Alzheimer's disease in people with Down syndrome: What we know and what we can do about it

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- NIH Grants: R01AG073979; R33AG066543; U19AG068054
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- Consultant to AC Immune and Ionis
- Data Safety Monitoring Board/Scientific Advisory Board for Alzheon, Aptah Bio, Biohaven, Embic, Keystone Bio and Positrigo.

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Overview

- Why are people with DS at such high-risk for developing AD?
- How does AD present in people with DS?
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- Are there any new treatments for AD in people with DS?

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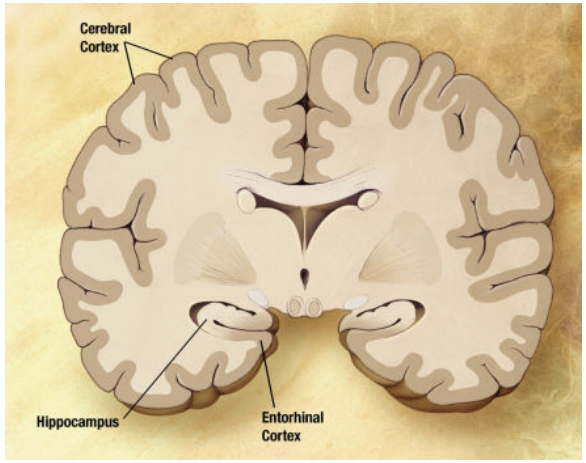
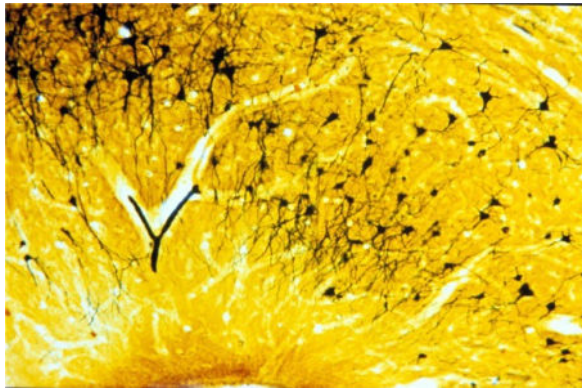
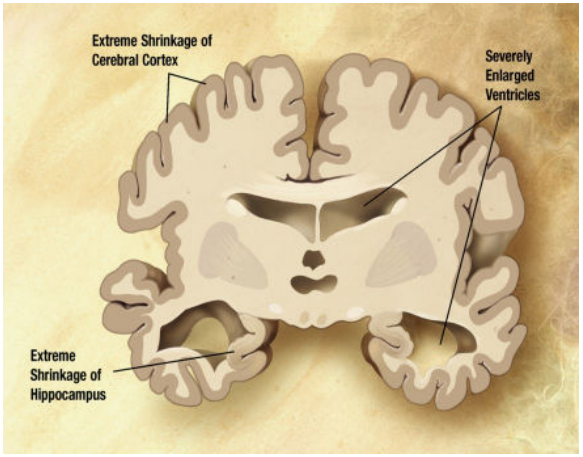
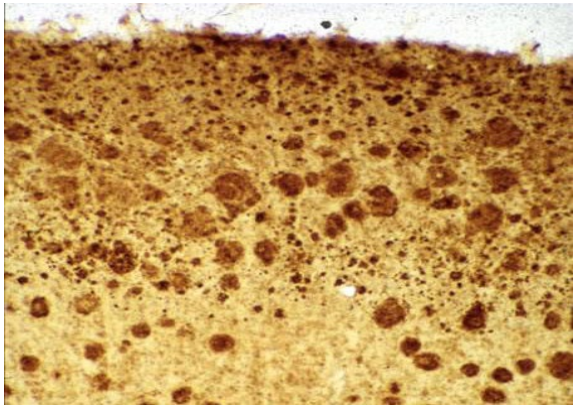
Healthy Brain





AD Brain





Dementia – '*De*' '*Mentis*' = 'without' 'thought'
Alois Alzheimer – Plaques, tangles and neurodegeneration
Glenner and Wong 1984

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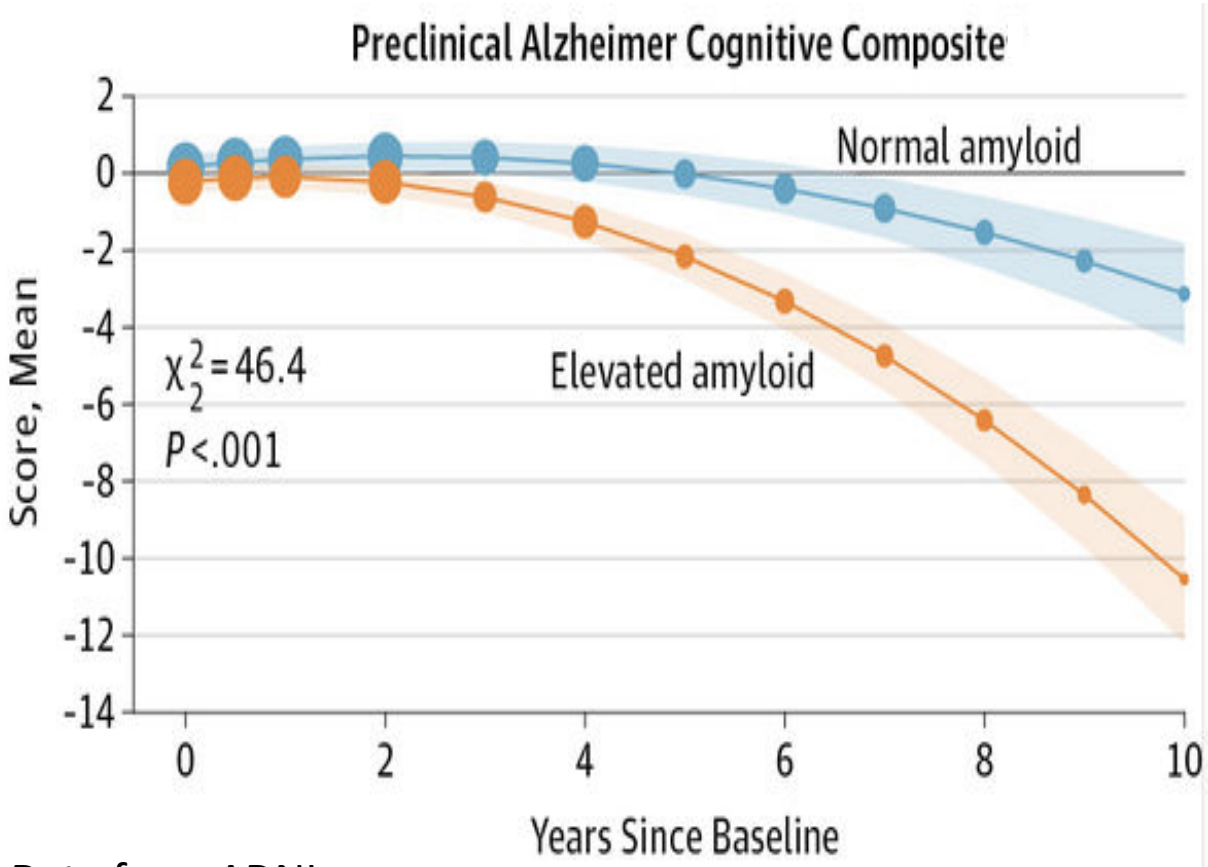
Amyloid and Alzheimer's Disease



Donahue et al, 2018

Data from ADNI

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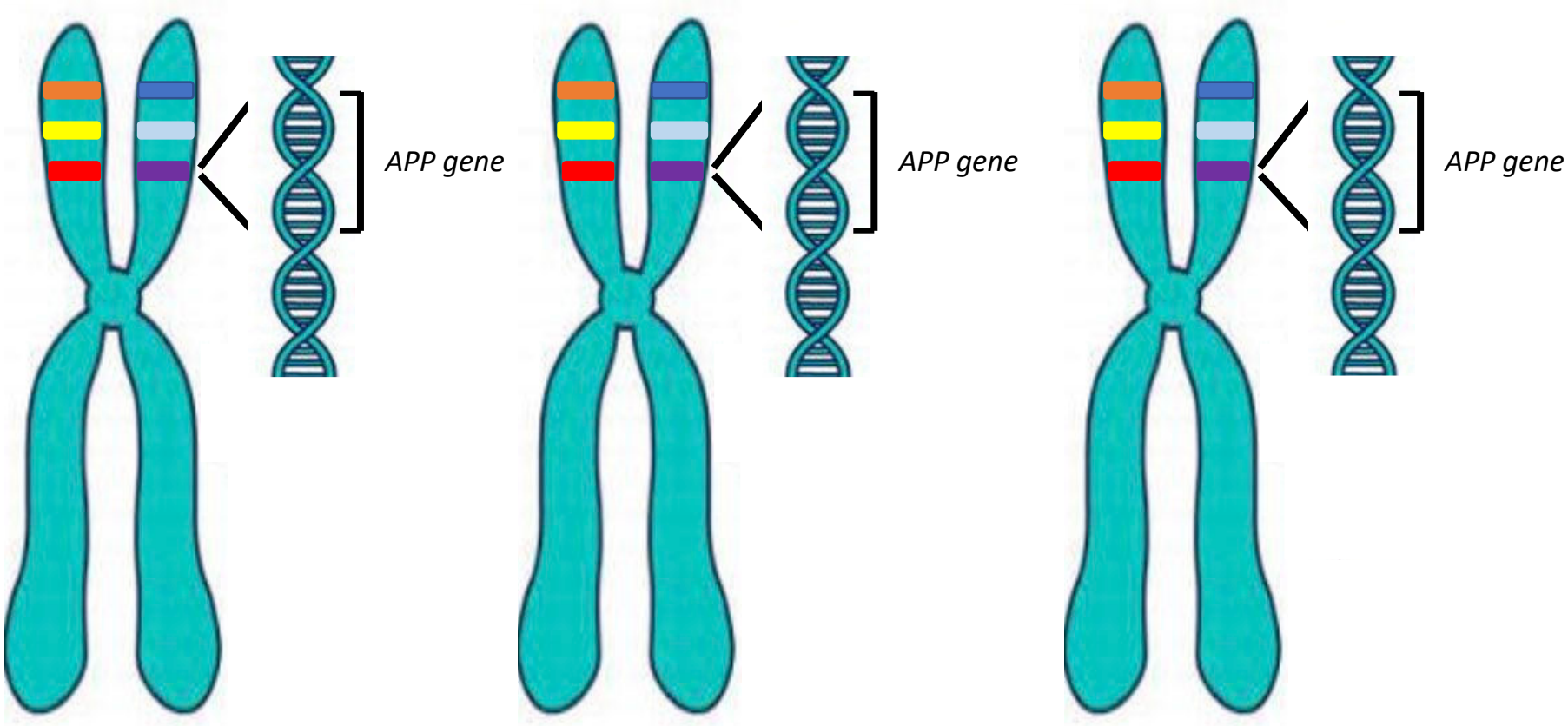
What is the genetic basis of AD in people with DS?



Chromosome 21

Chromosome 21

Extra Copy of Chromosome 21

Trisomy 21

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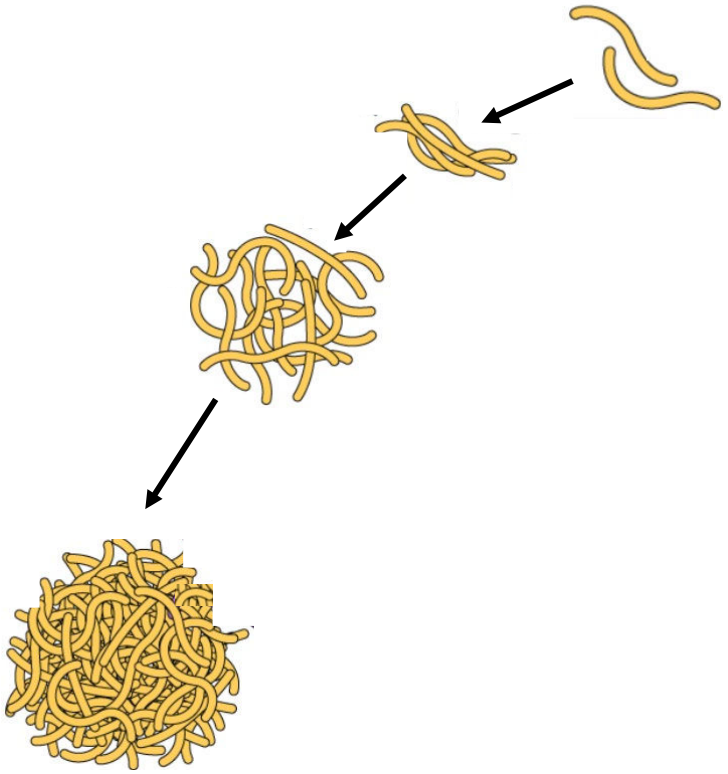
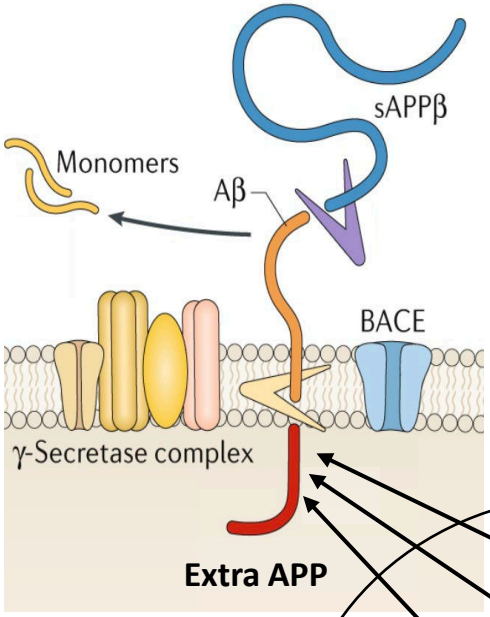
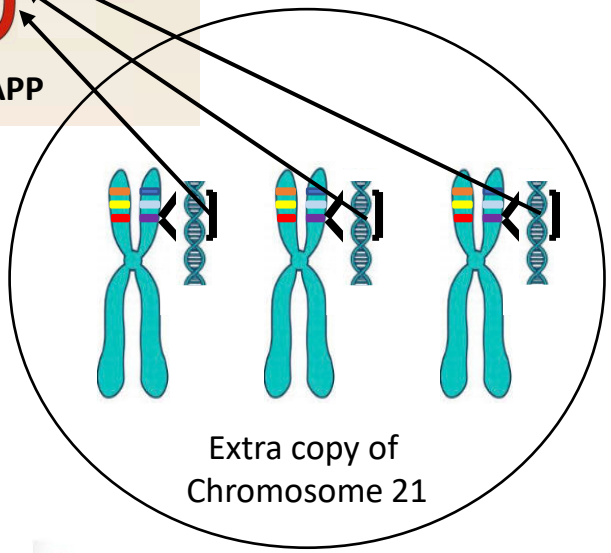


Fibrillar Amyloid plaques





Extra copy of Chromosome 21

APP duplication is basis for AD in DS

Partial trisomy
APP Dup mutation
Protective mutation

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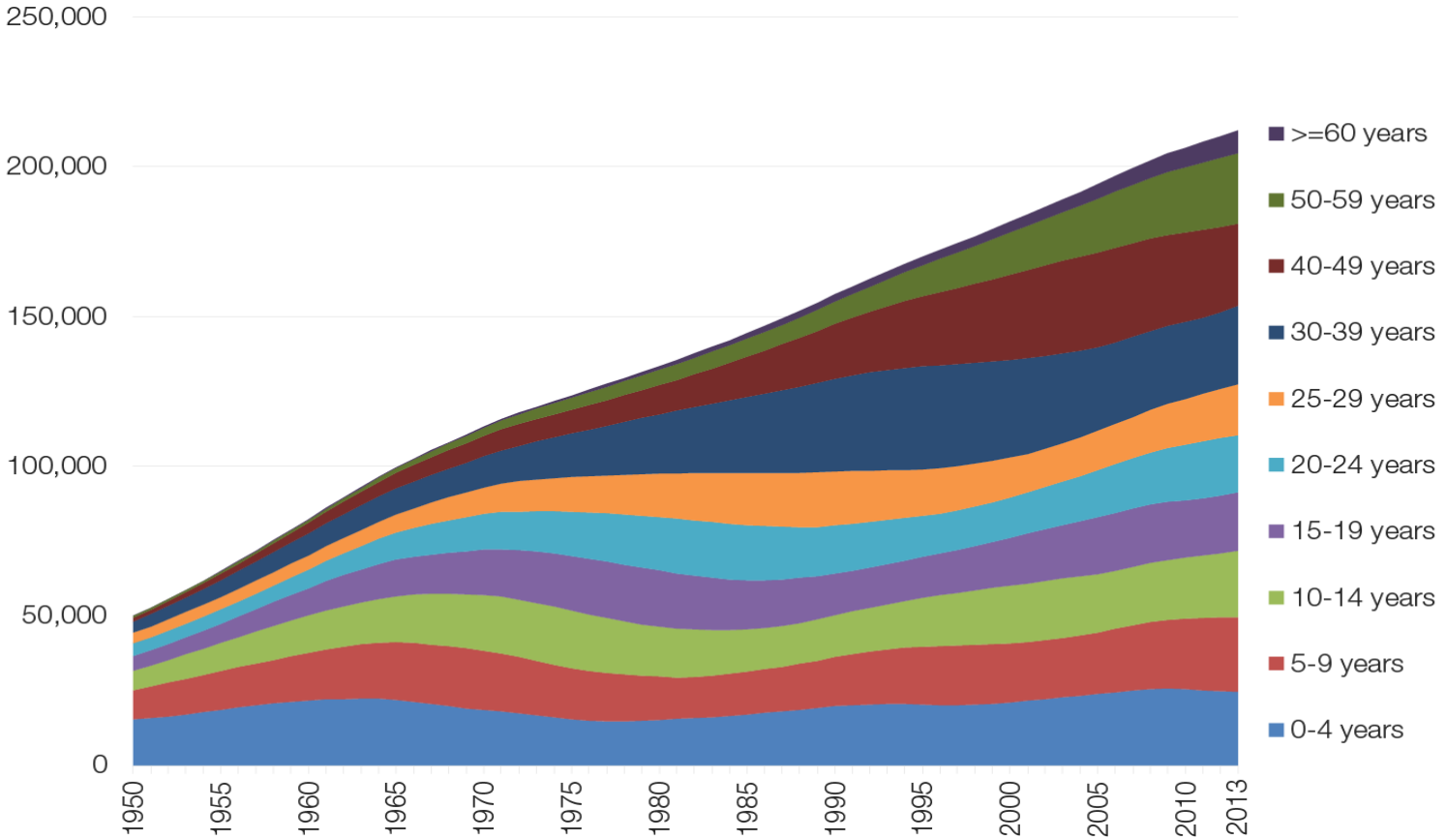
Population of People with DS in the USA



Li et al, 2013

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Life Expectancy

- 25 yrs in 1983
- 49 yrs in 1997
- 61 yrs in 2005

44% live to > 60 years
14% > 68 years

The most common causes of death in adults with DS over age 35 years are #1: Alzheimer's disease, #2: Pneumonia, #3: Cancer and leukemia, #4:congenital circulatory defects

Day et al, 2005

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Signs of possible dementia in a person with DS

- Memory loss
- Social withdrawal
- Disorientation
- Loss of daily living skills
- Changes in personality
- Development of seizures
- Change in sleep patterns
- Major weight change
- Aggressive behavior
- Loss of speech

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Differential Diagnosis of Dementia

- Depression, Anxiety, Psychosis
- Medical disorders e.g. hypothyroidism
- Sensory problems e.g. cataracts and otosclerosis
- Medication: Polypharmacy

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Self-Talk

- Common, developmentally appropriate, important coping tool. Imaginary friends common.
- Self-talk is not only “normal” but also useful. Essential role in cognitive development and to coordinate actions.
- Self-talk allows adults with DS to problem-solve, to vent their feelings, and to process the events of their daily lives.
- The amount and intensity of the self-talk reflects the number and emotional intensity of the daily life events experienced
- A dramatic change in self-talk may indicate a mental health or situational problem.

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Making the diagnosis

- Assess cognition and functioning by the age of 40 and then follow-up with annual reassessments, if decline is evident conduct a medical work-up.
- Screening tools such as www.the-ntg.org/ntg-edsd
- Labs (B12, TSH)
- Neurology Consultation
- Brain Imaging (MRI or CT)
- *Under age 40, consider Down Syndrome Regression Disorder (DSRD) or alternative diagnosis

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Labs and Consults

- Annual thyroid screening (TSH and T4).
- Ophthalmologic evaluation every two years (looking especially for keratoconus and cataracts).
- Fasting glucose, B12 and lipid profile
- Baseline cognitive testing

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Who makes the diagnosis?

- Primary Care MDs don't feel confident
- Psychiatrists and Neurologists don't often specialize in DS
- Pediatric DS clinics do not usually follow patients beyond age 18 years
- Often seems to be family member, support worker, case manager or manager of group home

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And how?

- Informant information: caregivers, family
- Physical and Cognitive evaluation compared to baseline
- Labs, neuroimaging

- Global Down Syndrome Foundation Listing of Down Syndrome Medical Care Centers in the U.S

https://www.globaldownsyndrome.org/research-medical-care/medical-care-providers/

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Why make the diagnosis?

For all the usual reasons

- Education of person, family and support workers
- To access additional support/care
- Planning/Residence
- Medication

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Down Syndrome Biomarker Initiative (DSBI)

- Launched in 2013; funded by Janssen (n=12)
- First multi-modal biomarker study of AD in persons with DS
- Cognition, MRI, PET (Amyloid, Tau and FDG); fluid biomarkers.
- Pilot study to evaluate feasibility, scalability of studying AD biomarkers in DS
- Results show that biomarkers of AD in people with DS are nearly identical to other forms of AD including autosomal dominant and sporadic forms
- All 12 participants completed the entire 3-year study

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Alzheimer's Biomarker Consortium – Down Syndrome (ABC-DS)

- Launched in 2015; funded by NIA.
- MPIs- Ben Handen, Liz Head, Brad Christian and Mark Mapstone
- 550 participants with DS >25 yo and 50 sibling controls across 8 sites.
- Cognition, MRI, PET (Amyloid, Tau and FDG); fluid biomarkers
- Visits every 16 months
- All data being made available to researchers on the USC LONI Image and Data Sharing platform
- >100 papers published so far
- ABC-DS is revolutionizing our understanding of AD in DS

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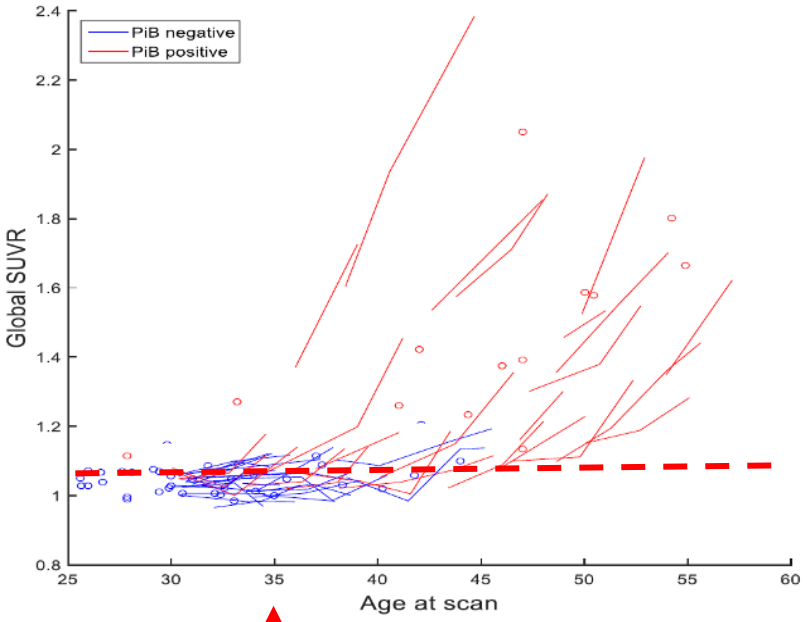
Brain Amyloid in People with Down syndrome

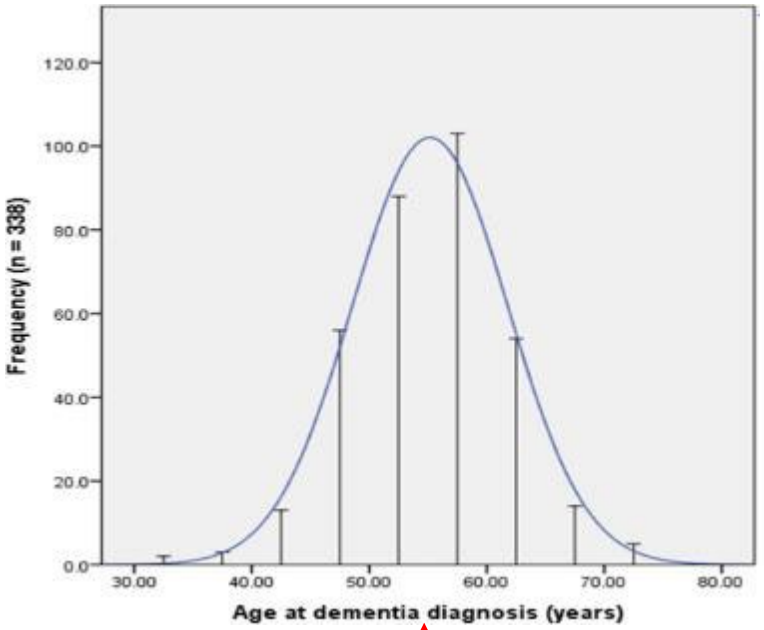
Longitudinal Amyloid PET Imaging



Lao et al, 2018

Amyloid PET positive

95% Lifetime Risk for AD Dementia



Strydom et al, 2017

Dementia diagnosis

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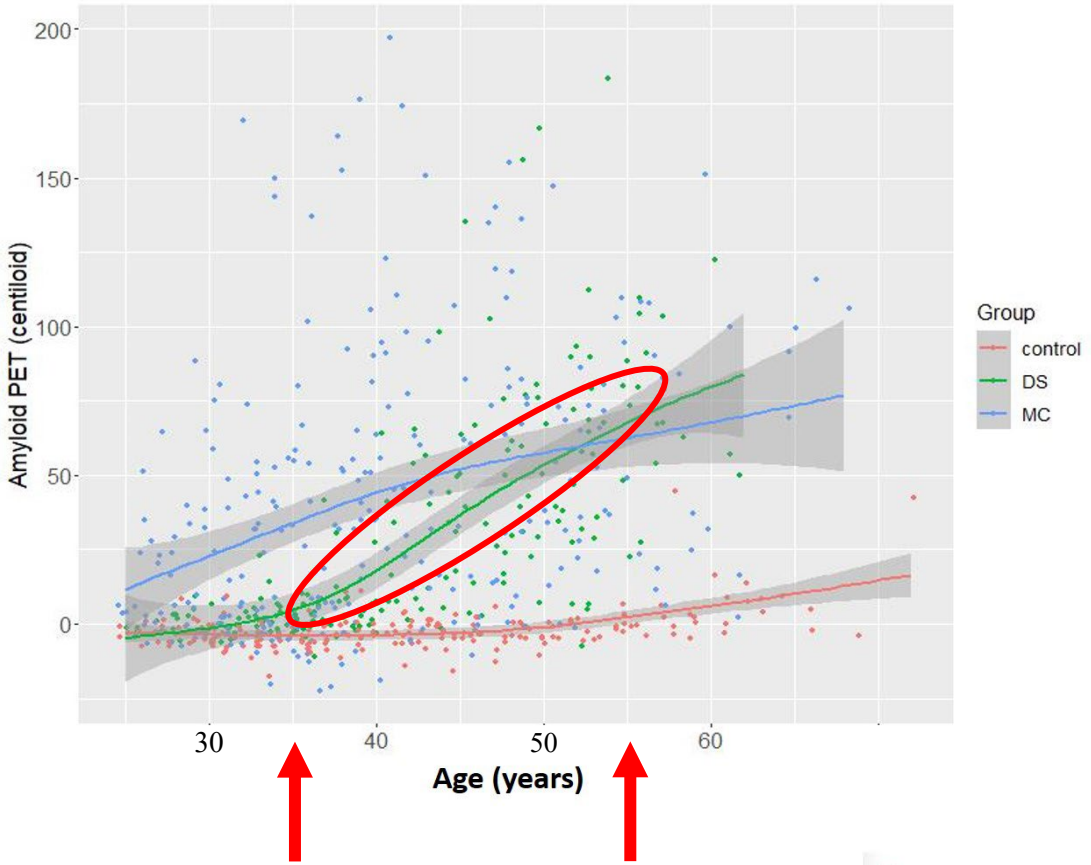
Conversion to Amyloid PET Positivity DSAD versus ADAD



Boerwinkle et al, 2023

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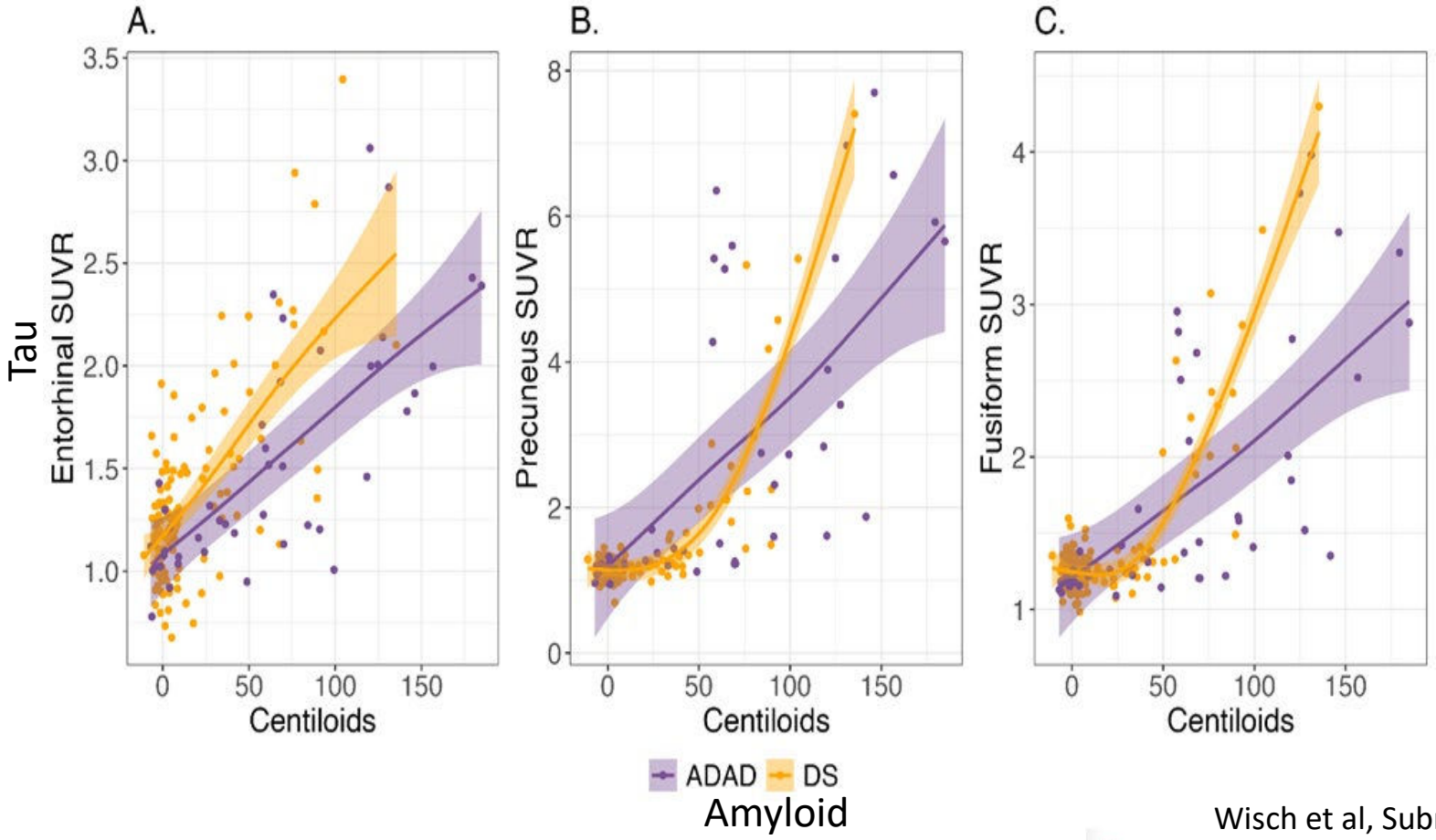
Tau PET burden with respect to cortical amyloid burden in DS



Wisch et al, Submitted

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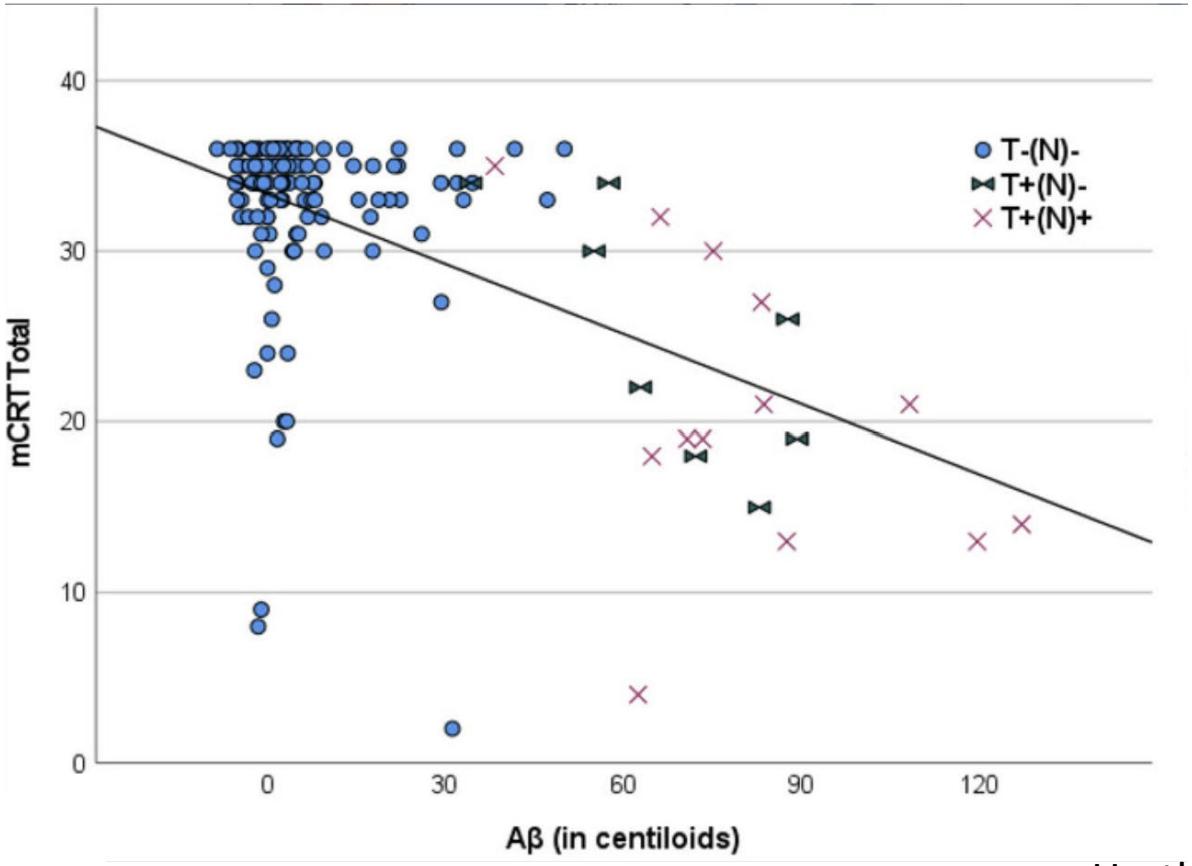
Association between A/T/N biomarkers and the Cued Recall Test



Hartley et al, 2023

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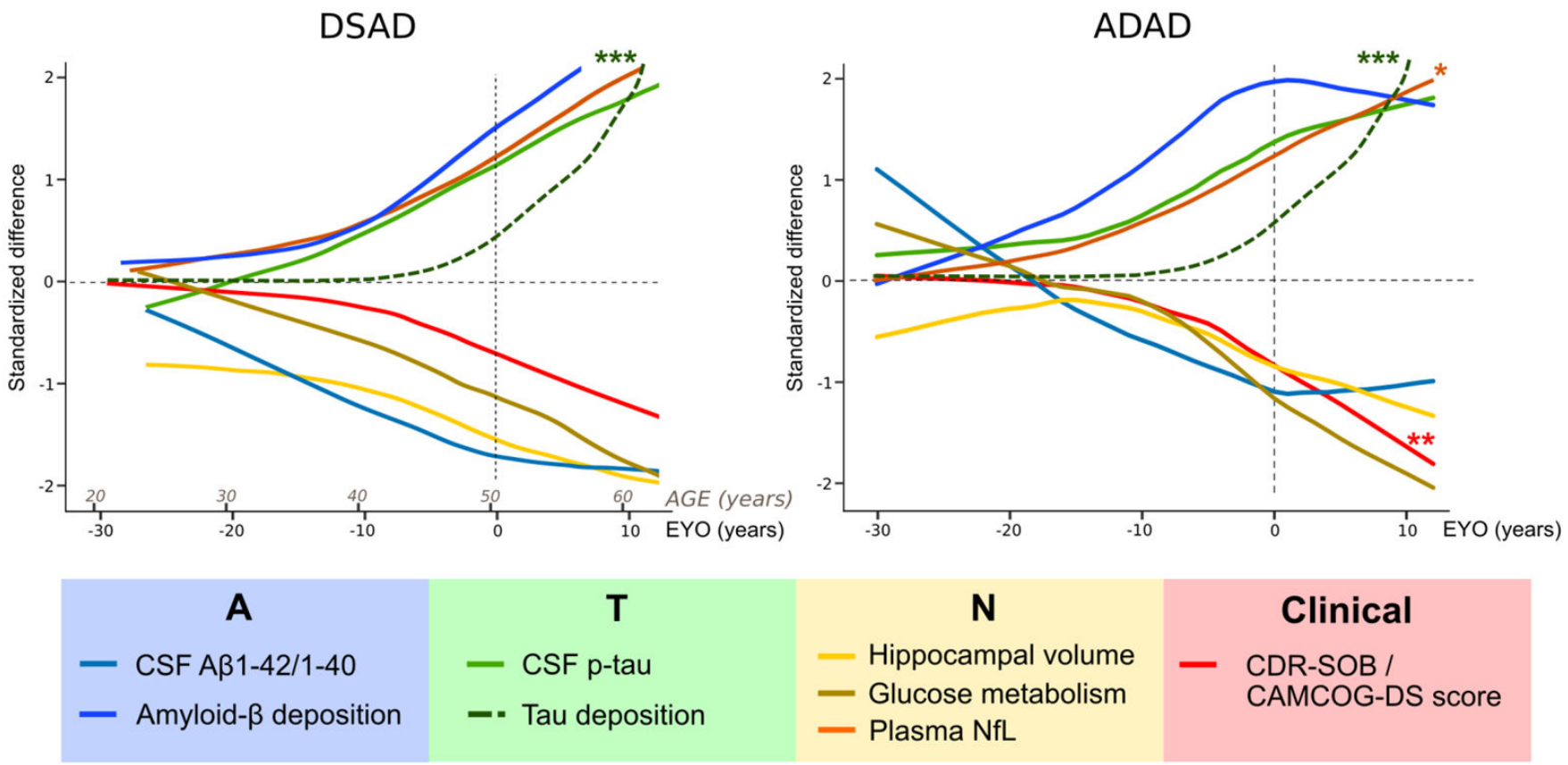
DSAD and ADAD



Fortea et al. Lancet Neurology 2021

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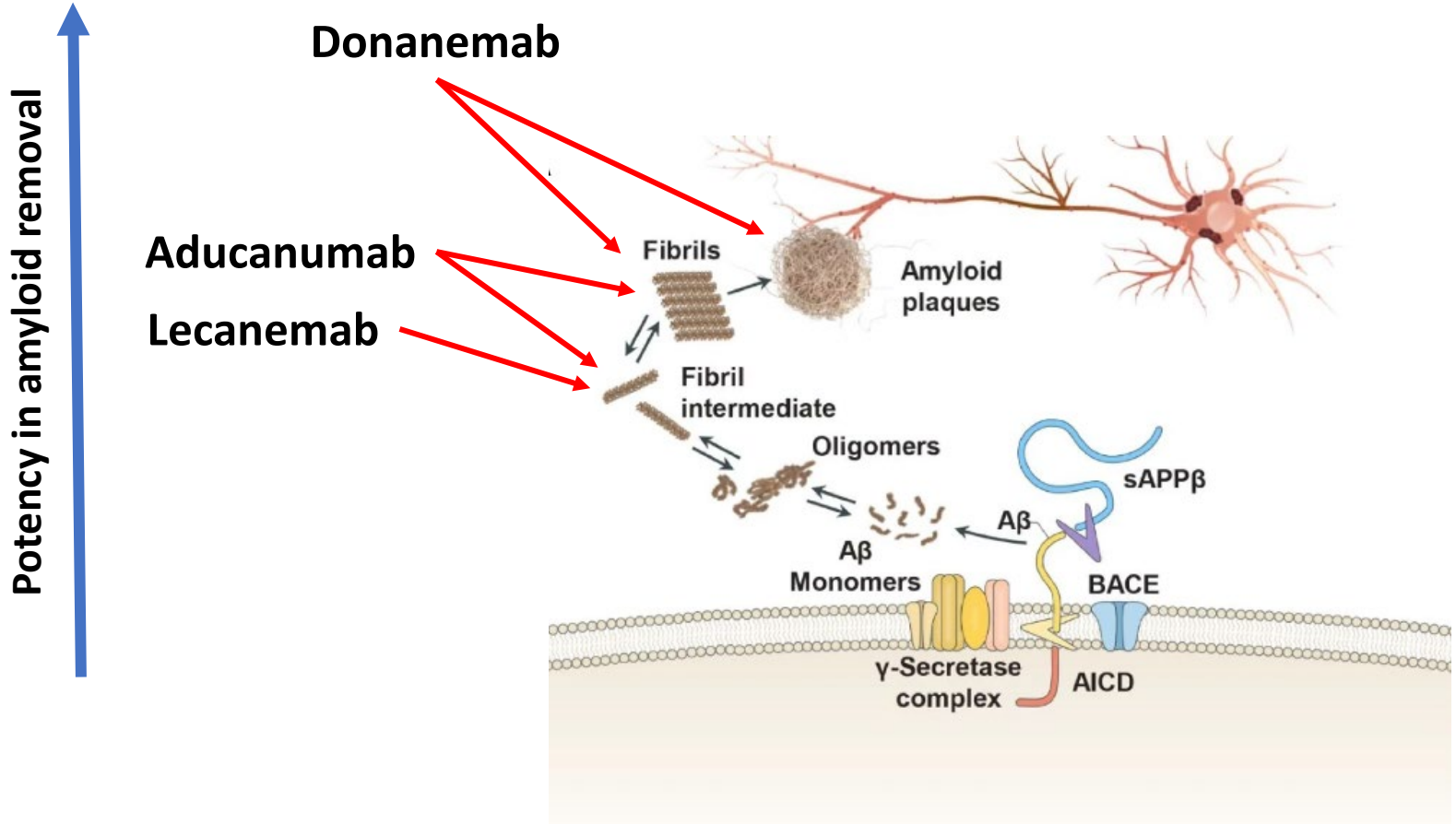
Amyloid-Lowering Monoclonal Antibodies



36% reduction in cognitive decline. 40% ARIA mostly asymp.

Two are FDA approved, 3rd expected in 2024 for Early AD

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Clinical Trials targeting amyloid in DS

Compound	Mechanism of Action	Phase	Status
Scyllo-inositol	Amyloid binding	2a (PK/PD)	Rafii et al, 2017
ACI-24	Anti-amyloid vaccine beta-amyloid	1b	Rafii et al, 2022
ACI-24.060	Anti-amyloid vaccine beta-amyloid	1b/2	ABATE trial - Recruiting

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ACTC-DS: A Clinical Trials Platform to Prevent Alzheimer's Disease in Down Syndrome

20 sites with unparalleled experience in DSAD.

Funded by the NIH INCLUDE Initiative.

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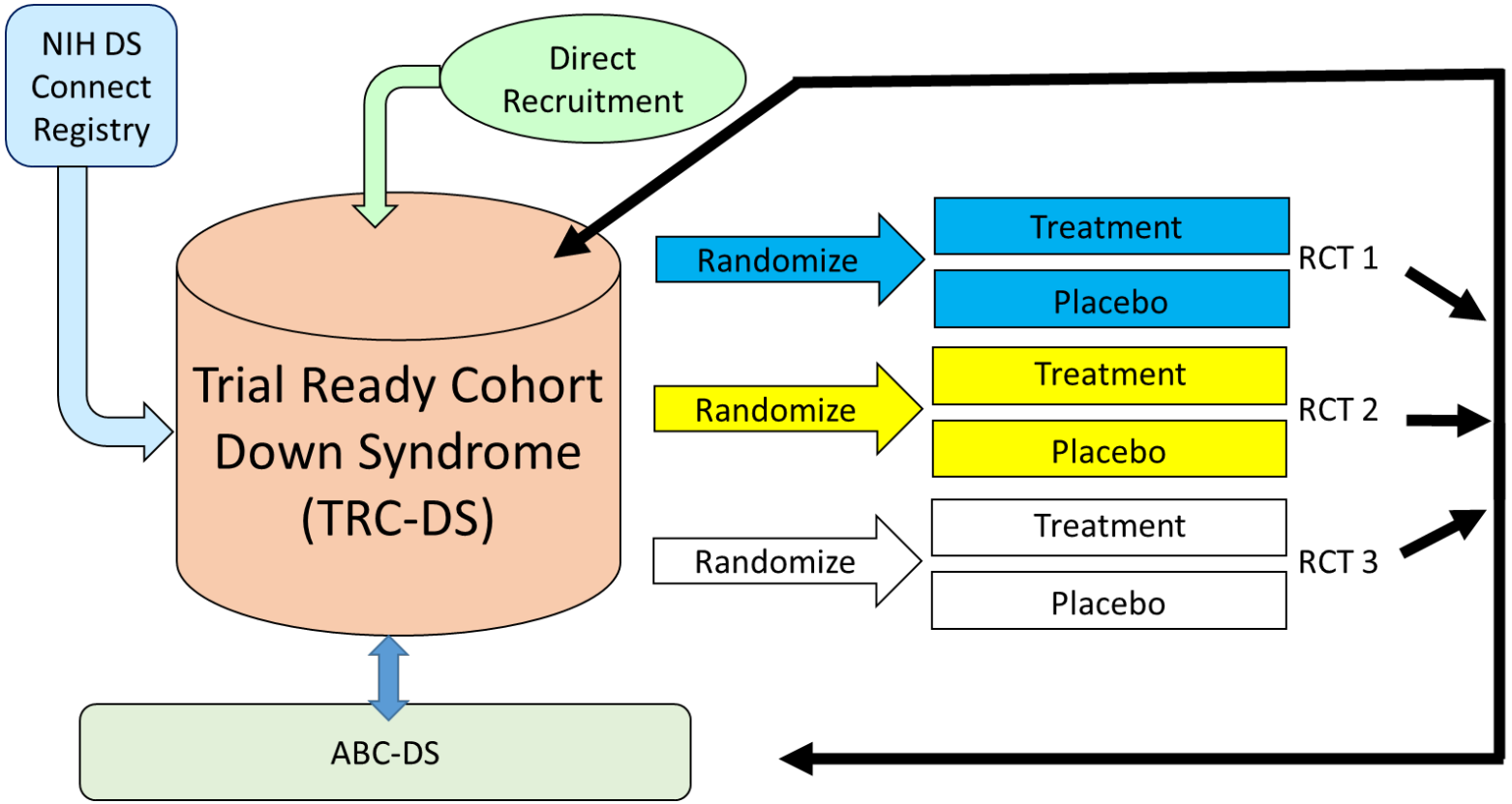
TRC-DS and Clinical Trials to Prevent AD in DS



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ACTC-DS Affiliated Clinical Trials

- ABATE Trial **www.abate-study.com**
- Participants 35-50 years old with DS
- The study is specifically designed for people with DS and is testing an investigational vaccine for Alzheimer's disease in people with Down syndrome.
- We want to see:
  - If the vaccine is safe
  - How the vaccine works inside the body
  - If it helps get rid of amyloid buildups
  - If it slows down memory loss and thinking problems

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Summary

- People with DS develop a genetic form of Alzheimer's disease
- Treatments are urgently needed for the DS population
- Studies show that DSAD is nearly identical to ADAD
- FDA approved treatments of Early AD are now available. Blood tests for elevated brain amyloid are now available and will soon be covered by CMS/insurance.
- Additional clinical trials designed specifically for people with DS will be launching in 2024.
- Please check the ACTC-DS website for updates and site locations:

www.actc-ds.org

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ACTC Leadership

Laurie Ryan, Paul Aisen, Reisa Sperling, Ron Petersen

Unit Leads

Administration | Pizzola
Biomarkers | Rissman
Biostatistics | Raman & Donohue
Clinical Outcomes Instr. | Rentz & Petersen
IDEA-CT | Raman & Sperling
Informatics | Jimenez-Maggiora
Medical Safety | Rafii
MRI | Jack & Weiner
Neuropathology | Frosch & Jicha
PET | Johnson
RER | Raman & Grill

Key Committees

Internal Ethics | Karlawish & Grill
Participant Advisory Board | Walter & Morales
Site Metrics and Budgets | Craft & Geldmacher

NIA Cooperative Agreement:
U24AG057437

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Sarah Savoia
Sean Kenelley

Thank you!

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