Understanding Alzheimer's Disease as a Co-Occurring Condition in Down Syndrome: Insights from the Alzheimer Biomarkers Consortium-Down Syndrome (ABC-DS) Study.

ABC-DS

Alzheimer Biomarkers Consortium- Down Syndrome

The Arc of New Jersey

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When you think of people with Down syndrome, who comes to mind?

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Children with Down syndrome grow up and even get old!

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Good news

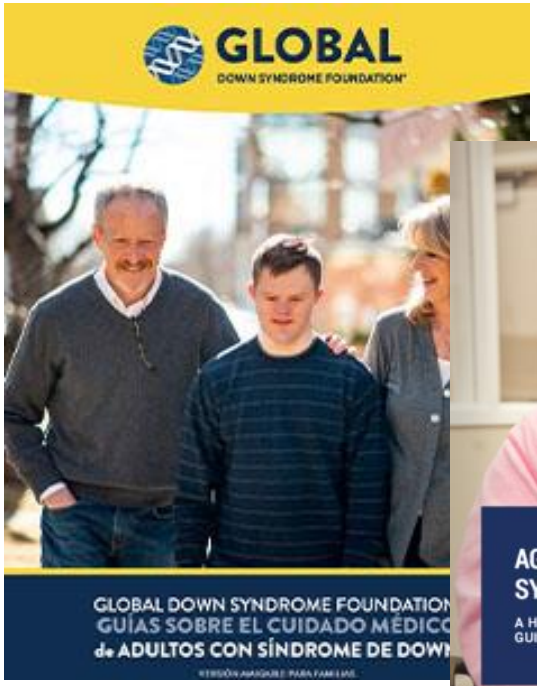
Adults with Down syndrome are living longer, healthier lives because of improved medical care and environmental conditions.

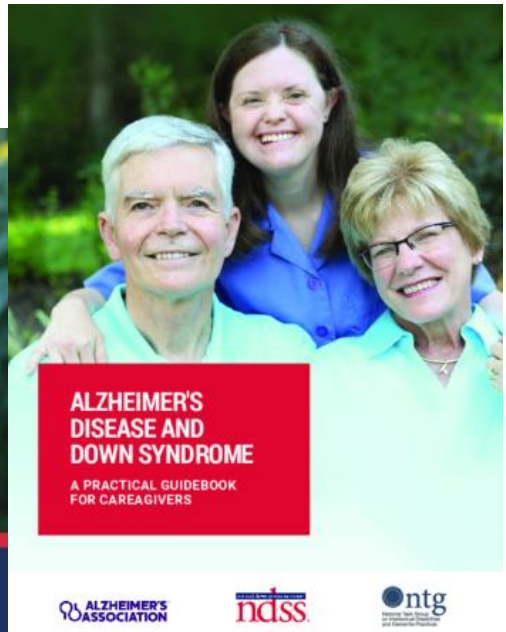
Associated challenges

We have limited knowledge and experience caring for adults with Down syndrome

Down syndrome scientific community efforts

Advance knowledge on aging and co-occurring conditions.





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Behavior and Dementia in Down syndrome

Healthcare Guidelines for Adults with DS recommend:

- **Annual review of factors** that may affect physical and mental well-being.
  - **Behavior**: mood, attention, and activity level
  - **Functional-adaptive skills**: social, communication, and daily living skills
  - **Psychosocial events**: major life events, bereavement, trauma

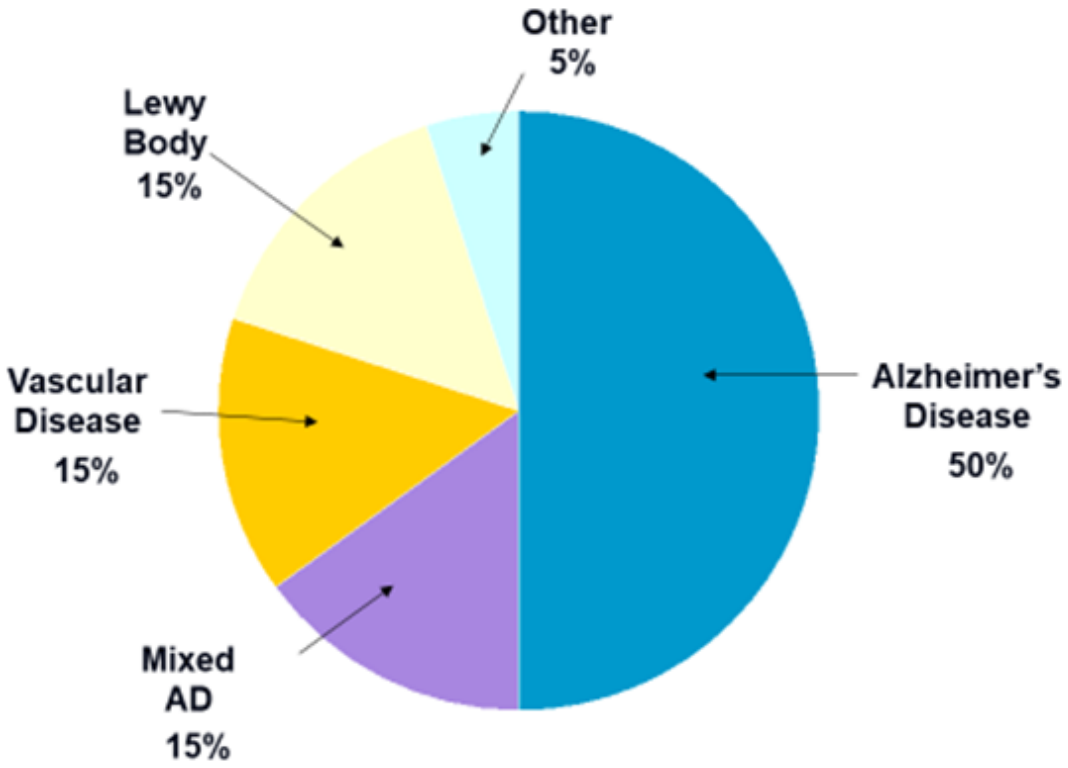
Consider changes in mood and behavior reported by family and caregivers. (Especially those who are part of the adult's daily life)

GLOBAL Medical Care Guidelines for Adults with Down Syndrome.

What is Dementia?

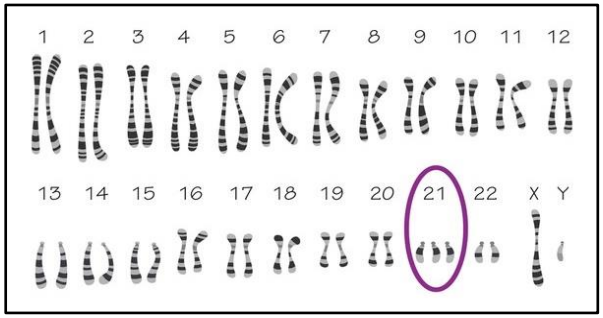
- Serious **loss of global cognitive ability** in a **previously unimpaired** person, **beyond** what would be expected in **"normal" aging**
- Typically occurs in geriatric populations
- Not a single disease, but associated with many underlying causes

Causes of old-age associated dementia in neurotypical adults



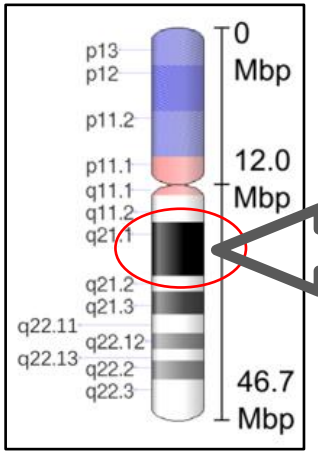
How is Alzheimer's disease associated to Down syndrome?

Chromosome 21 and the Amyloid Precursor Gene: APP



3 copies of chromosome 21

Chromosome 21



Amyloid precursor protein (APP) gene is located on Chromosome 21

- Over-expression of APP gene
- Larger production of Amyloid Precursor Protein
- More Amyloid accumulation in the brain
- Increased risk of Alzheimer's Disease in adults with Down syndrome

*Other genes may also be involved.

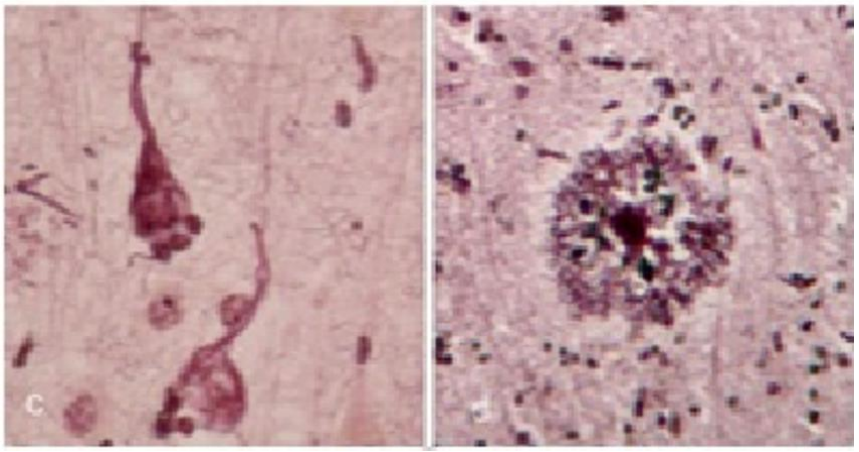
Alzheimer's Disease

- 1906. Dr. Alois Alzheimer identifies an "unusual disease in the cerebral cortex" of a 51 years old patient with dementia

- Post-mortem autopsy:
  - Thinner cerebral cortex
  - Senile Plaques
  - Neurofibrillary tangles

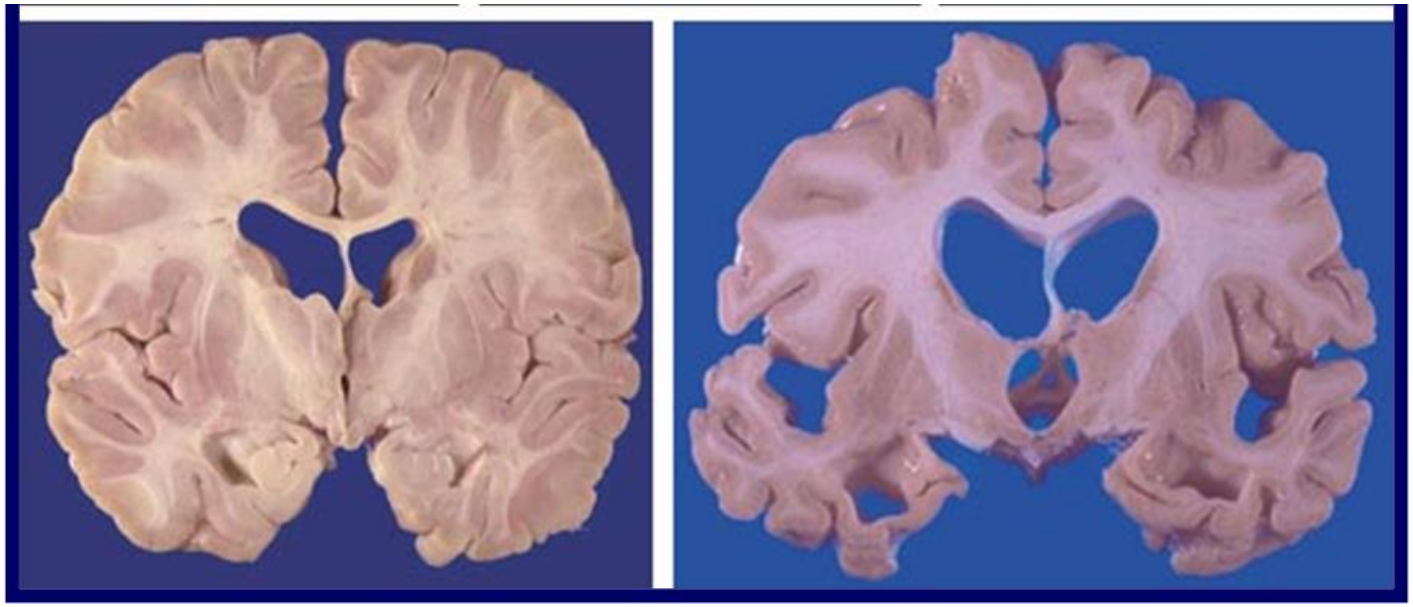
Alzheimer's Disease: Neuropathological characteristics

- Amyloid plaque formation
- Neurofibrillary (tau) pathology
- Loss of brain cells and brain mass
- Change in blood flow and glucose utilization



Neurofibrillary tangles Amyloid plaque

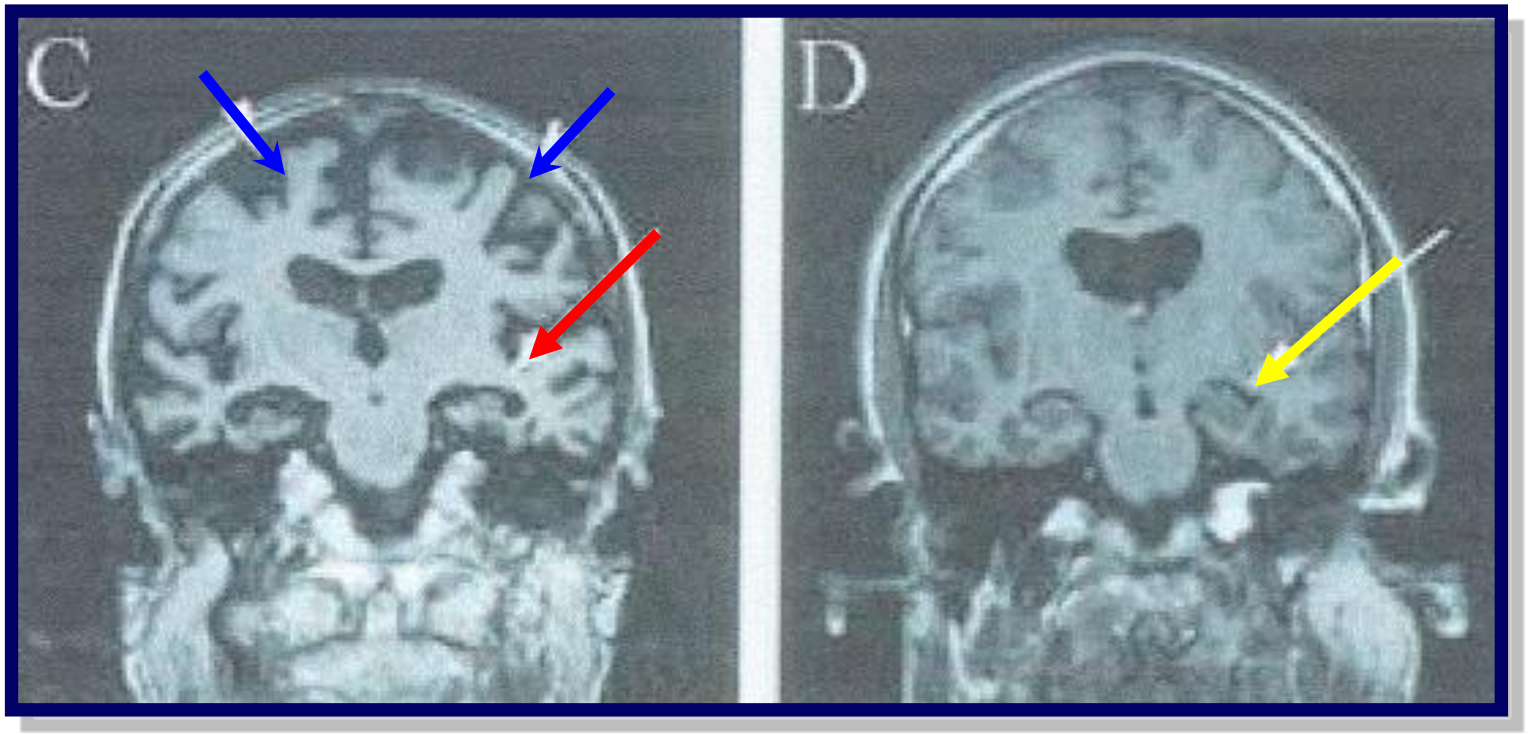
Postmortem Examination



Healthy elderly brain

Brain with AD

Magnetic Resonance Imaging (MRI)



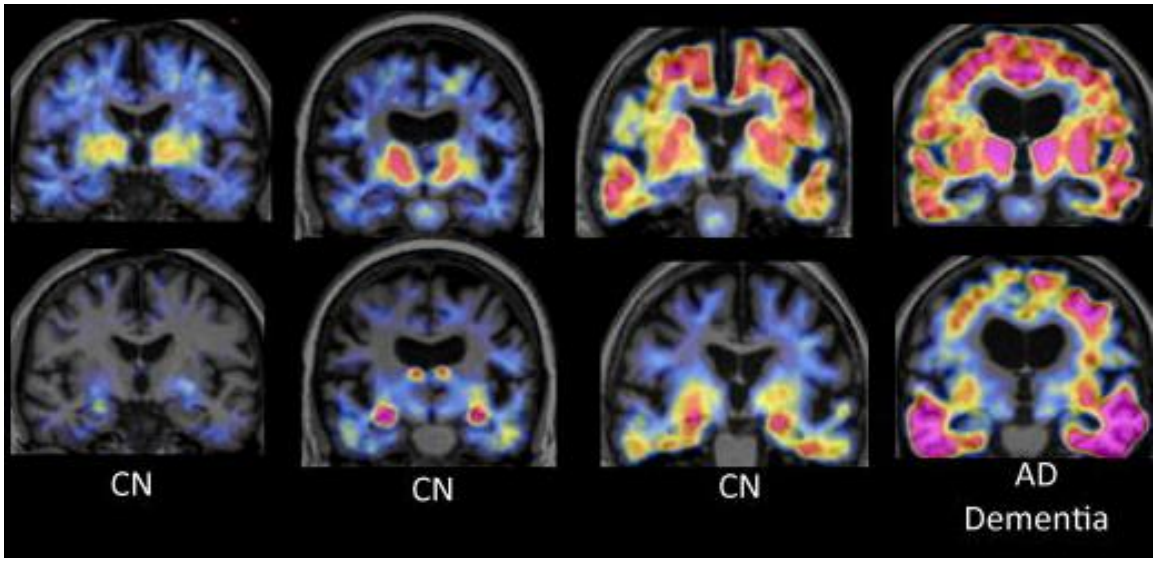
Alzheimer's Disease

Healthy elder person. Cognitive Stable

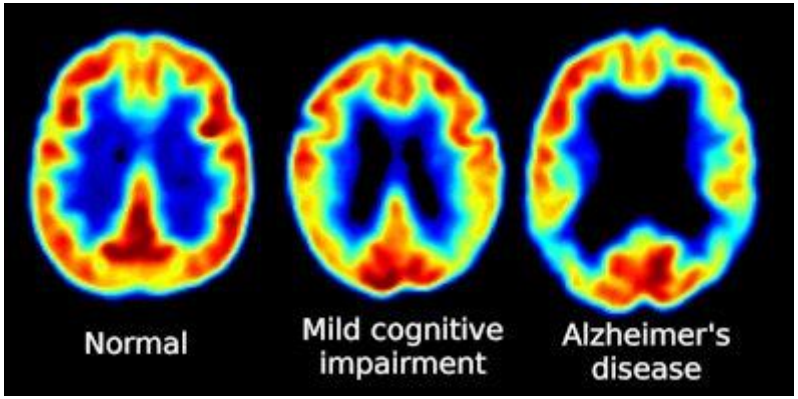
Positron Emission Tomography (PET)

Amyloid PET

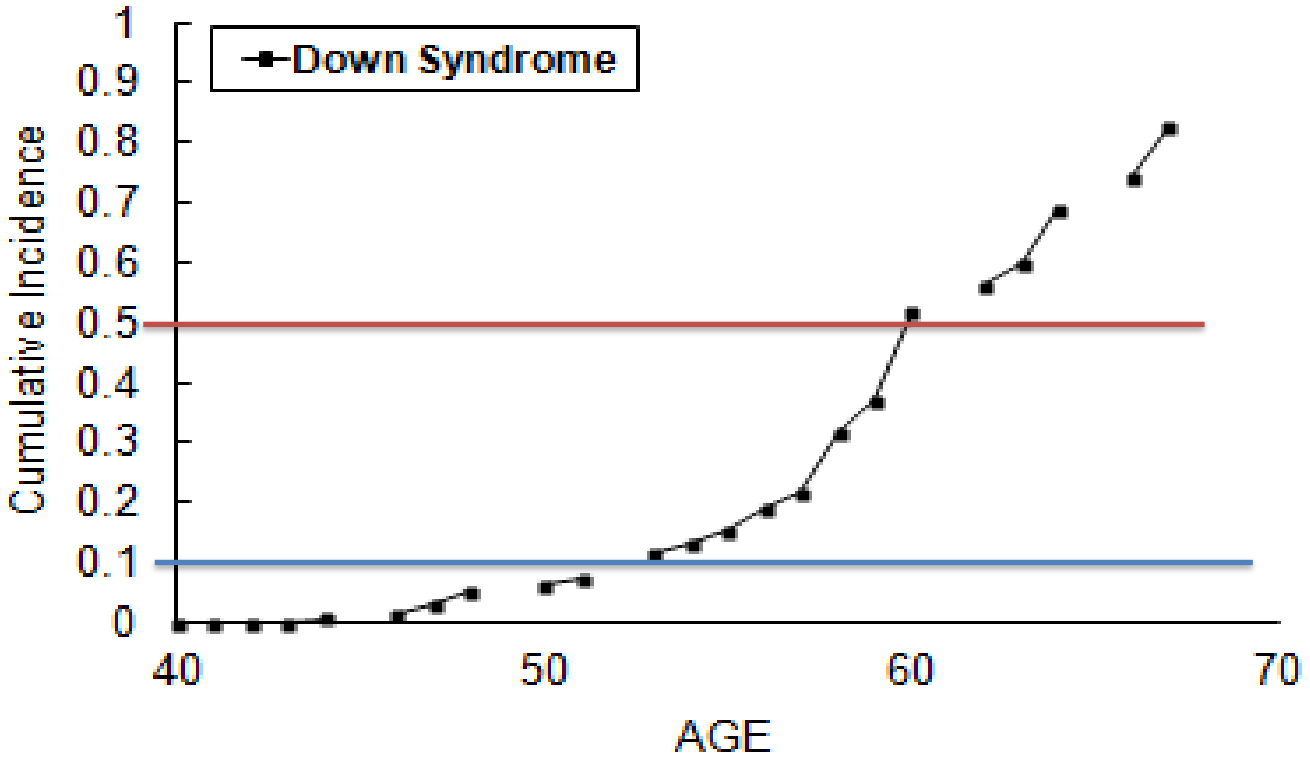
Tau PET



FDG-PET



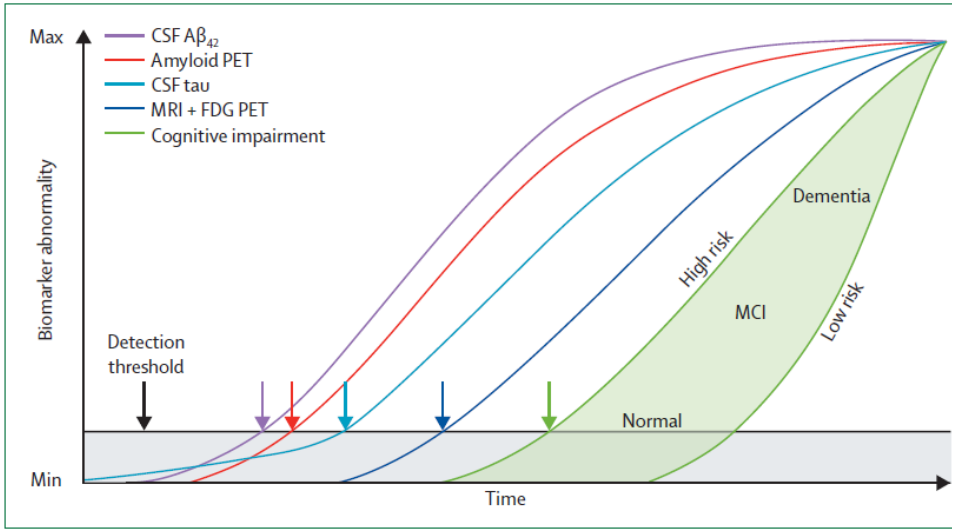
Cumulative incidence of Alzheimer's disease in Down syndrome



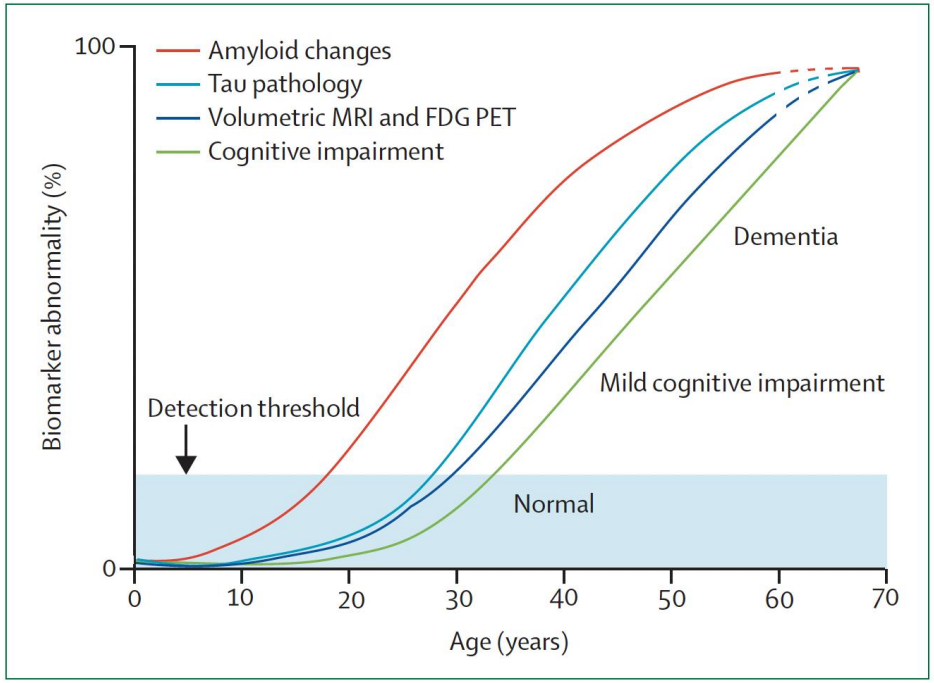
N. Schupf (personal communication).

Hypothetical model of biomarkers of the Alzheimer's pathological cascade

Neurotipical vs. Down syndrome



Jack and Holtzman et. al, Lancet Neurology, 2013



Adapted from Jack and Holtzman.
Ballard et. al, Lancet Neurology, 2016

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General facts about Alzheimer's disease in adults with Down syndrome

- Almost every adult over 40 years have neuropathological characteristics of Alzheimer's disease.
- Initial functional changes and decline progression, are similar to adults without intellectual disability.
- Risk factors are mostly the same as in any adult.
- Some individuals with Down syndrome do not exhibit indications of dementia.
- Wide variation in age of onset.

Diagnosis of dementia in Down syndrome: it's complicated…

- Pre-existing cognitive impairments (Intellectual Disabilities)
- Large differences in lifelong abilities amongst individuals
- No standard protocols for assessing dementia
- Caregivers may not notice early cognitive declines
- Other aging concerns, medical and psychological conditions and significant life events

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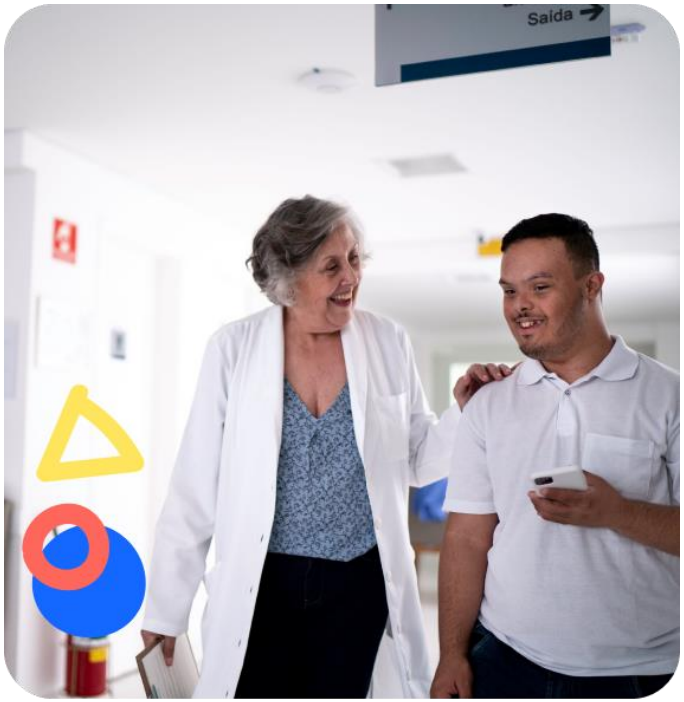

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ABC-DS

- ABC-DS is a **research project** where we follow a group of adult volunteers with Down syndrome to find signs and risks of Alzheimer's
- ABC-DS study **aims to better understand** the connections between Down syndrome and Alzheimer's disease to help with **treatment and prevention**
- As part of the study, **we gather data** through brain scans, blood tests, and exams that look at how people with Down syndrome think

ABC-DS

Alzheimer Biomarkers Consortium- Down Syndrome

Study Aims:

- Establish, follow, and comprehensively characterize a clinical cohort of ~600 individuals with DS
- Work within the community to increase the diversity of individuals in the cohort of adults with DS
- Examine biomarkers of DS-AD in the AT(N) framework and determine if risk is modified by selected factors.
- Examine genetic factors that modify DS-AD risk.
- Develop precision medicine ready biomarkers for DS-AD clinical trials.
- Disseminate data and biospecimens to qualified researchers outside of ABC-DS

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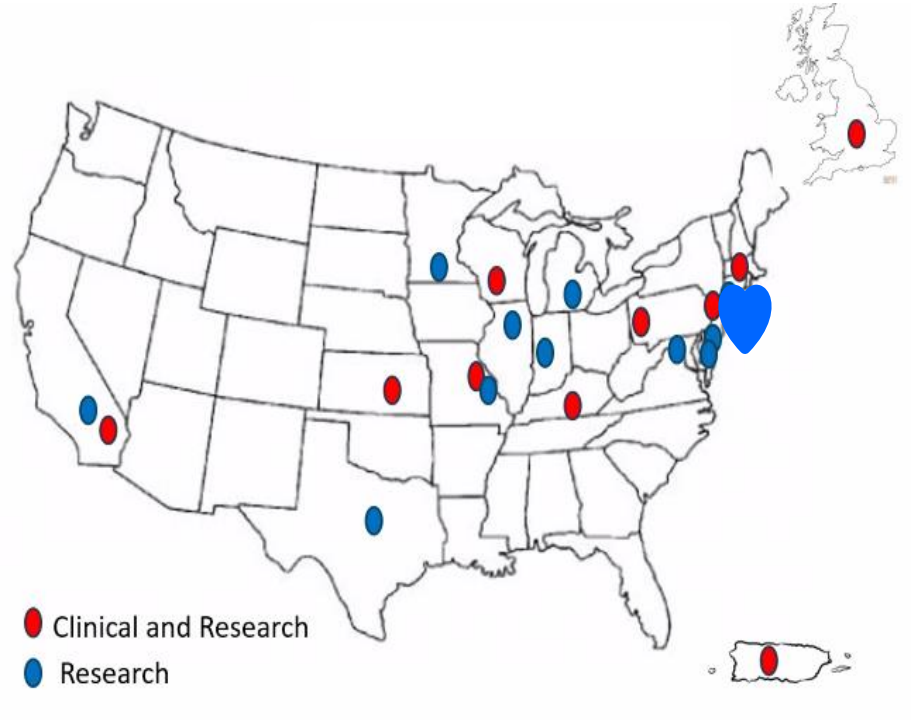
ABC-DS Performance Sites

ABC-DS is supported by the National Institutes of Health (NIH)

- National Institute on Aging (NIA)
- Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
- INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE **(INCLUDE) Project**.



https://www.nih.gov/include-project

New York Site

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Staten Island, NY

New York, NY

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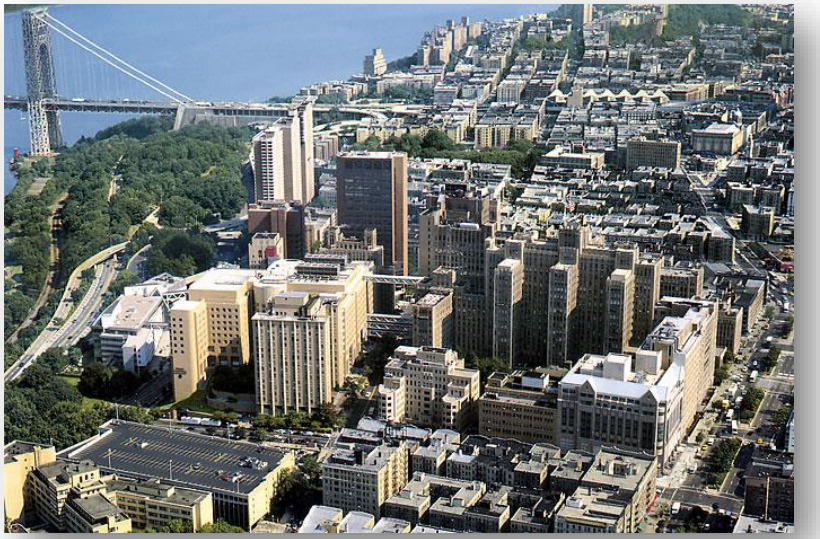

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NEW YORK STATE OF OPPORTUNITY. Institute for Basic Research in Developmental Disabilities (IBR)

New York State Institute for Basic Research in DD

Staten Island, NY

- Investigates brain development and pathology and elucidate their functional consequences
- Is the research arm of the NYS Office for People With Developmental Disabilities (OPWDD)
- Provide clinical services and educational programs

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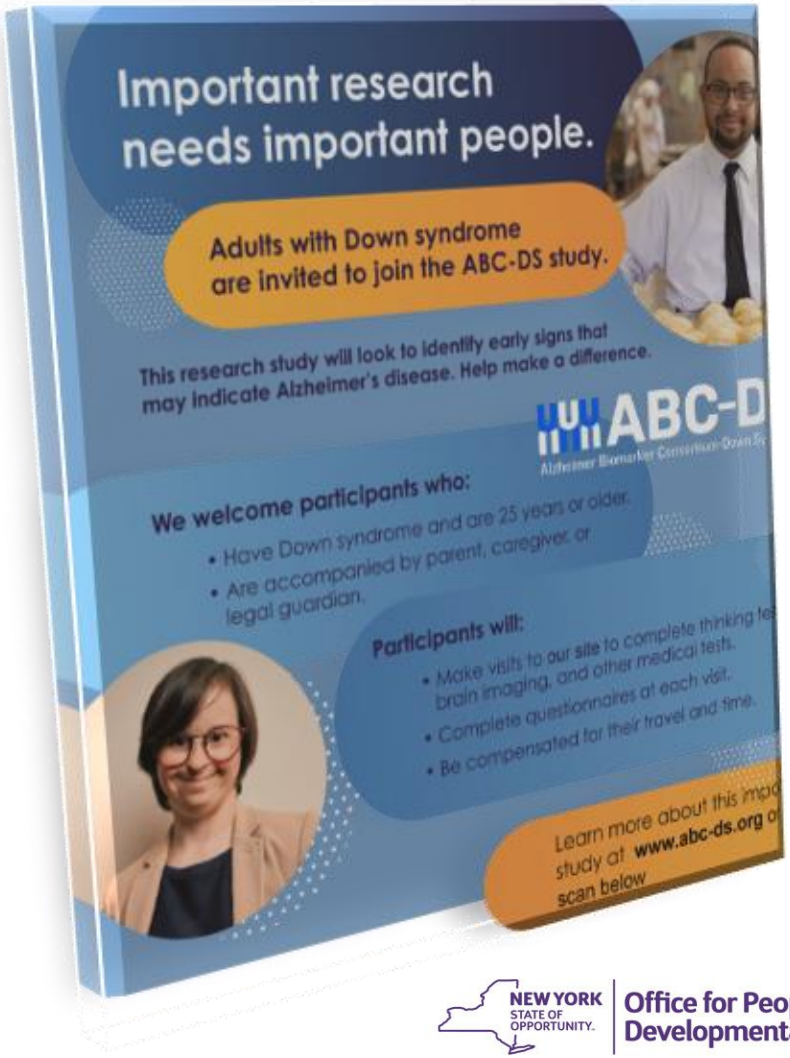
Recruitment Inclusion Criteria

- Age 25 years and older
- Down syndrome (including mosaicism and partial trisomy)
- No diagnosis of dementia
- Mental age ≥ 36 months
- Able to participate in cognitive testing and blood draws



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Assessments:

Performed every 16-18 months

- Medical history & clinical record review
- Caregiver measures of adaptive and behavioral functioning, neuropsychiatric and AD concerns
- Direct assessment of select cognitive functions & physical abilities

Assessments:

- Collection of blood samples for genetics, lipidomics and proteomics analyses
- Physical & neurological exam
- Neuroimaging biomarkers (MRI & Amyloid, Tau and FDG-PET scans)

- Lumbar Puncture for the collection of cerebral spinal fluid (CSF)
- Brain donation program

Our Neurocognitive Test Battery Assess:

- **Behavior**
  - Mood
  - Attention
  - Activity level
- **Functional-adaptive skills**:
  - Social
  - Communication
  - Daily living skills
- **Psychosocial events**
  - Major life events
  - Bereavement
  - Trauma

ABC-DS Future Directions

- Increase enrollment of participants with Down syndrome to ~700
- Increase the number of participants from underrepresented groups
- Examine additional biomarkers (e.g., gait, pTau-217)
- Make data available to outside researchers
- Prepare for prevention trials

Clinical Trials designed to address DS-AD

ABATE study, sponsored by AC Immune (ACI-24.060), is using a vaccine to train the immune system to make its own antibodies against amyloid plaques. Also designed to prevent amyloid in the brain.

ALADDIN study (Amyloid lowering for Alzheimer's in Down Syndrome with Donanemab Investigation), sponsored by Eli Lilly using an FDA-approved antibody therapy for Alzheimer's to clear amyloid plaques from the brains of people with Down syndrome.

Investing the safety and efficacy of donanemab, an anti-amyloid immunotherapy.

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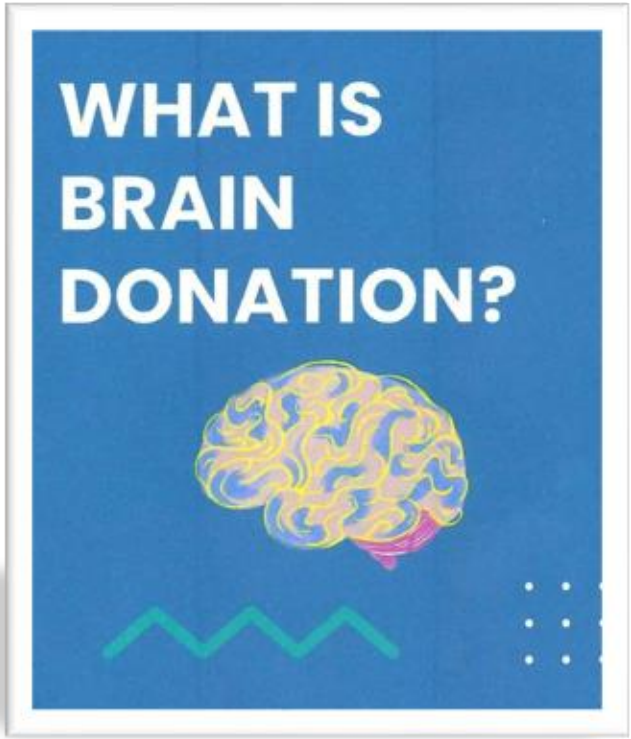
Brain Donation Program



- A medical procedure that takes place after someone dies.
- The brain is carefully removed and preserved for ongoing and future medical research.
- Brain donation is the only way to be sure that an individual had AD.

Thank you!

- Our participants & their families over the last 35+ years (~700)
- Agencies (100+) serving the needs of individuals with intellectual and developmental disabilities

- NIA, NIH and NICHD (U01AG051406; U01AG051412; U19AG068054)
- The New York State Office for People with Developmental Disabilities

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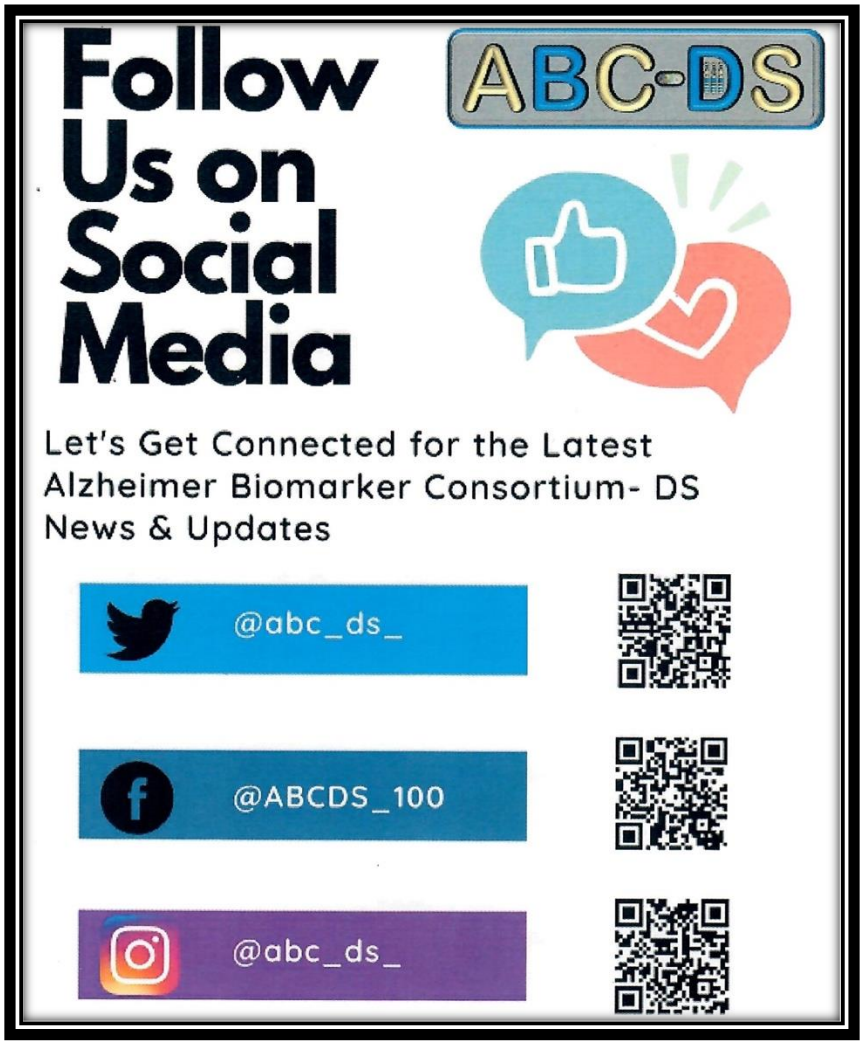

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