

The Convergence of Down Syndrome and Alzheimer's Disease — Scientific and Ethical Imperatives

**NAPA Advisory Council Meeting
August 3, 2026**

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Disclosures

- **NIH Grants:** R01AG073979; R61AG066543; R33AG066543; U19AG068054
- **Research Contracts:** Eisai and Eli Lilly
- **Data Safety Monitoring Boards/Scientific Advisory Boards:** AC Immune, Aerska, Alzheon, Alnylam, Ionis, Neusignal, Otsuka, Positron, Recall Therapeutics, Sumitomo Pharmaceuticals.
- **Philanthropic Support:** Linda and Mike Mussalem Foundation, John and Tami Marrick Foundation, Goldman Sachs Foundation

Who We Are and Our Work in Down Syndrome and Alzheimer's

The Epstein Family Alzheimer's Therapeutics Research Institute (ATRI)
is part of the **Keck School of Medicine of USC**:

- A team of **8 faculty and 200+ staff** focused on Alzheimer's clinical trials
- We lead and support clinical trials across **145+ research sites worldwide**
- Coordinating center for the **NIA Alzheimer's Clinical Trials Consortium (ACTC)**

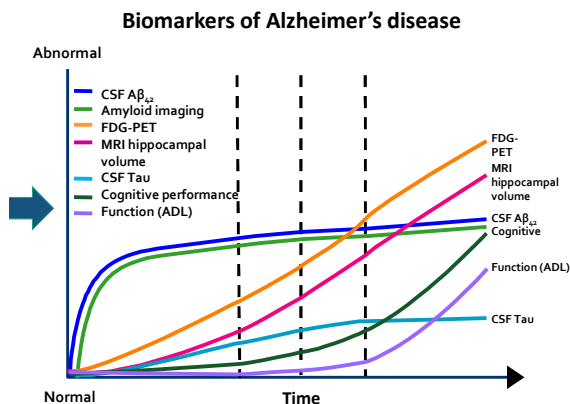
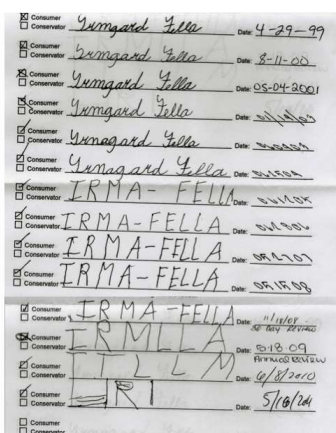
Our Mission:

To develop safe and effective treatments for
Alzheimer's disease, including for people with Down
syndrome

Overview

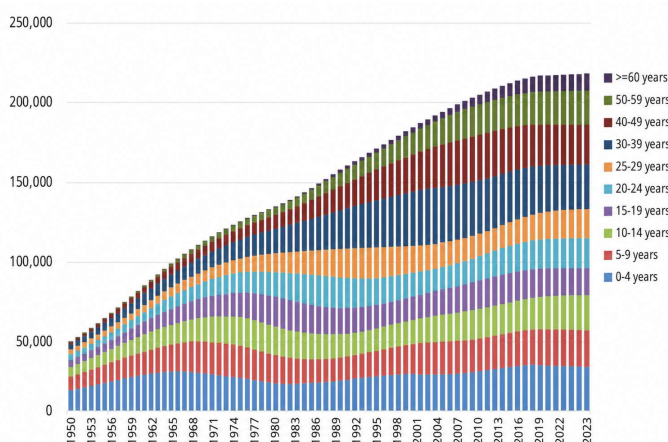
- Why are people with Down syndrome at such high-risk for developing AD?
- Is AD in people with Down syndrome the same as other forms of AD?
- Are there any new treatments for AD in people with DS?

The Alzheimer's Continuum in People with Down syndrome



With permission

Population of People with DS in the USA

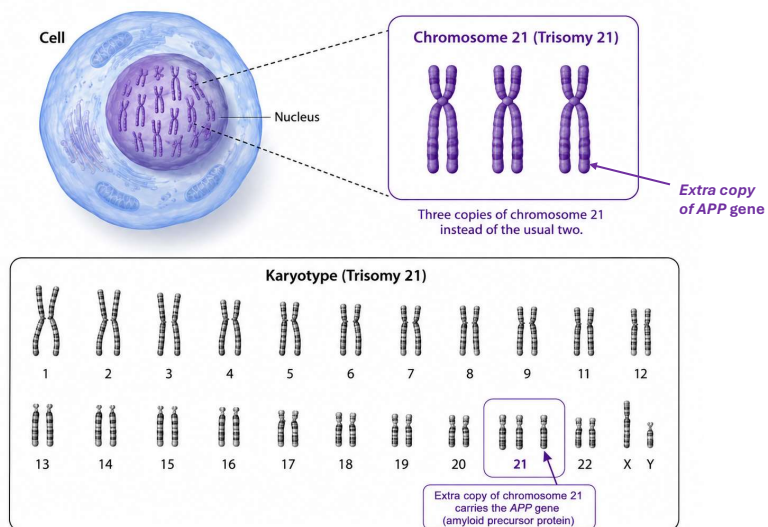


1. People with DS are living longer.
2. Life expectancy has plateaued
3. People with DS have a 95% lifetime risk of dementia.
4. Average age of dementia is 55.
5. AD is the leading cause of death in adults with DS.

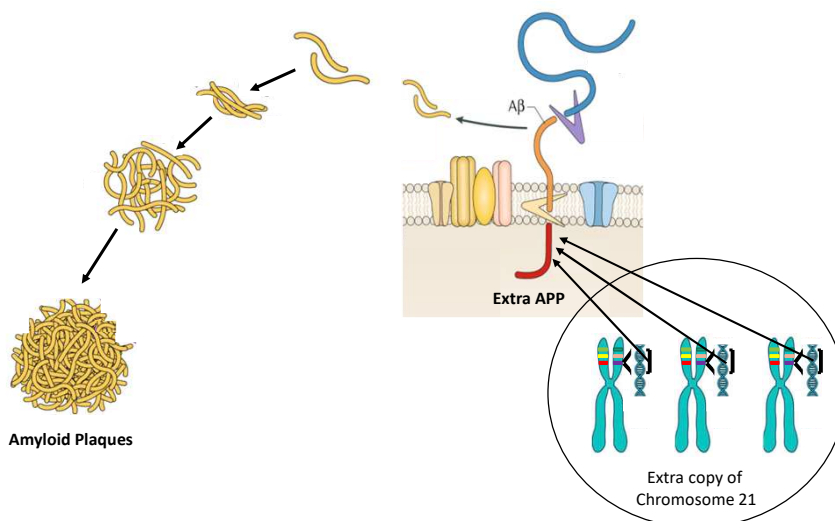
Adapted from De Graaf et al. 2020

What is the Genetic Basis of Alzheimer's in People with DS?

Trisomy 21: Cell with an Extra Copy of Chromosome 21



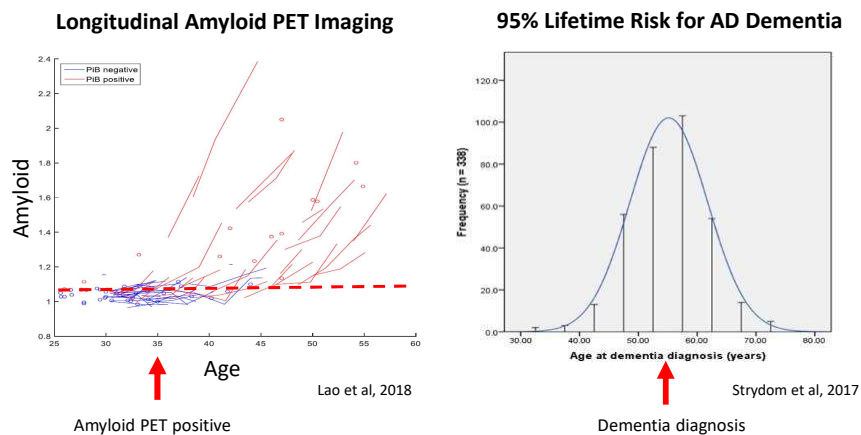
Where do Amyloid Plaques come from in DS?



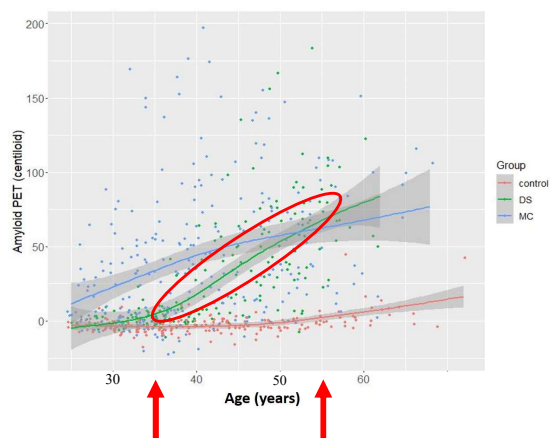
Amyloid plaques define AD

APP duplication is basis for AD in people with DS. Disomy for APP— no AD

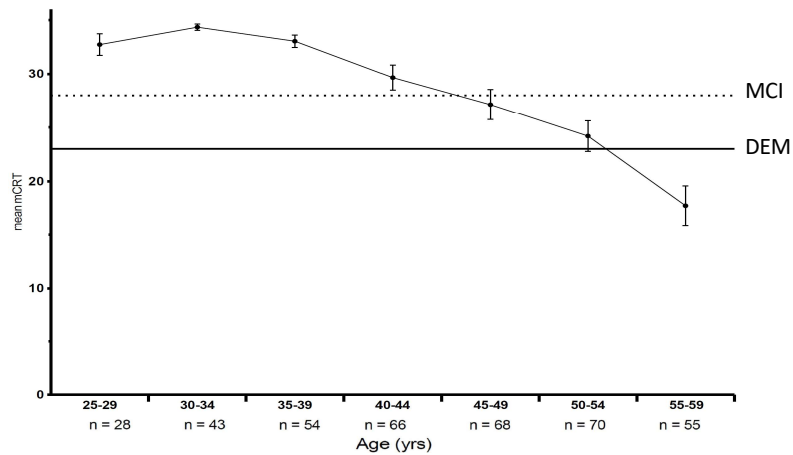
Brain Amyloid in People with Down syndrome



Conversion to Amyloid PET Positivity DSAD versus ADAD

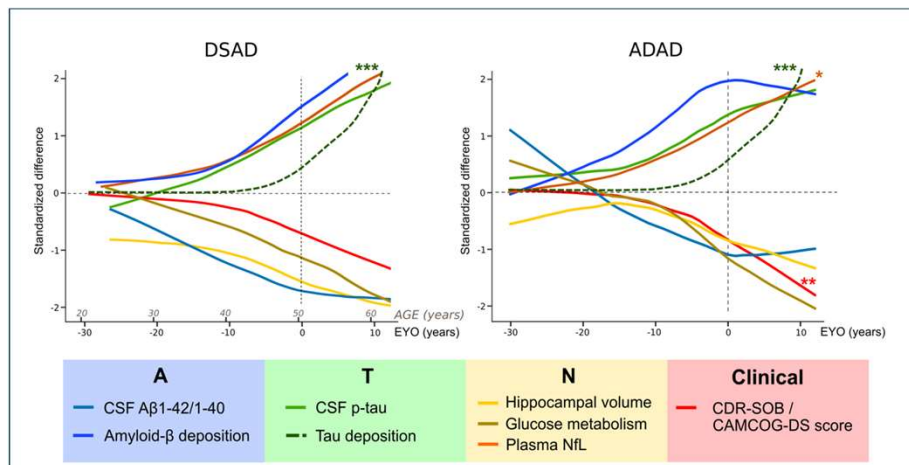


Mean modified Cued Recall Test (mCRT) scores by age



Krasny et al, 2024

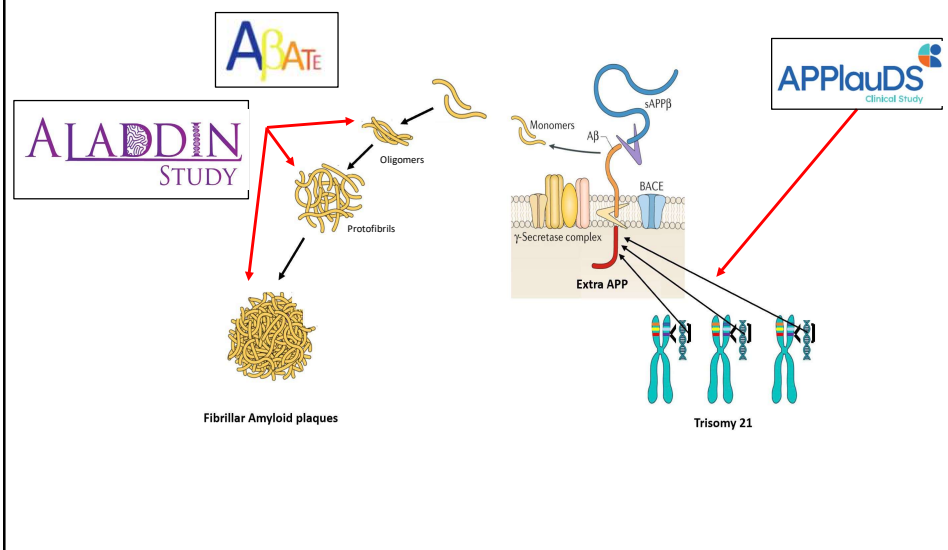
Genetically Determined Alzheimer's disease



Forte et al. Lancet Neurology 2021



Therapeutic Targets of Clinical Trials



ACTC-DS Affiliated Clinical Trial: ABATE

- Collaboration with AC Immune
- Active immunotherapy (ACI24.060) targeting amyloid
- Phase 2, randomized, double-blind controlled trial
- N=24
- Participants 35-50 years old with brain amyloid
- Top line results 2027

ABATE

ACTC-DS Affiliated Clinical Trial: ALADDIN

- Collaboration with Eli Lilly
- Passive immunotherapy (donanemab) targeting amyloid
- Phase 4, randomized, double-blind controlled trial
- N=60
- Participants 35-50 years old with brain amyloid
- Top line results 2027

**ACTC-DS Affiliated Clinical Trial: APPlauDS**

- Collaboration with Alnylam
- RNAi (mivelsiran) targeting APP
- Phase 2, randomized, double-blind controlled trial
- N=24
- Participants 40-55 years old with brain amyloid



Down Syndrome Research Partnership Board



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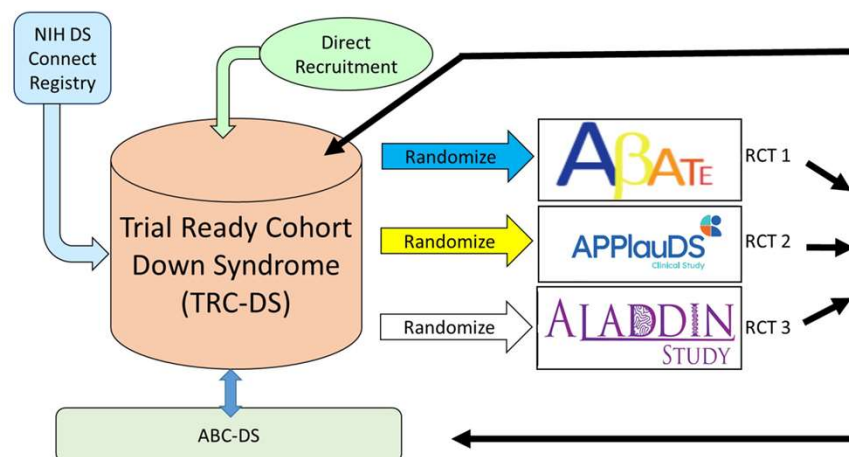
“Being brave, being seen, and having your voice heard”: Perspectives of self-advocates and families toward accessible and impactful research of Alzheimer's disease in down syndrome

[Sarah Walter](#) [Lauren Ptomey](#), [Elizabeth Head](#), [Ann Cohen](#), [Joseph Mike Briones](#), [Henry Shaw](#),
[Brandon Carter](#), [Jessica Kishner](#), [Willie Pestolesi](#), [Anthony Sciallo](#), [Katy Kolb Olmstead](#), [Aurelia Carter](#),
[Sara Kishner](#), [Amy Kolb Tucker](#), [Lissa Pestolesi](#), [Maria Briones](#), [Dana Sciallo](#), [Kay Sciallo](#), [Pam Shaw](#),
[Perry Chen](#), [Michael S. Rafii](#) ... See fewer authors ^

First published: 19 December 2025 | <https://doi.org/10.1002/alz.70999> | [VIEW METRICS](#)

Brain Health Report now used in all clinical trials to return results to participants with Down syndrome

Clinical Trials to Prevent AD in DS



Summary

- People with Down syndrome develop a genetic form of Alzheimer's disease
- Studies show that DSAD is essentially identical to other forms of AD
- ACTC-DS is providing the infrastructure to conduct specialized trials for people with DS
- Several clinical trials of disease-modifying treatments are now underway or planned in adults with DS
- Additional trials being planned including lifestyle modification and non-pharmacologic interventions

ACTC Leadership

Paul Aisen, Reisa Sperling, Ron Petersen,
Laurie Ryan

Unit Leads

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

Key Committees

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Participant Advisory Board | Walter & Morales
Site Metrics and Budgets | Craft & Geldmacher

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Paul Newhouse
Flo Lai
Diana Rosas
Sharon Krinsky-McHale
Sarah Savoia
Sean Kenelley
Matt Zammit



**Participants
with Down
syndrome and
their families!**

