Characterizing Disease Progression in the Target ALS Global Natural History Study

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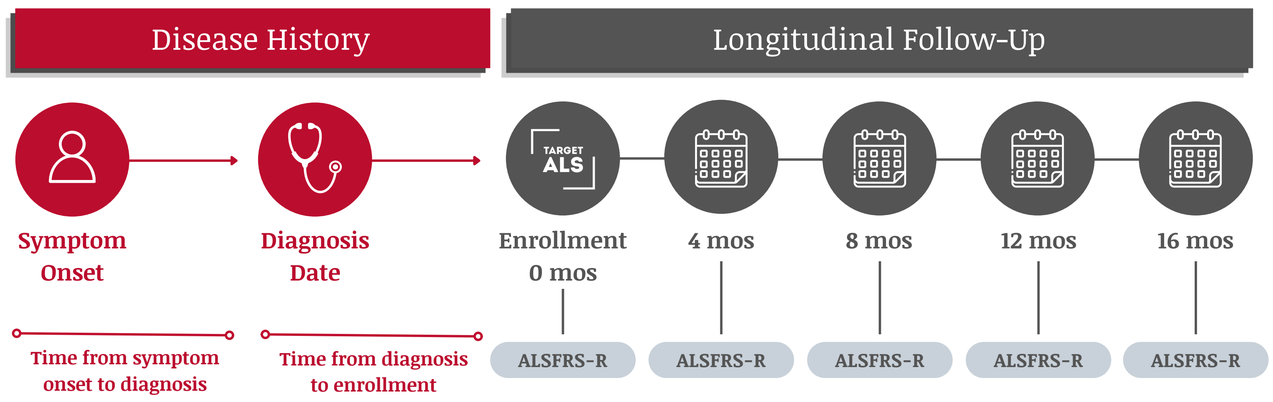
Background

The Global Natural History Study (GNHS), launched in 2021, has grown from six US centers into an international longitudinal biofluids study with 18 sites. GNHS collects clinical data and biospecimens from people living with ALS and healthy controls to generate clinical, molecular, and environmental datasets that are shared through the Target ALS Data Engine. Here, we evaluate symptom onset and diagnosis date relative to enrollment and ALSFRS-R scores during the study to characterize disease progression captured over the five study visits.

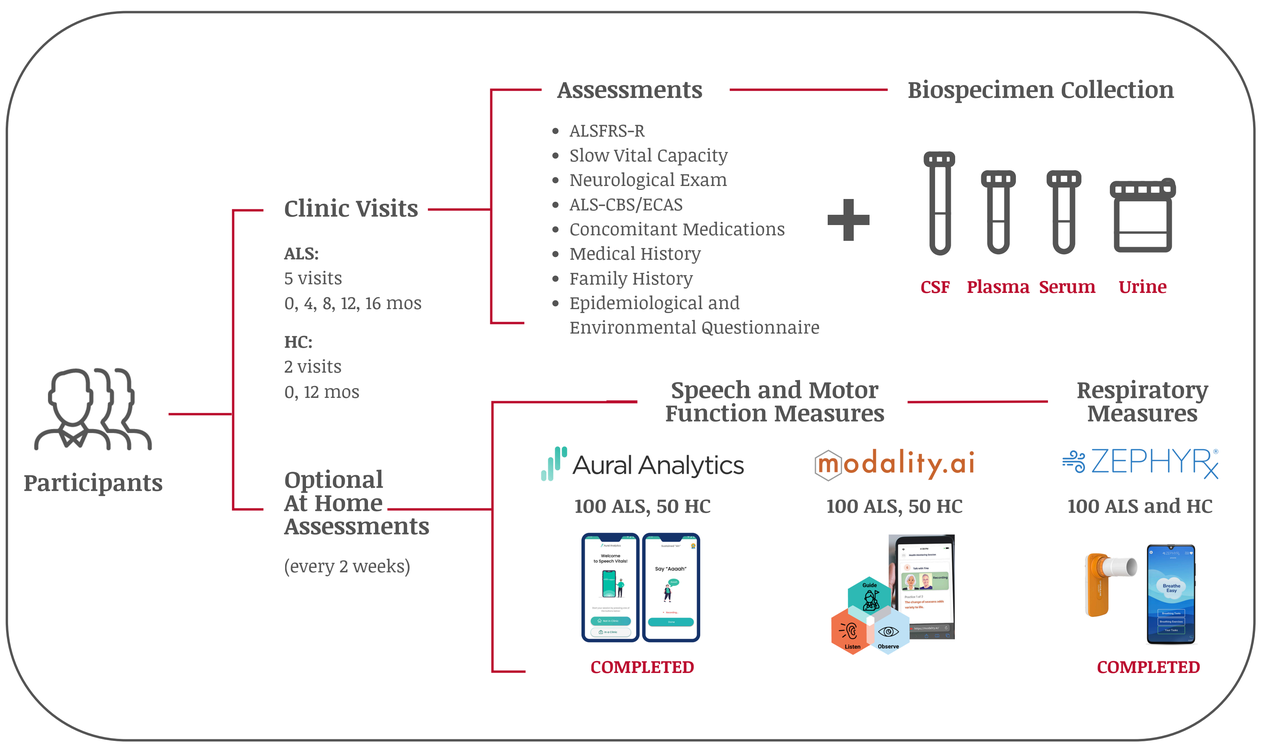
Methods

We calculated time from symptom onset to enrollment, time from diagnosis to enrollment, baseline ALSFRS-R, and change in ALSFRS-R across study visits. GNHS enrolls ALS participants for five study visits over 16 months (0, 4, 8, 12, and 16 months) and healthy controls for two visits over 12 months (0 and 12 months). ALSFRS-R analyses include all enrolled ALS participants with consecutive assessments.

Longitudinal Study Design



Study Assessments



Results

As of October 2026, GNHS has enrolled approximately 396 participants across 16 active sites in the United States, Puerto Rico, Colombia, Israel, Malaysia, and South Korea, including 226 ALS participants and 170 healthy controls.

For ALS participants, mean time from symptom onset to enrollment is 40.0 months (SD 39.7; median 27.1 months). Mean time from diagnosis to enrollment is 20.3 months (SD 23.0; median 12.5 months). Mean baseline ALSFRS-R score is 35.4 (n=192). Mean ALSFRS-R score decreased by 2.28 (n=140) from visit 1 to visit 2, decreased by 1.61 (n=100) from visit 2 to visit 3, decreased by 1.72 (n=72) from visit 3 to visit 4, and decreased by 1.32 (n=57) from visit 4 to visit 5.

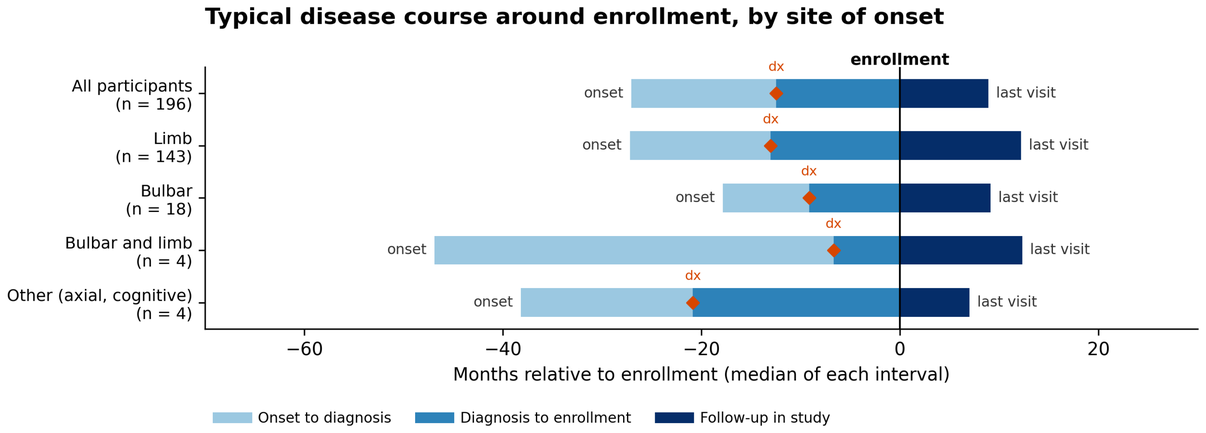
Enrollment Timing and Functional Outcomes

Time to enrollment and ALSFRS-R score in ALS participants

Measure	n	Mean (SD)	Median
Time to enrollment (months)			
Symptom onset to enrollment	196	40.0 (39.7)	27.1
Diagnosis to enrollment	196	20.3 (23.0)	12.5
ALSFRS-R total score			
Baseline (visit 1)	192	35.4 (7.3)	37.0
Change in score between visits			
Visit 1 to visit 2	140	−2.28 (4.21)	−2.0
Visit 2 to visit 3	100	−1.61 (4.33)	−1.0
Visit 3 to visit 4	72	−1.72 (3.63)	−1.0
Visit 4 to visit 5	57	−1.32 (2.57)	−1.0

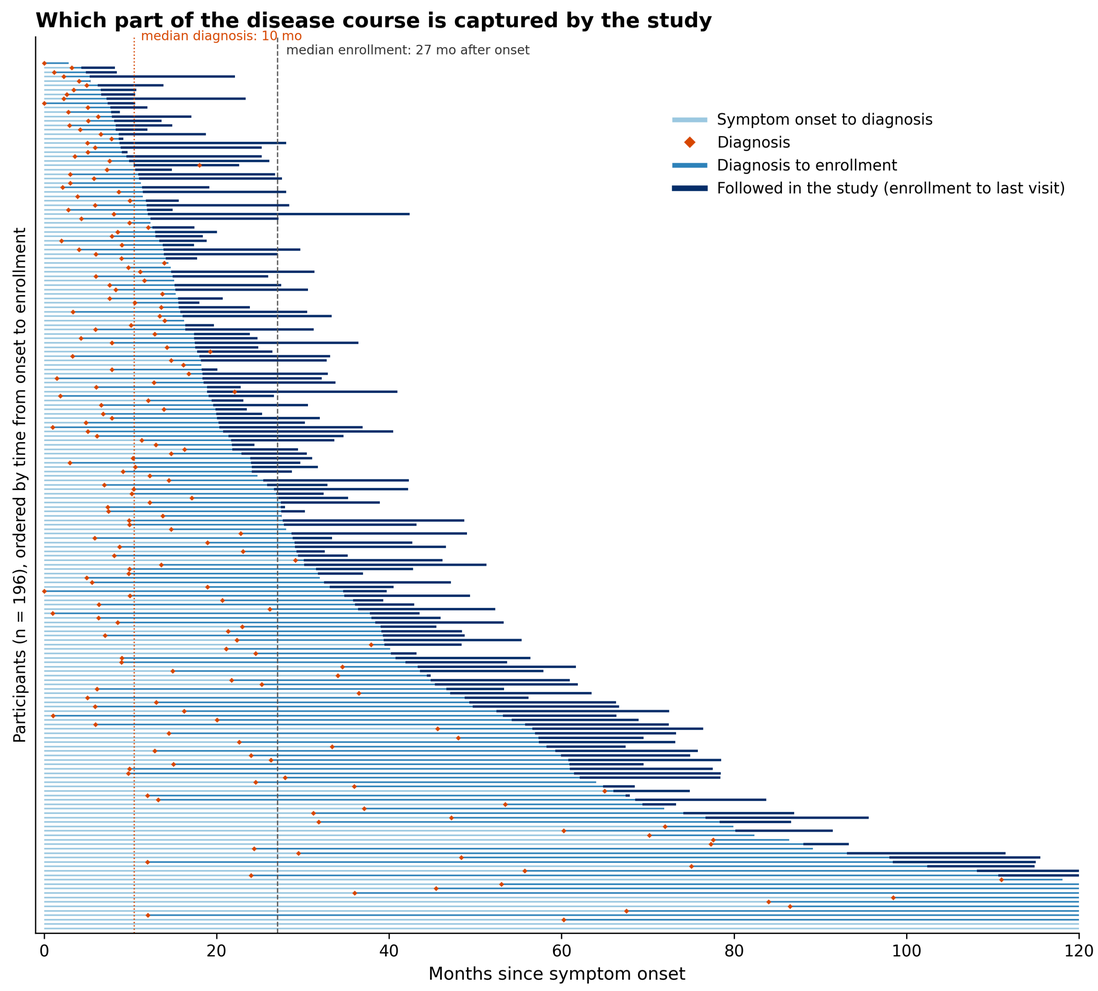
Time intervals use the 196 ALS participants with onset, diagnosis and enrollment dates (diagnosis not before onset). Enrollment = registration date. Onset and diagnosis dates use the most precise date available (exact, month/year taken as the 15th, or year only taken as July 1). ALSFRS-R changes are paired differences between consecutive visits (negative = decline); n is the number of participants with scores at both visits. Visit intervals vary, so changes are per visit, not per month. SD, standard deviation.

Enrollment by Site of Onset



Bars show the median time from onset, diagnosis and enrollment to the last visit with clinical data. Each position is a separate median, so segment lengths need not equal the interval medians in the table.

Individual Disease Histories



Each line is one ALS participant (time zero = symptom onset). 11 participants enrolled after 120 months from onset and are cut off at the axis edge. Enrollment = registration date; follow-up = enrollment to last visit with clinical data.

Discussion

Participants enrolled a median of 12.5 months after diagnosis, with substantial variability in the timing of enrollment relative to symptom onset and diagnosis. ALSFRS-R scores declined across successive visits, consistent with progressive functional impairment during follow-up. Characterizing enrollment timing and duration of follow-up is essential for understanding which portions of the disease course are captured during the 16-month study period. These findings provide important context for interpreting clinical and biospecimen data generated through GNHS and establish a framework for future studies leveraging this resource to investigate ALS progression and biomarker trajectories. These critical data can be found alongside multi-omic datasets generated from biofluid samples in the Target ALS Data Engine.