Alzheimer´s disease: the next challenge in Down syndrome

Neuroimage Core

Memory Unit Sant Pau

www.santpaumemoryunit.com

Outline

1. Alzheimer´s disease in Down syndrome

1. A population based health plan to detect and treat AD in DS

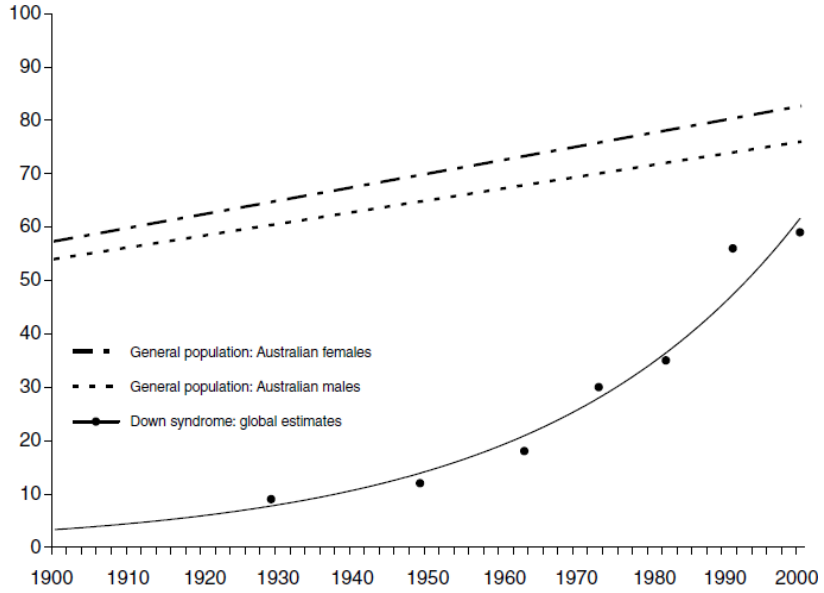
3. The Down Barcelona Neuroimaging Initiative (DABNI) project

4. Some good news in Down syndrome

Alzheimer´s disease
in
Down syndrome

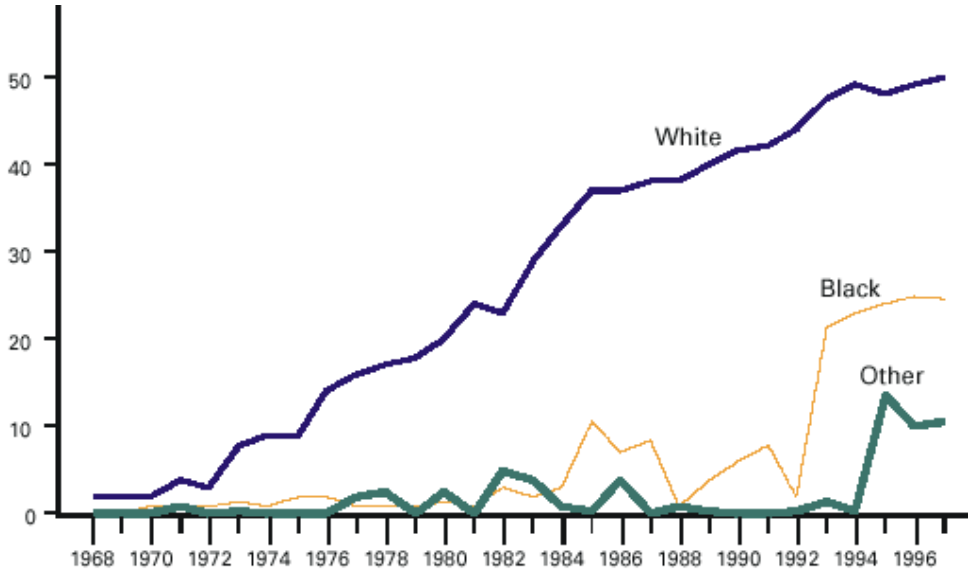
Life expectancy in Down syndrome

Life expectancy in Australian population



Bittles, Glasson et al. 2004

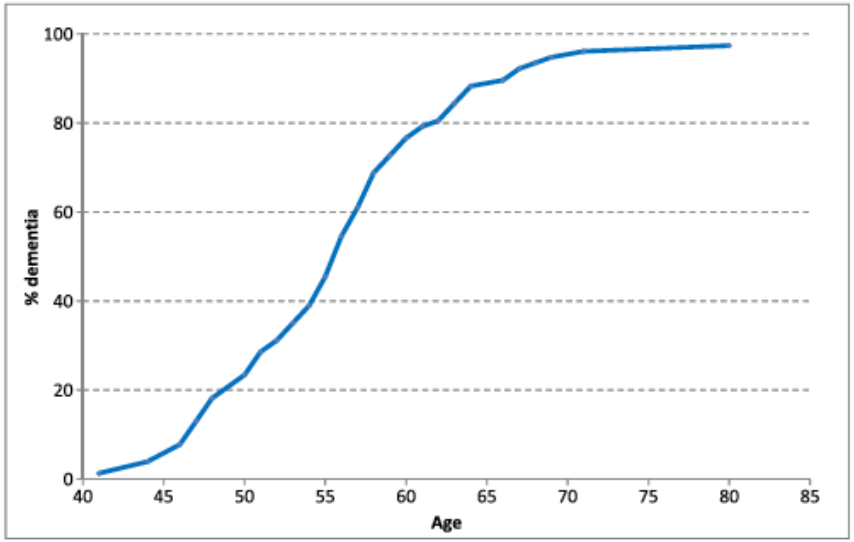
Median age of people with DS by race (US)



Lisa Wade. CDC data, 2010

DS is a vulnerable population that needs more care and health services than the general population

Alzheimer´s disease is the main medical problem in adults with DS



McCarron et al. JIDR 2017

Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria

IWG-2 criteria for presymptomatic AD (A plus B)

A Absence of specific clinical phenotype (both are required)
- Absence of amnestic syndrome of the hippocampal type
- Absence of any clinical phenotype of atypical AD

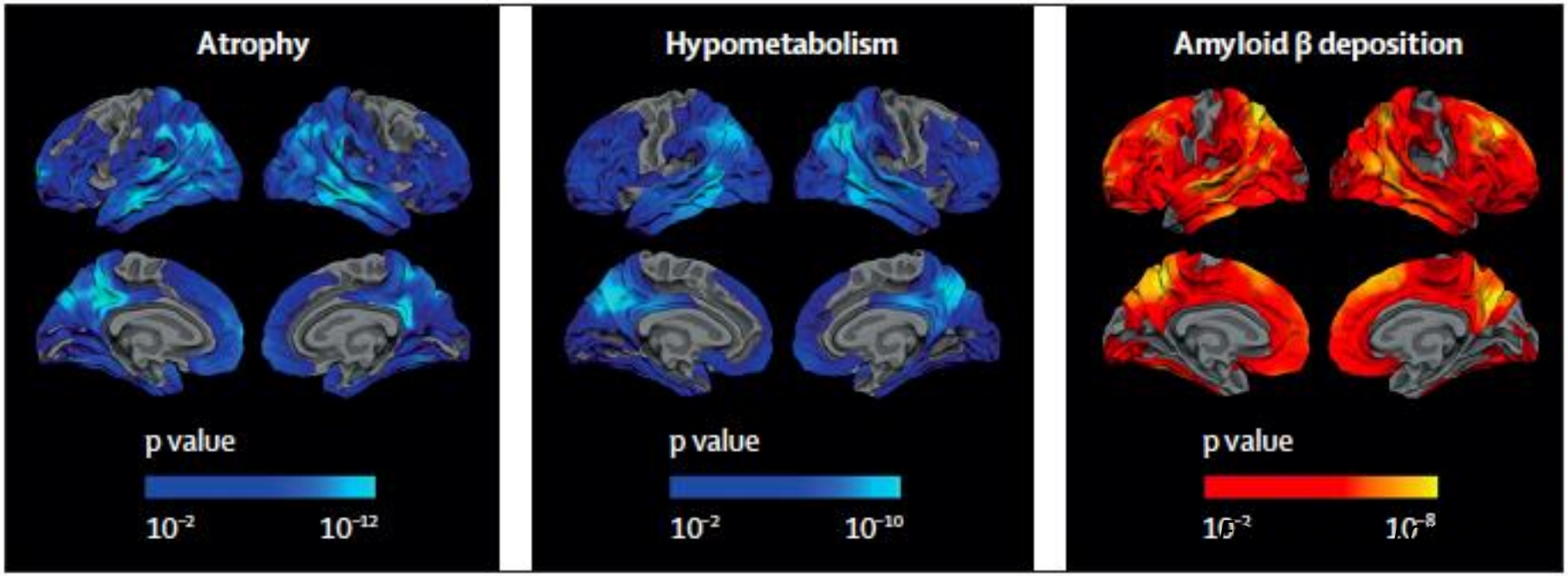
B Proven AD autosomal dominant mutation in *PSEN1*, *PSEN2*, or *APP*, or other proven genes (including Down's syndrome trisomy 21)

IWG-2. Lancet Neurol. 2014

Down syndrome is now conceptualized as a form of genetically determined Alzheimer´s disease

How is Alzheimer´s disease in Down syndrome?

Imaging signature of AD in DS



In short: “THE SAME” (with some small differences)

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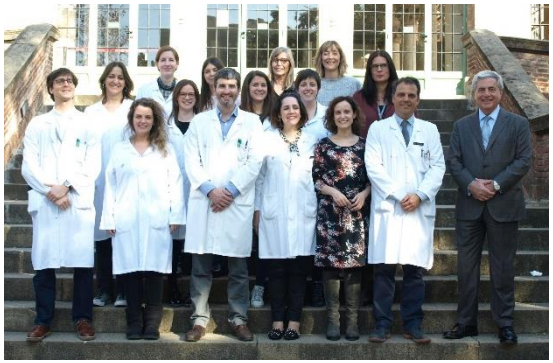
A population based health plan to detect and treat AD in DS

FUNDACIÓ CATALANA SÍNDROME DE DOWN

HOSPITAL DE LA SANTA CREU I SANT PAU

Alzheimer´s Down Unit



Health plan for adults with DS in Catalonia → **CLINICAL COHORT**

Annual NRL & NPS
Blood (+/-) EEG

N > 800

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DAVIS

"Domiciliary Alzheimer Visiting in Down syndrome"

1. To reach out for those who cannot come to Barcelona (or are too ill to come to the clinic)

2. *To help centers working with DS individuals*

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The Down Barcelona Neuroimaging Initiative (DABNI) project:

A research program to fight Alzheimer´s disease in Down syndrome

Proposal

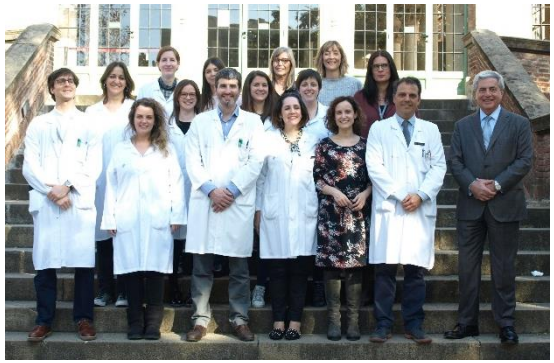
Sant Pau memory unit

FUNDACIÓ CATALANA SÍNDROME DE DOWN

HOSPITAL DE LA SANTA CREU I SANT PAU

DABNI

(Down Alzheimer Barcelona Neuroimaging Initiative)



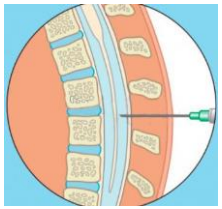
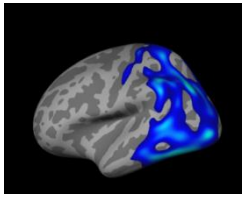
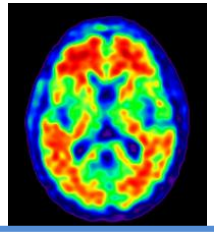
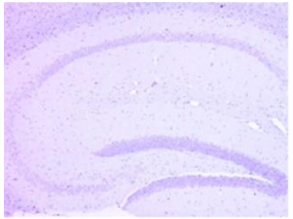
Health plan for adults with DS in Catalonia → **CLINICAL COHORT**

Annual NRL & NPS
Blood (+/-) EEG

N > 800

↓

BIOMARKER COHORT

Plasma & genetics	CSF study	Structural and functional MRI	FDG-PET Florbetarpir-PET Tau-PET	Polysomnography	Brain banking
					
N= 408	N= 157	N= 171	FDG, N= 123 FBP, N= 56	N= 74	N= 13

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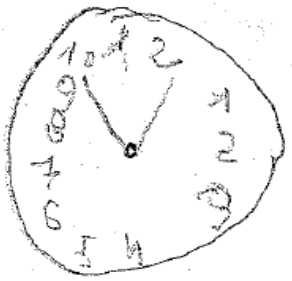
Why should we care about research in Down syndrome?

Why biomarkers?

AD dementia diagnosis is especially difficult in the context of Down syndrome

17-12-2008



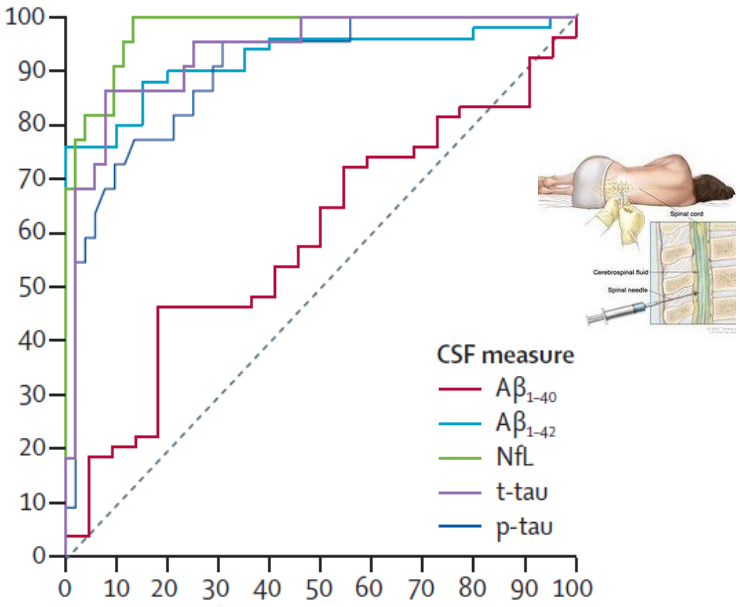
17-02-2010

07-04-2011

Biomarkers

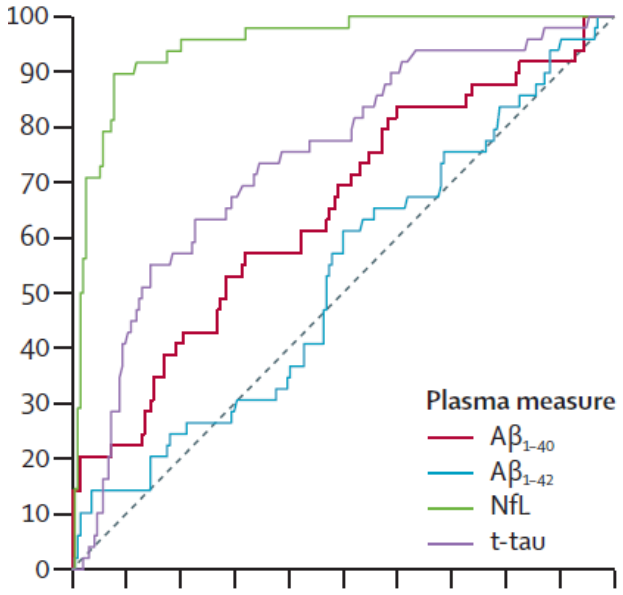
Biomarkers for AD diagnosis in DS

CSF



Carmonaet al. JAD. 2017

Plasma



Fortea et al. Lancet Neurology 2018

Good plasma biomarkers are already here!

Saint Paul memory unit

Longitudinal plasma NfL levels in Down syndrome

Multicenter international study: 608 samples from 236 participants

U. of Kentucky (L. Head)
193 samp/ 60 subjects

Hospital Sant Pau (J. Fortea)
275 samp/113 subjects

LonDownS (Strydom)
34 samp /17 subj

LUM (Munich J. Levin)
10 samp/5 subj

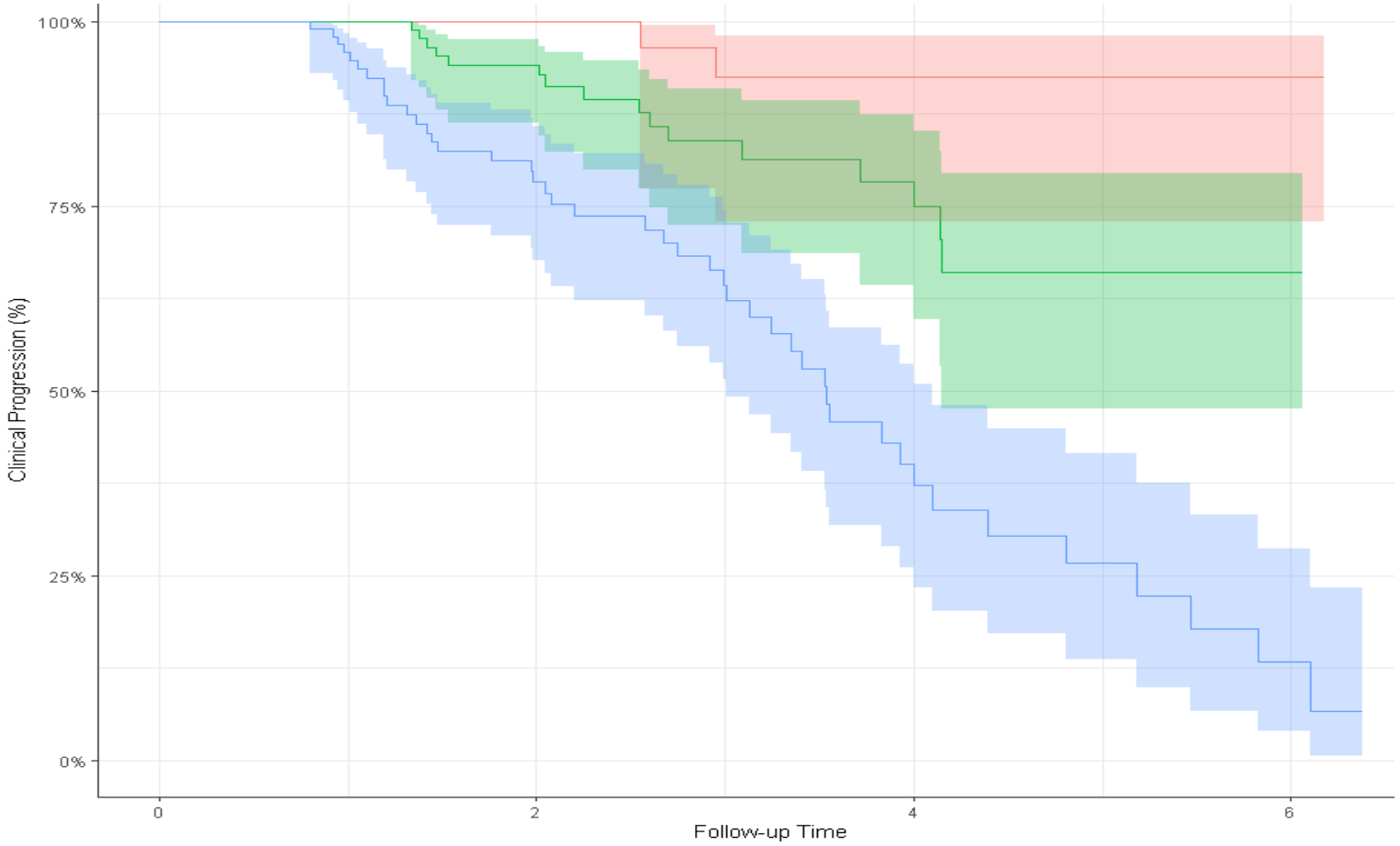
FJL (Paris; PI: A. Rébillat)
76 samp /31 subjects

U. of Cambridge (PI S.Zaman)
20 samp /10 subjects

Objectives

1. To confirm the dx performance of plasma NfL levels
2. To assess the px performance of plasma NfL levels
3. To assess the longitudinal trajectory of plasma NfL

Prognostic performance



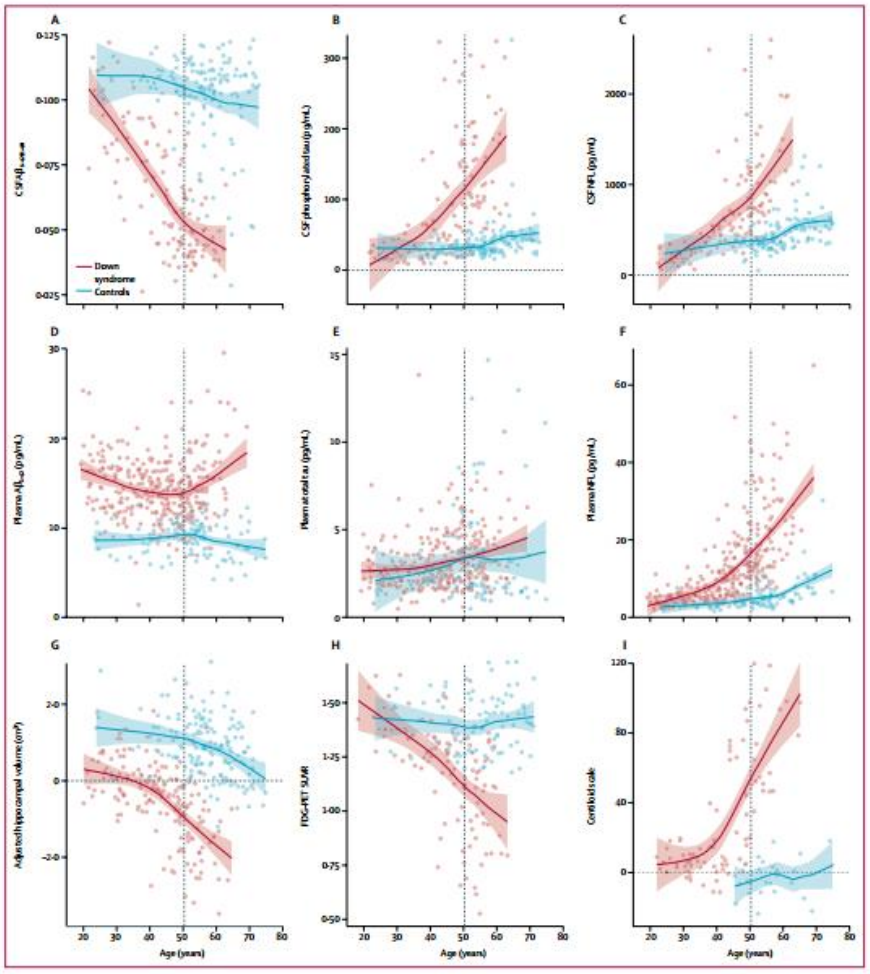
Clinical progression to symptomatic AD is higher in those adults with DS with elevated plasma NfL levels

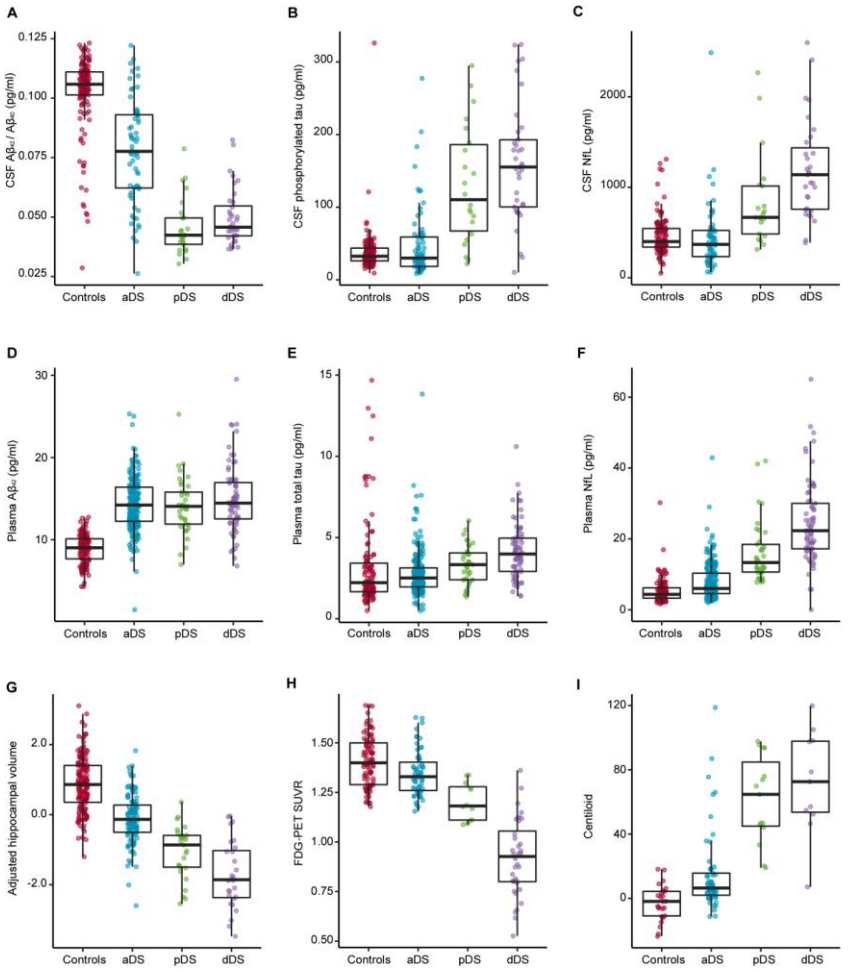
AD

Natural history

in DS

AD biomarker changes in DS



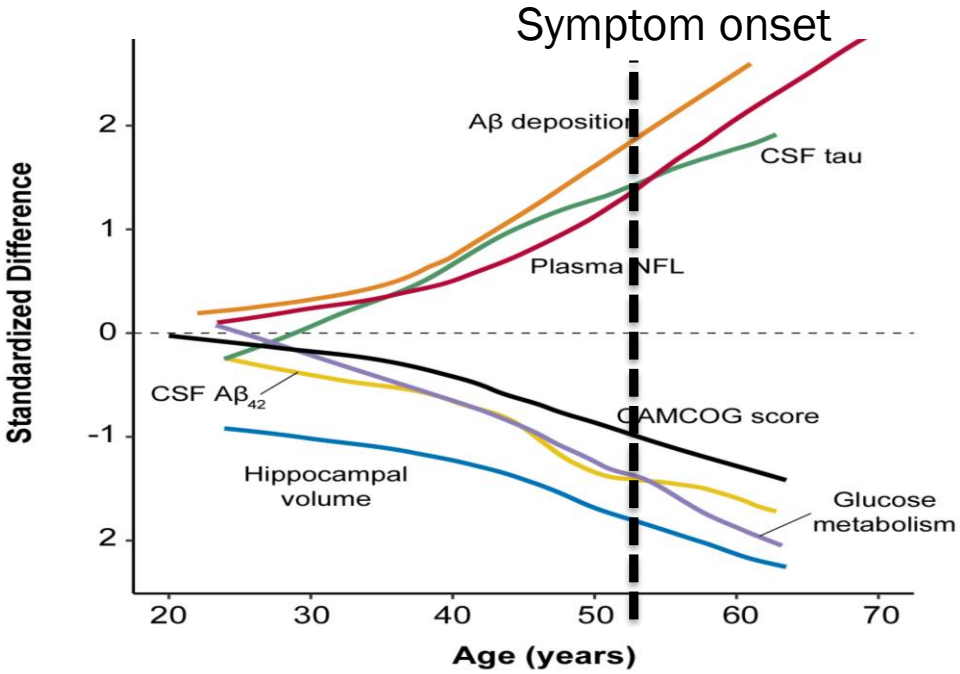


Fortea et al. Lancet 2020

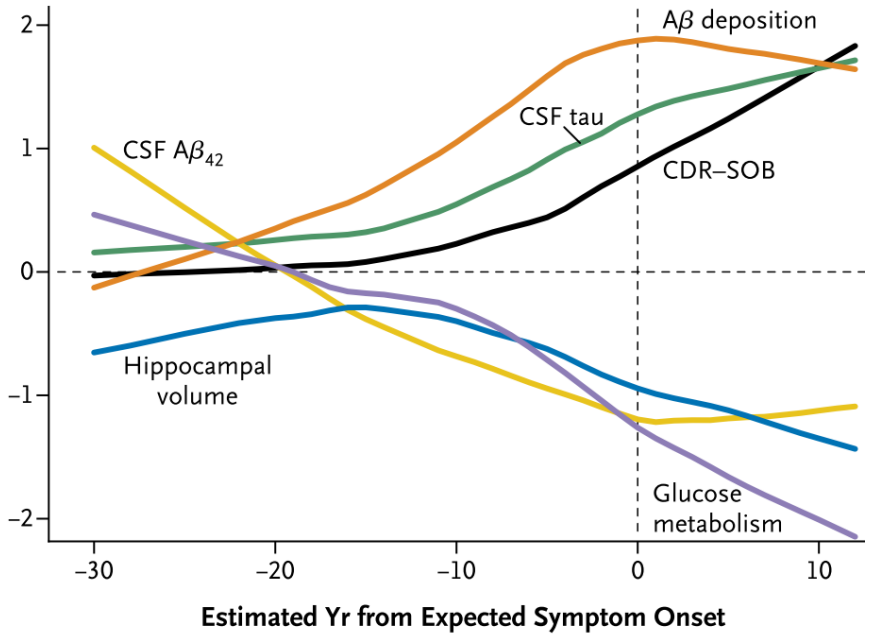
Changes with respect age

Changes along the AD continuum

Trajectory of changes strikingly similar to that in ADAD



Fortea et al. Lancet 2020



Bateman et al. Nejm 2012

Under review

There are very good news in AD research in DS!

- Collaborative efforts
- Trial Ready Cohorts
- Clinical Trials

International consortia

USA

ABC consortium
ACTC-DS
Lumind

Europe

Horizon 21

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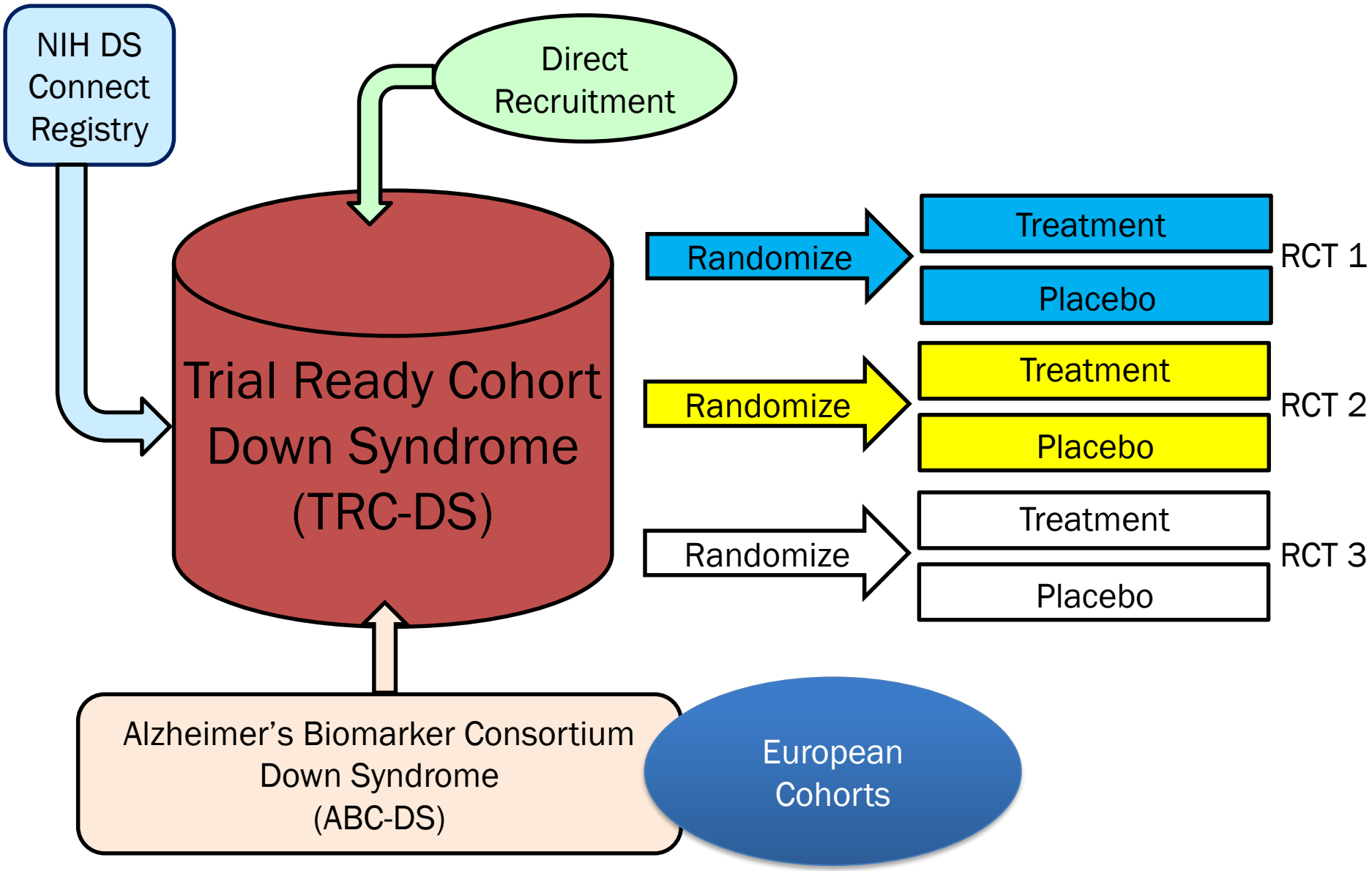
Horizon21
Stop Alzheimer's before it starts

Jerome Lejeune
FOUNDATION
Research, Care, Advocacy

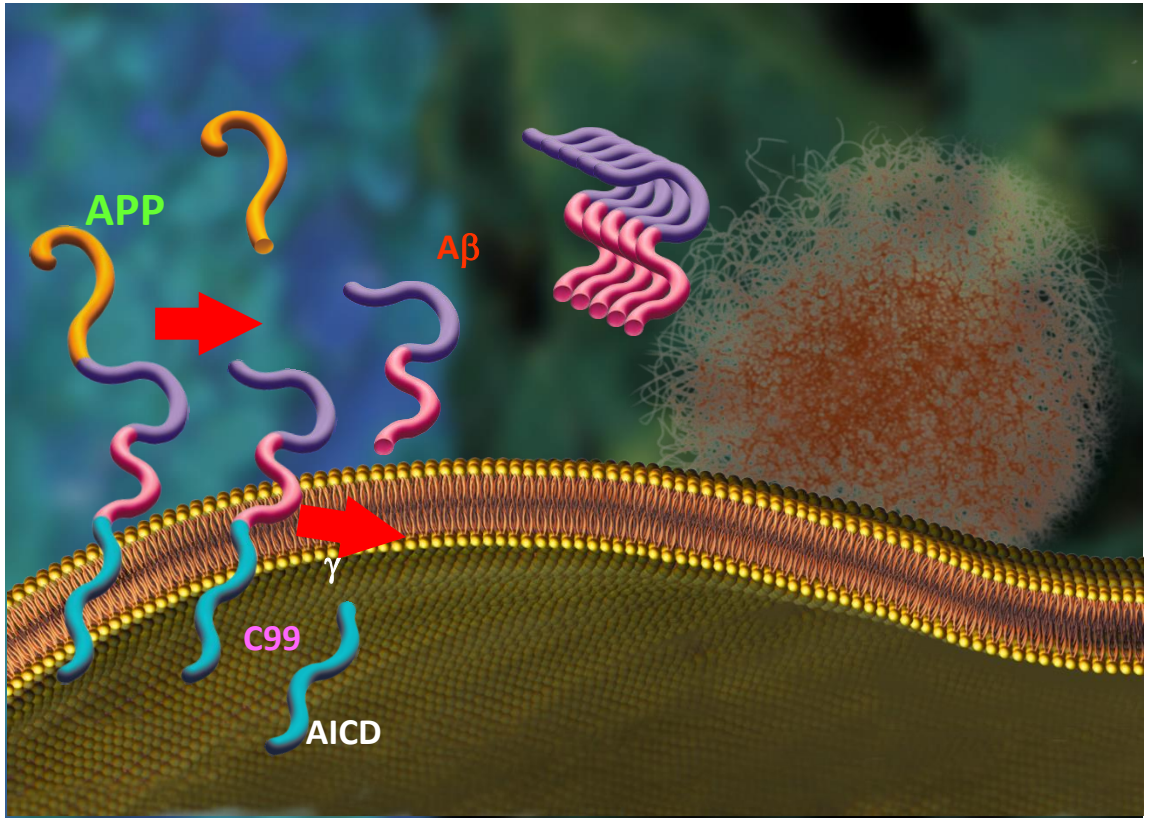
ACTC-DS: A CLINICAL TRIALS PLATFORM TO PREVENT AD IN DS

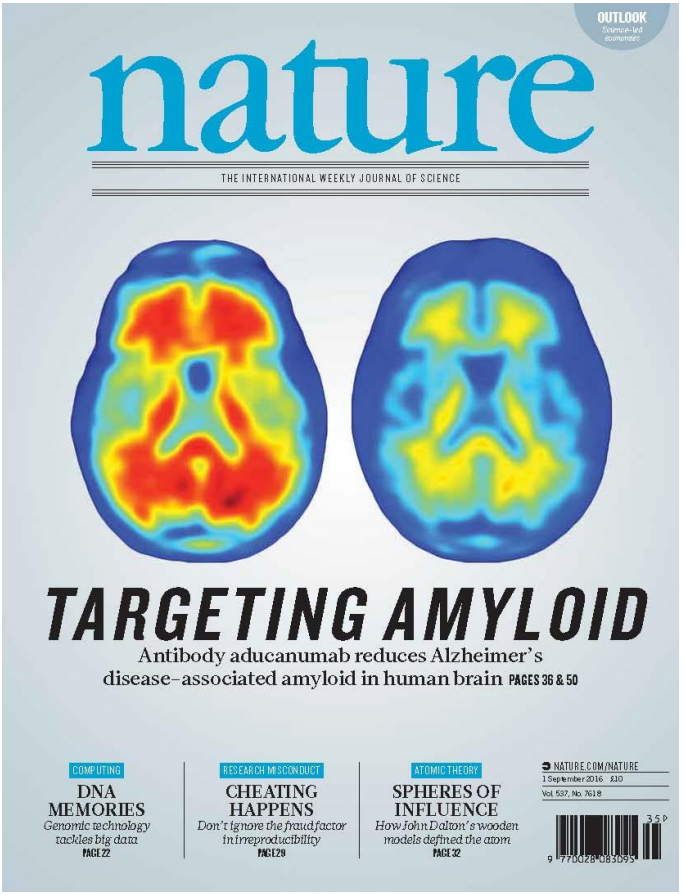
A network of 15 international clinical sites with experience in AD and DS clinical research. $4.7 Million award from NIH

Trial Ready Cohort



DS is all about amyloid (and tau) and the first drug targeting amyloid is being evaluated for aproval





Anti-amyloid (and tau) therapies must be tested in DS

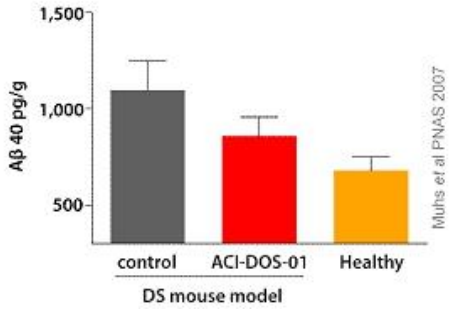
What about Down syndrome?

ACI-24 – Phase 1b in Down syndrome (DS)

Anti-Abeta therapeutic vaccine

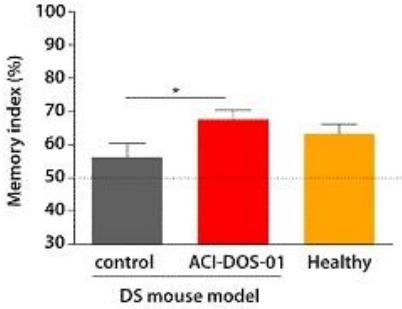
Target	Misfolded Abeta
Study rationale	▪ Down syndrome population is at high risk of developing AD ▪ 75 – 100% of people with Down syndrome have AD by age 60 ▪ Unique possibility to study prevention and treatment in defined genetic population
Key results	▪ Compelling memory enhancement in ORT[1] in Down syndrome mouse model[2]

Reduction of Abeta levels in brain[2]



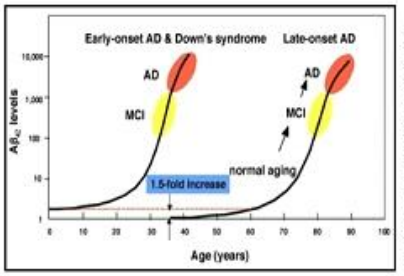
Muhs *et al* PNAS 2007

Memory restoration[2]



Belichenko *et al* PLOS ONE 2016

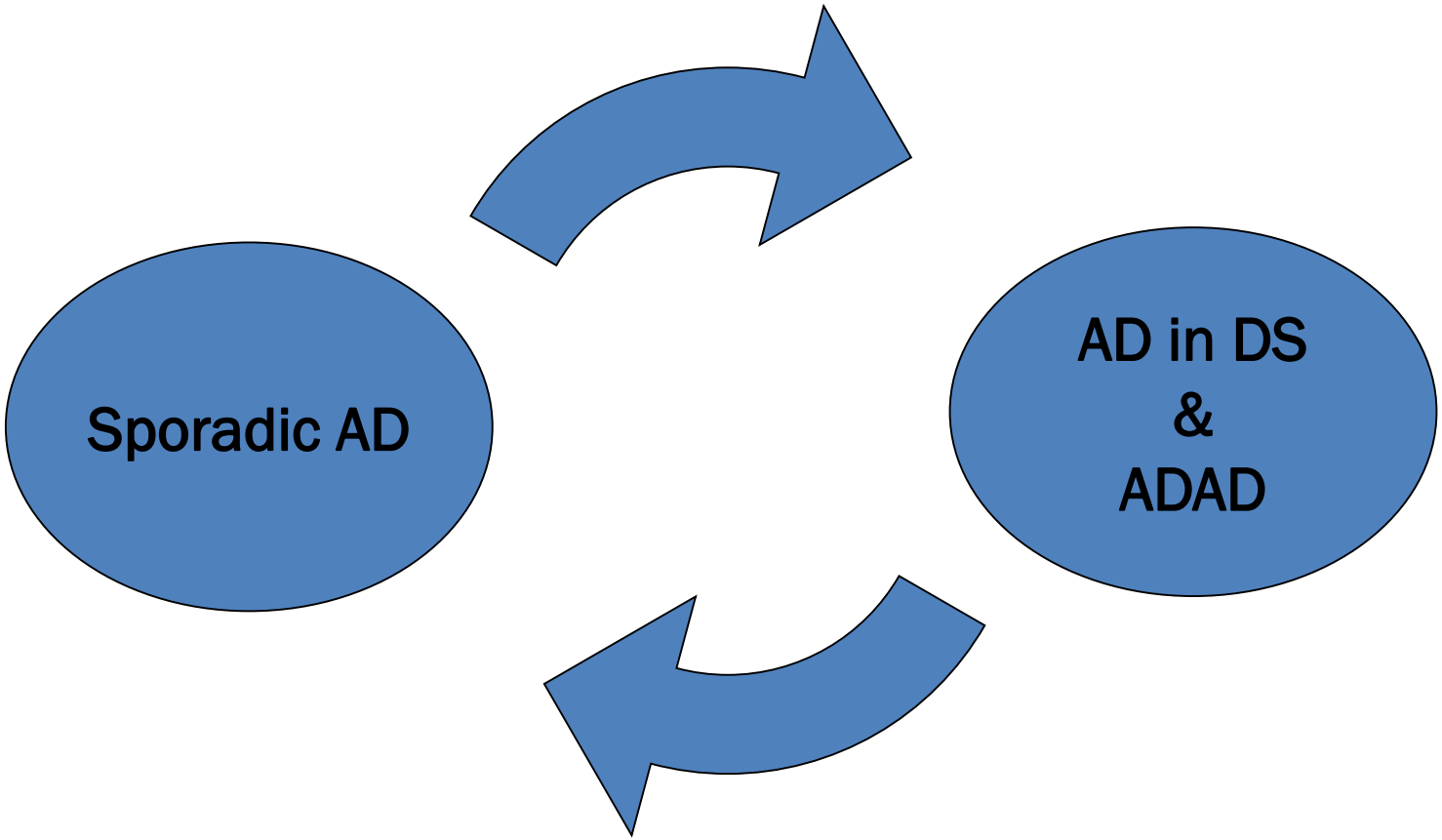
Down syndrome population is at high risk of developing AD



Alzheimer's Association, New York

An phase II anti-amyloid trial is about to start in DS later December 2020

“Virtuous Circle”



Not being able to perform research in DS is a new form of discrimination

Take home messages

1. Down Syndrome is a form of genetically determined AD

2. Trials AD are feasible due to advancements in AD pathophysiology and biomarker research

3. International networks & trial ready cohorts have been built

4. AD might be easier to cure in DS than in sporadic AD and it is the best population in which to perform prevention studies

5. **Clinical trials are about to start in DS!**

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ADNI
Alzheimer's Disease Neuroimaging Initiative

Instituto de Salud Carlos III
ciberned
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