One Disease, Many Presentations: Clinical Heterogeneity in the Target ALS Global Natural History Study

Jorge Zaragoza Zapiain[1], Sarah Berth[1], Laura Dugom[2], Daniel Weatherill[2], Amy Easton[2], Lizzi Neylon[3], Kyra Nagle[4], Cindy Ly[4], Timothy Miller[4], Kaycie Opiyo[5], Michael Weiss[5], Aeryn Hopwood[6], Senda Ajroud-Driss[6], James Berry[7], Lada Filippov[7], Huy Tran[8], Bjorn Oskarsson[8], Gilbert Gutierrez[9], John Ravits[9], Benjamin Hoover[10], Matthew Harms[10], Neil Shneider[10], Shakti Nayar[11], Cassandra Holmes[11], Frances Aponte Caraballo[12], Valerie Wojna[12], Brenda Deliz Roldan[12], Manuela Quiroga Carillo[13], Martha Peña Preciado[13], Lina Abd Alhalim[14], Marc Gotkine[14], Jiwon Choi[15], Seok Jin Choi[15], Jiwon Lee[15], Sherly Lam[16], Eduardo Locatelli[17], Nortina Shahrizaila[16], Donovan Mott[17], Noelle Lemme[3], Shafeeq Ladha[18], Robert Bowser[18, 3]

[1] Baylor College of Medicine, Houston, TX, USA; [2] Target ALS, New York, NY, USA; [3] Department of Neurology, Barrow Neurological Institute, Phoenix, AZ, USA; [4] Department of Neurology, Washington University in St. Louis, St. Louis, MO, USA; [5] Department of Neurology, University of Washington, WA, USA; [6] Department of Neurology, Northwestern University, Chicago, IL, USA; [7] Department of Neurology, Massachusetts General Hospital, Boston, MA, USA; [8] Department of Neurology, Mayo Clinic Jacksonville, Jacksonville, FL, USA; [9] Department of Neurosciences, University of California, San Diego, San Diego, CA, USA; [10] Department of Neurology, Columbia University Medical Center, New York NY, USA; [11] Department of Neurology and Pathology, Georgetown University, Washington, DC, USA; [12] University of Puerto Rico, San Juan, Puerto Rico; [13] Instituto Roosevelt, Bogotá, Colombia; [14] Hadassah Ein Karem Medical Center, Hebrew University, Jerusalem, Israel; [15] Seoul National University Hospital, Seoul, South Korea; [16] Universiti Malaya Medical Centre; [17] Nova Southeastern University; [18] Department of Translational Neuroscience, Barrow Neurological Institute, Phoenix, AZ, USA

Abstract

Background

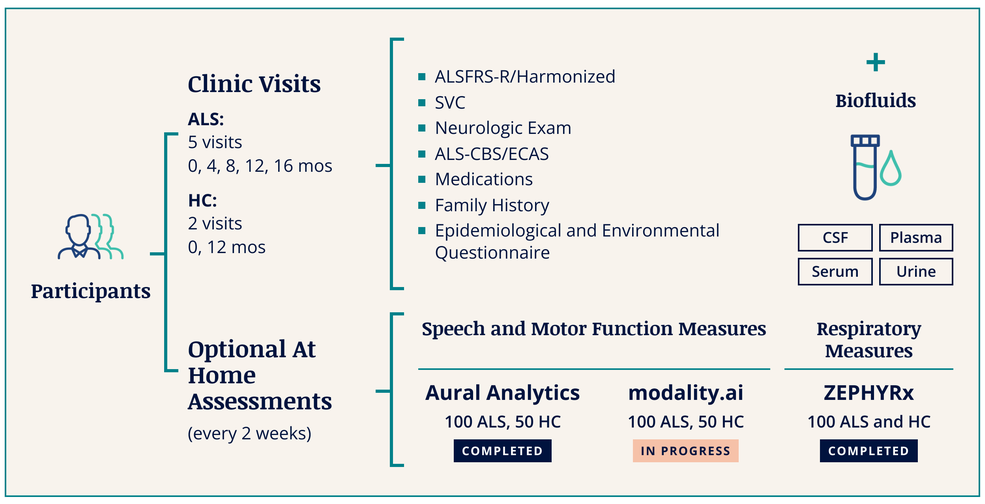
Amyotrophic lateral sclerosis (ALS) is a clinically heterogeneous neurodegenerative disease characterized by substantial variability in symptom onset, progression, cognitive involvement, respiratory impairment, and underlying genetic architecture. Understanding baseline heterogeneity is essential for improving disease classification, prognostication, and the development of precision medicine strategies.

Methods

The Global Natural History Study (GNHS) is an ongoing, prospective, multicenter longitudinal study enrolling individuals with ALS and healthy controls globally. Participants with ALS complete up to five visits over approximately 16 months, while healthy controls complete two visits over about 12 months. Standardized clinical, functional, respiratory, and cognitive assessments are conducted alongside longitudinal blood, urine, and CSF collection. Demographic, clinical, and genetic data from 398 participants were analyzed using descriptive statistics to characterize baseline heterogeneity. Data and biospecimens are available to researchers through the Target ALS Data Engine and biorepository to advance ALS research and biomarker discovery.

GNHS Study Design

Clinic visits with biofluid collection, plus optional at-home assessments



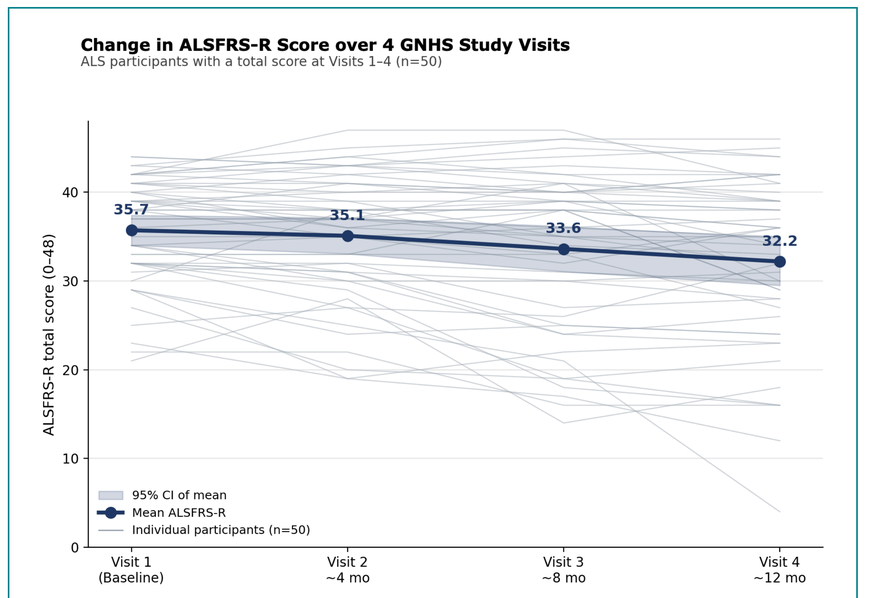
PARTICIPATING COUNTRIES United States (10 sites) · Puerto Rico · Colombia · Israel · South Korea · Malaysia · India (2 sites) ONBOARDING · Canada (1 site) ONBOARDING

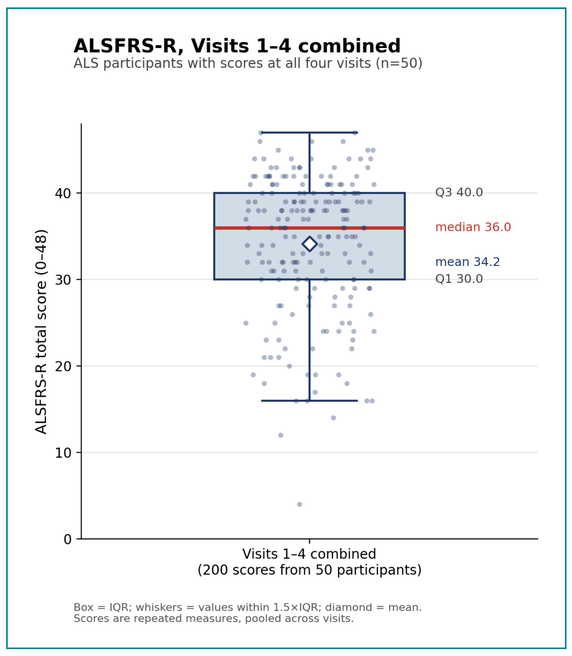
Demographics and Baseline Characteristics

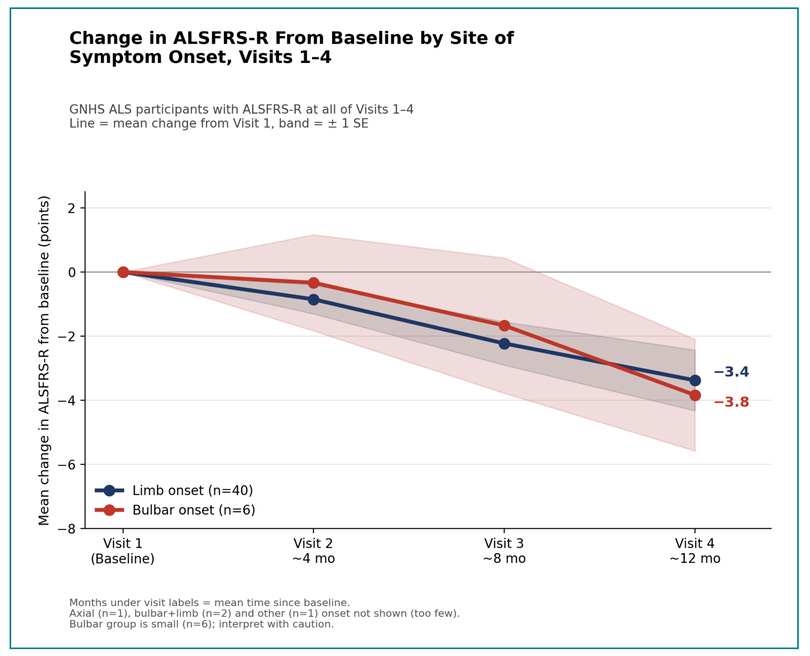
	ALS (n=219)	Control (n=169)
Male / Female	131 (59.8%) / 85 (38.8%)	80 (47.3%) / 88 (52.1%)
White	159 (72.6%)	92 (54.4%)
Black or African American	9 (4.1%)	11 (6.5%)
Asian	19 (8.7%)	18 (10.7%)
More than one race/ethnicity	22 (10.0%)	21 (12.4%)
Hispanic or Latino	44 (20.1%)	35 (20.7%)
Site of onset: limb / bulbar / axial / bulbar and limb / other	136 / 20 / 2 / 4 / 3	N/A
Site of onset not recorded	54 (24.7%)	N/A
ALSFRS-R, mean (SD)	34.8 (7.6), n=164	N/A
Months since symptom onset, mean (SD)	41.7 (41.1), n=165	N/A
Months since diagnosis, mean (SD)	21.3 (23.3), n=161	N/A

Results

In 50 ALS participants with four completed consecutive study visits, ALSFRS-R declined an average of 3.5 points over about 12 months (35.7 to 32.2), with substantial individual variability.







ALSFRS-R declined by 3–4 points over ~12 months in both limb and bulbar onset ALS, with no clear phenotypic difference. Larger bulbar cohorts are needed to detect potential differences in progression.



Nearly 30% of GNHS participants have non-European or admixed ancestry, providing a diverse foundation for characterizing clinical heterogeneity in ALS.

71%	European	**8%**	Mixed
7%	Euro-Native American	**5%**	East Asian
3%	Native American	**1%**	South Asian
1%	Afro-European	**1%**	Euro-South Asian
<1%	African	**<1%**	Euro-East Asian

Conclusion

Across four consecutive GNHS study visits, ALSFRS-R declined by an average of 3.5 points over about 12 months, with substantial individual variability. Limb- and bulbar-onset participants declined by a similar 3–4 points, and larger bulbar cohorts are needed to detect potential differences in progression. With nearly 30% of participants of non-European or admixed ancestry, the GNHS provides a diverse foundation for characterizing clinical heterogeneity in ALS. Data and biospecimens are available to researchers through the Target ALS Data Engine and biorepository.

Interested in joining the GNHS study?

SCAN TO LEARN MORE AND ENROLL ›

targetals.org/agri

References

1. Berger A, Locatelli M, Arcila-Londono X, Hayat G, Olney N, Wymer J, et al. The natural history of ALS: baseline characteristics from a multicenter clinical cohort. Amyotroph Lateral Scler Frontotemporal Degener. 2023;24(7-8):625-633.
2. Target ALS. (n.d.). Target ALS Data Engine. https://dataengine.targetals.org/
3. Benatar M, CReATe Consortium. Phenotype-Genotype and Biomarker Study (PGB1). Clinical Research in ALS and Related Disorders for Therapeutic Development.
4. Pinto S, Santos MO, Gromicho M, Swash M, de Carvalho M. Respiratory phenotypes in amyotrophic lateral sclerosis as determined by respiratory questions on the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised and their relation to respiratory tests. Eur J Neurol. 2023;30(7):e15765.
5. Rooney J, Murray D, Meldrum D, Al-Chalabi A, Bunte T, Chiwera T, et al. REVEALS: a longitudinal cohort study of multifaceted respiratory assessment in ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2024;25(7-8):661-671.
6. González-Sánchez M, Ramírez-Expósito MJ, Martínez-Martos JM. Pathophysiology, clinical heterogeneity, and therapeutic advances in amyotrophic lateral sclerosis: a comprehensive review of molecular mechanisms, diagnostic challenges, and multidisciplinary management strategies. Life (Basel). 2025;15(4):647.