# DOWN SYNDROME ASSOCIATED ALZHEIMER'S DISEASE:

## Early Data from the Longitudinal Investigation for Enhancing Down Syndrome Research (LIFE-DSR) Study

James A. Hendrix[1], Hampus Hillerstrom[1], David C. Airey[2], Angela Britton[1], Anna D. Burke[3], George T. Capone[4], Ronelyn Chavez[5], Jacqueline Chen[6], Brian Chicoine[7], Alberto C. S. Costa[8], Jeffrey L. Dage[2], Eric Doran[9], Anna Esbensen[10], Kelley M. Faber[11], Tatiana M. Foroud[11], Sarah Hart[12], Kelsey Haugen[13], Elizabeth Head[14], Suzanne Hendrix[15], Priya S. Kishnani[12], Duvia Ladesma[5], Florence Lai[16], Ira Lott[9], Jessie Nicodemus-Johnson[15], Cesar Ochoa-Lubinoff[6], Carolyn Revta[5], H. Diana Rosas[16], Tracie C. Rosser[17], Stephanie Santoro[13,18], Kim Schafer[5]. Thomas Scheidemantel[19], Frederick Schmitt[20], Brian G. Skotko[13, 18], Melissa R. Stasko[19], Amy Torres[13], Kristi Wilmes[11], Jason Woodward[10], Jennifer A. Zimmer[2], Howard H. Feldman[5], William Mobley[21]

[1] LuMind IDSC, Burlington, MA, USA. [2] Eli Lilly and Company, Indianapolis, IN, USA. [3] Department of Neurology, Barrow Neurological Institute, Phoenix, AZ., USA. [4] Kennedy Krieger Institute, Down Syndrome Clinic & Research Center, Baltimore, MD, USA. [5] Department of Neurosciences, Alzheimer's Disease Cooperative Study, University of California San Diego, San Diego, CA, USA. [6] Division of Developmental Behavioral Pediatrics. Department of Pediatrics. Rush University Medical Center, Chicago, Illinois, USA. [7] Advocate Adult Down Syndrome Center, Park Ridge, IL, USA. [8] Division of Neurology and Epilepsy, Department of Pediatrics, Case Western Reserve University School of Medicine, Cleveland, OH, USA. [9] Department of Pediatrics, The University of California, Irvine, Irvine, CA, USA. [10] Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA. and Division of Developmental and Behavioral Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA. [11] National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD), Indiana University School of Medicine, Indianapolis, IN, USA. [12] Department of Pediatrics, Duke University Medical Center, Durham, NC, USA. [13] Down Syndrome Program, Division of Medical Genetics and Metabolism, Department of Pediatrics, Massachusetts General Hospital, Boston, MA, USA. [14] Department of Pathology and Laboratory Medicine, The University of California, Irvine, Irvine, California. [15] Pentara, Salt Lake City, UT, USA. [16] Department of Neurology, Massachusetts General Hospital and McLean Hospital, and Harvard Medical School, Boston, MA, USA. [17] Department of Human Genetics, Emory University, Atlanta, GA, USA. [18] Department of Pediatrics, Harvard Medical School, Boston, MA, USA. [19] Department of Pediatrics, at Case Western Reserve University School of Medicine, Cleveland, OH, USA. [20] Sanders-Brown Center on Aging, University of Kentucky Lexington, KY, USA; Department of Neurology, University of Kentucky Lexington, KY, USA. [21] Department of Neurosciences, University of California, San Diego, CA, USA.

## ABSTRACT

**Background:** With improved healthcare, the Down syndrome (DS) population is both growing and aging rapidly with a life expectancy of >55 years of age compared to just 25 year of age in the 1980's. It is estimated that there are 210,000 people with DS in the USA and 40% are over the age of 30 years (de Graaf., 2019). However, with longevity comes a very high risk of Alzheimer's disease (AD). It is estimated that by age 55–60 years at least 70% will develop Alzheimer's dementia (Hartley, 2015). Furthermore, by their 40's virtually all adults with DS develop neuropathology consistent with AD (Lemere, 1996). The LIFE-DSR study is a longitudinal natural history study recruiting 270 adults with DS over the age of 25. The study is designed to characterize trajectories of change in DS-associated AD (DS-AD) via 3 annual visits that include physical exam, medical history, neuropsychiatric evaluation, and a blood draw for biomarker and genetic analyses. The use of Phosphorylated tau (P-tau) biomarkers in plasma is relatively new but may be associated with AD progression and the onset of dementia symptoms. Neurofilament light (NfL) levels which are a general marker of axonal injury and neurodegeneration, have demonstrated a strong association with progression in DS-AD (Lewczuk, 2018; Rafii, 2019; Strydom, 2018) and are a primary biomarker of interest in this study investigation.

**Objectives:** The LIFE-DSR study has been designed to better understand the factors that underlie symptoms and age of clinical presentation of DS-AD. During the pause in LIFE-DSR recruitment caused by COVID-19, the first 93 plasma samples banked will be analyzed for AD and neurodegenerative biomarkers P-tau181, P-tau217 and NfL. The biomarker data will be combined with clinical data from the baseline visit (detailed below).

**Methods:** Plasma P-tau biomarkers will be measured using previously published methods and NfL will be measured using the Quanterix NfL assay. The clinical data includes demographics and medical history as well as a series of neuropsychiatric exams of cognition, function, and behavior. The cognitive measures include the Severe Impairment Battery (SIB) with the Shoebox test and, optionally, the Down Syndrome Mental Status Examination (DS-MSE). The Vineland-3 is used to assess function while the Dementia Questionnaire for Persons with Learning Disabilities (DLD) and the Neuropsychiatric Inventory (NPI) is used to measure behavior. Biomarker distributions will be described and compared to historical data in non-DS populations. In addition, statistical associations between clinical measures, demographic characteristics, and biomarkers will be evaluated.

**Results:** Biomarker and clinical data at baseline will be presented on a subset of LIFE-DSR participants.

**Conclusion:** The biomarker data contributes to understanding of disease onset and progression and clinical profiles of DS-AD and will be applied to the full LIFE-DSR longitudinal study.

## OVERVIEW

The LIFE-DSR study (NCT04149197) is an observational, multi-center, longitudinal cohort study to characterize adults with DS ages 25 years and above enrolled at specialized care centers.

Longitudinal data collected: demographics, clinical, cognitive, behavioral and functional data, and blood collection

PRIMARY OBJECTIVE OF INTERIM ANALYSIS: To assess associations of baseline Alzheimer's biomarker data from 93 subjects with demographics, and measures of cognition and behavior. The plasma biomarkers include Phosphorylated tau (P-tau181 and P-tau217), neurofilament light (NfL) and APOE (e4 +/-) genotype.

- Cognitive measures
  - Severe Impairment Battery (SIB) and Shoebox test
  - The Down Syndrome Mental Status Examination (DS-MSE) is administered to participants with a SIB score of 60 or above.
- Behavioral measures
  - Dementia Questionnaire for People with Learning Disabilities (DLD)
  - Neuropsychiatric Inventory (NPI)

## METHODS

### BIOMARKER ASSAYS PRESENTED IN THE ANALYSES:

P-tau - were performed on a streptavidin small spot plate using the Meso Scale Discovery (MSD) platform. For the Ptau181 assay, Biotinylated-AT270 was used as a capture antibody (anti-Ptau181 antibody) and SULFO-TAG-Ru-4G10-E2 (anti-tau monoclonal antibody) for the detector. For the Ptau217 assay, Biotinylated-IBA493 was used as a capture antibody (anti-Ptau217 antibody) and SULFO-TAG-Ru-4G10-E2 for the detector. Both assays were calibrated using synthetic P-tau peptides.

NfL- was measured using the Quanterix Simoa® NF-Light Advantage Kit (103186) and followed the manufactures instructions.

### BASELINE CLINICAL SCALES PRESENTED IN ANALYSES:

SIB - developed to assess skills of people with severe dementia utilizing 40 simple one-step commands and gestural cues (Fish 2011); maximum score 100, with higher score indicating less impairment

DS-MSE – neuropsychological test battery measuring skills including recall of personal information, orientation to season and day of the week, short-term memory, language, visuospatial construction, and praxis (Haxby 1989); maximum score 87 using scoring method 2, with higher score indicating better performance.

Clinical scales available but not presented in analyses:

Shoebox, DLD, and NPI were not presented due to restricted distribution of the baseline scores.

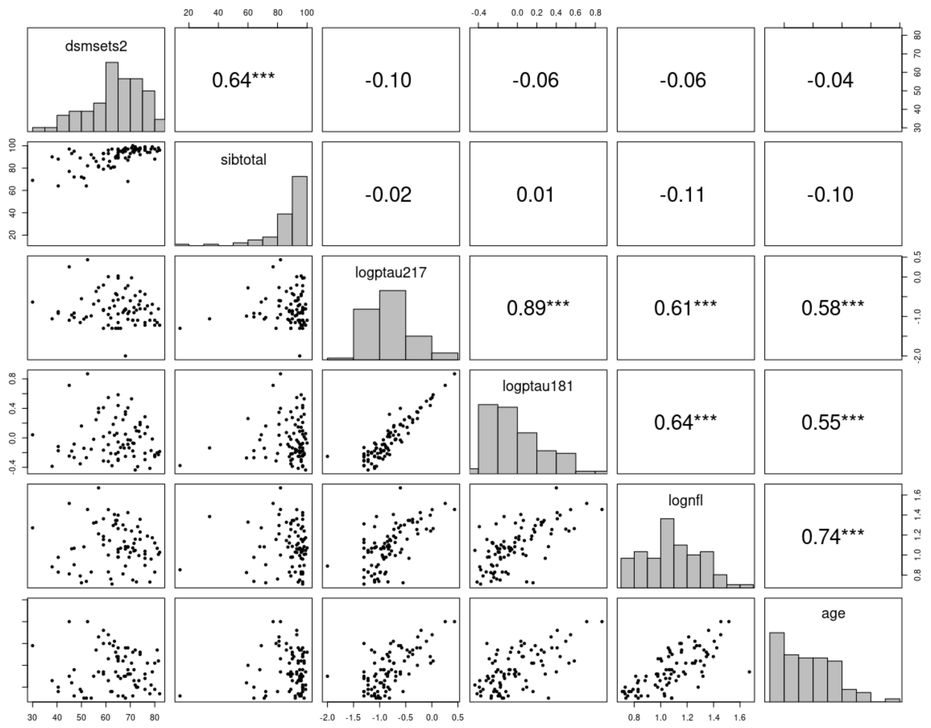
## FIGURES

### TABLE 1: PRELIMINARY BIOMARKER STUDY DEMOGRAPHICS AND BASELINE ASSESSMENT

| Characteristic | Value |
|---|---|
| Age, Median (Q1, Q3) | 37.0 (30.0, 45.0) |
| Sex, N Female (PCT) | 40 (46.5%) |
| E4 carrier , N (PCT) | 23 (25.6%) |
| DSMSE Total Score2, Median (Q1, Q3) | 65.0 (59.0, 72.0) |
| SIB Total Score, Median (Q1, Q3) | 93.0 (86.0, 96.5) |
| Ptau217 pg/ml, Median (Q1, Q3) | 0.136 (0.080, 0.250) |
| Ptau181 pg/ml, Median (Q1, Q3) | 0.813 (0.592, 1.448) |
| NfL pg/ml, Median (Q1, Q3) | 11.897 (9.278, 18.061) |

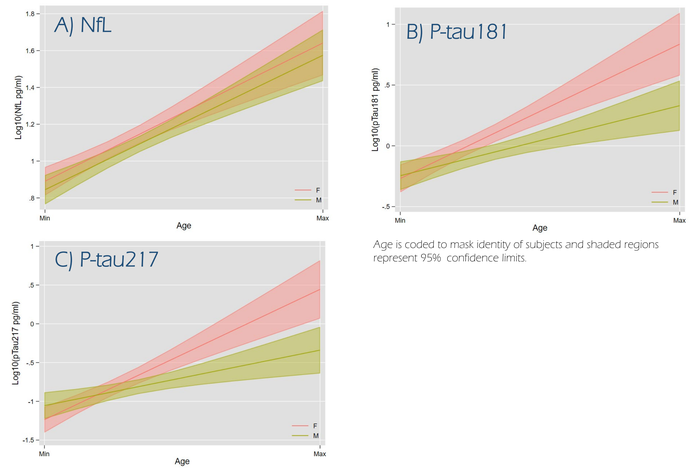
Biomarker samples were analyzed for 90 of 93 anticipated participants. The following data was available at the time of interim analysis for these 90 participants: demographic data for 86 (95.6%), SIB total score for 84 (93.3%) and DSMSE total score for 79 (87.8%).

### FIGURE 1: MULTICORRELATION ANALYSIS OF BIOMARKERS WITH COGNITIVE MEASURES AT BASELINE




Notes: Age values are hidden in Figure 1 to mask identity. Statistical significance for Spearman correlation is three stars for p < .001, two for < .01, and one for < .05.

### FIGURE 2: REGRESSION OF BIOMARKERS WITH AGE BY SEX




Age is coded to mask identity of subjects and shaded regions represent 95% confidence limits.

References

de Graaf, et. al. (2019) https://dsuri.net/us-population-factsheet

Hartley, et al. (2015) Down syndrome and Alzheimer's disease: Common pathways, common goals. Alzheimers Dement;11:700-709.

Lemere, et al. (1996) Sequence of Deposition of Heterogeneous Amyloid β-Peptides and APO E in Down Syndrome: Implications for Initial Events in Amyloid Plaque Formation. Neurobiol Dis 3(1):16-32.

Lewczuk, et. al. (2018) Plasma neurofilament light as a potential biomarker of neurodegeneration in Alzheimer's disease. Alzheimers Res Ther;10:71.

Rafii, et al. (2019) Plasma Neurofilament Light and Alzheimer's Disease Biomarkers in Down Syndrome: Results from the Down Syndrome Biomarker Initiative (DSBI). J Alzheimers Dis, 70(1):131-138.

Strydom, et al. (2018) Neurofilament light as a blood biomarker for neurodegeneration in Down syndrome. Alzheimers Res Ther 10:39.

Fish J. (2011) Severe Impairment Battery. In: Kreutzer J.S., DeLuca J., Caplan B. (eds) Encyclopedia of Clinical Neuropsychology. Springer, New York, NY (Book Chapter).

Haxby, J. V. (1989) Neuropsychological evaluation of adults with Down's syndrome: patterns of selective impairment in non-demented old adults. J Ment Defic Res, 33 (Pt 3), 193-210.

### Abbreviations in Tables and Figures

anyE4 = APOE e4 carriers; DSMSE Total Score2 or dsmsets2 = Down Syndrome Mental Status Examination method 2 score; lognfl = logarithmic transformation of neurofilament light; logptau = logarithmic transformation of Phosphorylated tau; NfL = neurofilament light; Ptau = Phosphorylated tau; SIB Total Score or sibtotal = Severe Impairment Battery total score

### Author Disclosures

David C. Airey, Jeffrey L. Dage, and Jennifer A. Zimmer are full-time employees and minor shareholders of Eli Lilly and Company. Lilly is exploring commercialization opportunities for the Lilly P-tau217 blood test.

## CONCLUSIONS

Preliminary study of baseline biomarkers in LIFE-DSR study indicates suitable performance for a full analysis once the study reaches full enrollment.

At current enrollment, correlation of biomarkers with neuropsychological testing results is not significant.

At current enrollment, the association of biomarkers with age is different between male and female participants and this could be due to small sample size, especially older participants, and will be further investigated once full enrollment is achieved.

The biomarker data contributes to understanding of disease onset and progression and clinical profiles of DS-AD and will be applied to the full LIFE-DSR longitudinal study.