# Appendix 1

**Appendix 1. Attendees of the First International Pre-Symptomatic ALS Workshop**

The First International Pre-Symptomatic ALS Workshop (January 27, 2020, in Miami, FL) brought together specialists in the field of neurodegenerative disorders, along with discovery scientists, statisticians, genetic counselor, legal researcher, and representatives from industry, the ALS Association, the Association for FTD and the National Institutes of Health. The goals of the Workshop were to learn from the experience of those studying the pre-symptomatic phases of other neurodegenerative diseases and to: (1) define the minimal assessments needed to declare an ALS gene mutation carrier as pre-symptomatic; (2) reach consensus on a conceptual framework for describing and understanding pre-symptomatic ALS; (3) develop operational criteria for both motor and cognitive/behavioral phenoconversion; and (4) review the landscape of pre-symptomatic ALS biomarkers to identify leading candidates. Attendees included:

Ammar Al-Chalabi (King's College London, UK)

Peter M Andersen (Umeå University, Sweden)

Jalayne Arias (University of California San Francisco, USA)

Michael Benatar (University of Miami, USA)

Bradley Boeve (Mayo Clinic, USA)

Stephanie Cosentino (Columbia university, USA)

Kuldip Dave (The ALS Association)

Toby Ferguson (Biogen)

Mary-Kay Floeter (National Institute of Health, USA)

Jonathan Rohrer (University College London, UK)

Stephanie Fradette (Biogen)

Tania Gendron (Mayo Clinic Jacksonville, USA)

Volkan Granit (University of Miami, USA)

Anne-Laure Grignon (University of Miami, USA)

Murray Grossman (University of Pennsylvania, USA)

Amelie Gubitz (National Institute of Health, USA)

Petra Kaufman (AveXis)

Isabelle Le Ber (ICM Brain and Spine Institute)

Suzee Lee (University of California San Francisco, USA)

Andrea Malaspina (University College London, UK)

Michael P McDermott (University of Rochester, USA)

Caroline McHutchison (University of Edinburgh, UK)

Corey McMillan (University of Pennsylvania, USA)

Katie Nicholson (Massachusetts General Hospital, USA)

Ronald Petersen (Mayo Clinic, USA)

Ronald Postuma (McGill University, Canada)

Richard Robinson (Freelance Science Writer)

Howard Rosen (University of California San Francisco, USA)

Christopher Ross (Johns Hopkins University, USA)

Jeremy Shefner (Barrow Neurological Institute, USA)

Christine Stanislaw (Emory University, USA)

Nadine Tatton (The Association for Frontotemporal Degeneration)

Neil Thakur (The ALS Association)

Martin Turner (University of Oxford, UK)

Jochen Weishaupt (Ulm University)

Joanne Wuu (University of Miami, USA)

**Appendix 2. CDR® plus NACC FTLD** 1,2

Some key scales have been developed for use in natural history and clinical trial studies in s- and f-FTLD. One of the most commonly used scales is the Clinical Dementia Rating Dementia Staging Instrument (CDR®) PLUS National Alzheimer Coordinating Center (NACC) Frontotemporal Lobar Degeneration (FTLD) Module Behavior & Language Domains, which is commonly abbreviated “CDR® plus NACC FTLD” 1,2. This measure involves clinician ratings based on separate patient and informant interactions, which expands the classic five-domain CDR® to include two additional domains pertinent to FTLD. The CDR® domains include Memory, Orientation, Judgement and Problem Solving, Community Affairs, and Home and Hobbies, which are each rated on a 5-point scale ranging from 0 (normal), 0.5 (questionably or minimally impaired), 1 (mildly impaired), 2 (moderately impaired) to 3 (most severely impaired). A sixth domain, Personal Care, is rated on a 4-point scale from 0 to 3 without a rating of 0.5. The Behavior/Comportment/Personality and Language domains were added to the CDR to reflect the two primary domains pertinent to FTLD; these domains are also scored on the 5-point scale ranging from 0 to 3 1,2.

Two scores are generated as part of the CDR® plus NACC FTLD scoring system: the global CDR® plus NACC FTLD score and the CDR® plus NACC FTLD Sum of the Boxes (SB). If any person has a change in cognition/behavior/language, this is reflected by the global and SB scores being >0. For the CDR® plus NACC FTLD SB score, the value is determined by simply adding all eight of the domain scores. The global CDR® plus NACC FTLD is more complex, and represents an algorithm that follows particular guidelines1,2. Importantly, a global CDR® plus NACC FTLD score of 0 represents normal cognition, behavior and language functioning; a global score of 0.5 represents questionably or mild changes in cognitive, behavioral, or language functioning; and a global scores of 1-3 represent definite changes in cognitive, behavioral, or language functioning of mild (1), moderate (2) and marked (3) severity. Generally speaking, those with a global score of 0.5 are considered in the MCI stage, and those with a global score of 1 or higher have an overt FTLD phenotype. Furthermore, among asymptomatic mutation carriers who are followed longitudinally, *symptom onset* is determined when the global CDR® plus NACC FTLD score goes from 0 to >0 (which is usually 0.5 at first instance).

**References**

1. Miyagawa T, Brushaber D, Syrjanen J, et al. Use of the CDR(R) plus NACC FTLD in mild FTLD: Data from the ARTFL/LEFFTDS consortium. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* 2020;16(1):79-90.

2. Miyagawa T, Brushaber D, Syrjanen J, et al. Utility of the global CDR((R)) plus NACC FTLD rating and development of scoring rules: Data from the ARTFL/LEFFTDS Consortium. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* 2020;16(1):106-117.