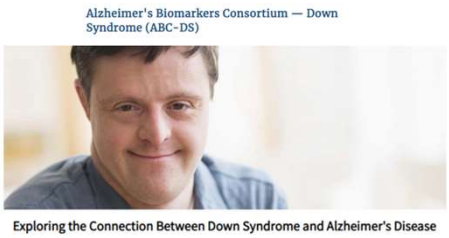
Down syndrome and Alzheimer's disease



Elizabeth Head, MA, PhD
University of California, Irvine
Irvine, CA
heade@uci.edu

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Disclosures

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- Research funded by NIH (NIA, NICHD, INCLUDE), Alzheimer Association and Brightfocus
- Section Editor: Alzheimer's & Dementia

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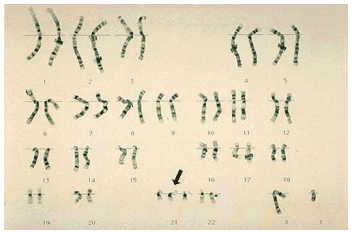
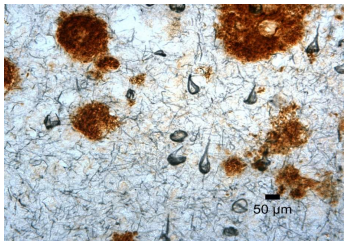
What is the link between Down syndrome and AD





Head & Lott, 2019

- Trisomy 21 most common cause
- APP on chromosome 21
- Early age of onset of Aβ – intracellular then extracellular
- Age-dependent Aβ accumulation
- By age 40 years – sufficient plaque and tangle pathology for a diagnosis of AD
- Genetic form of AD
- Over 400,000 people with DS in USA

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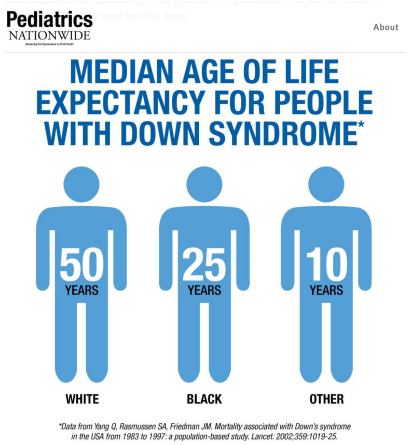
Down syndrome – aging and Alzheimer disease



- People with DS are living longer
- The most rapidly growing age cohort is people between 40 and 50 years
- Age of onset of dementia between 50-55 years
- Average age at death is 58.4 years
- Average disease duration is 4.6 years
- ~10-15% of people reach late 60's early 70's without cognitive decline despite AD neuropathology

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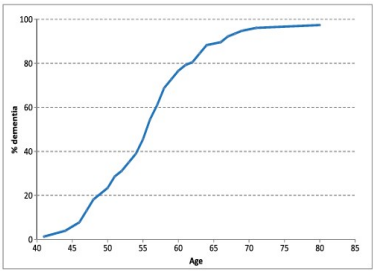
Down syndrome – aging and Alzheimer disease

Near full penetrance of AD dementia



McCarron et al. JIDR 2017

JAMA Network Open

Original Investigation | Neurology

Association of Alzheimer Disease With Life Expectancy in People With Down Syndrome

María Florencia Iulita, PhD; Diana Garzón Chavez, RN; Maria Klitgaard Christensen, PhD; Natalia Valle Tamayo, MSc; Oleguer Plana-Ripoll, PhD; Sonja A. Rasmussen, MD; Marta Roqué Figuls, PhD; Daniel Alcolea, MD; Laura Videla, MSc; Isabel Barroeta, MD; Bessy Benejam, MSc; Miren Altuna, MD; Concepción Padilla, PhD; Jordi Pegueroles, MSc; Susana Fernandez, MD; Olivia Belbin, PhD; María Carmona-Iragui, MD; Rafael Blesa, MD; Alberto Lleó, MD; Alexandre Bejanin, PhD; Juan Fortea, MD

- AD limits the life expectancy for people with DS
- We need a treatment.

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Developing treatments for people with Down syndrome to prevent or treat Alzheimer disease

Challenges

- "Due to the low quality of the body of evidence in this review, it is difficult to draw conclusions about the effectiveness of any pharmacological intervention for cognitive decline in people with Down syndrome." *Livingstone et al., 2015*.
- People with Down syndrome are excluded from clinical trials for Alzheimer disease

Opportunities

- Life span studies – biomarkers – age dependency
- Resilience (~10-15% > 60 years do not show significant cognitive decline)
- Patient/participant tracking of treatments received for Alzheimer disease in people with Down syndrome
- Including people with Down syndrome into ongoing studies as a separate cohort – are we ready?

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Preparing for clinical trials

ABC-DS
Alzheimer Biomarker Consortium-Down Syndrome

- ABC-DS is longitudinal study examining biomarkers of AD in adults with Down syndrome (ages 25 and older).
- The goal of ABC-DS is to understand biological changes underlying AD in people with DS and to develop biomarkers for future clinical trials.
- We have identified neuropsychological and clinical outcome measures that can be diagnostic for MCI or dementia and can serve as outcomes for clinical trials
- Participants are offered the opportunity to co-enroll in a trial ready cohort (ACTC - TRC-DS PI Rafii) for clinical trials.


Handen (UPitt)


Christian (UWisc)


Mapstone (UCI)


Head (UCI)

- 92 Investigators representing 19 Institutions
- NIH: Laurie Ryan, PhD; Melissa Parisi, MD, PhD; Erika Tarver, MSM,MPH; John Hsiao, MD
- https://www.nia.nih.gov/research/abc-ds

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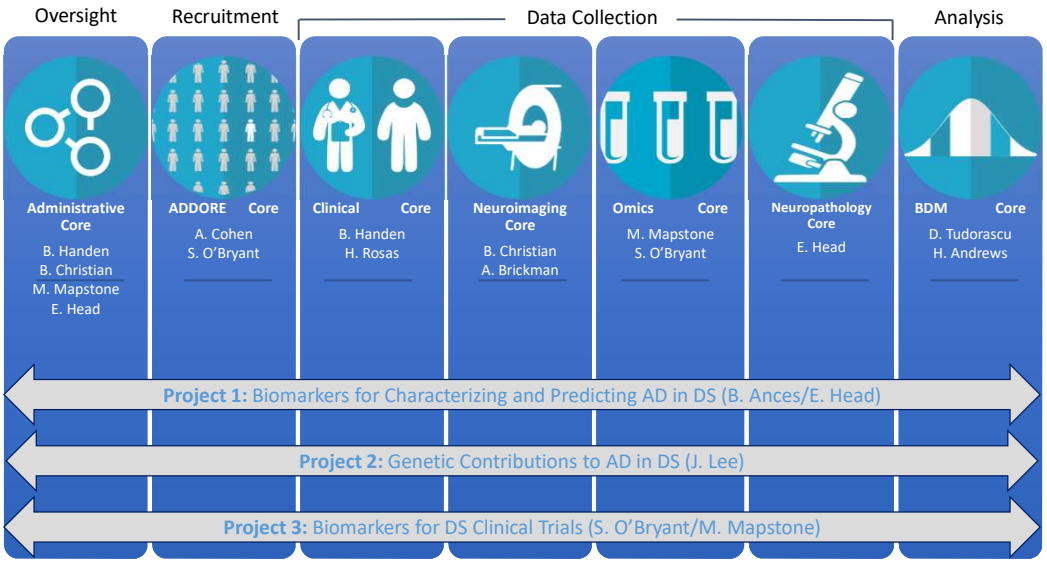
ABC-DS Structure (NIH/NIA U19)



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ABC-DS Outcomes and Available Data

Measure Type	Primary Use	Examples of Outcomes
Medical History	Modifier of trajectories	Medical comorbidities, medications, family history
Physical/Neurological Examination	Dementia determination/ Modifier of trajectories	Body mass index, balance, gait, sensorimotor function
Cognitive Assessment	Dementia determination	Level of intellectual disability, memory, attention, language function
Rating Scales/Questionnaires	Dementia determination/ Modifier of trajectories	Functional capacity, mood, behavioral disturbances
MRI	Biomarker	Resting state activity, cortical thickness, structure volumes, structural connectivity
PET	Biomarker	Regional amyloid SUVr, regional tau SUVr, FDG SUVr
Blood	Biomarker	Specific gene and transcript expression, specific protein and metabolite abundances (IL-6, CRP, phospholipids, acylcarnitines)
CSF	Biomarker	$A\beta_{1-42}$, p-tau_{181}, total tau, Neurofilament light Chain (NfL)***
Neuropathology	Confirmation of diagnosis/correlation with biomarkers	Braak staging, Thal staging, inflammation, cerebrovascular pathology

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Challenges and opportunities for 2024

- We know that people with Down syndrome will be asking for access to approved treatments for AD in the general population
- We know that people with Down syndrome will be recruited into clinical trials
- How to best balance the desire to be inclusive and offer clinical trials to participants in ABC-DS and other studies with longitudinal research
- How can we provide insights into clinical trial design
- How can we provide context for possible adverse events
- How do we balance the messaging to families and to investigators?

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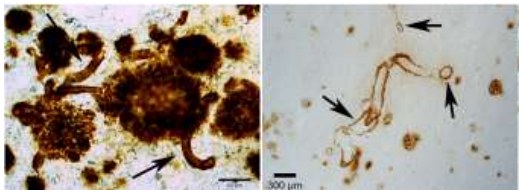
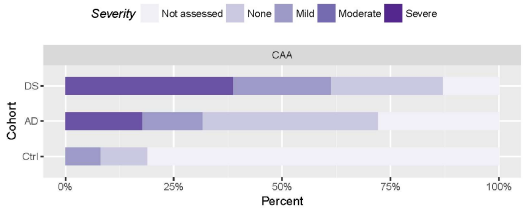
Example - Aβ Immunotherapy

- Lecanemab or Donanemab
- Benefits reported in late onset AD (cognition/biomarkers)
- Adverse events can affect a significant number of patients – ARIA
- People with DS have significant cerebrovascular pathology
- How might this impact a DS clinical trial?
- Again -How do we balance the messaging to families and to investigators?





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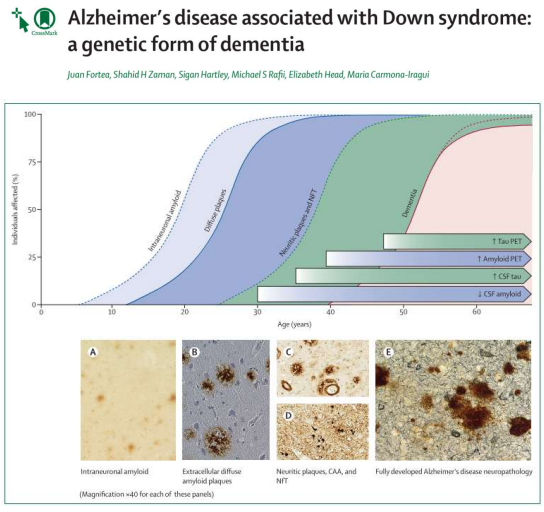
Leveraging unique features of brain aging and AD in DS and the AT(N) framework

- Age is the dependent factor (x axis) on AT(N) frameworks
- Identify sequence of events associated with AD initiation and progression
- Examples:
  - Neuroinflammation may have a unique phenotype in DS
  - More extensive and severe cerebral amyloid angiopathy after 50 years of age
- Understanding therapeutic windows
- Windows of safety for clinical trials



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How can working with people with Down syndrome contribute to AD treatments, prevention and the NAPA mission?

- Leverage prospective data from ABC-DS supported by NIA and INCLUDE (including other international efforts)
- Using age on the x axis for biomarker and neuropathology staging to identify treatment or prevention targets
- Helps to identify efficacious and safe therapeutic windows
- Allows us to assess the impact of risk factors (genetics, co-occurring illnesses, genetics)
- Evolving! Protective factors (resilience) – both in terms of the gap between onset of AD pathology and onset of dementia, as well as people that escape dementia

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Thank you to our research volunteers, their families and our brain donors.

ABC-DS Key Investigators

Site Leads
- UCI - Lott/Hom
- U Pitt-Handen
- U Wisc Mad - Christian/Hartley
- UKY -Schmitt/Harp
- IBR/Columbia - Krinsky-McHale/Lee
- MGH -Rosas/Lai
- Cambridge -Zaman
- Wash U -Ances

Core and Project Leads
- Admin Core – Handen/Christian/Mapstone/Head
- ADDORE - Annie Cohen/Sid O'Bryant
- Clinical Core – Handen/Rosas
- Neuroimaging Core – Christian/Brickman
- Omics Core - Mapstone/O'Bryant
- Neuropath Core –Head
- Biostats/Data Management – Tudorascu/Andrews
- Project 1 – Ances/Head
- Project 2- Lee
- Project 3 – Mapstone/O'Bryant

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