Target ALS Global Natural History & Longitudinal Biofluid Study

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ABSTRACT

Background Although ALS exists in people of all ancestries, research studies and clinical trial participants are mainly composed of white patients of European descent. Inclusion of historically underrepresented ethnicities and races is a critical part of understanding the genetic risk factors for ALS and developing effective treatments for all patients. We therefore launched the ALS Global Research Initiative (AGRI). Under this initiative, we expanded our Global Natural History Study to include underrepresented and genetically diverse communities at sites around the world, with the goal of enrolling 800 symptomatic ALS patients and 200 healthy controls. We are generating robust multi-omic, clinical and demographic datasets linked to longitudinal biofluids to provide investigators a comprehensive resource for research studies.

Methods Participant enrollment currently occurs across 14 international sites, with sites in India, Malaysia, South Korea, and South Africa on-boarding. Longitudinal clinical assessments and cognitive measures occur every 4 months, along with collection of blood, urine, and cerebrospinal fluid (CSF). At-home digital measures of speech, using Aural Analytics or Modality AI platforms, and respiratory function using the ZEPHYRx platform are collected in a subset of study participants. In addition, environmental and occupational history data are collected. ALS participants are followed for up to 18 months and healthy controls are seen in clinic twice, 12 months apart.

Results To date, 229 participants (145 ALS, 84 HC) have been enrolled. 27% of ALS participants are symptomatic genetic mutation carriers. While the majority of participants (64.2%) are White Caucasian, increased enrollment at our international sites is quickly enhancing the study's diversity. Currently, approximately 4% of participants identify as Asian, 19% as Hispanic/Latino, and 3% as African American/Black. Robust clinical and genomic datasets can be mined in the Target ALS data portal. The biorepository currently holds over 23,000 biofluid vials; samples are being distributed to researchers to help identify biomarkers critical for clinical use. Application for samples can be found on the Target ALS website.

Conclusion This global Natural History study will inform the heterogeneous nature of disease and allow for development of novel biomarkers that can predict and track disease progression. New insights from ALS populations outside of the USA will help further our understanding of the disease and provide the framework to enable future clinical studies indiversepartsof the world.

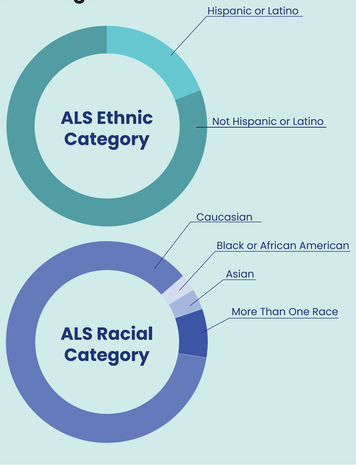
PARTICIPANT COHORT – ENHANCING GLOBAL DIVERSITY

Enrollment by Gender, Racial, and Ethnic Categories

Gender	ALS	HC
Male	93	40
Female	52	44
Total (229)	145	84

Ethnic Category	ALS	HC
Hispanic or Latino	28	16
Not Hispanic or Latino	117	68

Racial Category	ALS	HC
Caucasian	125	66
Black or African American	4	2
Asian	5	4
American Indian/Alaska Native	0	1
Native Hawaiian/Pacific Islander	0	0
More Than One Race	11	11



GENETIC MUTATIONS IN COHORT

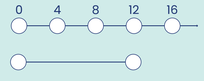
C9ORF72	FUS	SOD1	TDP43	SPG11	ATXN2
17	1 VUS	20	1 and 2 VUS	1	1 and 1 VUS (p.P3922)

GLOBAL NATURAL HISTORY STUDY DESIGN

Global NaturalHistoryStudy

1. 800 ALS symptomatic, 200 healthy
2. Efforts to enhance genetic and ethnic diversity
3. 19 sample requests approved and 3202 samples distributed
4. Longitudinal clinical data and biofluids (0, 4, 8, 12, 16 months)
5. Optional At-home functional measures include speech (Aural Analytics or Modality AI) and respiration (ZEPHRYx- subset of sites)
6. WGS, unbiased multi-omics, NFL

Visits and biofluid sample collection in months



Operations

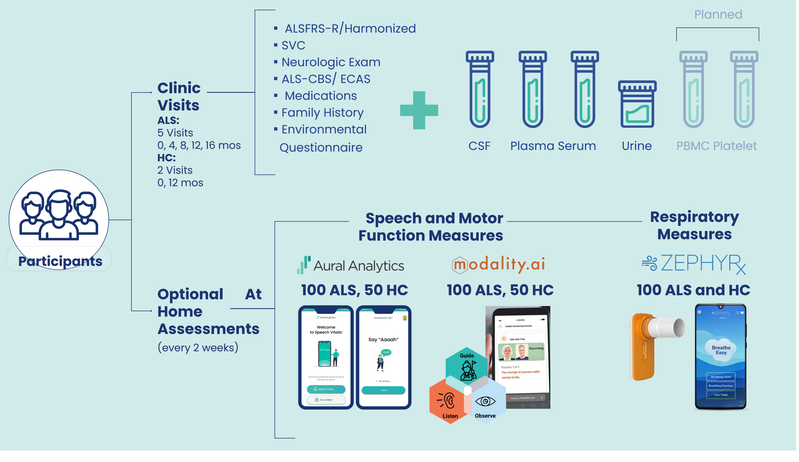
Biofluids sample collection process is standardized across 14 international sites

Biofluids stored at and distributed from Barrow Neurological Institute

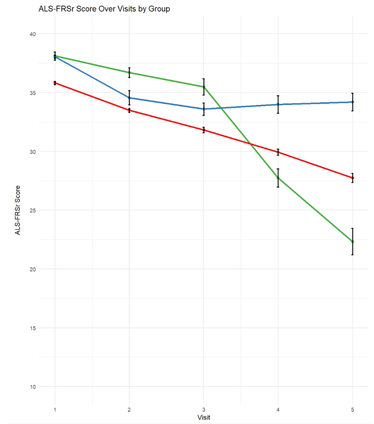
Biofluids datasets generated at:
Broad Institute
New York Genome Center
University of Gothenburg
Psomagen

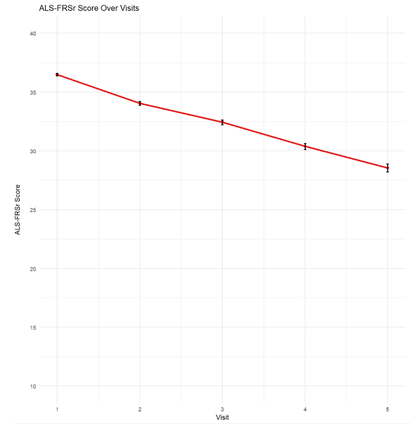
Data Engine for access and analyses

SCHEDULE OF ACTIVITIES



LONGITUDINAL ALS-FRSR SCORES





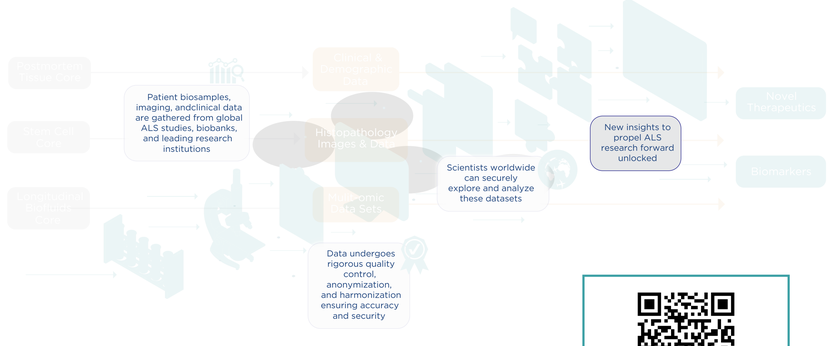
C9-ALS (n=8)
Mutation Negative ALS (n=59)
SOD1 ALS (n=16), 15/16 on Tofersen

ALS (n=83)

Graphs courtesy of Joji Thomas, PhD, Research Professor, Department of Translational Neuroscience, Barrow Neurological Institute

Patients with C9orf72 mutations and negative for genetic mutations progress throughout the 16-18 month time course. SOD1 patients treated with Tofersen (15 of 16) show stable ALS-FRS-R scores.

TARGET ALS DATA ENGINE



Requests for samples will be made through the Target ALS website https://www.targetals.org/. Research proposals will be reviewed by an independent review committee and samples distributed from the repository at BNI. All clinical, genomic, & functional meta-data will be available via a Target ALS Data Engine developed with DNAstack and Verily.

Scan the QR code to access the Target ALS Data Engine at dataengine.targetals.org