GLOBAL
DOWN SYNDROME FOUNDATION®

Alzheimer's Disease in Down Syndrome
Understanding the Connection

Welcome Remarks from Michelle Sie Whitten

President & CEO, Global Down Syndrome Foundation

GLOBAL Webinar Series – Tuesday, September 14, 2021

Today's Speaker – Dr. Michael Rafii

- **Dr. Michael Rafii:**
  - Medical Director of the Alzheimer's Therapeutic Research Institute (ATRI)
  - Associate Professor of Neurology at the Keck School of Medicine of the University of Southern California

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Welcome Remarks from Frank Stephens

Actor, Author, Advocate, Quincy Jones Exceptional Advocacy Awardee
and Member of the Board of Directors of GLOBAL

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THANK YOU & WELCOME!

- THANK YOU to the Global Down Syndrome Foundation and to all the participants who are attending this session today! You are in for a treat!
- Welcome to Alzheimer's Disease in Down Syndrome - Understanding the Connection with Dr. Michael Rafii.
- My name is Frank Stephens and I am so pleased to be here representing the Global Down Syndrome Foundation - as their newest board member!
- I have been involved with GLOBAL for nearly ten years. I am so proud to have been apart of GLOBAL's first ever congressional hearing on Down syndrome research—Together we tripled the NIH Budget!

A Personal Reason Why Research is Important

- "**Global Therapeutic Leverage**"- people with Down syndrome can be the key to solid tumor cancers and Alzheimer's disease
- **This is very personal to me**, as I am well aware of the risk I have for this terrible disease and because my much-loved mother is fighting Alzheimer's as we speak.
- **Grateful for any small part I play in ending the scourge of Alzheimer's.**

Cornelia, John and Frank Stephens at GLOBAL's DC Gala

Keep a Few Things in Mind

- **We are people, not just test subjects.**
- **Include our role prominently in the published results**
  - It's accurate
  - Reminds society that we have value
  - Acknowledges our role in your funding
- **Stand with us when we need you**
  - Promote an up-to-date view of life with Down syndrome
  - No discrimination in medical care

NIH Director, Dr. Francis Collins and Frank Stephens

Without Further Ado…

- I am honored to present a speaker who needs no introduction—but that's my job!
- Today's webinar is on ***Alzheimer's Disease in Down Syndrome, Understanding the Connection***
- It is my pleasure to introduce today's speaker, Dr. Michael Rafii!

Alzheimer's Disease in Down Syndrome Understanding the Connection

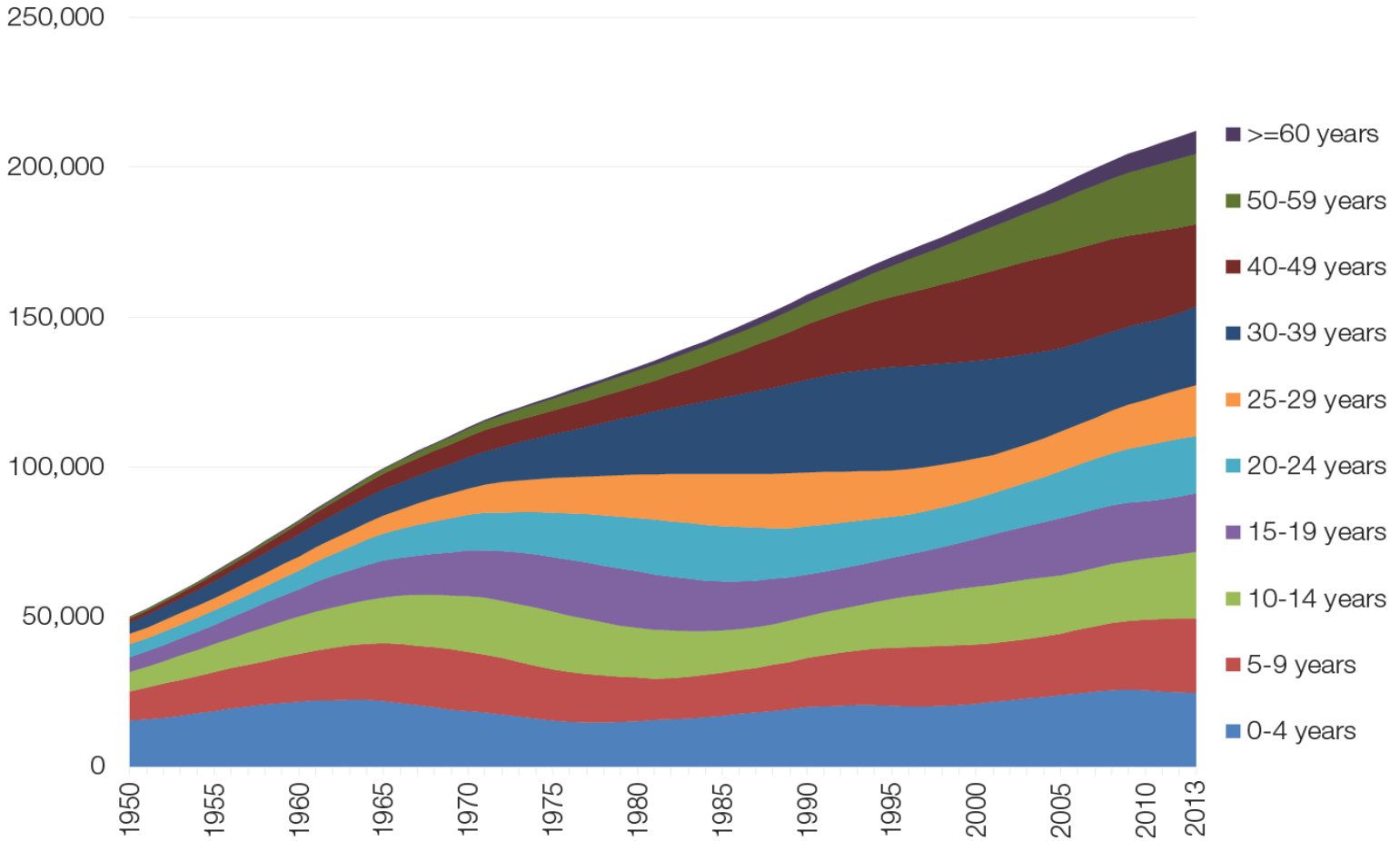
Michael S. Rafii, MD, PhD

Medical Director
Alzheimer's Therapeutic Research Institute
Associate Professor of Neurology
Keck School of Medicine of USC

DS Related Conditions

- Intellectual Disability
- Congenital Heart Disease
- Seizures
- Cataracts
- Hearing Loss
- Urinary Tract Issues
- Sleep Apnea
- Obesity
- Endocrine Disease
- Blood Disorders
- Respiratory Disease
- **Alzheimer's Disease**

Population of Persons with DS in the USA, 1950-2013



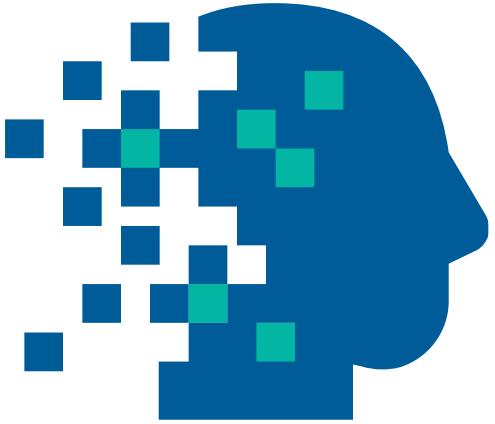
Li et al, 2013

Consequences of Increased Life-span

- More disorders of old age: mental and physical including dementia
- Aging parents no longer able to continue care at home
- Need residential options suitable for people with DS

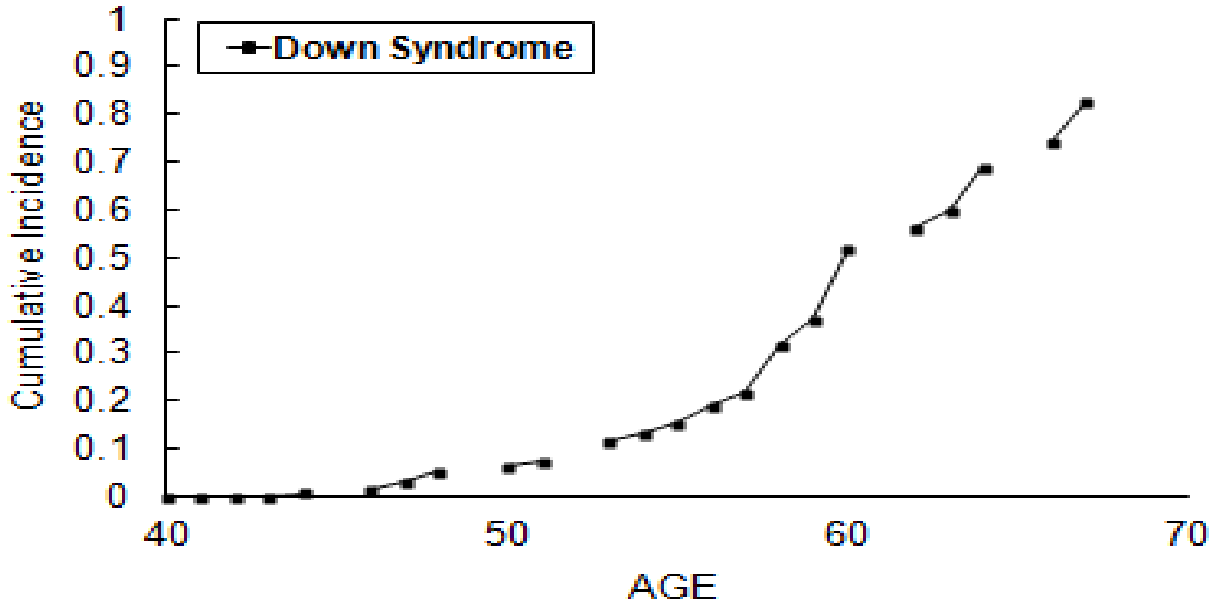
What is Alzheimer's Disease?

According to the National Institutes of Health:



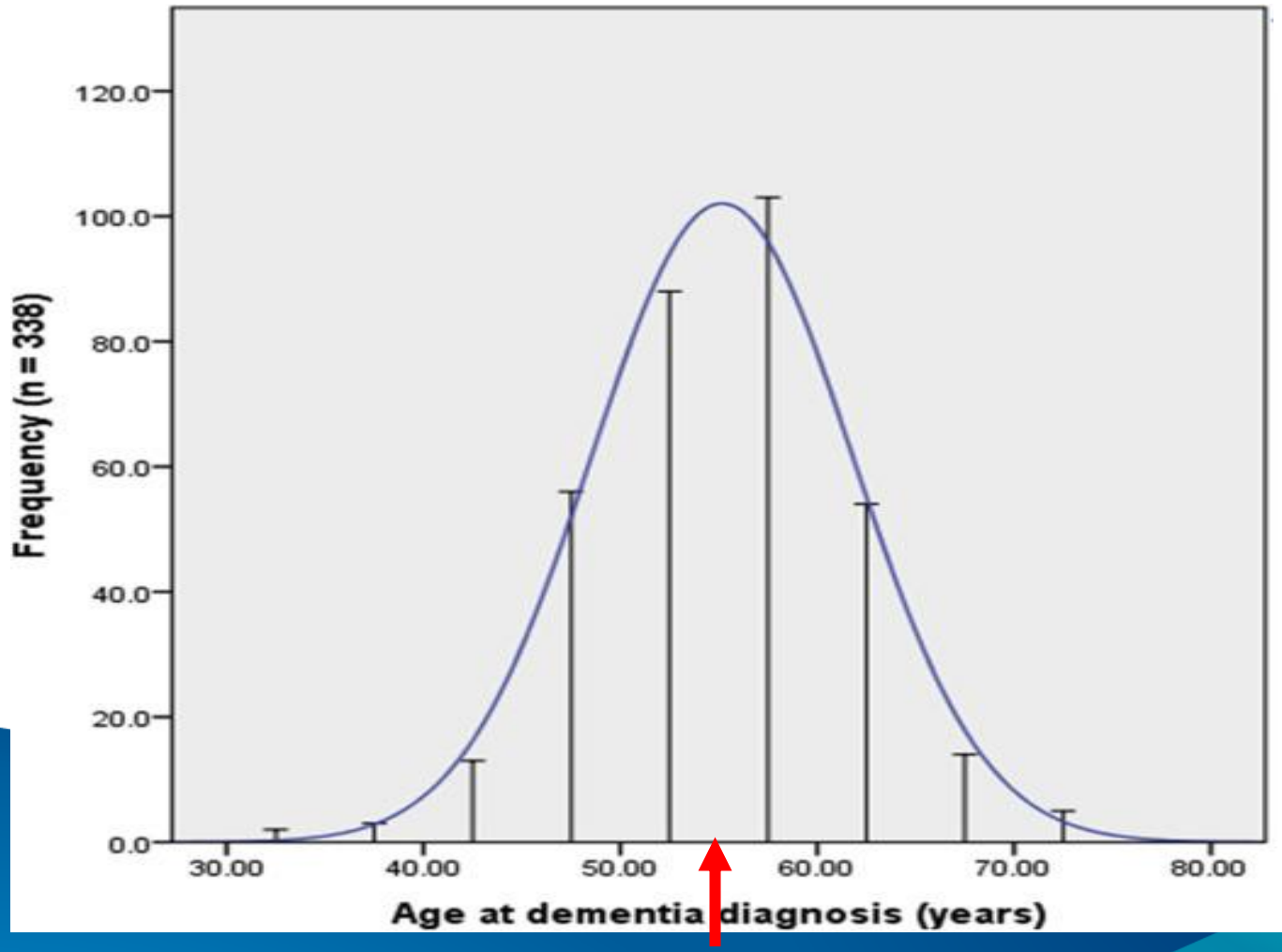
Alzheimer's disease is an irreversible brain disorder that slowly destroys memory and thinking skills...and eventually the ability to carry out the simplest tasks. It is the most common type of dementia.

Cumulative Incidence of Alzheimer's Disease in Down syndrome



Schupf et al, 2009

Average age of dementia diagnosis is ~55 years old

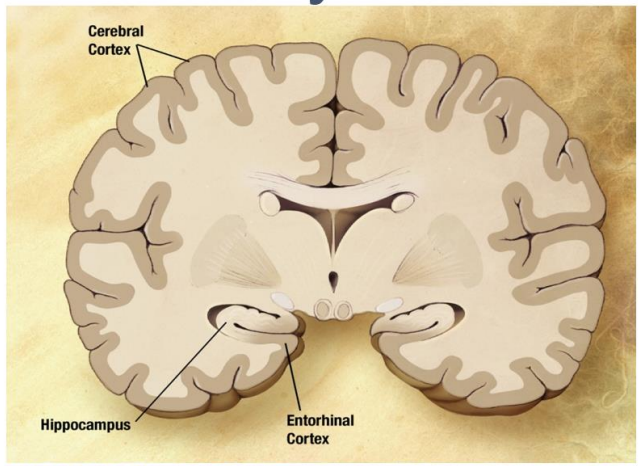


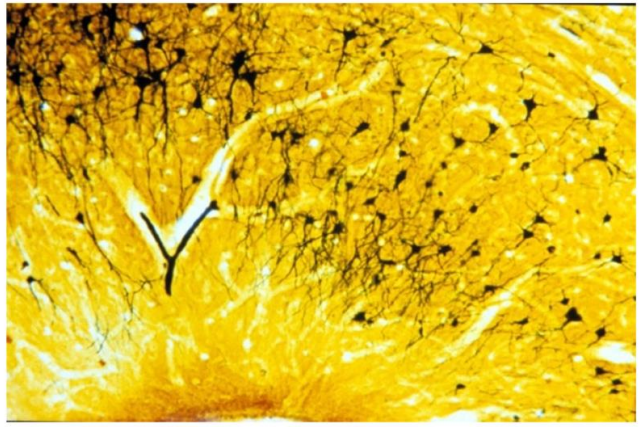
Strydom et al, 2017

Why do we call it Alzheimer's disease?

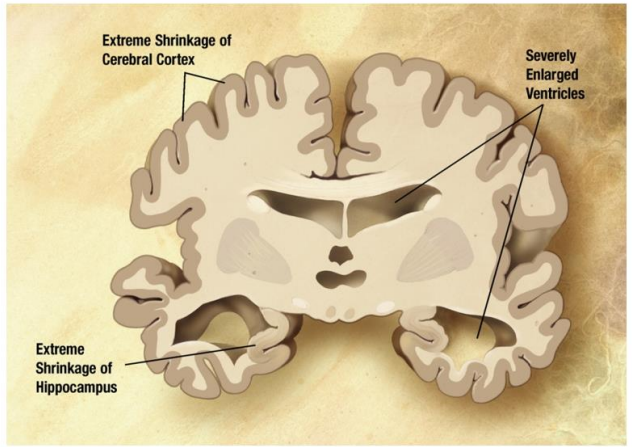
- The most common cause of dementia
  - 75% of dementia cases
- A degenerative disorder of the brain, with memory loss as its hallmark.

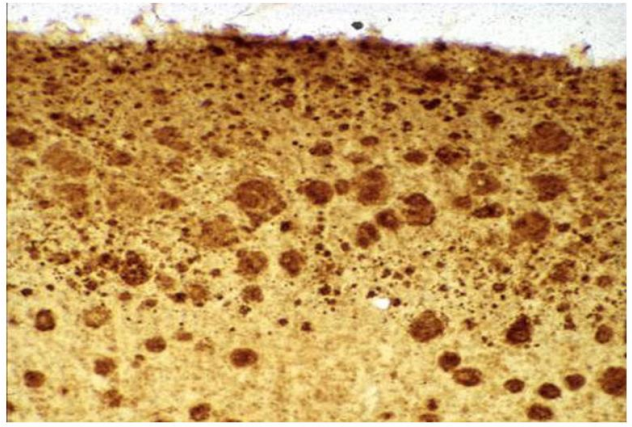
Healthy Brain

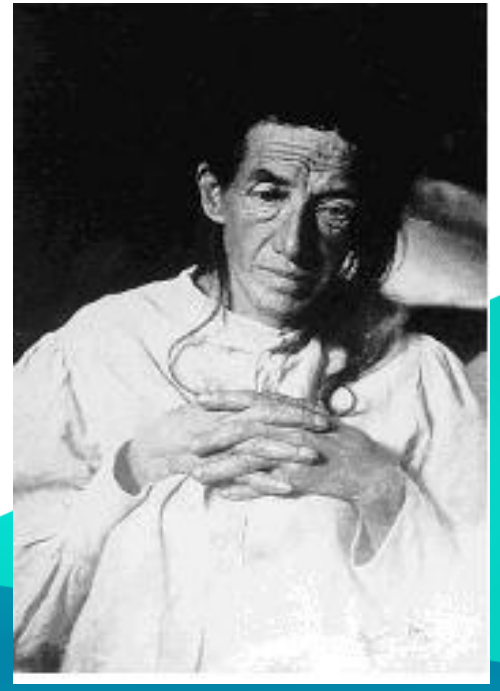




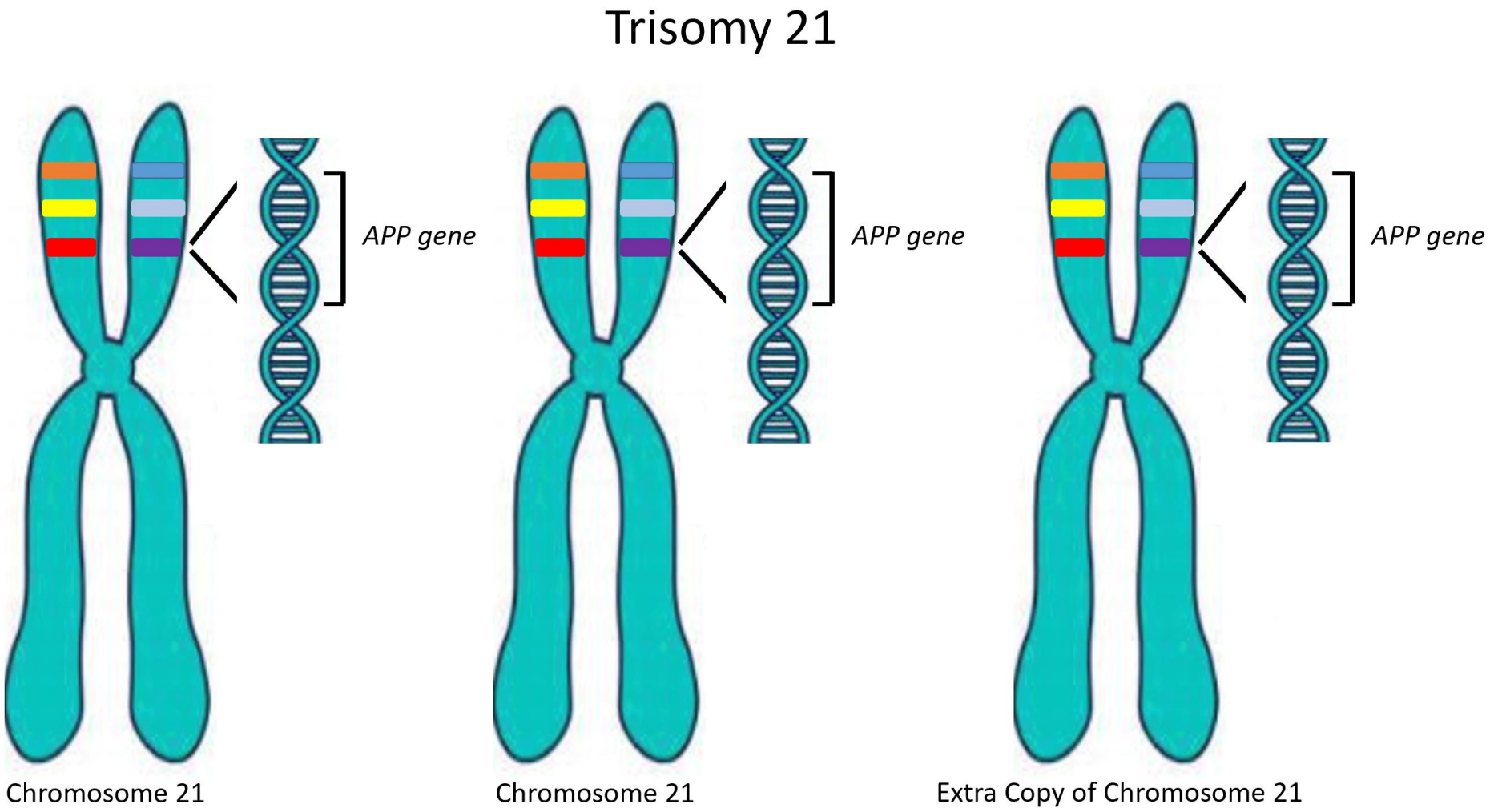
AD Brain



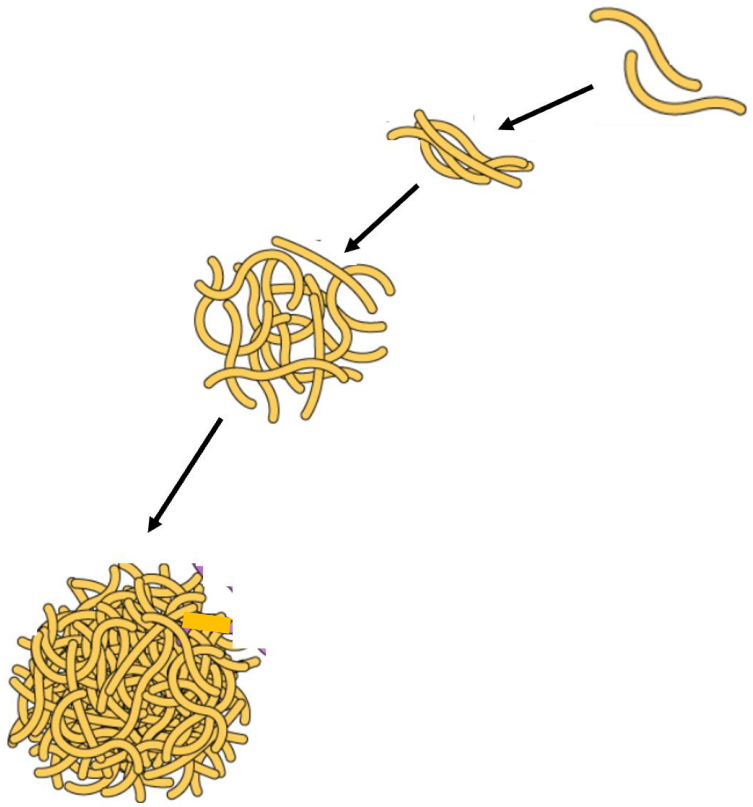




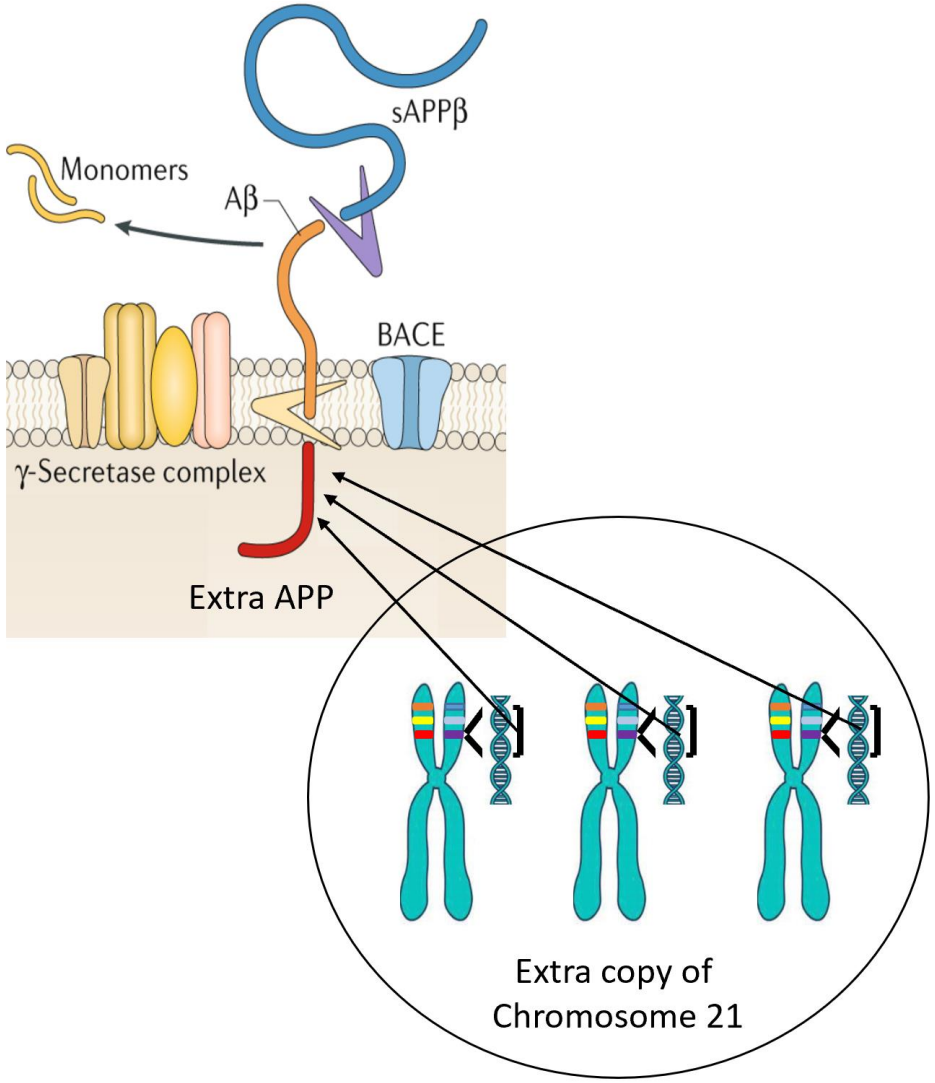
Why is Alzheimer's More Common in People with Down Syndrome?



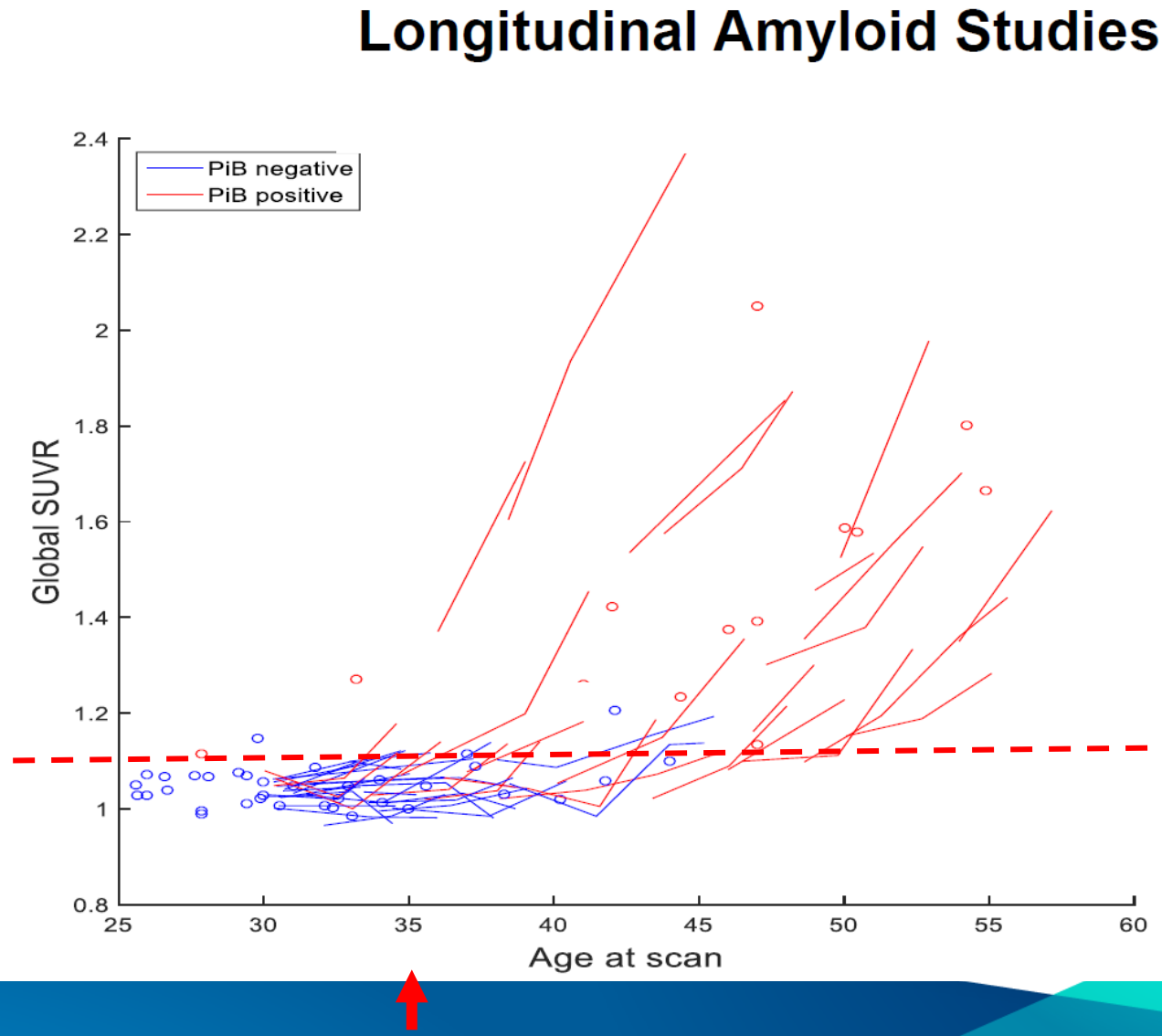
How Trisomy 21 Leads to Alzheimer's Disease



Fibrillar Amyloid plaques



But Amyloid PET positivity begins at age 35 years



Lao et al, 2018

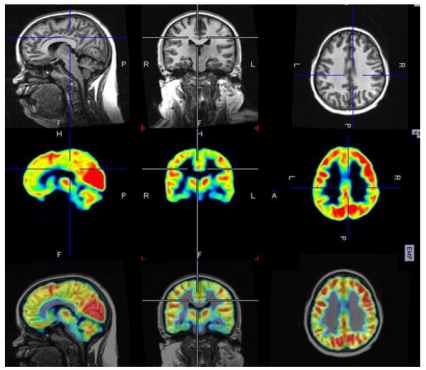
Biomarker studies will enable clinical trials for AD in DS

- The NIH-Alzheimer's Biomarker Consortium for Down Syndrome (ABC-DS), is collecting critical data on the natural history of AD in DS to enable clinical trials.
- Biomarker-enabled studies of AD in DS are feasible.
- Clinical trials for AD in DS are feasible.
- 500 participants with Down syndrome already enrolled

Down Syndrome Biomarker Initiative (DSBI)

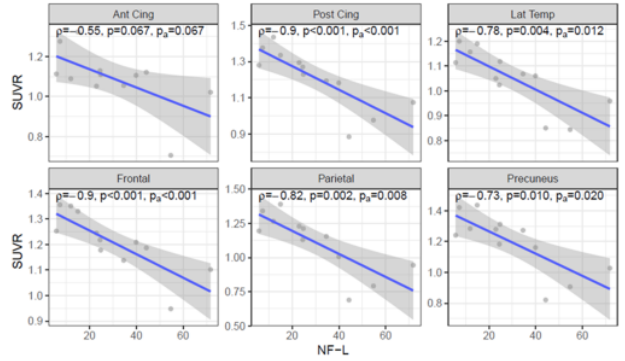
MULTIMODAL QUANTITATIVE NEUROIMAGING

Subject	Lateral Occipital	Entorhinal Cortex
DP03		
Amyloid Binding	1.17	2.88
FDG metabolism	-1.16	1.86
Cortical Volume	30.96	5.14
Percent change	N/A	N/A
DP04		
Amyloid Binding	1.15	3.35
FDG metabolism	1.95	-2.55
Cortical Volume	24.81	6.11
Percent change	N/A	N/A
DP05		
Amyloid Binding	2.95	3.05
FDG metabolism	-1.21	-2.39
Cortical Volume	37.15	7.31
Percent change	N/A	N/A
DP06…		



Rafii et al, 2015

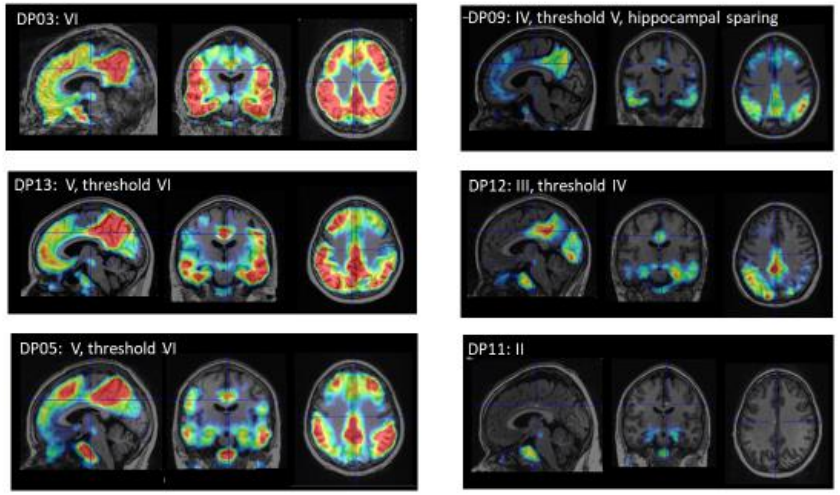
Plasma NF-L and Regional FDG PET



There is a statistically significant correlation of decreased regional glucose metabolism associated with increased plasma NF-L levels

Rafii et al, 2019

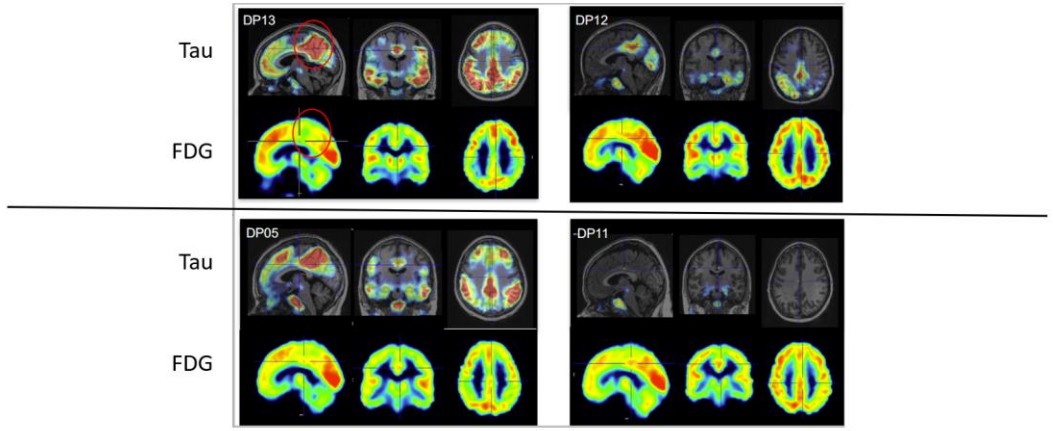
TAU PET IN DSBI PARTICIPANTS



Tau positivity only seen in amyloid-positive subjects but to varying degrees

Rafii et al, 201

INVERSE RELATIONSHIP OF TAU PATHOLOGY AND REGIONAL GLUCOSE METABOLISM



Areas with greater tau burden have less regional glucose metabolism

Rafii et al, 2017

What does AD look like in DS

- Duration of the disorder from first symptoms to death is 9 years (range, 6-11 y), and the duration from diagnosis to death is 6 years (range, 5-12 y).
- The main symptoms are memory loss, confusion, disorientation, and wandering.

- Social withdrawal/Apathy
- Disorientation
- Loss of daily living skills
- Changes in personality
- Aggressive behavior
- Self-abuse
- Development of seizures
- Change in sleep patterns
- Major weight change
- **Persistent forgetfulness**

Mimics of Dementia

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

The Signs of Depression

- Sad, apathy, irritable mood, along with disturbances of appetite, sleep, and energy, and loss of interest
- Skill losses, more extreme withdrawal.
- Strong reaction to loss: death of a family member, change in a roommate, retirement of a caregiver from a group home, etc.

Self-Talk

- Common, developmentally appropriate, Imaginary friends common.
- Self-talk is not only “normal” but also useful. Essential role in cognitive development and to coordinate actions
- Important tool for learning new skills and higher level thinking.
- Private nature of their self-talk: occurs behind closed doors or in settings where the adults think they are alone
- The amount and intensity of the self-talk reflects the number and emotional intensity of the daily life events experienced

Making the diagnosis

- Premorbid functioning by the age of 35 and then follow-up with annual reassessments, if decline is evident conduct a detailed work-up.
- Labs (B12, TSH)
- Neurology Consultation
- +/- Brain Imaging

Labs and Consults

- Annual thyroid screening (TSH and T4).
- Ophthalmologic evaluation every 1-2 years (looking especially for cataracts).
- Hearing testing every 1-2 years
- Fasting glucose, B12 and lipids
- Baseline cognitive testing

Who makes the diagnosis?

- PMDs don’t feel confident
- Physicians don’t often specialize in DS
- Often seems to be family member or support worker, case manager or manager of group home who identifies the issue

Why make the diagnosis?

For all the usual reasons

- Education: of person, family and support workers
- Support e.g. via Alzheimer's Association
- To access additional care ("age-related")
- Planning
- Medication

And how?

- Informant information: caregivers, family
- Physical and Cognitive evaluation compared to baseline
- Labs, neuroimaging
- Diagnostic criteria adapted to people with DS (National Task Group)
- Medical Care Guidelines – Global Down Syndrome Foundation

Diagnostic Criteria for Dementia in DS

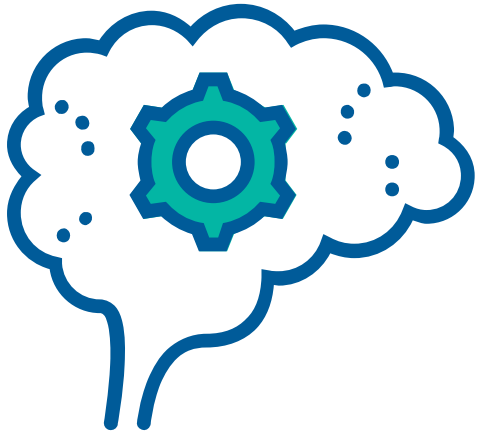
- Change in adaptive behavior which is recognized by loss of skills in self care
- Language difficulties, both of expressive language and comprehension
- Cognitive decline especially loss of skills of judgment and understanding

Response to Dementia Medication

Donepezil in Adults with Down Syndrome With and Without Dementia					
Author	**Journal**	**Year**	**No subjects**	**Study Type**	**Results**
Kishnani, P.S., et al.,	Lancet	1999	4	Case Reports No dementia	Improvement
Heller, J. H. et al	AJ Medical Genetics	2003	6	Case Reports No dementia	Improvement Language
Johnson, N. et al	AJMR	2003	19	RCT No dementia	Improvement Language
Prasher, V.P., et al.,	Intl J Ger Psych.	2002	27	RCT Alzheimer's Disease	Non significant improvement
Lott, I.T., et al.,	Archives Neurology	2002	15	Case Control Alzheimer's Disease	Significant Improvement
Prasher, V.P., et al	Intl J Ger Psych.	2003	25	Open label extension Alzheimer's Disease	Significant improvement
Kondoh, T. Et al	Annals Pharmacotherapy	2005	2	Case Reports Alzheimer's Disease	Improvement

People with Down syndrome can make a difference in Research

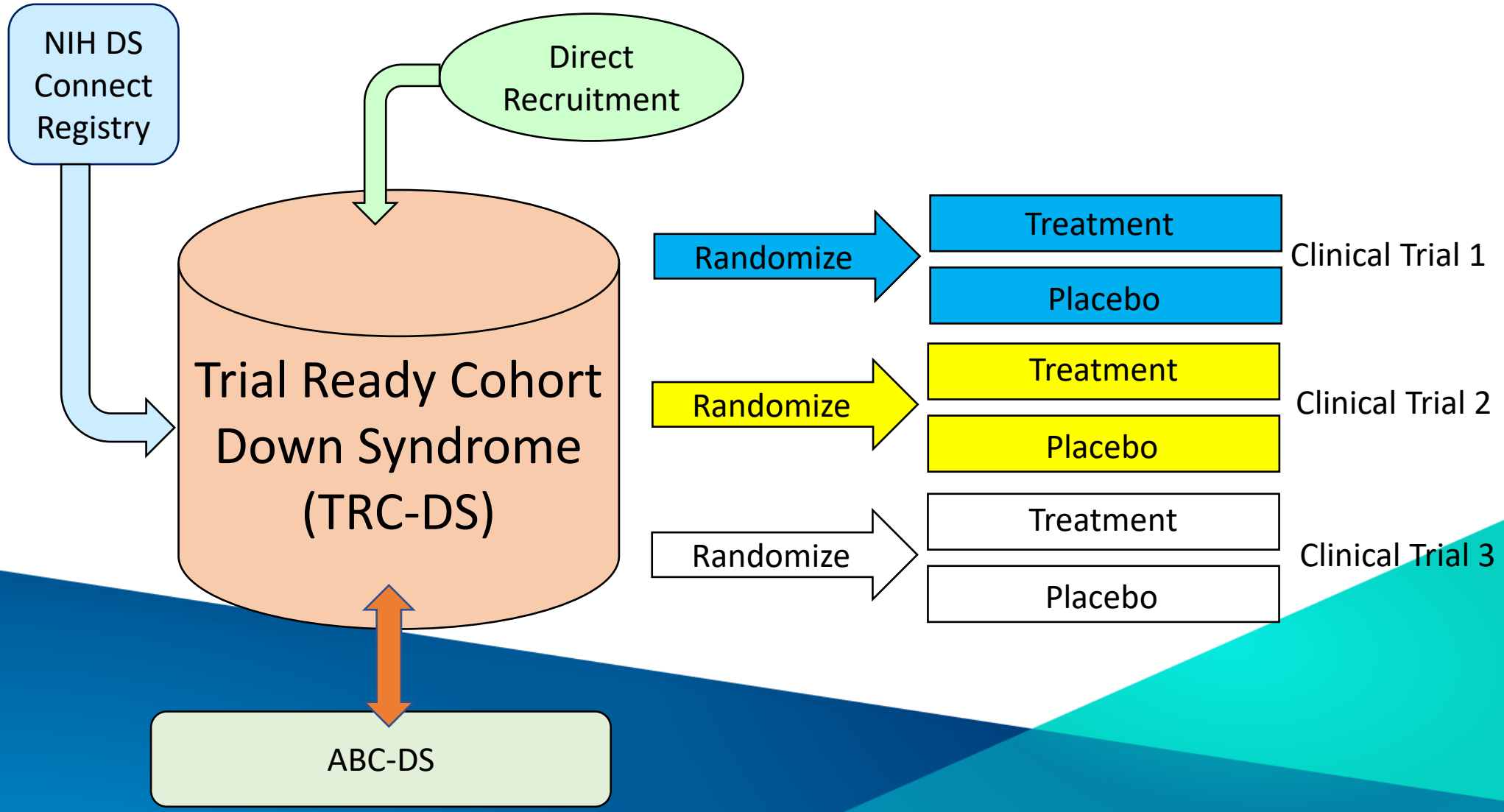
- There are similar brain changes in Down syndrome as there are in Alzheimer's disease
- Researchers want to provide treatments to this population



What can I do? Join TRC-DS

- The Trial-Ready Cohort-Down Syndrome (TRC-DS) needs 120 healthy people with Down syndrome
- Participants in the ABC-DS study can co-enroll in TRC-DS
- TRC-DS is funded by the National Institutes of Health's INCLUDE initiative in partnership with ABC-DS

Trial-Ready Cohort Down Syndrome



Who is eligible?

Eligible volunteers:

- Are healthy adults, between ages 35-55, with Down syndrome;
- Have an interest in participating in clinical research; and
- Will visit their nearest research center once every 16 months for routine exams and brain scans.

What is involved in the study?

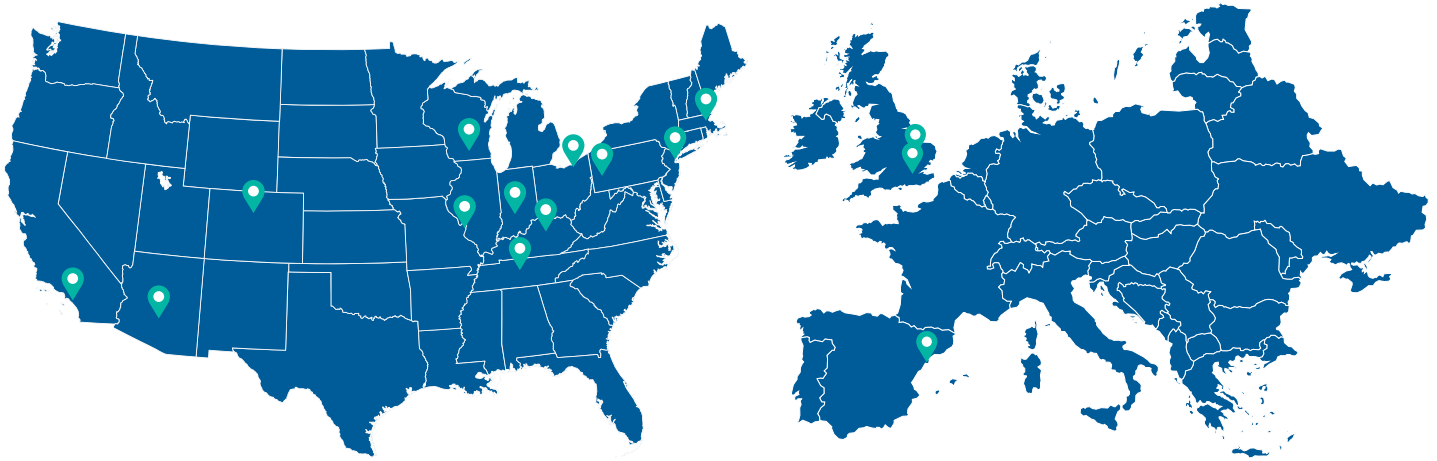
Volunteers visit their nearby research center every 16 months for:

- Physical exams like blood draws, blood pressure readings, and brain imaging scans
- Assessments to measure thinking ability

Make a difference. Join TRC-DS.

Contact your nearest research center and ask about TRC-DS

The research center will determine eligibility and schedule you for an in-person evaluation



Visit www.TRCDS.org for more information

Summary

- People with DS are living long enough to develop Alzheimer's disease
- Diagnosis is similar to that for other people, though some differences
- New treatments are urgently needed
- Research into the natural history of AD in DS is ongoing
- Clinical trials on new therapies are starting
- Trial-Ready Cohort will help bring the latest therapies to the DS population

Thank you!

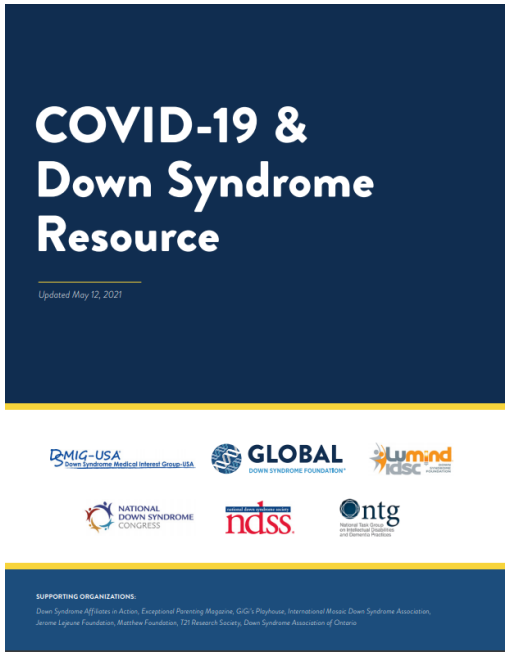
TRC DS

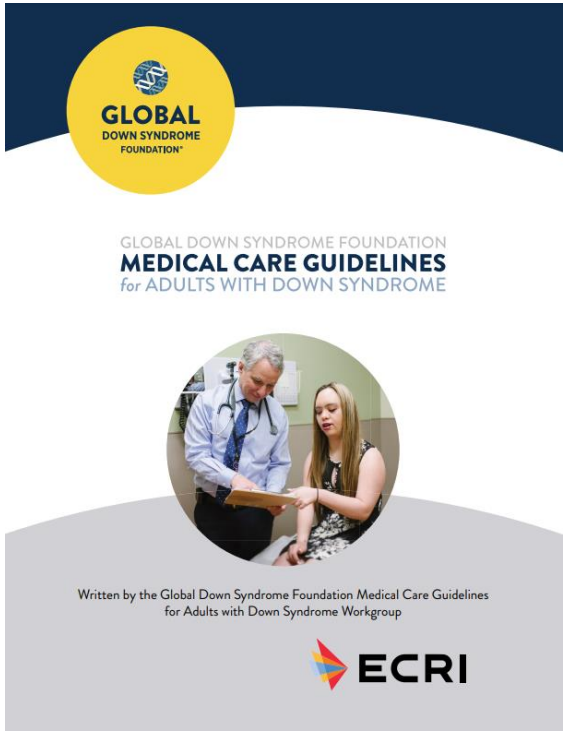
Trial-Ready Cohort-Down Syndrome

Thank you for attending!

Additional Resources:

- Trial-Ready Cohort-Down Syndrome (TRC-DS)
  - www.TRCDS.org
- GLOBAL Medical Guidelines for Adults with Down Syndrome
  - https://www.globaldownsyndrome.org/medical-care-guidelines-for-adults/
- COVID-19 & Down Syndrome Resource
  - https://www.globaldownsyndrome.org/covid-19/
- Alzheimer's and Cognition Center
  - https://medschool.cuanschutz.edu/alzheimer
- Alzheimer's Association Further understanding the connection between Alzheimer's disease and Down syndrome
  - https://alz-journals.onlinelibrary.wiley.com/doi/abs/10.1002/alz.12112
- Find a Down Syndrome Medical Care Center in your area!
  - https://www.globaldownsyndrome.org/research-medical-care/medical-care-providers/





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