This question definitely will be assessed in the future.

Juliet Pierce asked whether the research also would assess whether veterans with ALS are living longer and, if so, whether there is a commonality that points to their longevity.

Dr. Weisskopf indicated that with their data, the question will not be exactly whether veterans live longer than non-veterans, because they are only looking at veterans. They will be looking at whether some factors in the military experience lead to longer survival.

Dr. Stommel added that he thinks the majority of ALS patients who have a history of military service end up at the VA because the benefits for that diagnosis are so extraordinary that it would be foolish not to take advantage of that. They will build a house for someone who needs one.

Dr. Weisskopf agreed that the benefits are huge. He and others have been contemplating how to assess this in different ways. It is likely that several things affect incidence and survival. Examining survival as a separate issue and recognizing that it may have slightly different risk factor characteristics than those for incidence is an important question and is highly relevant because it may have implications for people currently with ALS.

ALS Risk Factors: Airborne Pure Lead and Lead Compounds

Meifang Li, PhD
Research Scientist
Geography Department
Dartmouth College

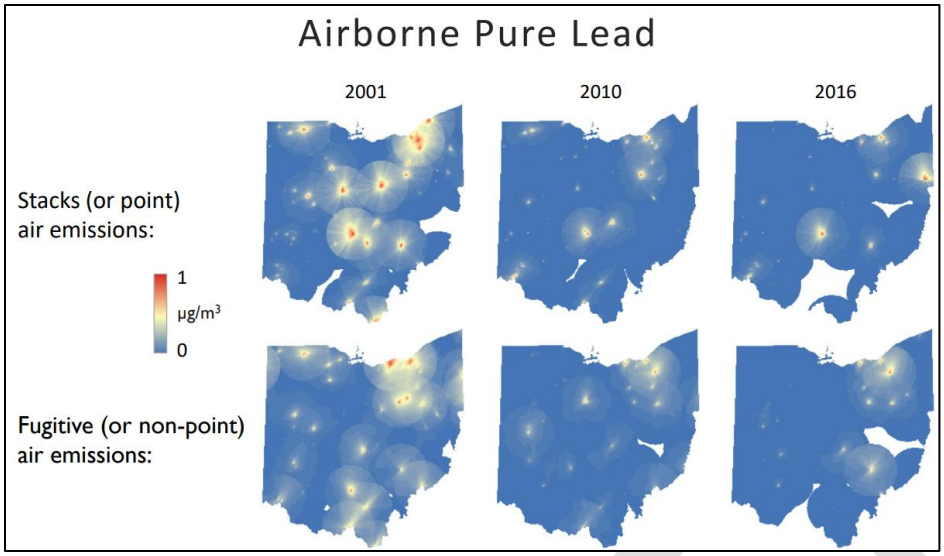
Dr. Li said it was an honor to present their team's recent work on the *ALS Risk Factors: Airborne Pure Lead and Lead Compounds* study. In terms of background, it is known that ALS is a fatal NMD with no cure. The vast majority (90%) of ALS cases are sporadic. The development of ALS has been linked to environmental contaminant exposures (e.g., lead), but the source and mechanism of lead (Pb) are not conclusive. Spatial analysis based on geographic information systems (GIS) can be a practical approach to detecting the association between disease and various environmental pollutants. Preliminary studies have found that population density may be associated with ALS, which impacts the detection of ALS-environment associations.

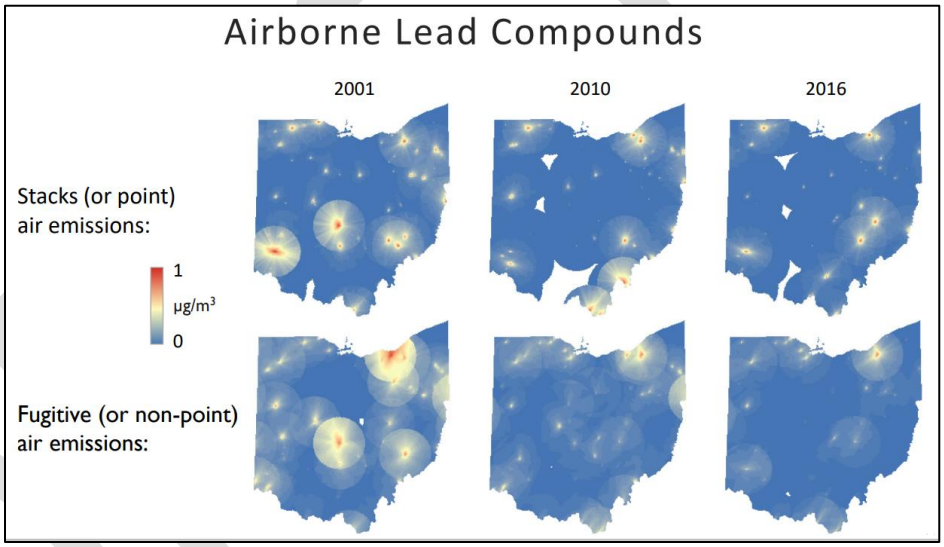
The hypothesis of the *ALS Risk Factors: Airborne Pure Lead and Lead Compounds* study is airborne pollution is a source of Pb and may contribute to ALS development. To test this hypothesis, the team developed a GIS-based method to examine the association between airborne pure Pb and Pb compound and ALS with GIS methods, excluding the impact of population density. They obtained approximately 700 ALS mortality cases that were attributed to "motor neuron disease" using ICD-10 code G12.2 in Ohio for the years 2012–2016. About 5 times as many controls were obtained. Approximately 3500 controls were randomly sampled in the population based on the expected demographic distribution of ALS cases. They have information on sex, age, and migration histories for cases and controls.

Population density was used as a confounding factor. The population density data were generated using the Landscan population dataset created by the Oak Ridge National Laboratory (ORNL). First, to represent the population distribution of the entire study period, the Landscan data of 2000–2015 were used to generate an average yearly population raster layer. To remove the artifacts in the population data, especially those pixels with unnaturally 0 population, a 7 x 7 moving window was used to smooth the average population raster. The smoothed average population raster is the population density data that were used in this study.

High-resolution, publicly available air quality data were sourced from the EPA's Risk-Screening Environmental Indicators model (RSEI) called AERMOD.[26] The AERMOD data estimate the concentrations of 770 individual Toxic Release Inventory (TRI) program-reported chemicals emitted from industrial facilities from 1988–2021 in 810- meter grid cells for 49 kilometers around each facility. The AERMOD air release dataset includes the media and/or method by which the chemical was released into the air, yearly chemical concentrations ($\mu g/m^3$), and spatial information. Stacks (or point) air emissions include releases to air through stacks, confined vents, ducts, pipes, or other confined air streams, and represent the majority of reported air releases. Fugitive (or non-point) air emissions include all other releases that are not stack air emissions. Lead in the air includes pure lead and lead compounds. The following maps show the spatial distribution of airborne pure lead and airborne compound emissions:

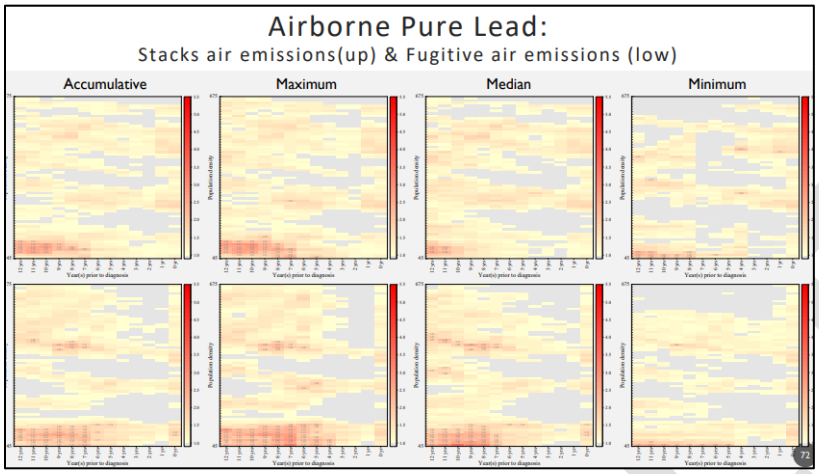
[26] https://www.epa.gov/scram/air-quality-dispersion-modeling-preferred-and-recommended-models#aermod

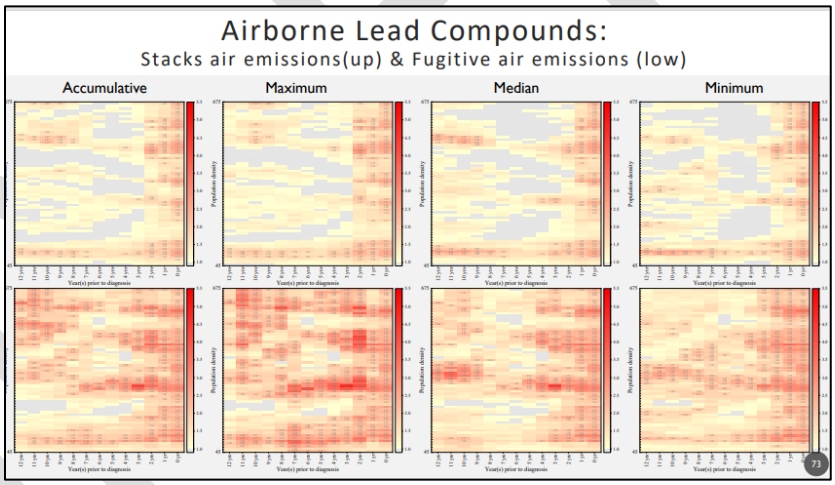




For the research design, the moving window based on population density was used to classify the cases and controls based on their surrounding population densities. Each window has 50 cases, and 63 windows were created in total. Annual samples were retrieved of airborne Pb concentration from 2000–2016 from the AERMOD dataset for ALS mortality cases and controls based on the subjects' historical residential locations. Considering migration history of cases and controls, subjects' accumulated, maximum, median, and minimum Pb exposure levels were compared using a logistic regression analysis in which age and sex were considered to be confounding factors.

These figures represent the association between airborne pure Pb and ALS and airborne lead compounds and ALS. In each figure, the colors from yellow to red have an odds ratio of >1.0. The redder the color the greater the odds ratio and the gray color indicates that the odds ratios are significant:





To summarize the findings, the odds ratios of the airborne lead compounds on ALS are higher than that of airborne pure lead. For pure lead, the impact on ALS is stronger in rural areas with lower population densities and has at least a 4-year lag effect. The 2 media present similar patterns. The maximum exposure in the years prior to the diagnosis year has the strongest odds ratio, and the minimum exposure has the lowest ones. For lead compounds, the impact on ALS is consistently significant in rural areas with lower population densities. Fugitive/non-point air emissions have a much greater impact on ALS than stack/point air emissions. The maximum exposure during the years prior to the diagnosis year has the strongest odds ratio, and the minimum exposure has the lowest ones.

In conclusion, both airborne pure lead and lead compounds from 2 different media have significant positive impacts on ALS development. The impacts of airborne pure lead from 2 different media on ALS development are similar, and the impacts are stronger in rural areas and have at least 4-year lagging effects. The impacts of airborne lead compounds from non-point air emissions are much stronger than those from point air emissions, and both impacts are without obvious lagging effects.

Discussion Highlights

Ms. Pauls Backman read some of the questions aloud during each discussion period. Questions that were posted during the registration process and raised during the meeting are included in the attachment sections for Days 1 and 2 at the end of this document.

Regarding a question from Dr. Brooks about whether there are comparable data for mercury, Dr. Li indicated that there are data for mercury, which is an elemental chemical.

Dr. Brooks asked whether Dr. Li has any data on reports of Pb intoxication in these areas (i.e., non-ALS Pb intoxication) to which she responded that she did not think they have these data but would like to explore this later.

In terms of a question from MC Collet regarding whether Dr. Li knew if anyone has studied lead in dishes and ALS and Lynn Brielmaier asked about shaving lead fishing weights, Dr. Stommel responded that they previously looked with their questionnaire data at led intoxication associated with various hobbies, including stained glass window making and making lead sinkers or bullets in one's basement or shop, which do seem to be correlated with ALS. While he was not familiar with shaving lead fishing weights per se, dealing with lead is certainly a risk factor. This includes removing paint from houses that have lead in them. There are several occupations and hobbies where one could be exposed to lead.

Dr. Weisskopf commented that there is an assumption that lead from any of these sources would act similarly. One of the advantages of using the airborne lead approach that Dr. Li and colleagues are using is that it is much easier to get good assessments of what people are exposed to. While it is more difficult with plates, lead sinkers, and those types of things, those are absolutely potentially very high exposure sources. He noted that one variable that was not included in Dr. Li's presentation was socioeconomic status (SES) variables. SES is worth considering, if possible, because his strong suspicion is that the exposure to airborne lead is not going to be evenly distributed. Underserved populations tend to get more exposure from airborne sources. The interesting point related to that, harkening back to Dr. Finger's comments earlier about how ALS assessment is not always as good in certain groups, and if it in fact turns out that lower SES populations have worse assessments of ALS or are not identified as much, the bias would be in the opposite direction of what is being found. That would tend to make lead look like less of a problem if still being found to be a problem. In addition, that type of bias from an SES point of view should not lead to different findings for lead in one year versus another, because SES is more or less constant. If windows of time are found when the lead matters more, that also argues somewhat against SES confounding the results. He recommended considering SES.

Dr. Stommel added that he recalled when training as a medical student in pediatrics at Boston City Hospital that the population in that neighborhood had a major problem with lead paint early in life because children were eating paint because it had a sweet taste to it. That issue should be considered in terms of SES.

Brian Kaplan asked whether there have been any studies in the age of the housing and ALS and blood lead levels (BLLs), as older homes have lead paint and may also have lead water lines.

Dr. Stommel responded that he had not thought enough about it and he was not aware of any data on this.

Dr. Li added that she was not aware of any data. They have only people's migration data where they have lived in the past several years, but no information on the age of the housing.

Jonathan Guest asked why airborne lead would be more significant in rural areas and if it is more likely to be well water.

Dr. Li indicated that their study results showed that for pure lead, the impact on ALS is stronger in rural areas with lower population densities and for lead compounds, the impact on ALS is consistently significant in rural areas with lower population densities. They needed to look at the spatial distribution of airborne lead and the specific pollution sources like industrial facilities. This is a very good point, and they will discuss it in their paper.

Regarding a question from MC Collet about how specific the location of ALS mortality cases was and whether they were able to drill down to the zip code level, Dr. Li responded that their data are at the individual level. They have the longitude and latitude of each case's residential location and geocode the location to estimate exposure levels based on their location.

A panelist noted that studies have shown elevated blood lead levels in children living near airports attributed to airborne lead from small airplanes burning leaded gasoline and asked whether there are similar findings of elevated ALS risk from living near airport.

Dr. Li indicated that they have not looked into whether cases were close to airports or other specific locations, although it is a very good point. For now, they are looking at the general spatial distribution but need to look at high-risk areas specifically.

Dr. Stommel added that there are a lot of nasty things around airports, including exhaust, nanoparticles, and all of the ingredients in fuel. Some studies have shown that the Air Force seems to have a higher rate than normal of ALS compared to other branches of the military.

Dr. Weisskopf added that there was an issue regarding pilots and crews. There are small airports throughout the country with prop plane fuel that until recently contained lead.

Dr. Stommel noted that Roger Pamphlett from Australia wrote some interesting articles about truck drivers and airline and stewards and pilots having a higher rate of ALS. There also are the people on the ground flagging the planes, who certainly would have a high exposure.

With respect to an inquiry about whether there are any data about childhood risk of ALS, especially among children of color, Dr. Li reiterated that age and sex are included as confounding factors. Perhaps in the future, they can pay attention specifically to childhood cases of ALS.

Brian Kaplan commented that ATSDR has done an extensive review of lead sources and recommended that they be consulted. There are a number of lead sources that are not necessarily captured in Toxics Release Inventory (TRI) data. Some of these sources include old forgotten mines and former military training sites.

Regarding an inquiry about whether Dr. Li's research is published and whether there is a link, Dr. Li indicated that they are preparing the manuscript and hope to submit it soon.

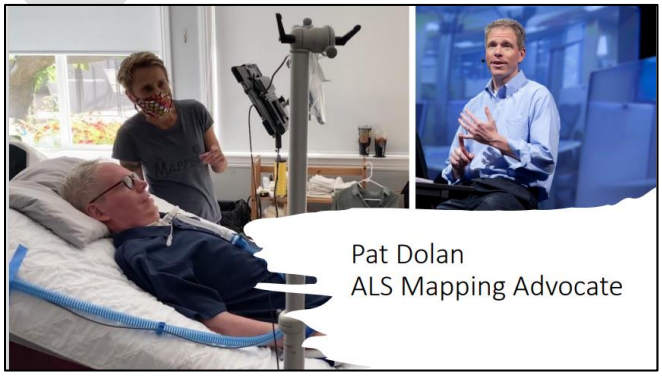
Mapping the National ALS Registry

Clare Durrett
Strategic Advisor
Advocacy, Legislation, & Communication
Team Gleason

Clare Durrett indicated that while she works directly with Team Gleason, she is part of this illustrious group and small group of unpaid volunteers. While she referred to them as a "merry band of misfits," she emphasized that their work has been very fruitful. About 2 years ago, Team Gleason was exploring ways to identify more people in the ALS community who remain uncounted unfortunately. They created an in-depth survey from which they now have several thousand responses from which they are hoping to establish who among them has ALS and then identify data deserts in order to deploy some outreach programs. While they had compelling data for those they serve, this basically validated that more data are needed to better understand the community and how everyone can help. She reached out to Danielle Boyce who did what she does brilliantly and quickly connected them to the CDC, Pat Dolan, and this band of GIS experts. She thought everyone would agree that the information that has been collected is compelling proof that much more can be done with added resources and access to more data. Their belief is that if they can commit to the end goal of counting everyone possible who is diagnosed with ALS, they can work backwards to identify solutions on how to get there collectively. She also thought everyone would agree that not one-person or one organization could solve this alone. There are multi-layered issues with this disease, but it is possible to count as many people as possible.

Earl Sarow, MA
GIS Professional, Retired from Esri
ALS Geospatial Hub

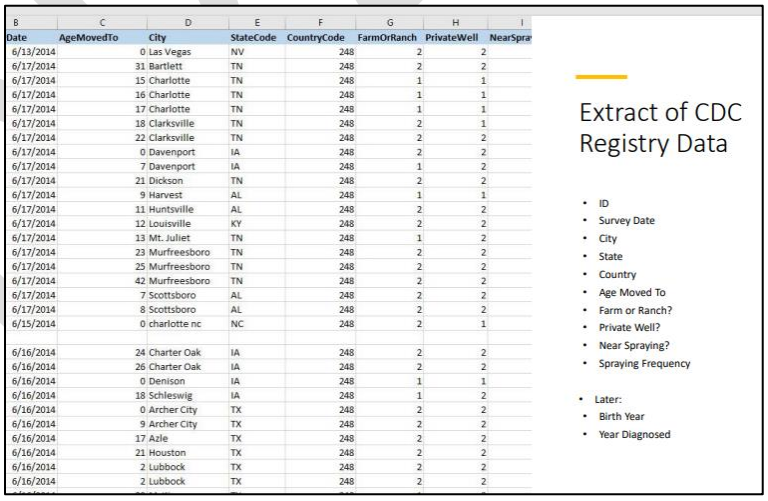
Earl Sarow reported that over the past few months, this group has been using GIS technology to map the ALS Registry to determine how mapping could help to understand things like access to care, identifying common lived locations, and locating communities that are underrepresented in the National ALS Registry. He began with an introduction of Pat Dolan, who has been a GIS professional for over 33 years. He was diagnosed with ALS in 2016. After his diagnosis, he wanted to use his GIS skills to help battle ALS. Though he can no longer move, speak, or breathe on his own, Pat continues his work as a GIS professional. Over the past 7 years, Pat has created hundreds of maps to support legislation, research, and clinical care. This is all thanks to his eye gazing device and the support of Esri and Team Gleeson:



In 2022 with the help of his former colleagues at Esri, Pat released the ALS Geospatial Hub[27] that as Pat stated, "Brings clinic information together by geography to discover patterns and relationships to improve care, accelerate research, and advocate for the ALS community." He invited everyone to join and explore the hub and the information it provides.

Mr. Sarow noted that he recently retired after 35 years with Esri, where he had the good fortune to work with Pat Dolan. Together, their claim to fame was working on the *Godzilla* movie during which they explained to the directors and writers how they would have used GIS to track and predict Godzilla's movements. Shortly after his diagnosis, Pat asked if he could help him analyze the history of ALS patients. Their goal was to map the places that registrants had lived and identify the environmental and demographic characteristics of those locations. They did this work in partnership with Danielle Boyce and Clare Durrett and were excited to show the results of this work. He first began by taking a moment to acknowledge the work done by all of the ALS advocates who have provided advice to the CDC on how the Registry could best serve the community. Sadly, they recently lost 2 of those advocates who were giants in the ALS community, Sandy Morris and Becky Mourey, to whom they dedicated this presentation. Sandy and Becky are a reminder that everyone needs to work with a sense of urgency, because this disease takes no breaks, and it continues to take lives at an alarming rate.

They undertook a spatial analysis of the place history data in the Registry to see what information could be extracted out of it. The goal of this analysis was not to offer any groundbreaking insights into ALS, but rather to raise awareness of how GIS could contribute to improving and understanding the information in the Registry. They hoped that by doing this, they would inspire some really smart and creative people to look at the Registry in a different way that could lead to new insights and new ideas for research. This is a sample of the data obtained from the Registry:

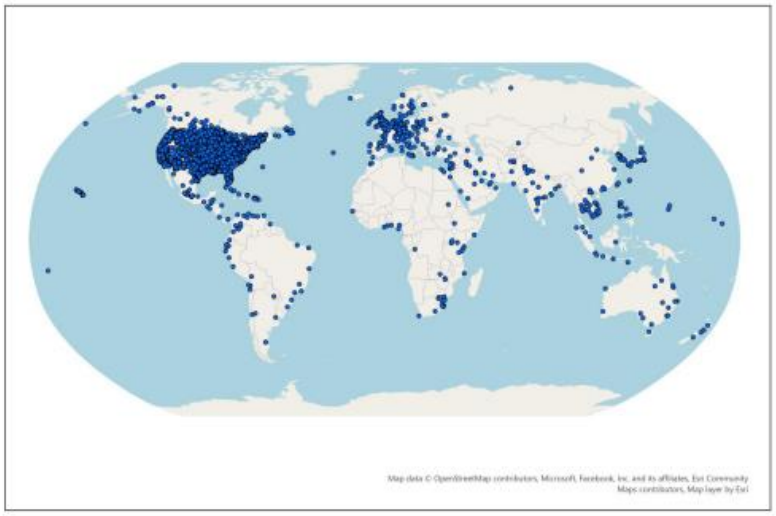


Date	AgeMovedTo	City	StateCode	CountryCode	FarmOrRanch	PrivateWell	NearSpra
6/13/2014	0	Las Vegas	NV	248	2	2	
6/17/2014	31	Bartlett	TN	248	2	2	
6/17/2014	15	Charlotte	TN	248	1	1	
6/17/2014	16	Charlotte	TN	248	1	1	
6/17/2014	17	Charlotte	TN	248	1	1	
6/17/2014	18	Clarksville	TN	248	2	1	
6/17/2014	22	Clarksville	TN	248	2	2	
6/17/2014	0	Davenport	IA	248	2	2	
6/17/2014	7	Davenport	IA	248	1	2	
6/17/2014	21	Dickson	TN	248	2	2	
6/17/2014	9	Harvest	AL	248	1	1	
6/17/2014	11	Huntsville	AL	248	2	2	
6/17/2014	12	Louisville	KY	248	2	2	
6/17/2014	13	Mt. Juliet	TN	248	1	2	
6/17/2014	23	Murfreesboro	TN	248	2	2	
6/17/2014	25	Murfreesboro	TN	248	2	2	
6/17/2014	42	Murfreesboro	TN	248	2	2	
6/17/2014	7	Scottsboro	AL	248	2	2	
6/17/2014	8	Scottsboro	AL	248	2	2	
6/15/2014	0	charlotte nc	NC	248	2	1	
6/16/2014	24	Charter Oak	IA	248	2	2	
6/16/2014	26	Charter Oak	IA	248	2	2	
6/16/2014	0	Denison	IA	248	1	1	
6/16/2014	18	Schleswig	IA	248	1	2	
6/16/2014	0	Archer City	TX	248	2	2	
6/16/2014	9	Archer City	TX	248	2	2	
6/16/2014	17	Azle	TX	248	2	2	
6/16/2014	21	Houston	TX	248	2	2	
6/16/2014	2	Lubbock	TX	248	2	2	
6/16/2014	2	Lubbock	TX	248	2	2	

This information came from people who self-enrolled in the Registry between 2016 and 2021. It does not include people who were found through other means, such as extracting data from government or insurance databases. They received one row of data for each location reported by each registrant. This place history information included the city, state, and country where the registrant had lived, as well as a few basic pieces of information about those places. Those records were geocoded to get latitude and longitude coordinates for the cities listed in the place

[27] https://als-geospatial-hub-nonprofit.hub.arcgis.com/

registry. They successfully located just over 23,000 place history records from a total of just over 4,000 registrants. This map shows where those locations were across the world:



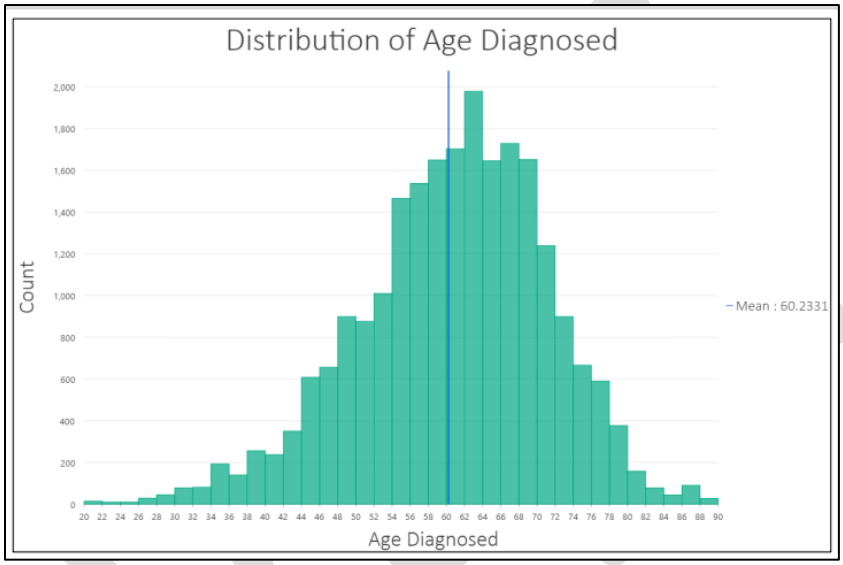
The first type of analysis performed was to look at the geographic distribution of the reported residence locations. Using just the data received in the extract, the locations were mapped and then broken out into different categories to get a better picture of where people had lived and when. The reported location for each of the registrants was extracted working on the assumption that each registrant's first reported location was the place where they were born. While these are located all around the globe, not surprisingly, most of them were within the US. Knowing the years that each person moved to and from each location and the year they were formerly diagnosed, they could start to divide the place histories into pre-diagnosis, diagnosis, and post-diagnosis groups. This information could be useful for researchers looking at potential exposure to environmental factors that could be contributing to ALS and could help direct outreach efforts for newly diagnosed patients. Information about where registrants reported living during or after the year in which they were diagnosed could be used to help determine whether ALS clinics are located in the places they are needed most, or if there are areas that are being underserved by the current set of clinics. It also could shed light on whether people moved in order to be closer to an ALS clinic.

GIS also can help to better understand where care is needed rather than making assumptions. Calculating the drive times from registrants' current locations to ALS clinics nationwide revealed that the average drive time to a clinic is about 51 minutes. However, not everyone lives near a clinic. This analysis showed that 16% of registrants have to travel 90 minutes or more to a clinic. The drive time to clinical trial locations also was calculated. For instance, the average drive time to a HEALY ALS Platform Trial location is about 83 minutes.

The number of years that each person lived at each location was calculated as well. That information can be summarized by geographic area to determine the number of person years that were spent living in different areas, which could be useful for a study of exposure to a specific environmental factor. The location each person lived at the time of the diagnosis also was mapped to see if there were any strong spatial patterns that could raise questions about what may have occurred in a specific area that would have caused a spike in diagnoses. No strong patterns were observed in the year that people were diagnosed, which is probably

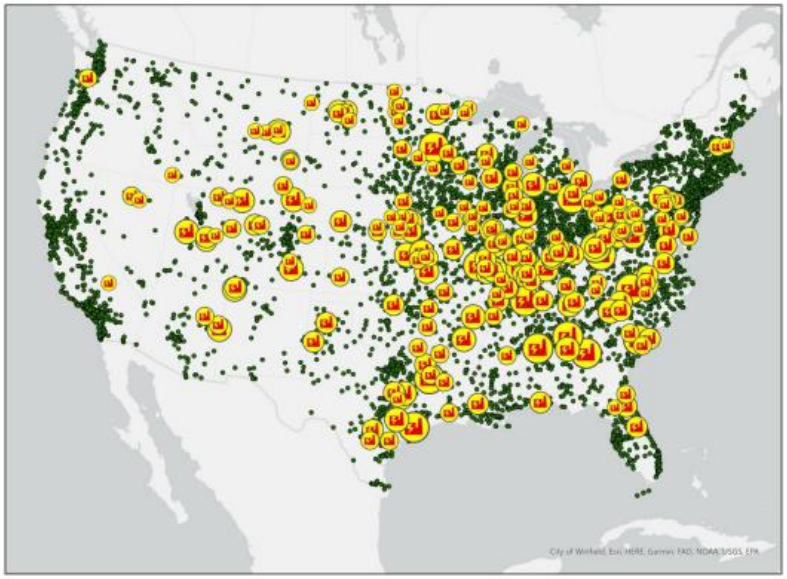
because the vast majority of diagnoses, at least within the Registry, occurred in the first few years after the Registry was established. The locations also were mapped to look for patterns in the age at diagnosis. For instance, strong spatial patterns in an area with an unusually high number of diagnoses at a fairly young age could raise questions about what kind of environmental factors might have been at play in that area that might cause an earlier onset of ALS.

This is a chart of the number of people diagnosed at each age from the 20 to 90 years old. Previous reporting on the Registry has indicated that ALS is most commonly diagnosed through a person's 60s. This chart supports that finding:



With GIS, another step that can be taken in the analysis is to look at relationships within the place histories of the registrants to detect spatial patterns in the data that are not evident from just looking at a map of points. This part of the analysis looked at just the pre-diagnosis locations of the registrants. This limited the analysis to the lower 48 states, which eliminates the distorting effects of long distances across the Pacific from Hawaii and from Alaska through Canada. One type of analysis that can be done is to identify places where registrants' locations tend to be lumped together. This type of analysis could help researchers identify geographic areas that might be of interest for detailed studies of environmental factors. Going one step further, the analysis can look for cases where multiple people have lived at the same location for some period of time. Yet another way to represent spatial patterns is with density maps, which can provide a general overall picture of the national pattern of the place histories. A hotspot analysis also can be performed, which is a methodology that finds statistically significant patterns in the distribution of a dataset.

One of the greatest strengths of GIS is its ability to link datasets together based on shared locations. If it is known where the observations from 2 different datasets occurred, such as place histories and county boundaries with demographic information, geography can be used to join those datasets together for further analysis. This is a simple example showing the locations where registrants have lived and locations of coal-burning power plants in the contiguous US:

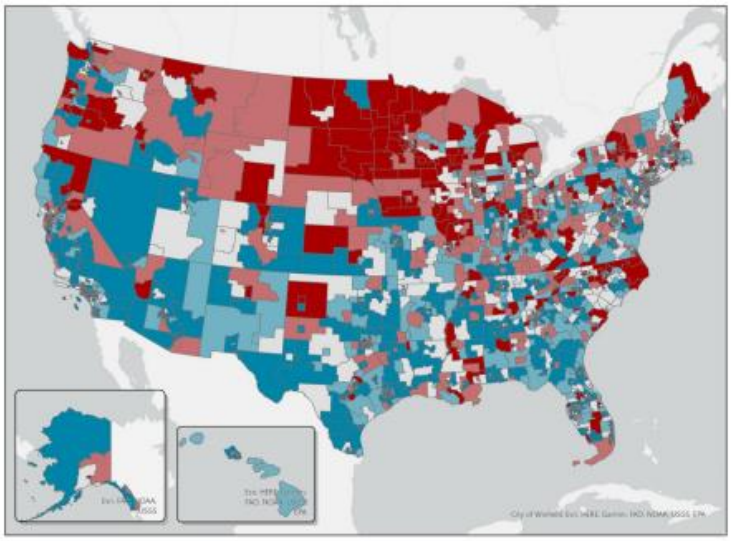


This kind of information could be combined with information about power plant emissions, prevailing winds, and health information from the Registry to look for relationships between them.

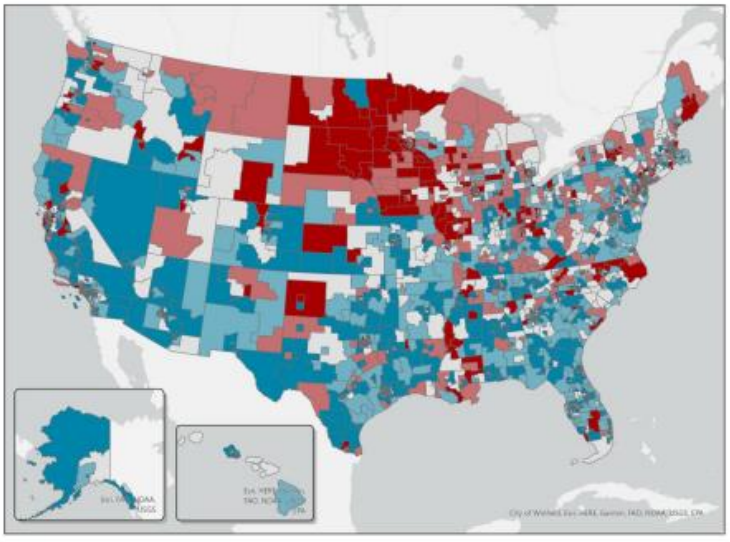
The EPA collects and makes available a lot of datasets dealing with environmental information, such as maps showing places where toxic chemicals have been released into the environment. These datasets can be mapped and GIS tools can be used to identify people who have lived in close proximity to any of these sites. Other EPA datasets have locations of industries that generate environmentally hazardous waste products that are regulated by the EPA under the Resource Conservation and Recovery Act (RCRA). Again, if the precise locations are known where people have lived, mapping can help to analyze their proximity to these sites. There also are EPA datasets that lists the amounts of various pesticides used by the county over approximately 70 years. That can be used for mapping aggregated numbers of person years lived at each location, which can be multiplied by particular pesticide usage rates in order to get a picture of the total potential aggregate exposure of registrants to a particular chemical.

GIS also can be used to identify relationships between the current or last reported locations of registrants and a number of demographic datasets to determine whether there are any geographic patterns that stand out, such as areas that are under- or over-represented. For this part of the analysis, the most recent location of each registrant was used. There was a question that asked registrants to identify their current location in the survey, which some registrants did. For those who did not, the last reported location was used. To link the registered locations to demographic data, they were overlaid with the boundaries of Public Use Microdata Areas (PUMAs) as defined by the US Census Bureau. Then the number of registrants within each PUMA were summed up. PUMAs are used because they are relatively equal in population as opposed to colonies or states whose populations vary greatly. This avoids problems like having small differences in the number of registrants causing huge differences in registration rates in areas with very small populations. Looking at PUMAs by registrant count, about 950 PUMAs had no registrants. One PUMA had 45 registrants, which was the highest number that they found.

The number of registrants was calculated per 100,000 persons, and the results were mapped. The red areas on the following map have a higher rate of registration than the national average, while the blue areas have a lower rate than average. This map shows that the rate of registration is higher in the upper Midwest and parts of the Northeast and lower in the South and Southwest, a pattern that is consistent with what other studies have found:

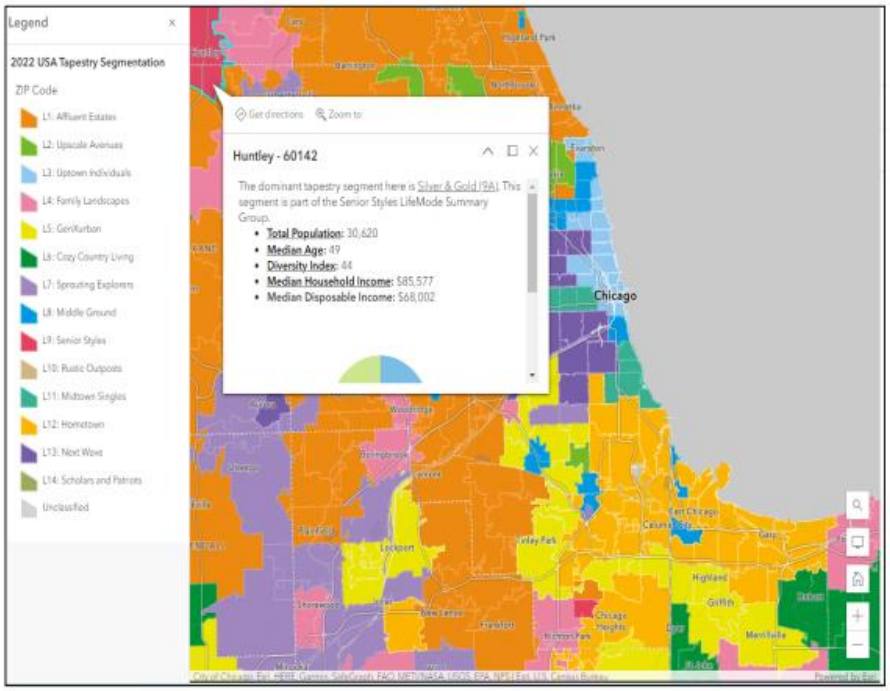


Veterans are several times more likely to be diagnosed with ALS than the general population, so for the next analysis, they wanted to see if there is a pattern to the rate of registration relative to the percent of veterans in the analysis areas. The number of registrations was calculated per 10,000 veterans and then mapped those results. In this map, the red areas show a higher rate of registrants relative to the number of veterans than the national average, and blue areas show a lower rate. In this map, the upper Midwest stands out more strongly than the rest of the country, but there are some other pockets of high registration in other parts of the country:



ALS tends to strike people in their late 50s and into their 60s, so registration rates were assessed relative to the population ≥50 years of age. The number of registrations were calculated per 10,000 persons ≥55 years of age and then were mapped to the areas above and below the national average. Again, the upper Midwest showed higher registration rates than most of the rest of the country. There were a lot more pockets of high registration scattered across the country, especially in the Eastern half of the country. These patterns also could be caused by several factors, like differences in the effectiveness of education and enrollment efforts in different areas, regional differences in the willingness among the population to provide personal information to the CDC, and/or patterns in the overall actual rate of occurrence of ALS within the population. The registration patterns observed using GIS are, in fact, similar to the regional patterns and deaths from MND.

One way to understand the characteristics of who is or is not joining the Registry is to look at demographic profiles of the areas where there are high and low numbers of registrants. Tapestry is a method of classifying geographic areas according to a number of demographic characteristics, such as race, ethnicity, average age, income, wealth, and buying habits. The following map shows the predominant tapestry classification by Zip Code for the Chicago area:



For this, a national map of tapestry classifications were overlayed onto registration locations in order to identify which tapestry segment each registrant lives in. The number of registrants were then summed up who lived in each tapestry category. The top 10 tapestry segments were identified based on the number of registrants who lived in each area. The characteristics of each of these segments can be further examined to find out more about the areas where people are or are not registering. For instance, one of the top 10 tapestry segments found is this group called "Comfortable Empty Nesters." There is a full description of that group online that describes their age, racial characteristics, income, spending habits, and occupations.[28] Looking

[28] esri.com/tapestry

at this kind of information in detail for areas with high or lower registration rates might provide insights into the demographics of who is joining the Registry and who is not.

Another area of great interest is identifying communities that are under-represented in the Registry. It is known that minority communities are under-represented, and GIS can be used to learn more about that. For this part of the analysis, areas were separated that have at least 1 registrant from areas that have no registrants. Then those areas were compared to determine whether certain population groups are more prevalent in the areas where no one has registered, which could help find out where the under-represented groups are. First, they looked at the Black population. This showed that in areas with registrants, 10.4% are Black and 89.6% are non-Black. In areas without registrants, 15.5% are Black and 84.4% are non-Black. This confirms that the Black population is probably under-represented, and that GIS could help to identify areas on which to focus to enroll more Black participants.

A similar analysis was performed to look at under-enrollment of the Hispanic population. In areas with registrants, the Hispanic population is 14.9% and non-Hispanic population is 85.1%. In areas without registrants, the Hispanic population is 24.% and the non-Hispanic population is 75%. Therefore, it also appears that the Hispanic population under-represented in the Registry. Again, GIS could be used to find areas on which to focus efforts to enroll more people of Hispanic heritage.

Another group that might be under-represented in the Registry are those without health insurance. Mapping this population showed the percentage of people living without health insurance in each area. In areas with registrants, 8.1% of the population is not insured and 91.9% are insured. In areas without registrants, 9.1% are insured and 90.9% are insured. While there is only a slight difference in the percentage of uninsured and un-insured between the areas with registrants and areas without, there might be a slight under-representation of people without insurance. However, this cannot be said for certain with the data available.

There may be a number of reasons that people do not join the Registry. Geographic data were used to try to evaluate whether some of those potential reasons hold true. One reason people do not join the Registry could be because they do not live near a specialty clinic. They might be seeing a neurologist or a general practitioner who either is not aware of the Registry or does not encourage their patients to join the Registry. One test of this theory would be if the rate of registration drops off in areas where clinics are less accessible. To start this analysis, the fastest route to drive to the nearest specialty clinic from each of the PUMA areas was calculated and travel times to get to those clinics were mapped for the contiguous 48 states. Those times from ranged <1 hour to 7 hours. Alaska and Hawaii were outliers that were removed from the rest of the analysis, given that there are no clinics within a practical driving time of Alaska and there is only 1 clinic on Oahu in Hawaii. Contrary to what was thought might be the case, there does not appear to be any relationship between accessibility to a specialty clinic and the rate of registration.

Lack of access to the internet might discourage some people from registering since the surveys are online. There also does not appear to be a correlation between the relationship of the percentage of households in each PUMA that do not have access to the internet and lower registration rates. Another possibility might be a language barrier in that non-English speakers might be less likely to join the Registry, so percentage of registrants who do not speak English was mapped. Again, no correlation was found between the percentage of people who do not speak English and the registration rates.

Researchers have identified other reasons that people give for not joining the Registry, including no mandate to register, lack of awareness of the Registry, lack of encouragement to register, not seeing the value of registering, and reluctance to share personal information with a government agency. GIS also can be used to examine demographic, economic, and other factors that might suggest other reasons for not registering.

Another challenge is the current state of the Registry data. The self-enrolled Registry data have limitations that prevent it from being used to make accurate assessments of the ALS community. The first limitation is the lower registration number. As Dr. Stephen Finger points out, the location information in the Registry represents only about 5% of the patients diagnosed during the time period it covers. A complete headcount is needed to make accurate predictions on the prevalence of ALS. A second issue is generalized address information. The Registry only captures locations down to the city level. This severely limits the value of the Registry because it makes it impossible to accurately analyze local patterns of patients or their relationship to localized environmental factors. Third, there is under-representation of minority populations. These GIS analyses verify that minority communities are under-reported, which impacts the understanding of ALS in those communities. It is important to be careful not to assume that the results found in this study apply to the ALS community as a whole.

Although there are several challenges to getting the entire ALS community to join the Registry in order to collect the level of detail needed for accurate analyses, there is still value in that effort. Using GIS tools could identify patterns and relationships within the ALS community and relationships to information in other data sources. Understanding those patterns and relationships can help accelerate research, improve access to care, inform policy decisions needed by the ALS community, and much more. To maximize the value of the Registry, timely reporting of the Registry data is needed so that research and policy can be carried out quickly and with current information. People need to see the Registry data in action so they can see the value of registering. An increase is needed in registration rates, especially for minority populations. The level of location detail needed for precise and accurate analyses need to be captured. In addition, a place is needed for researchers to share their analyses so that they can build upon each other's work.

In closing, Mr. Sarow shared contact information; invited anyone interested in additional details to visit the ALS Geospatial Hub to look at maps, applications, articles, presentations, and other resources that Pat Dolan has created; and invited persons living with ALS and/or their caregivers who attend an ALS clinic to take the ALS Clinic Survey to share their experiences at the clinic. Currently, surveys have been completed for about 65% of the ALS clinics in the US. All the survey results can be seen on the ALS clinic advisor dashboard. The contacts and resource links are as follows:

Contacts:

- ❑ Danielle Boyce: dboyce3@jhu.edu
- ❑ Pat Dolan: mapping4nonprofits@aol.com
- ❑ Clare Durrett: Clare@teamgleason.org

Resources:

ALS Geospatial Hub: http://bit.ly/ALSHub
ALS Clinic Advisor Survey: https://esriurl.com/alshubsurv
ALS Clinic Advisor Dashboard (survey results): https://esriurl.com/alshubdash

Danielle Boyce, DPA, MPH
Faculty, Johns Hopkins School of Medicine
Biomedical Informatics and Data Science Section
Johns Hopkins University

Pat Dolan, MBA
GIS Professional, ALS Advocate, and Living with ALS
ALS Geospatial Hub

Before beginning the discussion, Dr. Boyce indicated that Pat Dolan asked to say a few words on his behalf and that it was her honor to be his voice. Here are Pat and his wife Mara:

First, I want to thank Earl Sarow for his time and talents working on the Registry data with me. He came out of retirement to support this work, which I am incredibly grateful for. There are very few people who would spend 20 to 30 hours a week for 6 months dedicating their time and talents with zero pay. I am very blessed to have studied the movements of Godzilla and mapping the National ALS Registry with Earl. A few observations after mapping the Registry. First, authoritative PALs population data to build upon because we need to have a complete headcount of the ALS population. Next, we need a standard data model for collecting and mapping the ALS population. This will allow organizations that are collecting people with ALS to build upon. This includes the collection of residential addresses. Next, every person with ALS needs a unique identifier, which the CDC Registry creates. This needs to be used for all the other registries collecting information about PALs. My good friend Phil Green brought this up a few years ago, because this will prevent the duplication of data. We need a working group of researchers, neurologists, CDC scientists, and research advocates to enhance the data and data model based on the latest findings and research. This will allow us to build upon the latest research. Next, we need to make the Registry research-ready. This means having the full Registry map, required fields populated, and organized for researchers to start their analyses. Researchers should not be spending valuable time and resources getting the Registry ready for analysis. Next, we need researchers to share their work to build upon. We learned about the amazing work researchers have done with the Registry and data that came out of that analysis. This information has to be shared out for others to build upon. Finally, we need to see the Registry in action. I am tired of spending countless hours filling out surveys and never seeing the results of that work. When the community sees their information in action, trust me, people will want to join the Registry. This is for all surveys and registries, not just the CDC Registry. I want to thank Paul, Jamie, and the rest of the CDC National ALS Registry team for giving us the opportunity to work with them on the Registry data. I really appreciate your willingness to hear feedback and work with us.

Discussion Highlights

Ms. Pauls Backman read some of the questions aloud during each discussion period. Questions that were posted during the registration process and raised during the meeting are included in the attachment sections for Days 1 and 2 at the end of this document.

Dr. Li asked whether this great dataset is available and accessible for research purposes.

Mr. Dolan replied that they will share all of their work on the ALS Geospatial Hub, which can be accessed at the link provided in the materials that participants receive after the meeting.

Regarding the hotspot analysis indicating that there was a greater density of cases in the Northeast and Midwest, Ms. Pauls Backman asked whether the investigators overlaid that information with where registrants are located, who are in the Northeast and Midwest, and if sample bias was accounted for.

Mr. Sarow said they did not. They basically took those locations and ran a hotspot analysis. They did not adjust for population densities or anything like that. It was intended to be an illustration of one of the tools that is available that could be used in a more robust and statistically defensible way that could be used in peer-reviewed type studies. They were trying to throw out a hodgepodge of various techniques people could use that exist now to get people to start thinking about the data in a different way.

Ms. Durrett added that as Dr. Finger said, they probably were dealing with only about 5% to 10% of the population of people who filled out the location surveys. One of the biggest concerns was that people would draw correlations with the information that they are sharing in the maps, rather just illustrating what can be done with more and richer data and more details that could be deployed as tools for the research community.

Ms. Pauls Backman emphasized that an important takeaway from this presentation pertains to the importance of the survey information in the Registry. This sort of analysis can be done only if the data are available. While she understands that there are some limitations to the data, because the information received was at the city level and was not at the county or granular level because of limitations related to de-identifying participants.

Dr. Mehta confirmed that currently, they can ask for city level data only. They are discussing whether this can be modified, but this will require approval from the IRB and the OMB.

In response to a question from MC Collet regarding how long the particular survey used for the GIS mapping has been live, Ms. Raymond indicated that it was launched in 2012 or 2013. Patients who were already in the Registry could go back and complete that survey.

Anne Supplee asked whether there has been any effort to translate the questions into other languages, such as Spanish or Somali. Ms. Raymond responded that survey questions are available in Spanish, but that is the only other language to date. There is a link to the Spanish version on the website at https://www.cdc.gov/als/

Dr. Stommel reported that his experience, having worked in their ALS Clinic of Excellence at Dartmouth, is that a lot of patients do not want to go to the clinic anymore after 1 or 2 visits. The ALS Clinics of Excellence are a link to the National ALS Registry, so patients are told about the Registry there. However, if they are not going to clinics, they may not register with the National

ALS Registry. With that in mind, he asked whether anyone knew what percentage of ALS patients actually use ALS Clinics of Excellence and what percentage of those patients actually register with the National ALS Registry. A brochure is generally given out at the ALS clinics so that patients are aware of how to register.

Dr. Mehta responded that while those are great questions, they unfortunately do not know the answer because they do not specifically ask more than whether someone is going to a clinic.

Ms. Pauls Backman added that having been a member of one of the partner organizations for many years, she knows that MDA, Les Turner ALS Association, and the ALS Association are all involved in recruitment efforts with their specific patient populations to provide the information. Therefore, information should be coming from sources other than clinicians. Clinicians are pressed for time in clinic visits, but advocacy organizations also have been recruited to communicate the information.

Ms. Durrett reported that Team Gleason had 2800 responses in their survey questions, which included: Do you attend clinic? How long did you attend clinic? Why did you stop? They found that less than 60% of the respondents attended a clinic, but that very few continued as their disease progressed. This does limit the interaction at some of the clinics. This pertained to clinics across the country—not just one specific type of clinic. This is a problem, but also is an opportunity to create better outreach programs to reach people and encourage them to complete the surveys.

Dr. Mehta added that they have seen this same phenomenon. People with ALS will be seen in the clinic, but afterwards will receive their continuity of care from their local neurologist. This may be more common in rural areas where the nearest clinic may be hundreds of miles away.

Ms. Pauls Backman highlighted an issue that was raised a couple of times about the use of GUIDs consistently across all databases, which has been a problem in the ALS space probably since the invention of GUIDs.

Dr. Mehta indicated that they have been generating GUIDs since January 2017 and have been using the one form from Massachusetts General Hospital, which is more prevalent and common. Currently, they have generated about 5000 GUIDs. They also have the ability to use the NIH GUID, which is not as common. The Clinical Research in ALS and Related Disorders for Therapeutic Development Consortium (CReATe Consortium) uses the NIH GUID. ATSDR is in the process of working with Alex Sherman and the NeuroBANK® to do a comparison of ATSDR's GUID. So far, they have matched close to 800 GUIDs. The initial question Earl and Dr. Ostro were asking was about potentially having the National ALS Registry serve as the hub of the GUID for everybody. There is discussion about whether that is possible, but they do not want to "step on the toes" of others like NeuroBANK® who already have been doing this for a long time. In terms of a question about how people can get their own GUID identifier from the Registry, Dr. Mehta said he would have to check on that and report back to everyone.

Pat Dolan commented that the ALS Clinic Advisor survey shows that many people stop going to clinic when they do not feel it is worth the time and effort. A public announcement is needed about the ALS Registry. Plus, if they count on the ALS clinics to register people, it does not help in getting to under-represented communities.

Ms. Pauls Backman stressed that the lack of representation in the Registry is not necessarily limited to the Registry. There is clearly a lack of access to top-of-the-line ALS care among under-represented communities.

Ms. Durrett added that additionally, people see as many assistive technology representatives as they do doctors.

Ms. Pauls Backman agreed, emphasizing that all providers need to be aware of the Registry and of the benefits of having their patients register.

Dr. Mehta asked Ms. Durrett whether the Team Gleason survey asked people why they stopped attending clinic.

Ms. Durrett indicated that most people that answered that question said it was because the clinics were not telling them anything that they were not already aware of. They found that a lot of people start leaning on representatives for their mobility, comfort, and breathing needs rather than just going back to clinic. She thinks clinics are very valuable, but that is just the way a lot of families feel. It is a lot for families to get out of the house and go on an adventure to spend all day at a clinic. Many prefer not to attend once they have the information they need.

Dr. Mehta suggested that one possibility would be to implement mobile ALS clinics. While this is not something that ATSDR could do, there are organizations that certainly could go to people's homes to perform evaluations and provide care. There are numerous models throughout the country, such as mobile dental care.

Ms. Durrett agreed, but the issue is multi-layered. There are different areas where patients are being seen by the people they need at any given time (e.g., assistive technology representatives, speech and language pathologists, et cetera) who often engage with patients through telehealth. When representatives speak to patients via telehealth or are in their homes, they can find ways to share information about the Registry and explain the importance of registering.

Perspectives from Persons Living with ALS: Discussion Panel

Andrea Pauls Backman, MBA
Moderator, Annual Research Symposium and Meeting
Founder, ALS Strategy Consulting, LLC

Panelists:
Sunny Brous, MEd
Pat Dolan, MBA
Brooke Eby
Layne Oliff, PharmD

Ms. Pauls Backman introduced the session, explaining that 4 individuals living with ALS were invited to join this panel discussion because in addition to living with ALS, they all are tremendously well-informed, highly involved in the broader ALS community, open, honest with their thoughts, and definitely are not shy. She welcomed panelists Brooke Eby, Layne Oliff, Pat Dolan, and Sunny Brous. She noted that Pat Dolan would be communicating with an eye-gaze device that would take a little time and that his wife, Mara, was in attendance with him. The

format of this session was that Ms. Pauls Backman posed questions and invited the panelists to share their responses.

You are all active in many ALS groups and programs. What does it mean personally to you to contribute to scientific research as a person living with ALS?

Sunny Brous responded that she was always a "guinea pig" and always willing to contribute to the greater good. When she has an opportunity to jump in, she takes advantage of it. It makes her feel like she is contributing. She hopes she is paving the way for the next wave of ALS patients, even though it may not benefit her.

Layne Oliff said it is very, very personal. He takes this personally and is involved with many organizations because it is so important to find treatments for this disease. A cure may not be found during his stay here, but if treatments can be found to prolong Sunny's life, Brook's life, Pat's life—it is a win a step at a time. It is so important to take this personally and with passion and commitment. In terms of how to reach people with ALS to sign up for the Registry, a brochure is not a plan. He has been in strategic planning for many years and emphasized the importance of having a marketing plan in place to promote and raise awareness about the importance of the Registry—not just with NEALS members, but also all neurologists who care for people with ALS. He sees the ALS Registry as being as important as laboratory work. Many times when people leave an ALS clinic or doctor's office, they are given a prescription for laboratory work for the next visit. Handing them something about the Registry is just as important. While sometimes it is clinician-driven and clinicians have a lot of clout, doctors often are busy doing other things. The office staff, nurse, or nurse practitioner might be the real conduit to ALS patients.

Brooke Eby replied that she would echo what both Sunny and Layne said. It can feel like the ALS community is invisible at times because it is such a quick death sentence, so it feels like there are not that many people going through it. However, once in the community, she realized what a strong group it is. Research is a way that they can give back to each other and to future members of the community. It is one of those things that sometimes she does not want to do for herself, but she will do it because she knows it might help Sunny or Layne.

Pat Dolan said that for him, participating in research is essential. However, he wants researchers and organizations who support the ALS community to know that people living with ALS are more than a data point or a fundraising machine. Instead, they want to be active members of the research. The reason he loves working with Team Gleason is because they want people with ALS to be part of the research and learn from their personal experience. He referred to I AM ALS as another great organization that brings the ALS community together to create meaningful legislation and policies.

Regarding whether the National ALS Registry has a marketing plan, Dr. Mehta said that they work with the ALS Association, Les Turner Foundation, and MDA to raise awareness. They also work with Brunet-García, which developed a very robust communications plan though it is not a marketing plan per se. He agreed that they must do a much better job getting the word out to encourage people with ALS to join the Registry. Consideration is being given to potentially establishing an incentive program, which is very common in research. For instance, a $100 gift card might be provided for joining the Registry or taking the surveys. While it is not that much money, it is a way to incentivize people and give something back to them for their hard work and the time it takes to register and take the surveys. An incentive plan would have to be approved by the IRB and the OMB and could take 6 to 12 months, but that is one idea. They are certainly

willing to consider any suggestions anyone would like to make. There are a lot of print assets (e.g., brochures, infographics, et cetera) that they provide to their partners to give to persons with ALS, but those only go as far as someone actually reading them and acting on them. Some of them may just be tossed in the trash. There also are individuals who may never join no matter what because they just do not want to, which is certainly understandable. They cannot force anyone to join. There also has been discussion about focusing target enrollment efforts in diverse areas such as California, Texas, Florida, and New York. The voices of people living with ALS like Sunny, Brook, Layne, and Paul are very important and can be instrumental in encouraging others to get involved. There are many neurologists who do promote the Registry, provide materials, and explain the importance of the Registry.

Personally, when you first became aware of the Registry, what would have made it easier for you to register and want to register and go through the process?

Brooke Eby said that for her, it was about emphasizing the value of what the Registry can do for patients when they are first introduced to it. When she first heard about the Registry, it was through a pamphlet in a big folder that she was given by her ALS clinic that she shoved off to the side and did not pay attention to at first. In this case, doctors are the salespeople for the Registry or maybe it is the ALS Association who sent representatives to the clinics. Having someone who can help ALS patients understand that the Registry is something that can help everyone living with ALS and can help the future of ALS is very important. The value must be emphasized as opposed to just telling someone to sign up, which just gets added to the laundry list and administrative work someone has to take care of when they are first diagnosed. Somehow the message must be conveyed that the Registry is going to help everyone living with ALS and that participating in it is priority number one.

Did you have expectations about the Registry when you first heard of it? If so, have your expectations been realized? If not, could you explain?

Layne Oliff said it was interesting because the data from 2018 was just published the previous week. He was diagnosed in 2020, so he is not even officially part of the dataset yet. He understands dealing with the federal government and governmental agencies. Being in healthcare, he understands that data lag. However, in terms of a 4- or 5-year lag for a disease from which people die in 2 to 5 years, he was hoping the data would be more current. Hopefully, it will be possible to get the data a year or 2 out in the future.

Pat Dolan said this was a great question for him. He thought the Registry would have a complete ALS population, which he thought was a reasonable expectation in order to better understand the rate of ALS. He was surprised by the low registration rate, and wondered whether the self-enrolled surveys could be published, because that is the information that the ALS community is being asked to fill out.

Sunny Brous indicated that in preparation for this meeting, she got to meet with her neurologist for their quarterly meeting. In relation to expectations and realities, she asked him what came to mind. He said to make the Registry accessible for clinics to reference. Her example of that is with the current ALS Her Story, they have a WhatsApp group that is mostly "insane" but provides a lot of information. They talk about medicines, symptoms, side effects, at what point people started non-invasive ventilation (NIV), et cetera. To her, as an outlier not consistent with the white male population ALS diagnosis, that is what the Registry should be. She wants to be able to go to her neurologist and ask when she should do X or what other people do who may be around her age or in her cohort that is showing to be successful, consistent, or impactful. To

her, that is the expectation of the Registry so that the information is accessible to people's providers for those types of conversations.

Brook Eby said that while she did not have any expectations for the Registry itself, she does have very high expectations for every organization that is helping charge toward an end to ALS. She believes that every ALS organization is trying to do the right thing. She does not think that there are secret groups with an ALS organization that are pocketing the money and not actually working. Obviously, there is going to be some overhead that they can all accept and focus on how they want to drive forward. Her expectation is that every dollar is used very, very well. She has raised tons of money for ALS Therapy Development Institute (ALS TDI) and ALS ONE. She asks where the money is going, and she wants to see the fastest speed to an impact for the ALS community. The Registry receives $10 million per year, which probably includes a lot of overhead costs. She believes that CDC is working toward helping people with ALS and that they are all one team, but perhaps she would ask if they could work 1% more effectively. She thinks if everyone makes a 1% improvement, they could stretch that money to make it have an impact for the ALS community. Dollars are not easy to find in the ALS world, so she is very protective of where the money is spent when it comes to this community. She has very high expectations of how X amount of money is spent for the ALS community.

For those who may not have heard the previous day's presentation, Ms. Pauls Backman requested that Dr. Mehta briefly recap the roadmap of how the information is collected and why there is a time delay in getting it fully cleaned and then published.

Dr. Mehta indicated that these data do not belong to CDC/ATSDR. They belong to CMS and the VA. CDC has a robust data sharing agreement with these groups and request these data frequently. VA data tend to lag behind only about 1 to 2 years. CMS data tend to be older data and lag behind 2 to 3 years because the data come from all 50 states and include Medicaid data as well. CDC wants to make sure they get the entire dataset. The CMS lag itself is problematic. But once CDC has the data, it has to be validated, cleaned, and sent to NDI twice to make sure any deceased cases are removed because cumulative prevalence is used. That is, if someone is a case in 2017, they will remain a case until a death certificate is found for that person. Once all of that is completed, there is an internal process as well. Once cleared, it then goes to the journal. The 2019 data are in now and probably will be published in Winter 2024. They also are still in the process of requesting the 2020 dataset even though it is 2023. One hold-up is the CMS 2- to 3-year delay. CDC cannot release a report without having all 3 datasets (CMS, VA, Registry Portal). This is one of the terms of clearance from the OMB, given that there is under-representation. The capture-recapture method also is used to look at the number of missing cases. Some cases may never convert to the CMS system, so this helps to find them. Capture-recapture is still not perfect, but it is a methodology that has been used in epidemiology for many decades. Moreover, the CMS data are not free. CDC has to pay about $70,000 to $80,000 a year for them. In addition, CMS does not send the data electronically. They send them on a CD-ROM and they email Ms. Raymond a password so that she can open it and upload the files onto the secure server at CDC. They want to do everything they can to get the data out as soon as possible and they do not want to hear every year, "Where are the data? What's going on?" They do not like it either, but there are constraints that CDC has to deal with as well.

In terms of the surveys, Dr. Mehta indicated that surveys have been published already and can be found at cdc.gov/publications. Ms. Raymond has analyzed a number of these throughout the years, and at least 1 or 2 are published annually. These publications are peer-reviewed and are posted publicly on the website. In terms of the completeness of the Registry, cancer is a good example. Cancer is reportable at the state-level to health departments and cancer registries have existed in the US for decades. CDC tries to model after these. Other platforms are looking at the cancer model as well in terms of testing therapeutics. Cancer is more prevalent than ALS, so it gets more attention. But even cancer registries are not exhaustive and all-inclusive. They also are missing cases. ALS is more challenging because it is not notifiable to CDC, and ALS does not get as much attention. However, they are making strides in terms of case-ascertainment and in terms of increasing awareness.

Each year during this meeting, there are people who are recently diagnosed, have fallen into ALS, and are learning about it. A lot of questions came in during the registration process from people around the world about where to get help. In addition to M&Ms and tequila, which may or may not work for everyone but often are a very good idea, what advice does this panel have about what first steps they should take?

Brooke Eby said that a new free app/website[29] was released the previous week called "Roon" that contains over 1500 videos from people living with ALS, neurologists, caregivers, and every major ALS organization. They gave people making the videos list of hundreds of questions, so it is bite-sized content. For people who are newly diagnosed, she would recommend going to that site and following one of the guides that say something like, "I was diagnosed. What's next?" The guides will take them through what is next in bite-sized pieces that are not overwhelming.

Pat Dolan said the best advice for the newly diagnosed is that once they get through the grieving process, they should move from dying with ALS to living with ALS and getting involved with the ALS community and watch Brooke on social media. You will laugh, cry, and be inspired. It is better than "Cats."

Layne Oliff agreed with that. He pointed out that upon diagnosis, he would suggest taking a deep breath, calming down as much as possible, and realizing that ALS is as much mental as it is physical. It is important for people living with ALS to treat and manage their mental capacity and emotional capacity as much as their physical capacity. So, take a breath, get involved, and think about the mental and the physical. He also would say to keep in mind that the federal government, CDC, FDA, and NIH are well aware of ALS. ALS is on their radar screen because of the passage of the ACT for ALS. People living with ALS are on the minds of legislators and people in the federal government who want treatments, management, and a cure for ALS. Talking with people who have been involved with this for a long time say they are amazed at how much the federal government has suddenly become very interested in ALS. For anyone who has an idea or suggestion, now is the time to bring it forward. They are listening and will continue to listen as long as people living with ALS advocate.

[29] https://www.roon.com/

General comments and questions during this session:

Dr. Finger asked what ATSDR has heard from the partners in terms of the most effective ways to increase enrollment, how to build upon these efforts, and how the effectiveness of these efforts might be measured.

Dr. Mehta emphasized that ATSDR works very closely with its partners. He said that they know from Les Turner they have an individual who provides a concierge type of service in terms of reaching out to people living with ALS. That person provides information, calls people, and goes to their homes. That is in Chicagoland, which is a much smaller footprint within the entire nation. The ALS Association has someone who is very knowledgeable about the Registry, who provides information to their chapters and clinics. ATSDR does a lot of outreach at patient and research symposiums, virtually and in-person, throughout the year. Again, they cannot force anyone to join, but they can get the information out that hopefully will convince people to join. ATSDR has monthly meetings with its partner organizations to discuss what is and is not working, provide them with information about which states are under-enrolling, and so forth. At this point, he would like to try a different paradigm, such as the incentive program that he mentioned earlier. If it works on a small scale, potentially it could be rolled out nationwide. It is challenging. In their office are scientists, clinicians, epidemiologists, data scientists—they are not marketing experts. They do work with outside groups that have marketing expertise, but they are always willing to hear ideas and are open to partnering with other groups. They are open to partnering with Team Gleason in the upcoming fiscal year to look at that cohort and get the word out there as well.

Lauren Webb indicated that the Les Turner ALS Foundation has a dedicated Registry person who provides one-on-one assistance. They need help in doing outreach in communities most impacted by health disparities. She will be reaching out to the ALS Geospatial group to inform their outreach efforts.

Anne Supplee pointed out that the name of the Registry might be confusing because people say they have already registered, but it is with their local ALS organization—not THE Registry.

Dr. Mehta acknowledged that it is a valid point that sometimes there is confusion between registries, and that it is important to clearly explain the importance of the National ALS Registry, its Biorepository, and the surveys.

Regarding an inquiry about how long someone's name stays in the Registry and what happens to their information that is in the system when they pass, Ms. Raymond indicated that their name stays in the Registry. Though they are marked as being deceased, their information will remain in terms of tracking and inclusion in all analyses. This includes their survey data.

It was noted that the ALS community wanted a way to report hotspots of possible ALS clusters to investigate. When they asked about it previously, they were told it should be done at the state-level. However, states do not have the revenue and often have political reasons for not pursuing investigations. GIS data need to be correlated with the CDC Registry and for ATSDR to investigate. How do we work together to make that happen?

Dr. Mehta responded that he had a slide the previous day regarding a potential hotspot in Montgomery, Alabama. They talked to the state epidemiologist a few months ago and asked her whether she wanted to make an Epi-Aid request, which triggers CDC to deploy groups on the ground and potentially investigative more extensively through medical records and perhaps

performing blood sampling. As a federal agency, CDC/ATSDR cannot just go into a state and investigate without being invited. How it typically works is that a state has to make an official request, which will trigger an internal process within CDC/ATSDR. Another example is the East Palestine train accident. Dr. Horton's group was instrumental in conducting an investigation there, talking to the community, assessing the exposures, and so forth. That was triggered by the state requesting help from CDC/ATSDR. The same is true for hotspots of ALS throughout the country. The first step is for someone to contact the state health department, who must make the request. CDC does have the resources to investigate but must follow the hierarchy and be invited.

Ms. Pauls Backman noted that she and Pat Dolan were involved in the ALS Strategic Plan that was published earlier in the year by NINDS, and Pat also is actively involved in NEALS. She and Pat also are working together with some other working groups to implement the ACT for ALS and the strategic plan. She agreed that there are many governmental groups that not only are focused on ALS, but also a cohesive focus for the first time. This is a very pivotal time for ALS research.

Brooke Eby thanked CDC/ATSDR for hosting this panel. While sometimes it might be hard to remember what the ultimate goal is, she expressed her hope that seeing their faces would help bring inspiration and added motivation to all of the great work everyone is doing.

Dr. Mehta MD stressed that the panelists are all inspirational. He has been doing this work for 10 years and Dr. Horton has been doing it even longer. He was the one who took the bumps and bruises when this Registry was first starting off many years ago. They have made friends and lost friends throughout the years. This is not an easy disease to deal with and he wished everyone the best, emphasizing how inspirational they are and what a privilege it is to work with them.

Ms. Pauls Backman added what a privilege it had been for her to work with this amazing panel and to get to know them better. She expressed appreciation for their efforts, selflessness, authenticity, bringing all of their skills to this fight, and being willing to bear their souls like this and share their invaluable input.

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

Andrea Pauls Backman, MBA
Moderator, Annual Research Symposium and Meeting
Founder, ALS Strategy Consulting, LLC

During this session, Ms. Pauls Backman facilitated a meeting wrap-up discussion to address any final comments, questions, and suggestions.

Discussion Highlights

Patricia Stanco commented that the ALS Association is launching a trained volunteer ALS Registry enrollment program, similar to Les Turner's one-on-one approach, to provide direct assistance when requested. They also are working on a pilot to increase community-based outreach to people living with ALS who stop attending clinic because of language or cultural barriers. In addition, they are planning a workshop focused on developing an ALS diagnostic referral line to reduce the time to diagnosis and increase access to multi-disciplinary care,

genetic testing, treatments and the Registry. There are different strategies that are "2 sides of the same coin." One is to make sure that there is awareness that there is education so that people know about the Registry and understand its value, importance, and the role it plays in driving research so that that they are motivated to participate. The other side of the coin is to reduce barriers. They heard from Les Turner how successful their volunteer program is with those who might need direct assistance because they do not have a computer in the home, or they do not have reliable internet access or have internet access at all, their caregiver is overwhelmed, and/or there are just too many other competing demands. The volunteer program is a way to provide direct assistance when it is requested, so the ALS Association wanted to provide this as well. They also are increasing their outreach efforts with home visits and working within the clinics. They need to ask the clinics what the non-clinic-based needs are among underserved communities. They do hear about people with ALS and families who stop going to clinic. Sometimes it has been communicated that there is a language barrier and/or other factors. By working with some contractors in the community who can help bridge the gap, provide some health education, and help make sure that people are connecting to resources, the ALS Association can be working to increase support to the community while also increasing representation and diversity in the Registry.

Dr. Brooks asked whether the CDC ALS Registry has considered developing an ALS Caregiver's Forum to expand the information available across the different geographies and economical levels for those who are impacted by the disease ALS.

Dr. Mehta thought this was a great recommendation. While they have not looked into outreach to caregivers at this point, caregivers certainly are on the frontline taking care of their loved ones. An ALS Caregiver's Form certainly would be a very good way to reach out to caregivers and encourage them to speak with their loved ones about joining the Registry.

Kathleen Wilsbach asked how ALS advocacy groups could be informed so they could mobilize to put pressure on local governments to cooperate with the CDC if they are not being responsive about investigating specific potential hotspots, such as the one in Alabama.

Dr. Mehta emphasized that this was a tricky question because like other government agencies, ATSDR cannot lobby, engage in advocacy, or put pressure on other government entities. Certainly, what happens at the community level is greatly influenced by organizations like Les Turner ALS Foundation, the ALS Association, and MDA. These organizations have a lot of influence and a lot of clout. He would defer to them on any activities or measures they want to take or any information they want to provide.

Jenny Gore Dwyer recalled that some of the discussion centered around a lack of diversity in the Registry numbers. Because capturing diversity seems to be a major issue, maybe ATSDR could send an invitation to a member of the I AM ALS group "Many Shades of ALS" to explain what issues non-Whites have with registering. Maybe then the Registry could pivot to find ways to break down those barriers.

Along those lines, Michelle Lorenz suggested that an easy way to increase under-represented minority (URM) community enrollment is by outreach to the 102 Historically Black Colleges and Universities (HBCUs), especially the HBCU medical schools. Notably, Pat Dolan has mapped these HBCUs and found that very few have clinics or clinical trials in these locations.

Dr. Mehta MD appreciated these recommendations for reaching under-represented populations. They worked with BlackDoctor.org before publishing an article many years ago. He will look into perhaps working with the partners to send letters and/or convene a virtual seminar to reach out to the HBCUs.

Dr. Thakur said he would say the real value of the Registry is to keep people who share the reasons why a person has ALS from also getting ALS. This is the reason that experts are needed to figure out messaging. He often hears the question, "What does ALS mean for me and my family?" Inherent in that question is that they have people in their family who share their genes, eat the same foods, have been exposed to the same chemicals, et cetera which presumably led to their ALS. The research that the Registry has been funding is to help identify those risk factors. The next stage of that research is to figure out how to reduce and mitigate those risks. He does not want people who have ALS today not to have the opportunity to share their information with their family members about the reasons they think they got ALS and how their family members might do things differently to reduce their chances of getting ALS.

Dr. Mehta emphasized that CDC/ATSDR analyzes and provides data on potential risk factors. The more data points they have, the more they can analyze, and the more findings they may have on potential correlations, associations, or causes.

Ms. Pauls Backman that she was speaking with some folks about the ALS community who asked her to explain in layman's terms why someone gets ALS. She told them that essentially, there are three components: a genetic predisposition, an environmental trigger, and time. The ALS researcher sitting next to her said she forgot the fourth reason—luck. Her takeaway from that is that there are things that are still unknown about how the combination of various factors can work in any one individual to cause them to get ALS or not to get ALS.

Dr. Finger recalled that last year's stakeholder group stressed the need to examine the performance of the algorithm across different demographic groups, and he wondered what has been found.

Ms. Raymond replied that they did assess the algorithm and noticed that a certain proportion of the patients they get from CMS have only prescription data. This made them think about possibly including those who have only a prescription for riluzole or other medication now available to determine whether it could be added to the case count. They met with their neurologist and updated the algorithm. While they have not looked at the particular demographics of that group in terms of age or race yet, they were able to add about 1200 to 1600 cases and that was recently published.

Similarly, Dr. Thakur asked how the RFAs for ALS research coming from Registry funds have changed over time.

Dr. Ostrow commented that his impression is that prior to a couple of years ago, many ALS researchers were not aware of these funding mechanisms. Continued vigilance to promote these opportunities is important.

Dr. Mehta added that they typically like to fund between 1 to 3 applications per year. They have previously received 11 applications, so there are more that could be funded. Due to budgetary constraints, they are only able to fund 1 to 3 applications per year. Each year, there are current R01 grantees whose funding is expiring. Those funds are reallocated to new funding opportunities. That has been holding steady for the past few years, depending on what funds

are available. If more funding is received, more applications potentially could be funded. The most recent Request for Funding (RFA) that was published closes in December, issued earlier in August, and blanketed all of the potential areas of interest. To get the word out, they reached out to the group in Europe, NEALS, partner associations, previous grantees, and so forth to get the message to everyone possible. The RFA is open to domestic and international researchers, and they want to make sure that a diverse mix of applications are submitted. ALS does not stop at the border. A lot can be learned from colleagues across Europe and Asia because ALS affects everyone differently. It is very important to see the potential risk factors in other countries and understand if/how they correlated to what is occurring in the US. The hope is to fund another 1 to 3 applications in the next fiscal year.

Kuldip Dave asked whether Dr. Mehta could speak about the review committee for this RFA and whether they look at what already has gotten funded (e.g., looking at the portfolio across the Registry and NIH-funded) to make recommendations for funding.

Dr. Mehta answered that since they are interested in etiologies and factors related to environmental risks, that by itself is one area of focus. It is not basic science, genetics, or Biorepository studies. There is an Option A and Option B. Option A is for more rigorous applications, while Option B is for more novel proposals. Dr. Ostrow made the recommendation a couple of years ago to include Option B so that potential new concepts and ideas would be submitted. In terms of the peer review process, CDC follows the NIH model that has a very strict firewall. Therefore, Dr. Mehta does not know who submits applications until later in the process. ATSDR's Associate Director of Science (ADS) attends the peer review meeting with the other ADSs across the center. Once the reviews are completed and the panel makes suggestions, the ADSs make funding recommendations. The ADSs at the programmatic level are very influential regarding priorities. The final funding decisions are made by Dr. Aaron Bernstein, who is the Director of the National Center for Environmental Health (NCEH)/ATSDR. There is discussion about adding an Option C to better address diversity, equity, and inclusion (DEI) in terms of under-represented populations who are impacted by ALS.

Gudjon Sigurdsson asked about making the Registry international. Dr. Mehta replied that unfortunately, that is not possible with the framework regarding the CDC/ATSDR mandate. The ALS Registry Act, Public Law 110-373, governs only the US and its territories. That does not necessarily preclude participation with a consortium or other group that wants to have a larger Registry or larger cohort of individuals. Otherwise, the Registry cannot expand beyond US borders in terms of epidemiology or case counting, beyond comparing the US data to other countries' data, but can actually enroll only US citizens and legal US residents.

Wrap-Up, Adjourn

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

Dr. Mehta thanked everyone for their attendance and contributions, particularly persons living with ALS who shared their personal stories and invaluable perspectives. He emphasized that ATSDR is listening to everyone's concerns and suggestions and will continue to make changes to the National ALS Registry for the better accordingly. He said he also hoped that through the presentations, everyone could see the value in the work that is being done by the National ALS

Registry's Biorepository and how the clinical trials are supported. There are currently over 100 publications on the website that either CDC/ATSDR has conducted itself and with partners, or that other organizations have published that the agency is funding. Without research, it would be difficult to figure out what causes ALS and the risk factors. He also expressed gratitude to the "small but mighty" ALS Registry Team for their hard work and to Ms. Pauls Backman for her excellent moderation of this meeting and expressed hope that she would serve as moderator for the 2024 National ALS Registry Annual Research Symposium and Meeting.

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

Dr. Horton stressed that this is a collective effort among ATSDR, the National ALS Registry, researchers, organizations, patients, and others who can talk about and promote the Registry. ATSDR values everyone's comments and wants this Registry to be the best that it can be. That can only be done by hearing from and listening to each and every patient, caregiver, ALS organization, clinician, researcher, and others. In closing the meeting, he emphasized that ATSDR cannot do this alone, that the effort has to be community-wide, and that they look forward to seeing everyone at the next annual meeting.

Attachment #1: Day 1 Q & A Report

Time (EST)	Question Asked	Asked By	Answer	Answered By
8:53	Will this be recorded? Thanks.	t s	Hello t s, Thank you for your question. Due to limitations regarding consent, the meeting will not be recorded for publication, but a transcript will be available on the CDC website, cdc.gov/als. Thank you for joining us today!	Tori Bahe (Ross Strategic)
9:06	Transmission still garbled ? pods	Benjamin Rix Brooks MD	Thank you, Benjamin. We will have Paul remove his headphones to help with the audio.	Tori Bahe (Ross Strategic)
9:10	5-year-old numbers? Is this the best we can do?	Gudjon Sigurdsson	Thank you, Gudjon. Paul is answering this question now.	Andrea Pauls Backman (Moderator)
9:11	The overall prevalence and incidence of ALS cases is more in whites compared to blacks. Any thoughts?	Nitesh Sanghai	live answered	Andrea Pauls Backman (Moderator)
9:12	How is it that each demographic group is estimated to be missing over 30% of cases but the overall rate is 27%? How much confidence do you have in the 27% figure?	Stephen Finger	live answered	Andrea Pauls Backman (Moderator)
9:12	How is it that each demographic group is estimated to be missing over 30% of cases but the overall rate is 27%? How much confidence do you have in the 27% figure?	Stephen Finger	Yes, we do feel confident regarding the 27% figure. The race data has 17.2% missing race which makes the % missing slightly more unstable and gives a higher percentage. The overall missing of 27% is a more accurate number because it includes all of the ALS cases the Registry has.	Jaime S. Raymond (ATSDR)
9:13	Re clinical trial notification -- The registry's list of interventional trials continues to be < 10% of recruiting interventional trials for ALS. I don't think people depending on notification realize that. How about just pulling all ALS recruiting trials from clinical trials dot gov and featuring one each week? Just cycle through them. It's public info on clinical trials dot gov. Or just send a link for a list of recruiting interventional trials on clinicaltrials.gov and a link for observational trials there to people every quarter?	M. C. Collet	live answered	Andrea Pauls Backman (Moderator)

9:13	Re clinical trial notification -- The registry's list of interventional trials continues to be < 10% of recruiting interventional trials for ALS. I don't think people depending on notification realize that. How about just pulling all ALS recruiting trials from clinical trials dot gov and featuring one each week? Just cycle through them. It's public info on clinical trials dot gov. Or just send a link for a list of recruiting interventional trials on clinicaltrials.gov and a link for observational trials there to people every quarter?	M. C. Collet	The clinical trial research notification tool is currently used to help researchers recruit Registry-enrolled PALS into active trials and studies. We don't control what types of studies that researchers want us to recruit for (e.g., interventional trials).	Kevin Horton (ATSDR)
9:14	How often are you now running the death data against the database? Thanks.	M. C. Collet	live answered	Andrea Pauls Backman (Moderator)
9:14	How often are you now running the death data against the database? Thanks.	M. C. Collet	We send data to NDI twice a year and then update our web portal once it is finalized annually.	Jaime S. Raymond (ATSDR)
9:16	Hello from the Karolinska Institute in Sweden: in the US, is the registry used by research teams to pre-screen for ALS trials?	Juliette Foucher	The Registry data is not used as a pre-screening tool for ALS clinical trials since the Registry does not collect current clinical data. There is a research notification tool letting people with ALS know that a sponsor or researcher has an open trial or study.	Andrea Pauls Backman (Moderator)
9:17	We know that respiratory failure is linked with ALS pathology, how could you crosslink the cardiovascular comorbidity with ALS. Is it a new signal, which we shouldn't miss?	Nitesh Sanghai	live answered	Andrea Pauls Backman (Moderator)
9:29	On missing cases and demographics , it is not just race. It is age and gender.	Stephen Finger	Yes, that is correct.	Jaime S. Raymond (ATSDR)
9:29	How many HCPs completed the continuing ed? Do you have info on their specialties? What is the cost to provide CE? Thanks.	M. C. Collet	The CE just launched so we don't have any of this information regarding completions. The CE was done in house so there was no additional cost.	Jaime S. Raymond (ATSDR)
9:29	How many HCPs completed the continuing ed? Do you have info on their specialties? What is the cost to provide CE? Thanks.	M. C. Collet	We have just relaunched as Jaime stated. For this relaunch, our CE module and post-tests are linked to internal service which can provide us with the statistics on how many people have visited and taken the CE. Any result from this is pending as this has just started.	Moon Han (ATSDR)
9:29	Hello from Switzerland, how do you avoid double data using different data bases? Thanks	Peter Ambühl	live answered	Andrea Pauls Backman (Moderator)

9:29	Hello from Switzerland, how do you avoid double data using different data bases? Thanks	Peter Ambühl	We have an extensive deduplication process that is done within each dataset as well as between the datasets. This is done each time the data is updated to ensure we are not counting ALS cases more than once.	Jaime S. Raymond (ATSDR)
9:34	Why were the stakeholder sessions concluded?	Stephen Finger	Paul is answering this now. Looks like stakeholder groups are continuing.	Andrea Pauls Backman (Moderator)
9:36	On the registry home page, there are references to two different kinds of "Dashboards." Confusing.	M. C. Collet	We will look into that. Thank you.	Jaime S. Raymond (ATSDR)
9:36	On the registry home page, there are references to two different kinds of "Dashboards." Confusing.	M. C. Collet	One is the dashboard of ALS estimates and pertaining information. The other is the Enrollee/Registrant dashboard which displays surveys and such. We can definitely look into making it a better distinction.	Moon Han (ATSDR)
9:39	I don't think the slides are progressing through Dr. Mehta's narrative. It seems as if the presentation is stuck on one slide.	Juliet Pierce	Transition does seem low, but the past few slides have been tables of similar format recapping on the topics discussed/addressed from the Stakeholder meeting and such.	Moon Han (ATSDR)
9:40	We saw last year that people with ALS we surveyed would be motivated far more by understanding the use and importance of the data and by seeing reported results of their participation than by any tangible gift. I hope this will be probed more.	M. C. Collet	live answered	Jaime S. Raymond (ATSDR)
9:40	We saw last year that people with ALS we surveyed would be motivated far more by understanding the use and importance of the data and by seeing reported results of their participation than by any tangible gift. I hope this will be probed more.	M. C. Collet	Yes, we are in the process of creating bite size pieces of information regarding epidemiologic studies that have been published. We hope this way of presenting the information will be well received.	Jaime S. Raymond (ATSDR)
9:42	Could substances from the Anniston site in AL be contaminating the aquifer?	Antoinette Harrison	live answered	Andrea Pauls Backman (Moderator)
9:42	Could substances from the Anniston site in AL be contaminating the aquifer?	Antoinette Harrison	Hi Toni! Checking now. Bart Guetti (not Meifang Li (Dartmouth College))	Meifang Li (Dartmouth College)

9:42	Could substances from the Anniston site in AL be contaminating the aquifer?	Antoinette Harrison	Just sent you a map of Anniston to mt-pharma, but it bounced. Please send me your address if you would like to see the map. There are a lot of superfund sites in the city.	Meifang Li (Dartmouth College)
9:44	Why completely new people on stakeholder groups every year? Most businesses find continuity important. I can see cycling new people on, but completely new groups?	M. C. Collet	A wide group of stakeholders is always important to get a diverse group of opinions. Of course, there are people who continue to give input to the Registry year over year, which is very helpful.	Andrea Pauls Backman (Moderator)
9:44	Why completely new people on stakeholder groups every year? Most businesses find continuity important. I can see cycling new people on, but completely new groups?	M. C. Collet	We want to make sure that we're hearing from different subgroups. We will be meeting with ALS healthcare providers soon to hear how we can better promote the registry through them.	Kevin Horton (ATSDR)
9:45	We don't have to pick between the two. We can motivate using data and incentives. This is not an either-or situation.	Sarah Parvanta	Good point, thank you, Sarah.	Andrea Pauls Backman (Moderator)
9:46	Being a participant in a study in the Netherland at the UMC, Sponsor is a US company, as well as in others in Sweden, Switzerland I guess, that checking can't be done unless I have a single ID for all studies worldwide.	Peter Ambühl		
9:47	Is there a way to save the Q&A? Thanks.	M. C. Collet	Thank you for your question. The questions and answers will be included in the meeting summary.	Tori Bahe (Ross Strategic)
9:47	Can you say more about why post-mortem donations are no longer accepted?	Anne Supplee	The National ALS Biorepository coordinates and plans both in-house (premortem) and postmortem donations. We can reach out and get more information.	Moon Han (ATSDR)
9:47	Can you say more about why post-mortem donations are no longer accepted?	Anne Supplee	A percentage of the Biorepository funding was shifted to the Johns Hopkins/Temple ALS for their post-mortem collections. So, at this point, any new postmortem tissue samples will be directed to them	Kevin Horton (ATSDR)
9:50	Have you seen any helpful, interesting trends, changes in data over the years the Registry has existed?	Diane Hoey	live answered	Andrea Pauls Backman (Moderator)
9:52	Do you have any thoughts on the use of ICD-10 code G12.21 to identify ALS patients in various claims databases? Will the use of the code leave out a lot of patients?	Maithili Deshpande	live answered	Andrea Pauls Backman (Moderator)
9:53	Thank you, Andrea and Dr. Paul, for answering the questions.	Nitesh Sanghai		

9:53	If you missed over half of blacks in Massachusetts, do you think you are underestimating missing cases in the prevalence estimates?	Stephen Finger	live answered	Andrea Pauls Backman (Moderator)
9:53	Why is the data on webpages so old? "Page last reviewed: April 28, 2017"	Lynn Brielmaier	The contents on the webpages do get updated regularly. We will also make sure to update the dates that we "reviewed" as well.	Moon Han (ATSDR)
9:55	Considering the multifactorial nature of ALS, do you think there is the need of cocktail treatment? Further, do we need a new drug discovery area incorporating multiple molecules in single capsule in the future? Any thoughts?	Nitesh Sanghai	live answered	Andrea Pauls Backman (Moderator)
9:55	Considering the multifactorial nature of ALS, do you think there is the need of cocktail treatment? Further, do we need a new drug discovery area incorporating multiple molecules in single capsule in the future? Any thoughts?	Nitesh Sanghai	Yes. A cocktail treatment regimen should also be investigated. This has proven successful in HIV care. As for drug discovery, these need to be further investigated for safety and efficacy.	Paul Mehta (ATSDR)
9:55	https://www.atsdr.cdc.gov/about/mission_vision_goals.html#	Lynn Brielmaier	Lynn, I believe the webpages are updated regularly. The date in the webpage footers may not have been updated, however.	Andrea Pauls Backman (Moderator)
9:58	But they missed over 50%	Stephen Finger	Thanks for the follow up, Stephen. Sorry we ran out of time. I think this is a question for follow up between you and Dr. Mehta.	Andrea Pauls Backman (Moderator)
10:01	Dr. Paul, I have a question, which I want to understand with a regulatory perspective. What is more important ALSFRS positive outcomes or the positive survival outcomes with QoL	Nitesh Sanghai	live answered	Andrea Pauls Backman (Moderator)
10:01	Dr. Paul, I have a question, which I want to understand with a regulatory perspective. What is more important ALSFRS positive outcomes or the positive survival outcomes with QoL	Nitesh Sanghai	ALSFRS and QOL are measuring two different areas. ALSFRS is the disease progression itself while QOL looks at how the person with ALS is dealing on a daily basis. Both are important, but it is hard to say if one is more important than the other.	Paul Mehta (ATSDR)

10:09	Can you speak to how COVID has changed tissue acquisitions?	Lynn Brielmaier	COVID/Pandemic had definitely affected the logistics of visiting in-home for blood donation by the National ALS Biorepository. It has limited the visits, thus the number of biospecimen acquisition. Processing these biospecimen in the lab has also been affected, as labs were shut down as well. We are hoping to rebound and resume to normal activity level processing what is in the inventory and also encouraging the registrants to consent to receive Biorepository information.	Moon Han (ATSDR)
10:19	In the past over 97% of biorepository patients were white. What is the current rate? What is the rate in the tissue bank ?	Stephen Finger	live answered	Andrea Pauls Backman (Moderator)
10:19	In the past over 97% of biorepository patients were white. What is the current rate? What is the rate in the tissue bank ?	Stephen Finger	The portal is currently 94.5% White. It has become slightly more diverse. As for the Temple tissue bank, I will defer to Dr. Ostrow.	Paul Mehta (ATSDR)
10:22	Thank you, Dr. Paul. EMA looks for survival whereas, FDA looks for ALSFRS, which seems to be subjective	Nitesh Sanghai	Correct. Both of them have differing ways to approve drugs.	Paul Mehta (ATSDR)
10:23	Are these samples from original NIH ALS station (Chen) or from Canadian studies (Strong) and subsequent Mayo studies (Kurland)?	Benjamin Rix Brooks MD	live answered	Andrea Pauls Backman (Moderator)
10:24	I would recommend blurring patient's names on pictures.	Juliette Foucher	live answered	Andrea Pauls Backman (Moderator)
10:27	Introduce cells or tissues to correct mutation at the site, like sequencing information a 2-component system. Could ALS not use a DNA tool to fix individual DNA cut, paste, edit text? like repairing double strand ?	Lakeia Nard		
10:29	Thank you, Dr. Paul.	Nitesh Sanghai		
10:32	Great work out there.	Nitesh Sanghai		
10:35	programmable protein that in nature is programmed by two separate molecules of RNA. A single protein and a single RNA provide scientist with ability to program this enzyme as molecular scalpel to cut double stranded DNA at sites directed by piece of RNA, can this method be beneficial?			

10:36	Further, I feel like most of our scientific community is working towards G93 mice models. It is a highly aggressive mice model, compared to other ALS mice models. Sometimes, I believe the drug discovery in these models could give misleading information, also, the new molecules effects could be converted in this highly expressed mice models	Nitesh Sanghai	Thank you for this information.	Paul Mehta (ATSDR)
10:37	Expanding the ALS registry under 18 can be beneficial to finding cures/treatment.		Agree. This is something we can look at, but we would need approval/consent from those below the age of 18.	Paul Mehta (ATSDR)
10:38	Very good point for linking the samples with the studies	Nitesh Sanghai		
10:40	Pedi-ALS expand the registry to under 18 and the melanated communities please			
10:40	How about the biorepository?	Stephen Finger	live answered	Andrea Pauls Backman (Moderator)
10:41	Are there any demographic data on the HCPs who take the continuing ed? Thanks.	M. C. Collet	This information is currently not available. Whether this data is collected by the organization who would provide us with the statistics is unknown. We can inquire.	Moon Han (ATSDR)
10:41	why is the registry not expanded to under 18????		This was mentioned by Dr. Mehta during his presentation. It is not approved by IRB for us to collect information on those under 18 years of age.	Moon Han (ATSDR)
10:42	Stephen Finger (You): How about the biorepository?	Stephen Finger	The biorepository patients are only tracked by state representation, not race, but it is about the same as the web portal.	Jaime S. Raymond (ATSDR)
10:43	My son was 7 when he passed. i donated his samples to the NIH, why is the ALS not expanded to 18 ??			
10:43	Most of the Guam samples are not from white people and that will increase the diversity of our biorepository.	Kathleen Wilsbach	It is definitely a great addition.	Moon Han (ATSDR)
10:43	Most of the Guam samples are not from white people and that will increase the diversity of our biorepository.	Kathleen Wilsbach	Good point.	Paul Mehta (ATSDR)
10:43	18 and under?		This would require approvals on our end and is something we have discussed internally and will revisit. Our condolences on the passing of your son. We will review again including those below 18. Thank you.	Paul Mehta (ATSDR)

10:44	This question was answered for the portal but not for the biorepository	Stephen Finger	The team is working on this answer.	Andrea Pauls Backman (Moderator)
10:44	This question was answered for the portal but not for the biorepository	Stephen Finger	Jaime answered the question above.	Andrea Pauls Backman (Moderator)
10:48	I am with Melanin Children Matter Inc,			
10:48	Melanin Children Matter Inc			
10:49	Do you think that the lack of ethnic representation in the prevalence reports impacts the lack of diverse participation in the registry? Not just the %, but the way it is presented as White, Black and "other" — I'm curious to understand why more ethnicities are not pulled out.	Aditi Narayan Minkoff	This is a great insight. There is always a possibility of the degree of visibility affecting willingness. As for the data, due to the multiple databases that are being used to get our estimate, harmonizing the race category can be challenging. Some databases may lack a more detailed racial subgroup. Due to inconsistencies, stratification with sufficient sample count for proper estimation may be challenging.	Moon Han (ATSDR)
10:50	As a pharmacists would you support having a designation of ALS drugs for the US Formulary?	Benjamin Rix Brooks MD	live answered	Andrea Pauls Backman (Moderator)
10:50	I was denied when I tried registering my son who passed away at 7. between misdiagnosis and racial disparities i am fighting for child ALS and other rare diseases.		Yes, we have submitted a brief report regarding JALS cases in our data (18-24 years due to our current constraints of not collecting data for persons less than 18). Adding younger patients is on our radar and we are exploring what we would need to do in order to start collecting this data. Thank you for your support in this effort.	Jaime S. Raymond (ATSDR)
10:52	Thanks. I was curious as to whether the CE was reaching physicians in minority groups. We'll never fix DEI in patient data until we address DEI in the ranks of physicians represented. Thank you.	M. C. Collet	You are welcome.	Moon Han (ATSDR)
10:52	Thanks. I was curious as to whether the CE was reaching physicians in minority groups. We'll never fix DEI in patient data until we address DEI in the ranks of physicians represented. Thank you.	M. C. Collet	Agree, DEI needs to be addressed/improved in healthcare.	Paul Mehta (ATSDR)

10:56	These questions were not answered in the first session. 2018 Prevalence. Why did you choose to use the model that excluded demographic variables from the analysis for your main results? What were the range of estimates for the other specifications that were not selected? Why do you think each of the three models that allowed for variation by the demographic characteristics produced significantly higher estimates of missing cases?	Stephen Finger	While an estimate of the overall 2018 prevalence was our main target, we also sought estimates within strata of key demographic variables (sex, age, and race). It is to be expected that the total adjusted case count obtained using a covariate-free log-linear capture-recapture modeling strategy would differ from the summed estimates across strata based on applying such a strategy accounting for covariates. Generally speaking, however, the total case count and prevalence estimates were found to be quite consistent either way. This is the reason that the results from the model excluding demographic variables were highlighted in the text of the report, while the more granular stratum-specific estimates are also reported in Table 1. The estimated total case count is in the neighborhood of 30,000 (ranging from about 26,000 to 31,000), regardless of whether covariates were ignored, or of which stratified analysis is considered.	Paul Mehta (ATSDR)
10:56	These questions were not answered in the first session. 2018 Prevalence. Why did you choose to use the model that excluded demographic variables from the analysis for your main results? What were the range of estimates for the other specifications that were not selected? Why do you think each of the three models that allowed for variation by the demographic characteristics produced significantly higher estimates of missing cases?	Stephen Finger	Regarding estimates from other specifications, no we do have those estimates for those not selected.	Jaime S. Raymond (ATSDR)
10:57	Updated algorithm. The updated algorithm identified approximately 1,600 additional patients for 2017. What are the demographics for that group? Has the new algorithm improved case ascertainment of minority patients?	Stephen Finger	We have not analyzed those specific 1600 likely ALS cases by demographic factors. It is possible they are younger and possibly more diverse.	Jaime S. Raymond (ATSDR)
11:02	Payers are using Inclusion & Exclusion data from the clinical trials. This leaves PLWALS >24 months post Dx out in the cold.	Lynn Brielmaier	live answered	Andrea Pauls Backman (Moderator)

11:03	I extend my sincere gratitude for your condolences. Over a year ago, I initiated contact with the ALS Registry, demonstrating my commitment to the cause. I kindly request that you keep me informed about any developments concerning the decision to expand the ALS Registry to include individuals under the age of 18. In my capacity as a representative of Melanin Children Matter Inc., I remain steadfast in my ad		Lakeia, I send my condolences. As a mother, this is heartbreaking. We thank you for your support and please do reach out to us if there is anything we can do together to include this vulnerable population and advance the research that can benefit the children.	Moon Han (ATSDR)
11:04	remain steadfast in my advocacy efforts to broaden the ALS Registry's scope. Furthermore, I emphasize the critical importance of facilitating early access to whole genome sequencing within this context. Your cooperation and support in this matter are greatly appreciated. I eagerly await updates and look forward to continued collaboration in advancing these crucial initiatives.		Thank you for your support. We will keep you updated.	Jaime S. Raymond (ATSDR)
11:05	formulary data is usually out of date.	Lynn Brielmaier		
11:06	I am participating in both the CDC and TDI ARC repository studies. Are they sharing data? Also, I asked my doctor at major ALs university Als clinic if they were interested in this, and the answer was no		We are not sharing data at this time, but this may change in the future.	Paul Mehta (ATSDR)
11:08	Can we be confident in this range if the two estimates using complete demographic data fall outside of the range? What were the estimates from the other specifications that were not selected ?	Stephen Finger		
11:11	I need to be in another meeting this afternoon and will miss Dr Weisskopf. I have two questions related to his expertise. 1. What have been the results of the studies of military outside the US? Has there been any consensus on ALS in other countries' military members? 2. Has anyone used the Million Veterans project to look at ALS? Thank you.	M. C. Collet	These are excellent questions. It would be great if someone can ask Dr. Weisskopf during the session this afternoon.	Lyle Ostrow (Temple University)

11:11	I need to be in another meeting this afternoon and will miss Dr Weisskopf. I have two questions related to his expertise. 1. What have been the results of the studies of military outside the US? Has there been any consensus on ALS in other countries' military members? 2. Has anyone used the Million Veterans project to look at ALS? Thank you.	M. C. Collet	I will pose these to Dr. Weisskopf this afternoon. Also, all Q&A will be transcribed and added to the home page of the website at the end of each day's session.	Andrea Pauls Backman (Moderator)
11:12	When I have to break away for another meeting, I lose the Q and A. Is there a way for you to save the whole Q and A for us so that we can see questions answered while we were off of this zoom temporarily? Thank you.	M. C. Collet	We are looking to include the full list of answered questions in the Executive Summary that will be posted on the CDC website, cdc.gov/als	Tori Bahe (Ross Strategic)
11:12	When I have to break away for another meeting, I lose the Q and A. Is there a way for you to save the whole Q and A for us so that we can see questions answered while we were off of this zoom temporarily? Thank you.	M. C. Collet	They will be included in the Executive Summary as well.	Paul Mehta (ATSDR)
11:13	I didn't explain my second question well about my doctors seeming disinterest in digging deeper into these databases and me as their patient. With your talking about the lack of databases sharing/working together, I am disheartened. This is my life and impending death, and it sounds like politics, egos and profits are standing in the way of true - and faster help.		The Registry collaborates with a number of groups, and we are always looking to expand our partnerships. Throughout the years we have partnered and continue to partner with the NIH, Neurobank, Johns Hopkins, Temple. We are always open to productive and constructive partnerships than can benefit persons with ALS.	Paul Mehta (ATSDR)
11:13	I didn't explain my second question well about my doctors seeming disinterest in digging deeper into these databases and me as their patient. With your talking about the lack of databases sharing/working together, I am disheartened. This is my life and impending death, and it sounds like politics, egos and profits are standing in the way of true - and faster help.		I'm sorry to hear of your experience, Myra. One of the goals of the ALS Strategic Plan that was approved earlier this year is to encourage more collaboration and partnerships. The follow up steps are taking place as we speak.	Andrea Pauls Backman (Moderator)
12:40	What do we know of why the Vagus nerve is not affected like UMNs & LMNs?	Lynn Brielmaier	live answered	Andrea Pauls Backman (Moderator)

12:40	What do we know of why the Vagus nerve is not affected like UMNs & LMNs?	Lynn Brielmaier	The Vagus nerve does appear to be impacted in bulbar onset of ALS, see link: https://pubmed.ncbi.nlm.nih.gov/33167079/#:~:text=In%20controls%20and%20ALS%20patients,in%20bulbar%20affected%20ALS%20patients. In general vagus nerve is linked to gastro conditions such as GERD and others.	Paul Mehta (ATSDR)
12:44	How do we start getting Natural History Studies to include and analyze fecal samples?	Lynn Brielmaier	live answered	Andrea Pauls Backman (Moderator)
12:50	Are the controls in the human study household controls?	Sarah Parvanta	live answered	Andrea Pauls Backman (Moderator)
12:50	Awesome talk Dr. Benjamin. Could you please let me know are these pathologies, i.e., decrease in microbiome is a result of Aggressive SOD1 mutation. As your studies are in G93A mice models. OR can we think in opposite manner, whether microbiome decrease leads to SOD1 aggregation. How confident are you in the risk factors involved	Nitesh Sanghai	live answered	Andrea Pauls Backman (Moderator)
12:53	Could you please let me know the microbiome you looked into ALS mice models. I was wondering whether the same microbiome is found in humans. Are we comparing apples to apples	Nitesh Sanghai	live answered	Andrea Pauls Backman (Moderator)
12:53	Are gut microbiome results related to amount of stool produced	Benjamin Rix Brooks MD	live answered	Andrea Pauls Backman (Moderator)
12:56	Given the importance of the comparator groups, have you compared them to other disease groups, and how were the controls matched? Similarly, have you performed any longitudinal analyses to identify changes with meds or diet or disease progression?	Emily vonScheven	live answered	Andrea Pauls Backman (Moderator)
12:59	Could you please explain how the pathologies in your ALS models affects mostly the brain axis rather than spinal cord axis. Or are they both correlated--Just for curiosity	Nitesh Sanghai	live answered	Andrea Pauls Backman (Moderator)
13:01	When you look at family members are you looking at people with similar history or pre-symptomatic patients?	Stephen Finger	live answered	Andrea Pauls Backman (Moderator)

13:04	For PWALS would you suggest that they use probiotics to promote lipids?	Jonathan Guest	live answered	Andrea Pauls Backman (Moderator)
13:09	the main advantage of family members is similarities of diet?	Lynn Brielmaier		
13:10	I was asking this question because in the mouse models the pathologies are restricted to the spinal cord axis.	Nitesh Sanghai		
13:10	Since there seems to be fewer anti-inflammatory bacteria in ALS patients, do you think focusing on consuming foods that decrease inflammation in the gut would be beneficial?	Morgan Quinn	live answered	Andrea Pauls Backman (Moderator)
13:17	Dr. Benzamin was awesome. Thank you Dr. Benzamin for your efforts in ALS research.	Nitesh Sanghai		
13:23	Has algal blooms been considered as a pollution source?	Brian Kaplan	live answered	Andrea Pauls Backman (Moderator)
13:24	How is diesel exhaust similar and different? (many engines are exempted from emissions controls)	Lynn Brielmaier	live answered	Andrea Pauls Backman (Moderator)
13:26	Do the models consider indoor air?	Brian Kaplan	live answered	Andrea Pauls Backman (Moderator)
13:30	How do we add our own data for this study?		Thanks, Myra. If you have submitted your environmental surveys in the Registry, you are part of this database.	Andrea Pauls Backman (Moderator)
13:35	How do you control for other geographically associated predictors of health and medical care, including access to care, income, other resources and other SoDH?	Emily vonScheven	live answered	Andrea Pauls Backman (Moderator)
13:39	Dr. Goutman, can you talk more about your team's role in environmental health policy? How do you share your impressive work to create change?	Lauren Webb	live answered	Andrea Pauls Backman (Moderator)
13:40	Can you speak a little more about the potential impact of agriculture and related exposures on ALS?	Sheri Strahl	live answered	Andrea Pauls Backman (Moderator)
14:03	Can you share more about Camp Lejeune toxic water victims and connections to ALS?	Tyler Gaetano	live answered	Andrea Pauls Backman (Moderator)

14:06	Marc, I am assuming this database contains the participants from the Million Veteran Study; individuals in this study have consented to genetic studies. Do you have access to these data--this would allow you to investigate a genetic link to exposure risk. Thanks, Eva Feldman	Eva Feldman	live answered	Andrea Pauls Backman (Moderator)
14:08	The Sagiaju paper found vast demographic differences between cases identified as "definite" and those classified as "possible " indicating that disadvantaged patients were missed when you require multiple visits to qualify as "ALS." You may need to be careful with these definitions.	Stephen Finger	live answered	Andrea Pauls Backman (Moderator)
14:12	Your comments on Statins are very interesting. Are you looking at Creatine Kinase as a factor? I have been told that a high CK level is a reason not to use Statins.	Jonathan Guest	live answered	Andrea Pauls Backman (Moderator)
14:48	From the latest prevalence report. I am concerned that the estimate of only missing 27% of cases overestimates our ability to identify cases and is in conflict with other findings. 38% of cases were missed in Massachusetts. Roughly 40% of patients use private insurance and would not be picked up by the new algorithm.	Stephen Finger	live answered	Andrea Pauls Backman (Moderator)
14:50	Can we be confident in the range from the latest paper if the two other estimates using complete demographic data fall outside of the range ? What were the estimates from the other specifications in that paper that were not selected?	Stephen Finger	live answered	Andrea Pauls Backman (Moderator)
14:53	How much funding $ would be needed to set up a national registry?	Peter Ambühl	live answered	Andrea Pauls Backman (Moderator)
14:56	Francois Gand from NURO. I have two questions for Dr. Metha. 1. Have you looked at how ALS FRS-R score is being affected by QOL ? 2. Would you be interested in learning how Brain-based Communication (from non-communicative ALS patients) can affect the ALS FRS-R score?	Francois Gand	live answered	Andrea Pauls Backman (Moderator)
15:01	I am back n	Stephen Finger		
15:06	>> We could help you at that level. (www.nuro.world)	Francois Gand	Thank you, you can email me.	Paul Mehta (ATSDR)

15:09	MUNIX adds objective muscle electrophysiology to ALSFRS-R	Lynn Brielmaier	live answered	Andrea Pauls Backman (Moderator)
15:09	Thank you, Dr. Metha. Will do shortly.	Francois Gand		
15:10	I don't remember whether Relyvrio or Radicava claims that life may be extended by a couple of months. Does this mean quality of life will be improved or just we may live longer		live answered	Andrea Pauls Backman (Moderator)
15:15	Are there any CDC studies looking at USA distribution of ALS and Enterovirus D68	Benjamin Rix Brooks MD	live answered	Andrea Pauls Backman (Moderator)

Attachment #2: Day 2 Q & A Report

Time	Question	Asker Name	Answer	Answered By
9:07	Brooke & Sunny, as former athletes, how many cumulative Traumatic Brain Injury events do you think you might have had in your lives?	Lynn Brielmaier	live answered	Andrea Pauls Backman (Moderator)
9:30	What is being done to address the back log?	Stephen Fray	We are working with CMS to try to get the data as soon as it is available. CMS is typically not available for 2 years after the end of the calendar year and the data request is time consuming.	Jaime S. Raymond (ATSDR)
9:30	I found the National ALS Registry when I went on a tear, researching clinical trials. I filled out the surveys, but now new things come to mind. There is no append/ update option.		Thank you for this information. The only survey/information that is made available to be updated is the Disease progression survey for which the email get sent out as reminder to update at certain intervals. We will discuss your input of considering update/append option to other surveys beyond post-submission of the information in the future.	Moon Han (ATSDR)
9:38	Would you put a status meter on the website to continuously show us where we are in acquiring and processing and reporting on the next year's data, please?	M. C. Collet	Yes, we can provide an informational page on what data are received and being analyzed. Perhaps, we can say what year is currently being analyzed on the Registry Dashboard.	Paul Mehta (ATSDR)
9:38	The CDC refused to meet with last year's stakeholder group after our presentation at the meeting and ignored the majority of our action items. How will the new sessions be different?	Stephen Finger	We have never refused to meet with the stakeholder group. The action items were listed on my talk yesterday and many of the recommendations were implemented.	Paul Mehta (ATSDR)

9:38	The CDC refused to meet with last year's stakeholder group after our presentation at the meeting and ignored the majority of our action items. How will the new sessions be different?	Stephen Finger	As it was briefly addressed yesterday, the plan to meet with Stakeholders is in place. The exact detail is tentative, however. We value insights from different arms of ALS community, so we are also seeking people of various experience, profession, and other attributes for diverse input. We continually address our limitations, and this often takes actions of other agencies outside the Registry. We value the immediate need and call for change, and we will continuously put our effort in addressing them.	Moon Han (ATSDR)
9:38	The CDC refused to meet with last year's stakeholder group after our presentation at the meeting and ignored the majority of our action items. How will the new sessions be different?	Stephen Finger	We met with the first stakeholder group for months last year to get feedback on how to improve the registry. Further, we implemented many of the suggestions that were given to us as was discussed by Dr. Mehta in yesterday's talk. To say that we ignored the majority of the action items is, at best, disingenuous. Additionally, we feel it's important to broaden these stakeholder engagements to hear ideas from other groups (e.g., healthcare professionals). Regardless, any stakeholder may reach out to us at any time to discuss additional ways that we can make the Registry better. Any suggestion that we feel is reasonable and feasible, we do our best to implement.	Kevin Horton (ATSDR)
9:40	Hello what mobile applications are really helpful for ALS and why?	Vitaliy Hrynchyshyn	All of our webpages are responsive to mobile and tablets. We have made improvements to the interface and will be making more. At this time, we do not have an app for registering.	Paul Mehta (ATSDR)
9:40	'@Brooke - was the information about the provided within the registry as a single line within the paperwork, or as a stand-alone brochure?	Michelle Schmitz	live answered	Andrea Pauls Backman (Moderator)

9:42	that's question from me as senior developer from Ukraine. My uncle have that and he cannot talk, so preparing app which can use text to speech interface...		Thank you, utilizing technology is very important for persons with ALS.	Paul Mehta (ATSDR)
9:42	In addition to the 2024 public engagement sessions, building an ongoing feedback mechanism would be great to continue to learn from the community. That way updates can be more timely and responsive to the community's needs.	Aditi Narayan Minkoff	live answered	Andrea Pauls Backman (Moderator)
9:42	In addition to the 2024 public engagement sessions, building an ongoing feedback mechanism would be great to continue to learn from the community. That way updates can be more timely and responsive to the community's needs.	Aditi Narayan Minkoff	Hi Aditi, we always welcome feedback. Our email address is als@cdc.gov where feedback can be sent. Thanks	Paul Mehta (ATSDR)
9:42	Last year we asked about when we would be able to register pediatric patients. Has any progress been made on this as we have so many people with juvenile onset under the age of 18 yrs old & their data isn't being captured.	Michelle Lorenz	We are currently looking into the requirements to include patients less than 18 years. We just recently analyzed juvenile ALS cases in our database (18-24 years). We hope it will be published soon.	Jaime S. Raymond (ATSDR)
9:42	Can you talk more about what user-friendly means to the community? It would be super helpful to create a document that uses "technical spec/requirements" to provide the Registry with actionable steps to go through approval processes. The approval process takes time and phases would be helpful. I'll reach-out after the meeting.	Lauren Webb	live answered	Andrea Pauls Backman (Moderator)
9:47	yes, to status meter (as someone who helps others complete the surveys)!!	Anne Supplee	Thank you for your feedback.	Paul Mehta (ATSDR)

10:06	What does FoB stand for?	Antoinette Harrison	live answered	Andrea Pauls Backman (Moderator)
10:14	How have the RFAs for ALS research coming from registry funds changed over time?	Neil Thakur	Neil, the team can answer this live at the end of day wrap up. Thank you.	Andrea Pauls Backman (Moderator)
10:14	How have the RFAs for ALS research coming from registry funds changed over time?	Neil Thakur	Most notably, I believe it was two years ago that they started a new mechanism to fund novel ideas / pilot projects in the early stages as opposed to only R01-level projects.	Lyle Ostrow (Temple University)
10:14	How have the RFAs for ALS research coming from registry funds changed over time?	Neil Thakur	I just looked it up. It is "Option B" - "intended to support novel ALS risk factor research... exploratory and development in nature." Scroll down to "additional information" - https://www.grants.gov/web/grants/view-opportunity.html?oppId=343085	Lyle Ostrow (Temple University)
10:14	How have the RFAs for ALS research coming from registry funds changed over time?	Neil Thakur	Further, I believe another *change* was not to the RFA language itself, but rather to the number of proposals they received. Prior to a couple of years ago, my impression is that many ALS researchers were not aware of these funding mechanisms. Continued vigilance to promote these opportunities is important!	Lyle Ostrow (Temple University)
10:15	Dr. Fang, higher BMI is also associated with slower progression?	Lynn Brielmaier	live answered	Andrea Pauls Backman (Moderator)
10:15	Estimated peak incidence age for ALS continues to increase, do you believe that you will see an even later peak with your detailed methodology?	Bjorn Oskarsson	live answered	Andrea Pauls Backman (Moderator)
10:20	Is anyone collecting data on those patients who are diagnosed as not having ALS	Benjamin Rix Brooks MD	live answered	Andrea Pauls Backman (Moderator)
10:23	Thank you everyone.	Nitesh Sanghai		

10:40	Do you have detailed history of previous immunizations at time of entry to military Is there a relationship to results	Benjamin Rix Brooks MD	live answered	Andrea Pauls Backman (Moderator)
10:42	Does your data indicate a particular branch of service with a higher incidence of ALS?	Juliet pierce	live answered	Andrea Pauls Backman (Moderator)
10:48	Dr. Bjornevik, this DoDSR study does not include VA data?	Lynn Brielmaier	live answered	Andrea Pauls Backman (Moderator)
10:58	Will your research also assess if Veterans with ALS are living longer? If so, is there a commonality that points to their longevity?	Juliet pierce	live answered	Andrea Pauls Backman (Moderator)
11:12	Is there comparable data for mercury?	Benjamin Rix Brooks MD	live answered	Andrea Pauls Backman (Moderator)
11:17	How specific was the location of ALS mortality cases… zip code? Thank you,	M. C. Collet	live answered	Andrea Pauls Backman (Moderator)
11:17	Do you have any data on reports of Pb intoxication in these areas i.e., non-ALS Pb intoxication	Benjamin Rix Brooks MD	live answered	Andrea Pauls Backman (Moderator)
11:18	Do you know if anyone has studied lead in dishes and ALS? Thank you.	M. C. Collet	live answered	Andrea Pauls Backman (Moderator)
11:19	Why would airborne lead be more significant in rural areas? is it more likely to be well water?	Jonathan Guest	live answered	Andrea Pauls Backman (Moderator)
11:20	What about shaving lead fishing weights?	Lynn Brielmaier	live answered	Andrea Pauls Backman (Moderator)
11:21	Is your research published already? Would love to read more.	Adriana Martinez	live answered	Andrea Pauls Backman (Moderator)
11:21	Data for child ALS and its links to SPTLC2?	Lakeia Nard	live answered	Andrea Pauls Backman (Moderator)

11:23	Has there been any studies in the age of the housing (older homes have lead paint) and ALS and blood lead levels?	Brian Kaplan	live answered	Andrea Pauls Backman (Moderator)
11:24	Older homes may also have lead water lines.	Brian Kaplan	live answered	Andrea Pauls Backman (Moderator)
11:29	ATSDR has done an extensive review of lead sources and I recommend they be consulted. There are a number of lead sources that are not necessarily captured in TRI data. Some of these sources include old forgotten mines and former military training sites.	Brian Kaplan	live answered	Andrea Pauls Backman (Moderator)
11:31	Data rising in child ALS link to SPTLC2 in people of color?	Lakeia Nard	live answered	Andrea Pauls Backman (Moderator)
1:12	So as to not to conflict with HIPAA and OMB confidentiality rules, can a map be shown for ALS counts by County using the ALS registry?	Evelyn E Talbott	We do not have county level data, just city for this survey.	Jaime S. Raymond (ATSDR)
1:25	Is there any effort to translate the questions into other languages like Spanish? Somali?	Anne Supplee	live answered	Andrea Pauls Backman (Moderator)
1:25	Is there any effort to translate the questions into other languages like Spanish? Somali?	Anne Supplee	We do have survey questions in Spanish. That is the only other language to date.	Jaime S. Raymond (ATSDR)
1:28	thanks, Jaime , I was about to email you, as we have county of blood draw for the study , I don't believe county is considered a HIPA prohibitive descriptor, can a map be used in our NATA paper to show where the 260 cases and controls are located (we were asked to do a spatial analysis with Morans I as part of the revision, do you see a problem with that or should I also ask Wendy this questions? I can send you the map to take a look, Thanks Evelyn	Evelyn E Talbott	Yes, let's talk offline.	Jaime S. Raymond (ATSDR)

1:28	Fantastic, where does one access that? Could send the link?	Anne Supplee	https://www.cdc.gov/als/ALSJoinALSRegistry_Spanish.html	Jaime S. Raymond (ATSDR)
1:31	yes	Evelyn E Talbott		
1:35	Could this analysis be done at a street address level instead of city level?	Stephen Finger	The survey only asks for city, not county nor street level.	Jaime S. Raymond (ATSDR)
1:37	How long has the particular survey used here been live?	M. C. Collet	live answered	Andrea Pauls Backman (Moderator)
1:41	Great work Pat, Earl, Danielle and Earl. Thank you for doing work this in addition to your day jobs.	Diane Hoey	live answered	Danielle Boyce (Johns Hopkins University)
1:42	^ Opps thanks Clare.	Diane Hoey	Thank you for coming and for your kind words, Diane!	Danielle Boyce (Johns Hopkins University)
1:43	We heard two anecdotes that clinic education and outreach amounted to brochures in a "welcome to ALS" packet. How can ATSDR raise the bar on what ALSA, MDA, LTALS are paid to do? How are their results being measured?	M. C. Collet	We are working on a new approach which will allow us to see how Registry information is actually going out. We hope to see if this approach is more effective.	Jaime S. Raymond (ATSDR)
1:45	What does it mean that ALS clinics are linked to you? Is there actually any specific data transmitted to you? It seems there are so many different researchers/databases that just don't communicate with each other. So disheartening.	Myra Taksa	We have no direct links to the clinics, but the organizations such as ALSA, MDA, and Les Turner who have staff members at these facilities.	Paul Mehta (ATSDR)
1:46	Mda, ltals, and ALS association here been paid to market the registry for the past decade. Which efforts have they found most effective to increase enrollments? How do we build upon these efforts?	Stephen Finger	All of these groups have been instrumental in getting the word out to persons with ALS and caregivers. They have direct contact at the clinic and support level. Without their efforts, outreach and awareness would be very difficult, if not possible. We don't have the resources to have "boots on the grounds" as these groups do.	Paul Mehta (ATSDR)
1:47	"Stepping on toes"???? Politics are killing us pALS.			

1:49	Also, paying attention to the person and not just their ALSFRS scale and loss of speech. Folks often say that they get depressed by going to clinic.	Anne Supplee		
1:50	People stop going to Clinic due to futility. Once you are > 24 months post Dx, you are excluded from clinical.	Lynn Brielmaier		
1:51	excluded from clinical trials.	Lynn Brielmaier		
1:58	Not a question, but to add to what Layne just said, we need to remember - "You can't fix what you don't measure."	M. C. Collet	live answered	Andrea Pauls Backman (Moderator)
1:58	great question!	renene rivera-serra		
2:00	Last year when we surveyed people w ALS on what would motivate them to take surveys, they clearly ranked an incentive very low. The big motivators were to see the results and importance of their participation!	M. C. Collet		
2:01	What metrics are you using to measure the effectiveness of marketing efforts?	Stephen Finger	live answered	Andrea Pauls Backman (Moderator)
2:02	Which efforts have partners found most effective to increase enrollments? How do we build upon these efforts?	Stephen Finger	live answered	Andrea Pauls Backman (Moderator)
2:04	When we asked, "What might motivate you to self-enroll?" responses were 79% More info about what my data would contribute 33% More results from the registry 30% More timely reporting of results < 10% An incentive like a gift card	M. C. Collet	Yes, we have heard that as well. In the past, we have made our manuscripts Open Access, but we have realized that is not enough. We are now working on creating "bite size" information that highlights the manuscripts that utilize the survey data.	Jaime S. Raymond (ATSDR)
2:05	The name is also confusing because people say "I've already registered" but it's with their local ALS organization, not THE Registry!	Anne Supplee	live answered	Andrea Pauls Backman (Moderator)

2:07	How do you measure the effectiveness of these efforts?	Stephen Finger	Each organization sends us reports on a monthly basis regarding persons with ALS contacted at the clinic or support group level. Since we cannot force anyone to join, these data are important, but not exhaustive.	Paul Mehta (ATSDR)
2:09	My question is why you are so focused on an incentive when we had a strong signal that an incentive is not an important motivator to people with ALS???	M. C. Collet	Incentives have been used in research in the past. If the pilot program, when launched, does not show to be effective, we would not pursue this effort and shift gears.	Paul Mehta (ATSDR)
2:09	How cancer does it, including quarterly updates: Cancer Prevention Study-3 (CPS-3): https://www.cancer.org/research/cps3-cancer-prevention-study-3.html	Lynn Brielmaier	Thank you for the information. As it is common to learn from a strong study model such as cancer study, we also continuously learn from literature. One difference to note is that ALS is not notifiable disease as cancer is. This makes it challenging to estimate concrete disease burden.	Moon Han (ATSDR)
2:09	How long does a name stay in the registry? When I die will you erase my info?		live answered	Andrea Pauls Backman (Moderator)
2:10	Les Turner ALS Foundation has a dedicated Registry person and provide one on one assistance. We do need help in doing outreach in communities most impacted by health disparities. I'll be reaching out to the ALS Geospatial group to inform our outreach efforts	Lauren Webb	live answered	Andrea Pauls Backman (Moderator)
2:11	Do people from CMS and VA databases get GUIDs, or only those who self-register?	Michelle Lorenz	Good question. Only those who self-register accept to have a GUID created for them will receive a GUID.	Jaime S. Raymond (ATSDR)
2:13	What would each ALS patient consider as something that they thought that the ALS Registry would help them with their ALS journey and was this that they saw has been accomplished?	Benjamin Rix Brooks MD	live answered	Andrea Pauls Backman (Moderator)
2:14	What year was the last year that registry names were compared to the NDI? It someone died in 2020 are they still receiving emails?	Stephen Finger	For NDI analysis, through 2018 about to complete the match for 2019.	Jaime S. Raymond (ATSDR)

2:14	Why not make it international?	Gudjon Sigurdsson	live answered	Andrea Pauls Backman (Moderator)
2:17	Does what I just read about NDI mean that families of people who died in 2020, 2021, 2022 are still getting emails and clinical trial notification?	M. C. Collet	We have implemented measures to allow the caregivers who would receive information/notification to unsubscribe from further communications. As we do not know the passing of the registrants unless the family member or caregiver contacts us directly, we rely on NDI to confirm the passing of the registrant. It is then, that we indicate in the database to remove them from further communications.	Moon Han (ATSDR)
2:20	The ALS community wants a way to report hot spots of possible ALS clusters to investigate. When we have asked about it previously, we were told that should be done at the state level. But states don't have the revenue and often have political reasons for not pursuing investigations. We need to be able to correlate Pat's GIS data with the CDC registry and need ATSDR to investigate. How do we work together to make that happen?	Michelle Lorenz	live answered	Andrea Pauls Backman (Moderator)
2:22	5 years' delay is far too long. Must find a way to speed this up asap. Make this simpler "We are on the ALS clock"	Gudjon Sigurdsson	live answered	Andrea Pauls Backman (Moderator)
2:23	An easy way to increase URM community enrollment is by outreach to the 102 HBCUs and especially at the HBCU med schools. Pat has mapped these HBCUs and very few have clinics or clinical trials are in these locations.	Michelle Lorenz	live answered	Andrea Pauls Backman (Moderator)

2:27	The ALS Association is launching a trained volunteer ALS Registry enrollment program (similar to Les Turner's one-on-one approach) to provide direct assistance when requested. We're also working on a pilot to increase community-based outreach to people living with ALS who stop attending clinic because of language or cultural barriers. In addition, we are planning a workshop focused on developing an ALS diagnostic referral line to reduce the time to diagnosis and increase access to multi-disciplinary care, genetic testing, treatments and the Registry.	Patricia Stanco	live answered	Andrea Pauls Backman (Moderator)
2:30	what's the name of the WhatsApp group	Myra Taksa	It is through Her ALS Story.	Andrea Pauls Backman (Moderator)
2:31	Has CDC ALS Registry considered developing an ALS Caregiver's Form to expand the information available across the different geographies/ economical levels for those who are impacted by the disease ALS?	Benjamin Rix Brooks MD	live answered	Andrea Pauls Backman (Moderator)
2:31	Has CDC ALS Registry considered developing an ALS Caregiver's Form to expand the information available across the different geographies/ economical levels for those who are impacted by the disease ALS?	Benjamin Rix Brooks MD	This is a great recommendation. We will discuss internally.	Paul Mehta (ATSDR)
2:32	How could ALS advocacy groups be informed so they could mobilize to put pressure on local governments to cooperate with the CDC, if they are not being responsive about investigating specific potential hotspots like the one in Alabama?	Kathleen Wilsbach	live answered	Andrea Pauls Backman (Moderator)

2:41	A bit off topic and not really a question but more of an ask. I was only able to listen to a little bit of yesterday's webinar, so this comment pertains to yesterday discussion because I didn't get a chance to comment! Some of the discussion centered around a lack of diversity in the registry numbers. Because capturing diversity seems to be a big issue maybe an invitation to a member of the I AM ALS group "Many Shades of ALS" to explain what the issues that non- whites have issues with registering. Maybe then the Registry could pivot to find ways to break down those barriers. Thank you.	Jenny Gore Dwyer	live answered	Andrea Pauls Backman (Moderator)
2:41	A bit off topic and not really a question but more of an ask. I was only able to listen to a little bit of yesterday's webinar, so this comment pertains to yesterday discussion because I didn't get a chance to comment! Some of the discussion centered around a lack of diversity in the registry numbers. Because capturing diversity seems to be a big issue maybe an invitation to a member of the I AM ALS group "Many Shades of ALS" to explain what the issues that non- whites have issues with registering. Maybe then the Registry could pivot to find ways to break down those barriers. Thank you.	Jenny Gore Dwyer	That is a great suggestion, you can me so we can discuss it further. Thank you.	Paul Mehta (ATSDR)
2:42	I would say the real value of the Registry is to keep people who share the reasons why a person has ALS from also getting ALS	Neil Thakur	live answered	Andrea Pauls Backman (Moderator)
2:49	sure	Neil Thakur		

2:51	Last year's stakeholder group stressed the need to examine the performance of the algorithm across different demographic groups. What have you found?	Stephen Finger	live answered	Andrea Pauls Backman (Moderator)
2:53	Why not?	Stephen Finger	We did not see a significant difference in the 2018 overall prevalence by demographics. Nothing caught our eye regarding a change in age at diagnosis, race, sex, etc.	Jaime S. Raymond (ATSDR)
2:56	I think that Stephen's point about the whole algorithm and demographic groups would be valuable to pursue in the coming year.	M. C. Collet	Thank you, Cathy.	Andrea Pauls Backman (Moderator)
2:56	Can Dr. Mehta speak about the review committee for this RFA? Do they look at what's already gotten funded (looking at the portfolio across registry and NIH funded) to make recommendations for funding?	Kuldip Dave	live answered	Andrea Pauls Backman (Moderator)
2:56	What are the barriers to reporting ethnicity like the MENA and differentiating Asian communities where we know there are different genotypes prevalent among those ethnicities?	Michelle Lorenz	Small numbers in the Registry makes it difficult to look at particular races and ethnicities. We are looking at a comparison in age at diagnosis, site of onset, etc. for white vs. black vs. other races. We have discussed internally at specific races that might be affected differently.	Jaime S. Raymond (ATSDR)
2:59	I have a hard stop at 3. Nice job hosting Andrea!	Neil Thakur	Thanks, Neil - great to have you join!	Andrea Pauls Backman (Moderator)