

The Changing Landscape of Care for Adults with Down Syndrome associated Alzheimer's Disease (DS-AD): Preparing for Improvements in Diagnostic Assessments, Biomarkers and Medical Therapeutics

Summary and Recommendations of ICW meeting held at the 2023 Annual Conference of the American Academy of Neurology, Boston, Massachusetts

An event organized by the National Task Group on Intellectual Disabilities and Dementia Practices (NTG) and LuMind IDSC Foundation including stakeholders at a 'In Conjunction With' (ICW) meeting held on Tuesday April 25th, 2023 (2:30pm – 6:00pm) and held at the Element Seaport Boston Hotel during the annual meeting of the American Academy of Neurology (AAN). This document is a summary of the meeting. This meeting championed the need for equity, inclusion, and accessibility for people with intellectual disability within the current framework for dementia treatment, research, assessments, and care practices.

The focus of this event was to discuss viable current and future clinical assessment and care practices of adults with Down syndrome suspected or diagnosed with Alzheimer's disease (AD) and other forms of dementia. Many of the discussion points would also be relevant to those with IDD (non-DS). This event was created to tie into the *Working Group on Criteria for Access to Alzheimer's Therapeutics for Adults with Down Syndrome*. Additionally, our meeting also connected to the recent publication *Examining Adults with Neuroatypical Conditions for MCI/Dementia During Cognitive Impairment Assessments – Report of the Neuroatypical Conditions Expert Consultative Panel* developed collaboratively by the NTG and Lu-Mind. The overall scope of this meeting focused on how the impact of new biomarkers that would be able to provide a diagnosis of Down syndrome associated Alzheimer's Disease (DS-AD) often years before the onset of the symptoms of dementia, the advent of equitable assessment tools which would help provide a more objective evidence of change in function, as well the rapidly evolving and recent approvals of anti-amyloid disease modifying therapeutics (DMTs). These various DMTs may change the current landscape on how care and supports would be provided in the years to come from the way in which they are being offered now.

The meeting was a hybrid event, with most attendees in place and several joining virtually. An overview of the scope and intent of the meeting was provided by Dr. Seth Keller, the moderator. There was a round robin of introductions and all participants gave a brief overview of their background. Special acknowledgement for supporting the meeting was given to Dr. Philip McCallion of Temple University and the facilitator of the Butz Family Aging Research Fund.

- **Hampus Hillerstrom**, the CEO of the LuMind IDSC Foundation, presented an overview of the *Expert Panel on Equivalency Criteria for Access to Alzheimer's Therapeutics for Adults with Down Syndrome*.
 - DS-AD and Late Onset AD (LOAD) share many of the same clinical and pathological characteristics and as beta amyloid accumulates, Tau protein development follows leading to neurodegeneration.

- Some of the differences in Down syndrome include age of onset, shorter course of the disease leading to death, both earlier seizure frequency and rate of cerebral amyloid angiopathy (CAA) are higher in those with DS-AD.
 - Current anti-amyloid drug trials only included neurotypical participants; no one included had Down syndrome (DS). The concerns that their safety have not been demonstrated yet in those with DS was reviewed. The realization that safety studies often take many years to implement as well as the numbers who may need to be in a drug trial. With a 90% or more lifetime risk, people with DS are at a very high risk for the development of Alzheimer's disease. Given what is known about the marked risk, many adults with DS do not have the remaining life years to wait for completion of these studies. Access to emerging disease modifying therapeutics for Alzheimer's disease will be significantly delayed for adults with intellectual disability, including Down syndrome, unless there is active advocacy to include this group in clinical trials and in prescriber guidelines. Acknowledged was that a significant part of a generation of adults with Down syndrome, with estimates of perhaps up to 14 years, have already been deprived of access to life-extending therapeutics, because individuals with DS were not included in clinical trials of recently FDA approved or most promising anti-amyloid therapies including Aduhelm™ (aducanumab), Leqembi™ (lecanemab), and donanemab).
 - Anti-amyloid therapies will all require a biomarker proving the presence of the pathologic signs of AD (currently the presence of amyloid in the cerebral spinal fluid (CSF) obtained via lumbar puncture or on PET Scan) before therapy is initiated. Brain MRIs will be required before treatment and periodically after treatment is initiated. These studies will look for any evidence of amyloid-related imaging abnormalities (ARIA). These changes may have a negative impact upon which of the anti-amyloid therapies are safe therefore may influence which should be prescribed and be continued for therapeutic purposes. How people with DS would be able to tolerate testing and whether appropriate assessments could be done was discussed with commentators noting that much is variable and individually driven.
 - The challenges of recruiting people into drug trials were discussed; these included the limited pool of age-appropriate and naïve subjects available for enrolled in mass scale studies.
 - The work of the Expert Panel on Equivalency Criteria for Access to Alzheimer's Therapeutics for Adults with Down Syndrome was discussed and it was noted that the final report of the panel will soon become available.
- **Richard Fisher**, Chief Scientific Officer of the LuMind IDSC Foundation, presented an overview of the nature and current research on biomarkers.
 - A preclinical diagnosis of DS-AD may be possible. Would people with DS and their care supports be interested to know years before symptoms begin wish to be tested?
 - Cerebral spinal fluid (CSF) obtained through lumbar puncture and PET Scan (current test means for presence of amyloid) are expensive and challenging for people with DS; however, there are several on-going trials now to support the validation of blood-based biomarkers (BBM) for staging AD.
 - Timing of treatment in the amyloid cascade is critical and adds weight regarding the urgency for inclusion in the clinical trials.
 - Blood biomarker research for LOAD is advancing rapidly.
 - Adoption could lead to \$400M-\$700M in savings to US healthcare systems.

- Wide use will increase equitable access to care including adults with DS and ID.
- Remaining issues for adoption in LOAD or DS-AD
 - Universal assay cut points not yet established or in wide use.
 - Not validated in real-world populations.
 - Consensus guidelines are not yet established. The Alzheimer’s Association is working on an update to the NIA-AA Guidelines.
 - Risk for underdiagnosis of non-AD pathologies.
- **Seth Keller**, Co-President, NTG, and Past Chair of the AAN’s Intellectual Disability Interest Section, reviewed assessment tools.
 - Current assessment tools are not easily and accurately available to determine the presence of functional decline (i.e., change from their baseline) and to be able to track change. Research centers have expert testers and higher-level assessment tools available. Currently available tools for the general Alzheimer’s population that are used to test for evidence of cognitive decline are often not applicable to many people. However, adults with intellectual disability and other neuroatypical conditions have cognitive, sensory, language, cultural and ecological background differences which keep them from being able to receive equitable dementia assessments and care.
 - Functional assessment tools may be too subjective and inaccurate, and biomarkers may be needed to not only help determine the presence of AD, but also be able to track the disease.
 - There is a need for an expert group to be formed to establish a recommended protocol for assessing adults with ID/DS during annual wellness visit or during referrals for possible MCI or dementia in DS-AD, building off the work of Moran et al., that was done with the NTG and published in the Mayo Clinic Proceedings.
- Health and Wellness
 - Diet, physical activity, sleep/stress management, social and cognitive engagement as well as care of specific underlying health conditions may be able to mitigate cognitive decline associated with aging as well as that of dementia onset. People with DS or other forms of IDD and their caregivers may not fully embrace life span health and wellness practices.
 - The realization that many (if not most) people with DS will eventually present with dementia due to Alzheimer’s disease is very difficult to accept and consider. The idea of wanting to know about this, give some thought to it, and plan for this eventuality presents several inherent challenges in being able to do research, educate, and provide appropriate care and support strategies.
 - Consideration for much needed sensitive awareness strategy is needed.
- Healthcare Provider (HCP) Supports
 - HCPs are currently inadequately educated and trained in being able to care for and support most people with DS/ID who may develop cognitive decline and dementia.
 - The AAN has a formalized “Section” that specifically focuses on the neurologic complications of adults with IDD and is expanding in membership each year.

- The AAN has now guaranteed a specific course to be offered at each year's annual meeting that will focus on adult ID neurologic issues starting in 2024. The Adult ID Section will now begin to plan for the 2024 meeting in Denver to help further advance education and training.
 - The AAN magazine *Brain and Life*, in cooperation with the Adult ID Section, is looking at creating a special edition on the issues and concerns inherent in DS-AD, as well as non-DS ID Dementia to help provide these various to the general neurology community.
 - The Adult ID Section would work with others within the AAN to help push for improving standards of care practices within the community but also of that in tertiary memory centers.
 - Targeted education via various professional organizations (e.g., American Academy of Neurology (AAN), American Geriatrics Society (AGS), International Association of Gerontology and Geriatrics (IAGG), American Psychological Association, (APA), Gerontological Advanced Practice Nurses Association (GAPNA), etc.) is needed to increase the base knowledge among potential prescribers to better understand the issues in assessment of adults with ID and DS when looking for presence of dementia.
 - Currently available DS specialty clinics across the US only provide approximately 5% of expertise and most of these often focus upon pediatrics. Helping to provide education and training (such as through the use of the Project ECHO model) can be made more broadly available.
 - Organizations including DSMIG, DDNA, NTG, LuMind IDSC, AADMD can help to provide education and training.
 - Establish a routine series of webinars for practitioners to heighten awareness about dementia in ID/DS and how to assess and offer treatment.
 - Need a published article on dementia and medical aspects when dementia is present in ID/DS for medical practitioners.
 - Need a fact sheet for PCPs on non-pharmacological interventions (NPIs) recommendations for referral for paid personnel and families once PCP has made diagnosis.
 - DS national and local advocacy organizations at the center of additional education and training that also would connect back to their HCPs.
 - Engagement with GSA., particularly regarding modification of their KAERS tool kit which is specifically for PCPs to initiate conversations regarding brain health, detecting and diagnosing dementia and providing community-based supports.
- Engagement with pharmaceutical and biomedical research organizations
 - LuMind IDSC shared about its continuous efforts over the last 5 years engaging with all the key pharmaceutical companies in the Alzheimer's space and the creation of the LuMind IDSC Research Consortium to further include these companies in DS-AD research. Currently, the LuMind IDSC Research Consortium includes AbbVie, Alkermes, Eli Lilly, and Merck.
 - Pharmaceutical companies have a key role to play in establishing the safety of their most promising anti-amyloid treatments in DS-AD and in including adults with DS earlier in future clinical trials (moving from Phase 4 to Phase 2 clinical trials). This shift is urgent and critical to provide equitable access to the most promising Alzheimer's treatments to the DS population that has a 90% lifetime risk of developing Alzheimer's, causing up to 79% of the deaths of adults with DS.

Acknowledgement

Special appreciation is extended to the Butz Family Aging Research Fund for providing primary financial support for the meeting and to Dr. Philip McCallion, the Fund's principal officer.

Attendees/Invitees

- James Bishop, PharmD, Neuroscience Medical Science Liaison, Lilly
- Elizabeth Bodien, Family Advocate (Virtual)
- Mary Bolster, *Brain and Life* Magazine, Managing Editor (Regrets)
- Kendra Croker PharmD, Neuroscience Medical Science Liaison, Lilly
- Lucy Esralew, PhD, Geriatric Neuropsychology, California Department of Developmental Services (DDS) /NTG (Virtual)
- Richard Fisher PhD, Chief Scientific Officer, LuMind IDSC Foundation
- Forrest Foster, MD Neurologist, University of Cincinnati (Virtual)
- Hampus Hillerstrom, President and CEO LuMind IDSC Foundation
- Forrest Foster, MD Neurology, Univ Cincinnati (Virtual)
- Tom Hubbard, Senior Vice President of Policy Research, Network for Excellence in Health Innovation (NEHI)
- Matthew Janicki PhD, NTG/University of Illinois, Chicago
- Seth Keller MD NTG/AAN/AADMD/Advocate Neurology
- Florence Lai, MD Neurology, Down Syndrome (DS) Research, McLean Hospital/Harvard Medical School
- Christina Massrey, MD Baylor College of Medicine, Neurodevelopmental Disabilities
- Philip McCallion, PhD, Social Work, Temple University, NTG (Virtual)
- Julie Moran, DO, Geriatrician, Mass DDS Harvard Medical School Boston (Regrets)
- Nicolas Oreskovic, MD PhD, MGH DS Clinic
- Steve Perlman DDS, AADMD, Special Care Dentistry Special Olympics
- Jennifer Pettis, MS, RN, The Gerontological Society of America
- Kandi Pickard, President and CEO, National Down Syndrome Society (NDSS) (Regrets)
- Daniel Press, MD Chief, Cognitive Neurology, Harvard Medical School (Regrets)
- Margaret Pulsifer PhD, Neuropsychologist/Researcher, MGH DS Clinic (Virtual)
- Rick Rader, MD, NTG/AADMD/American Association on Health and Disability (Regrets)
- Mike Rafii, MD Professor of Clinical Neurology at the Keck School of Medicine and Medical Director of the Alzheimer's Therapeutic Research Institute (ATRI) (Regrets)
- Margot Rhondeau, Senior Director Health and Wellness, NDSS (Virtual)
- Jennifer Santoro, MD, Director of Quality Improvement Research, MGH DS Program (Virtual)
- Jonathan Santoro, MD Neurology, USC School of Medicine/ Children's Hospital, Los Angeles CA
- Dana Sciallo, Research Associate, NDSS
- Heather Snyder, PhD, vice president, Medical and Scientific Relations, Alzheimer's Association (Regrets)
- Jessica Solomon Sanders, MD, Children's Hospital, Neurodevelopmental Disabilities, Denver, CO
- Kathy Service, FNP/BC, NTG/Mass DDS (consultant.)
- Jo Ann Simons, Exec Director Northeast Arc, MA (Parent)
- Brian Skotko, MD MGH DS Clinic, Boston, MA
- Kristen Tenglin, Massachusetts Down Syndrome Congress
- Doug Wells, MD Baylor College of Medicine Neurodevelopmental Disabilities