Using Active Digital Phenotyping to Quantify Function and Cognition in Amyotrophic Lateral Sclerosis (ALS)

Zoe Scheier[1], Alison P. Clark[1], Mackenzie Keegan[1], Kelley Erb[2], Evan Remington[2], Sheena Chew[2], Roland Brown[2], Jessey Ouillon[1], Nicole Eklund[1], Stephen Johnson[1], Vineet Pandey[3], Krzysztof Z. Gajos[3], Anoopum S. Gupta[1], Katherine M. Burke[1], James D. Berry[1]

1) Healey Center for ALS, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. 2) Biogen Inc, Cambridge, MA, USA. 3) Harvard School of Engineering and Applied Sciences, Cambridge, MA, USA

Background

- ALS clinical trials rely on a standard set of outcome measures, including:
  - ALS Functional Rating Scale – Revised (ALSFRS-R)
  - Vital Capacity (VC)
  - Handheld Dynamometry (HHD)
- Digital Quantitative Monitoring (DQM) are tasks performed on digital devices
- DQM can obtain more frequent quantitative and granular measurements of function than current outcome measures
- Used alongside patient reported outcome measures, DQM can help improve standard ALS outcome measures

Objective

The purpose of this study is to:

1. investigate the utility of digital tools for quantifying in-clinic neurological examinations; and
2. utilize digital tools to examine patient behavior outside of clinic

for use as biomarkers of neurological change over time in people with ALS.

Methods

- Enrollment Goal: 25 People with ALS (PALS), 25 Healthy Controls (HC)
- **Initial Pre-COVID in-person study design (N = 8)**
  - Two clinic visits separated by 1 week of daily self-administered tests and continuous passive data collection
  - Clinic visits involved a traditional neurological exam, a digital neurological exam, standard ALS outcome measures, and various cognitive tasks.
- **Remote longitudinal redesign (in the setting of COVID, N= 42)**
  - Weekly self-administered testing via mobile app
  - Weekly self-administered fine-motor assessment
  - Telemedicine visits at baseline, week 12, week 24
    - Staff administered ALSFRS-R, Neurological Fatigue Index – Motor Neuron Disease (NFI-MND), and quality of life scale
- **Digital Quantitative Monitoring (DQM)**
  - Digital Artefacts Mobile Application - WatchALS
    - Downloaded on study provided iPhone and Apple Watch
    - Includes symptom questionnaire, self-administered ALSFRS-R and NFI-MND, fine motor, gait, stance, speech, and cognitive tests, and collected continuous passive data
  - Hevelius Computer task
    - Self-administered point and click fine motor assessment
    - Completed on participants' personal computer

We present preliminary analysis of Hevelius and WatchALS data for the remote portion of this study.

Results

Table 1. Participant demographics

Characteristic	Percent (N) or Mean (SD)	
	Remote PALS (N =19)	Remote HC (N = 23*)
Age (years)	60.6 (5.6)	58.0 (8.2)
Male	73.7% (14)	39.1% (9)
White	94.7% (18)	91.3% (21)
Location of Onset		
Lower Extremity	47.4 (9)	
Upper Extremity	31.6 (6)	
Bulbar	10.5 (2)	
Generalized	10.5 (2)	

*1 HC terminated study participation before contributing any DQM data. This participant has been included for demographics but was removed from data analysis.

WatchALS App Data

Table 2. Overall app session compliance out of 695 possible sessions

Complete Sessions	85.99%	(675/785)
Incomplete Sessions	3.57%	(28/785)
Missed Sessions	10.45%	(82/6785)

Figure 4. WatchALS session adherence plot

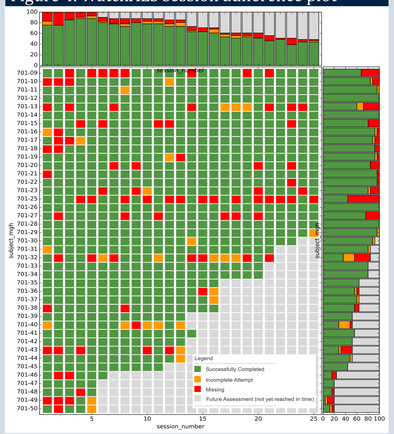
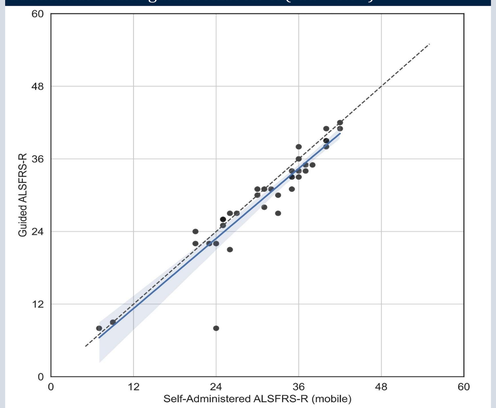


Figure 5. Strong intraclass correlation between self-administered and guided ALSFRS-R (ICC = 0.96)



Hevelius Computer Task Data

Figure 1. Individual z-scores for normalized jerk without pauses for participants with ALS and healthy controls

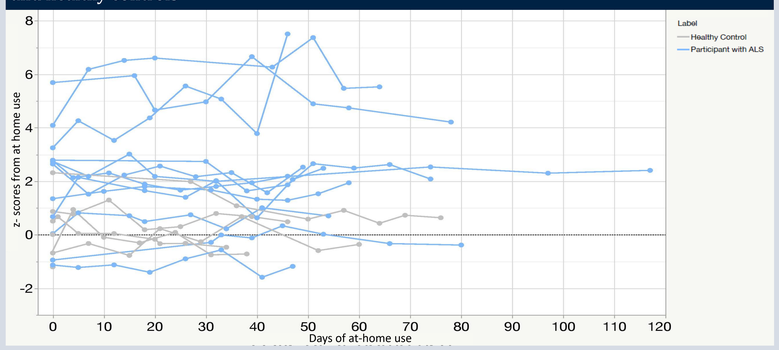


Figure 2. Individual z-scores for movement direction changes for participants with ALS and healthy controls

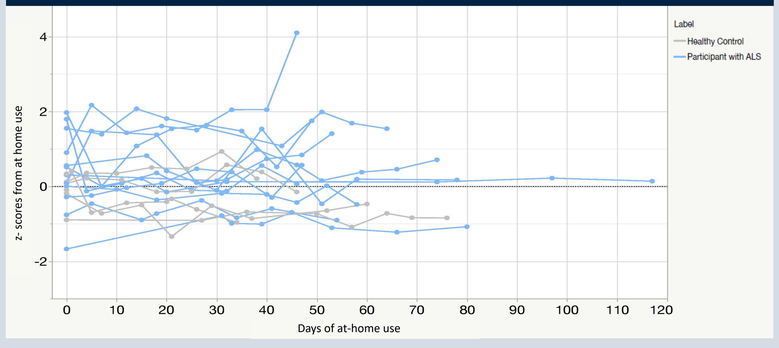


Figure 6. AWS transcription of a participant with ALS reading the Bamboo Passage

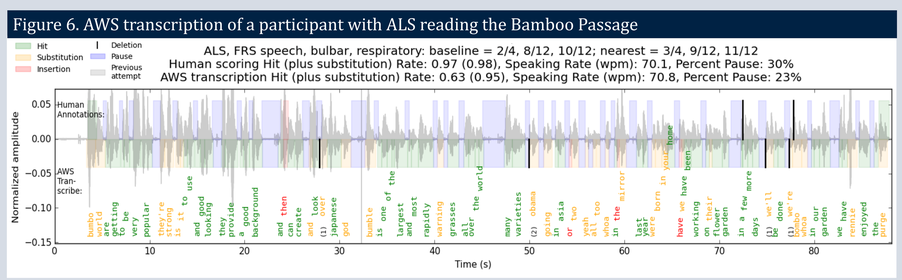


Figure 3. Many metrics measured by the Hevelius task demonstrate strong correlation with ALSFRS-R handwriting scores

Figure 3.1. Normalized Jerk (r = -0.88)

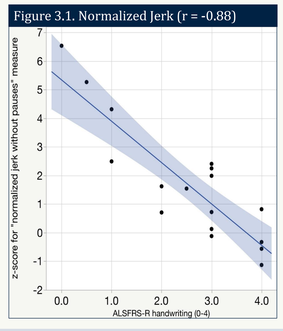


Figure 3.2. Max speed coefficient of variation (r = - 0.84)

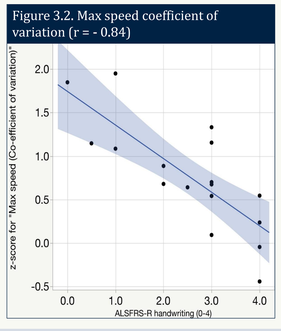
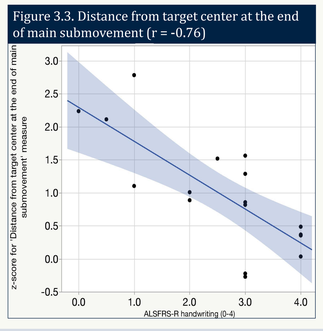


Figure 3.3. Distance from target center at the end of main submovement (r = -0.76)



Conclusion

- Early WatchALS data suggests compliance is acceptable
- Normalized jerk, speed variation, and target distance correlating with ALSFRS-R handwriting score indicates potential for Hevelius to reliably assess fine motor impairment
- Self-entry and guided ALSFRS-R show very high correlation, though self-entry scores are just over one point higher, on average.
  - Self-entry is a reasonable means for obtaining ALSFRS-R data
  - Self-entry and guided ALSFRS-R are not interchangeable

Future Directions

- Remote longitudinal data collection is scheduled to complete in March of 2022
- In-person data will be used to assess test-retest validity
- Further data analysis is needed to evaluate the WatchALS app data for
  - Evaluation of fine motor, gait, and cognitive function at baseline
  - Ability to identify changes over time related to ALS disease progression

Acknowledgments

We would like to thank our patients and their families for their kind contribution to research on amyotrophic lateral sclerosis.