DIAN TU
Dominantly Inherited Alzheimer Network
Trials Unit

Clinical and Biomarker Changes in Alzheimer's Disease

Randall J. Bateman M.D.
Washington University School of Medicine

Washington University in St. Louis
School of Medicine

DIAN
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Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

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Comparison of Autosomal Dominant and Sporadic AD

Measure	Autosomal Dominant AD	Sporadic AD
Clinical presentation	Amnestic	Amnestic
Cognitive deterioration	Memory, frontal/executive, generalized cognitive decline	Memory, frontal/executive, generalized cognitive decline
MRI	Hippocampal atrophy and whole brain atrophy	Hippocampal atrophy and whole brain atrophy
PiB PET	Cortex **plus basal ganglia**	Cortex
FDG PET	Parieto-occipital hypometabolism	Parieto-occipital hypometabolism
CSF Aβ 42	Decreased by 50%	Decreased by 50%
CSF tau	Increased by 2-fold	Increased by 2-fold

DIAN Research Aims

1. Establish an **international registry** of participants at risk for autosomal dominant AD (mutation carriers and non-carriers; presymptomatic and symptomatic).

2. Evaluate clinical and cognitive measures with imaging, CSF, and blood biomarkers in a uniform manner at entry and **longitudinally** thereafter.

3. Determine the temporal **order** and **rate of change** of AD changes in clinical, cognitive, neuroimaging, and biomarker indicators.

4. **Compare** the clinical, cognitive, imaging and biomarker indicators, and neuropathology of autosomal dominant AD to those **of late-onset "sporadic" AD**.

5. Design and perform DIAN with **future treatment trials**, per NIH request.

DIAN Mutation Distribution – based on data from January 25, 2012

Gene	Frequency
PSEN1	91 (77.8%)
PSEN2	9 (7.7%)
APP	17 (14.5%)

Participant Entry Characteristics

	Asymptomatic 219 (72.04%)		**Symptomatic** 85 (27.96%)	
N = 304* *(Target 80% Asymptomatic, 20% Symptomatic) (*Table based on 272 participants. **32** Mutations in Process- Missing)*	Confirmed Mutation Status: 196		Confirmed Mutation Status: 76	
	98 (NC-)	98 **(MC+)**	7 (NC-)	69 **(MC+)**
Age	39.65 (SD 9.85)	35.05 (SD 8.85)	42.71 (SD 13.37)	45.03 (SD 9.89)
Gender (% Female)	58.76%	57.14%	71.43%	57.97%
Parental Age of Onset	46.73 (SD 6.85)	47.22 (SD 6.41)	46.28 (SD 7.8)	44.03 (SD 10.07)
Education	14.74 (SD 2.56)	14.35 (SD 2.69)	13.43 (SD 2.29)	13.54 (SD 2.66)
MMSE	29.07 (SD 1.27)	29.02 (SD 1.30)	28.71 (SD 1.38)	22.76 (SD 7.11)
ApoE4+ ***1 E4***	27	22	0	13
2 E4	1	2	0	4

MC = Mutation Carrier; NC = Non-carrier

*Table statistics based on 272 participants with NCRAD confirmed mutation data available as of 15NOV2012.

- Total N = 304

Evidence for a presymptomatic Alzheimer's disease phase

- Incidence of dementia is delayed by 10-15 years from the prevalence of Alzheimer's pathology in population pathological studies
- Alzheimer's disease biomarkers are abnormal in asymptomatic individuals in an age dependent fashion (e.g. low CSF Aβ42, fibrillar amyloid deposition are rare <50 years, ~10% 60's, ~25% 70's and above).
- Given the long pathobiological progression, observational studies needed over many years, unless we can predict **who will have AD and when**.

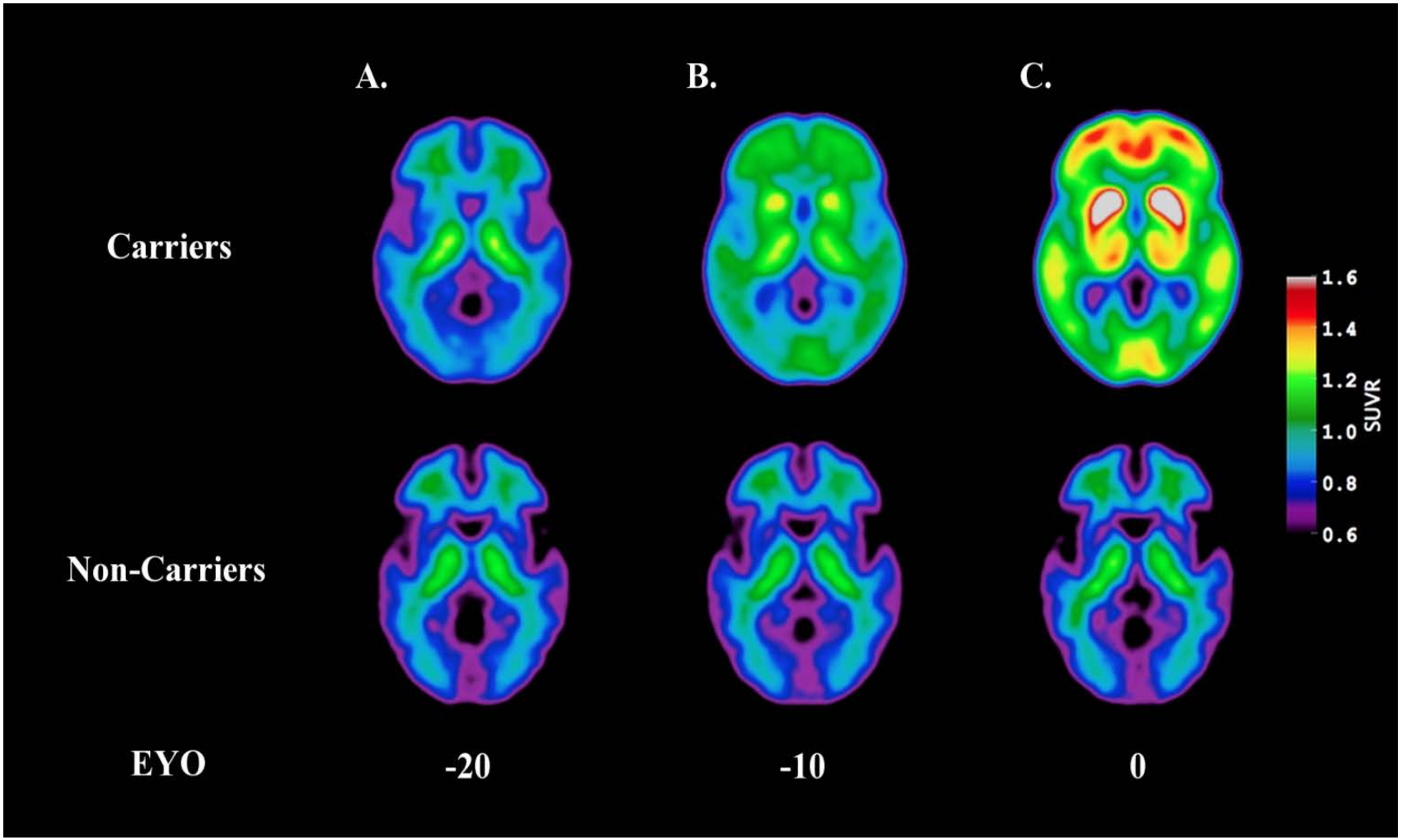
Map of DIAN sites

WashU Coordinating Center

DIAN sites

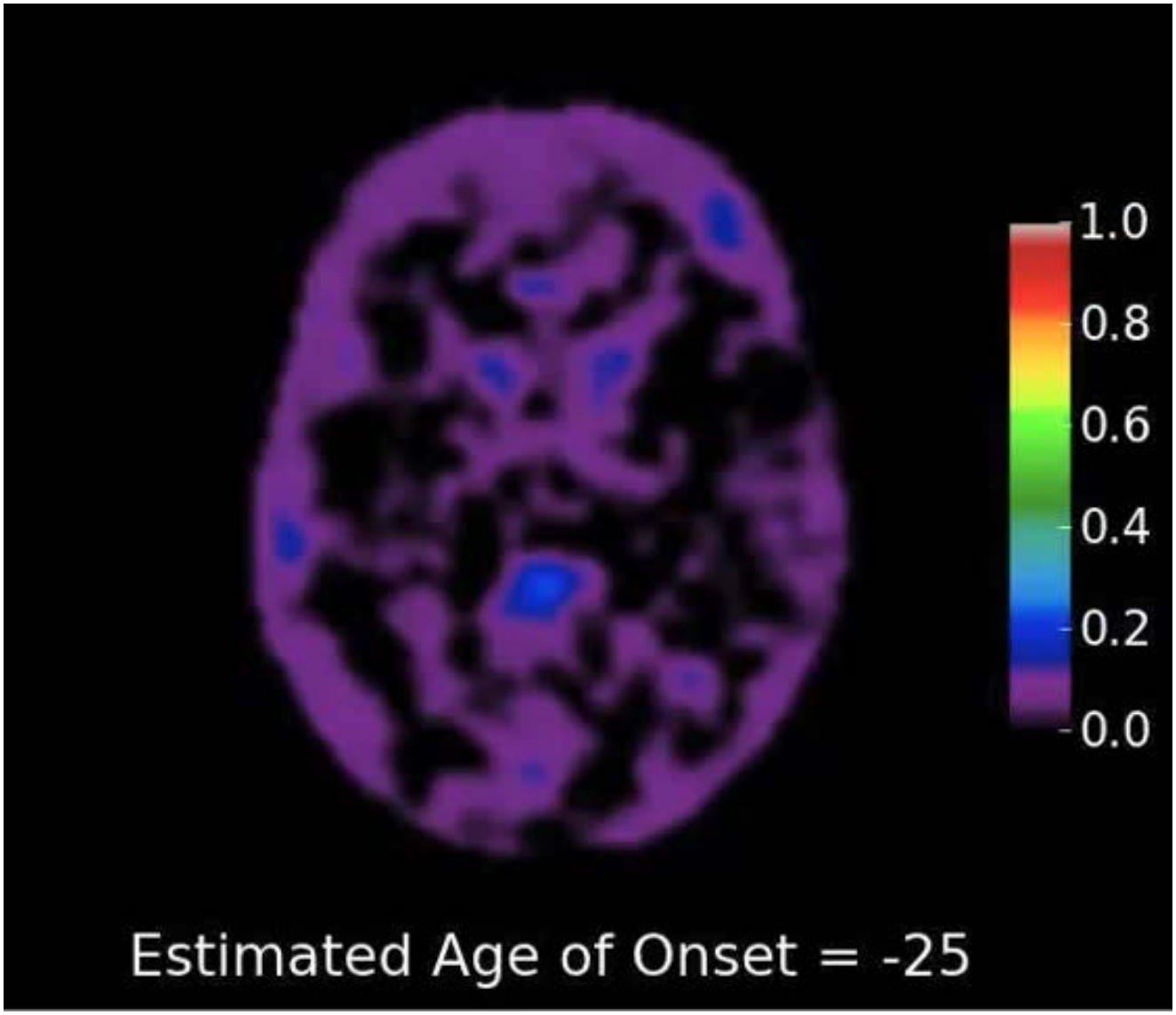
DIAN trial sites

Amyloid deposition begins at least 15 years prior to dementia onset in mutation carriers

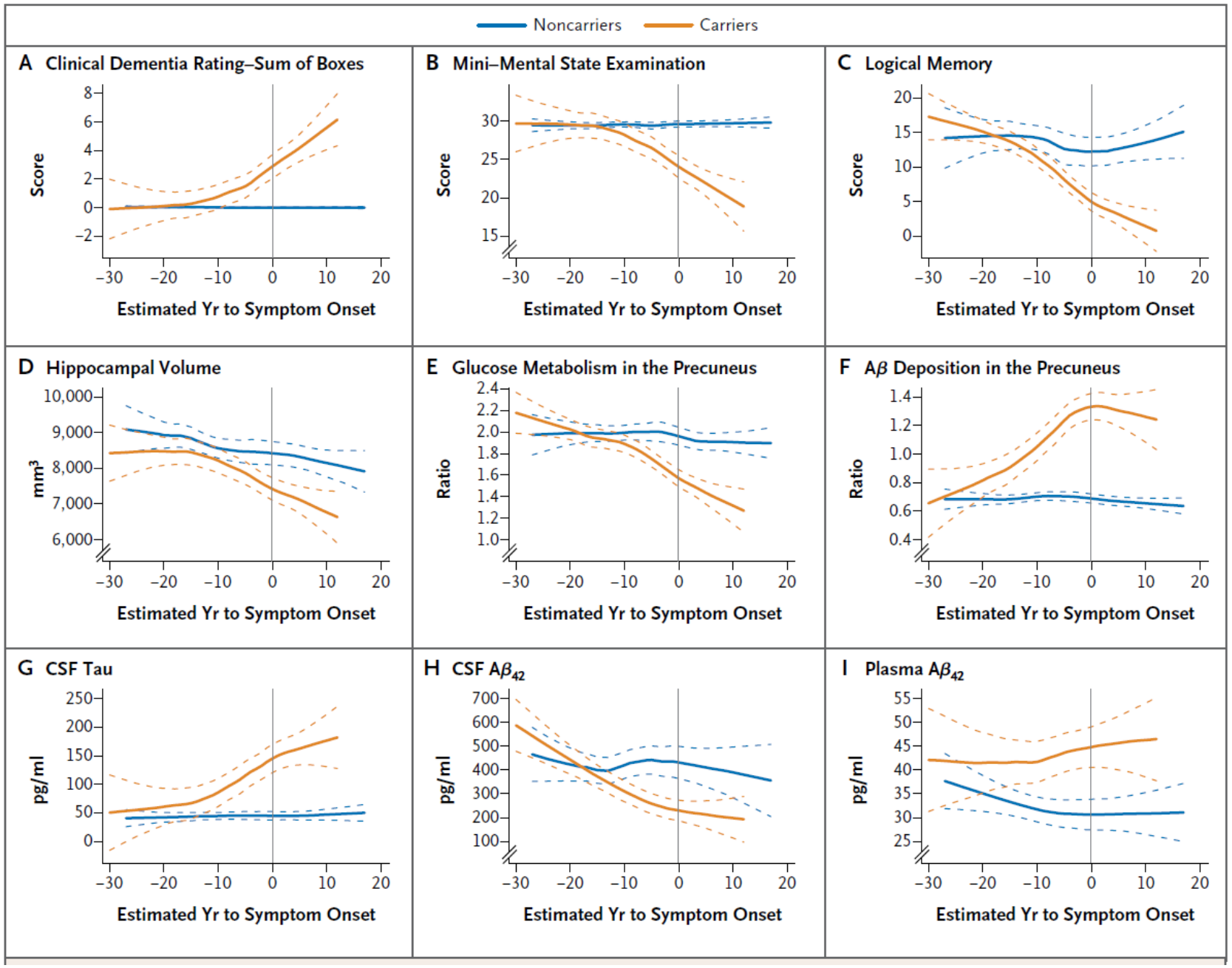


Courtesy of Tammie Benzinger; Bateman et. al NEJM 2012

DIAN amyloid deposition by estimated age of onset

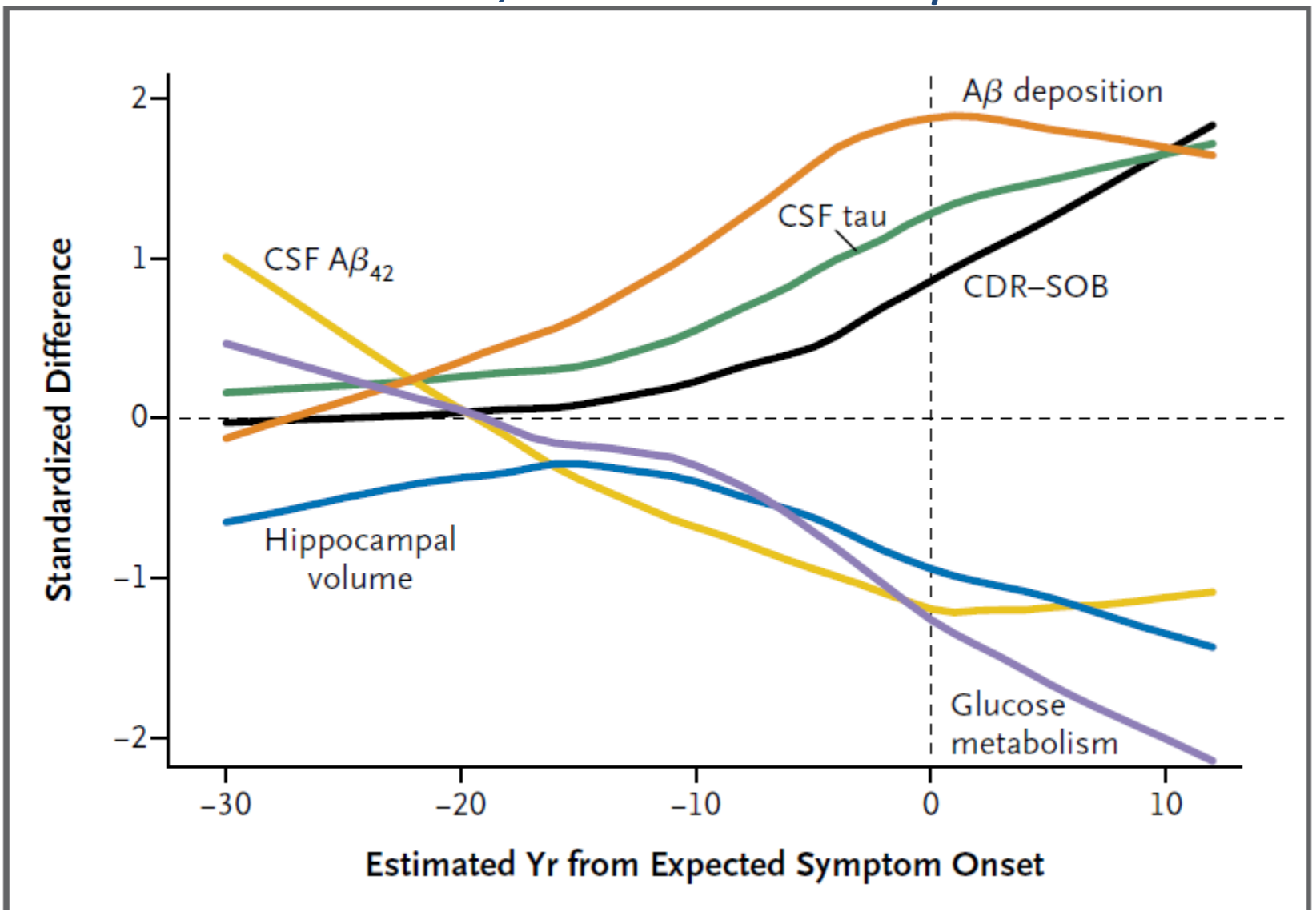


Courtesy of Tammie Benzinger; Bateman et. al NEJM 2012



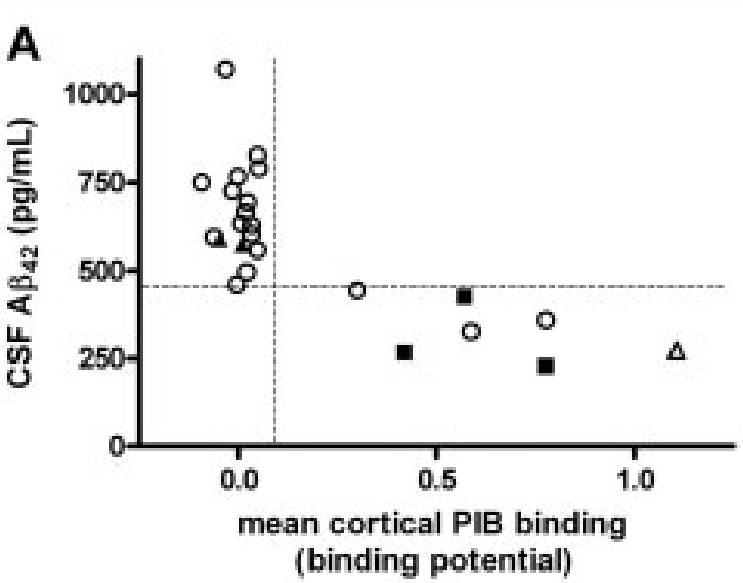
The DIAN; Bateman et. al NEJM 2012

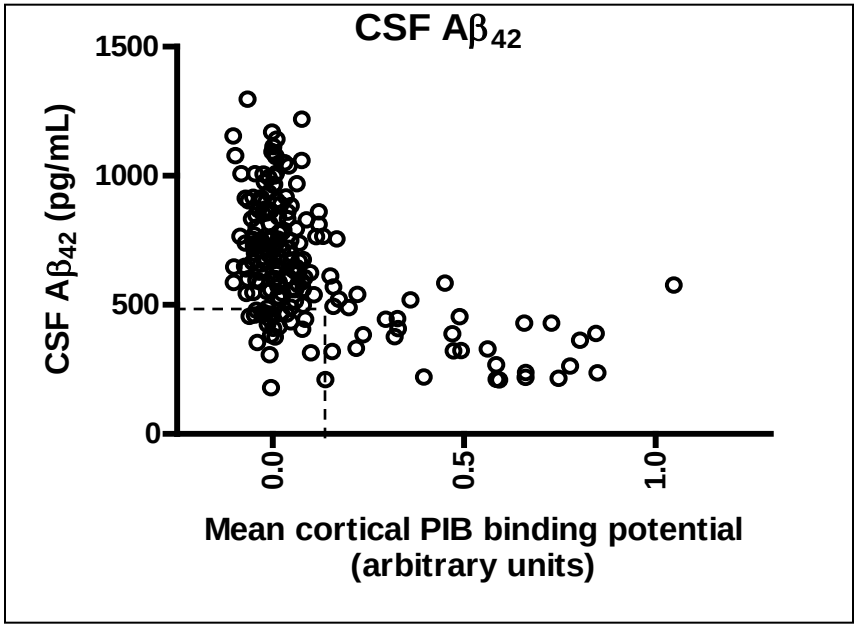
Comparison of Aβ, tau, brain atrophy, metabolism, and clinical impairment



The DIAN; Bateman et. al NEJM 2012

Low CSF $A\beta_{42}$ is a marker of cortical amyloid as detected by PET PIB, even in the absence of cognitive symptoms (CDR 0)





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Forsberg et al., 2008, Neurobiol Aging, 29:1456-65
Grimmer et al., 2009, Biol Psychiatry, 65:927-34
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Tolboom et al., 2009, J Nucl Med, 50:1464-70
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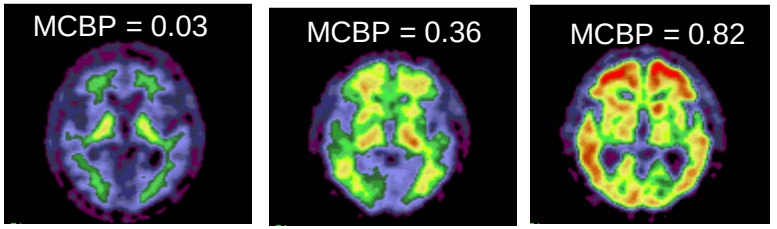


Interim Conclusions

- Currently more than 300 participants enrolled in DIAN
- The clinical, cognitive, imaging, and biochemical biomarkers of AD in mutation carriers is similar to late-onset sporadic Alzheimer's disease and can be detected at least **20 years** before estimated age of onset of dementia.
- The first clinical and cognitive changes begin at least **5 years** prior to estimated age of onset of dementia.
- The DIAN cohort is well-suited for proof-of-concept studies (drug effect on biomarkers) and for dementia prevention studies in pre-symptomatic carriers.

Rationale and design of Dominantly Inherited Alzheimer's disease trials

- **Current therapeutic trials may be too late**: Currently target slowing or halting the underlying disease (**disease modifying**), **but are not likely reverse the extensive neuronal death present at the onset of symptoms**.

- There is **certain risk** (~100% with known mutation in PS1, PS2 or APP) enabling prevention studies.

- **Disease modifying therapeutics are largely developed with animal models based on human disease causing mutations**. Thus, AD caused by known autosomal dominant mutations is **most likely to respond** to these proposed disease modifying treatments.

- Results from treatment trials in autosomal dominant AD will likely **bridge** cellular and mouse therapeutic research with sporadic AD therapeutic research.

Through public/private support and partnership, DIAN TU will launch trials to provide advancement of treatments, scientific understanding and improvements in the approach to Alzheimer's disease drug developments.

alzheimer's association®

DIAN Pharma Consortium

biogen idec · élan · Genentech A Member of the Roche Group · janssen · ALZHEIMER'S IMMUNOTHERAPY PROGRAM INNOVATION TO REMEMBER™ · Pfizer · Lilly · Mithridion · NOVARTIS · Pfizer · Roche · SANOFI

DIAN Biomarker Trial Design

- **3 different drugs** each with a unique target to alter the disease course
- 4 arms: 3 active drug, 1 placebo (**75% chance of active drug**)
- 160 mutation carriers, 40 per arm
- Estimated 80 non-carriers (placebo)
- Drug treatment duration = 2 years
- **Extend study if positive results**

Biomarker Outcomes

Primary biomarker outcome

- Based on drug mechanism of action and CNS target engagement

Secondary ‘downstream’ biomarker outcomes

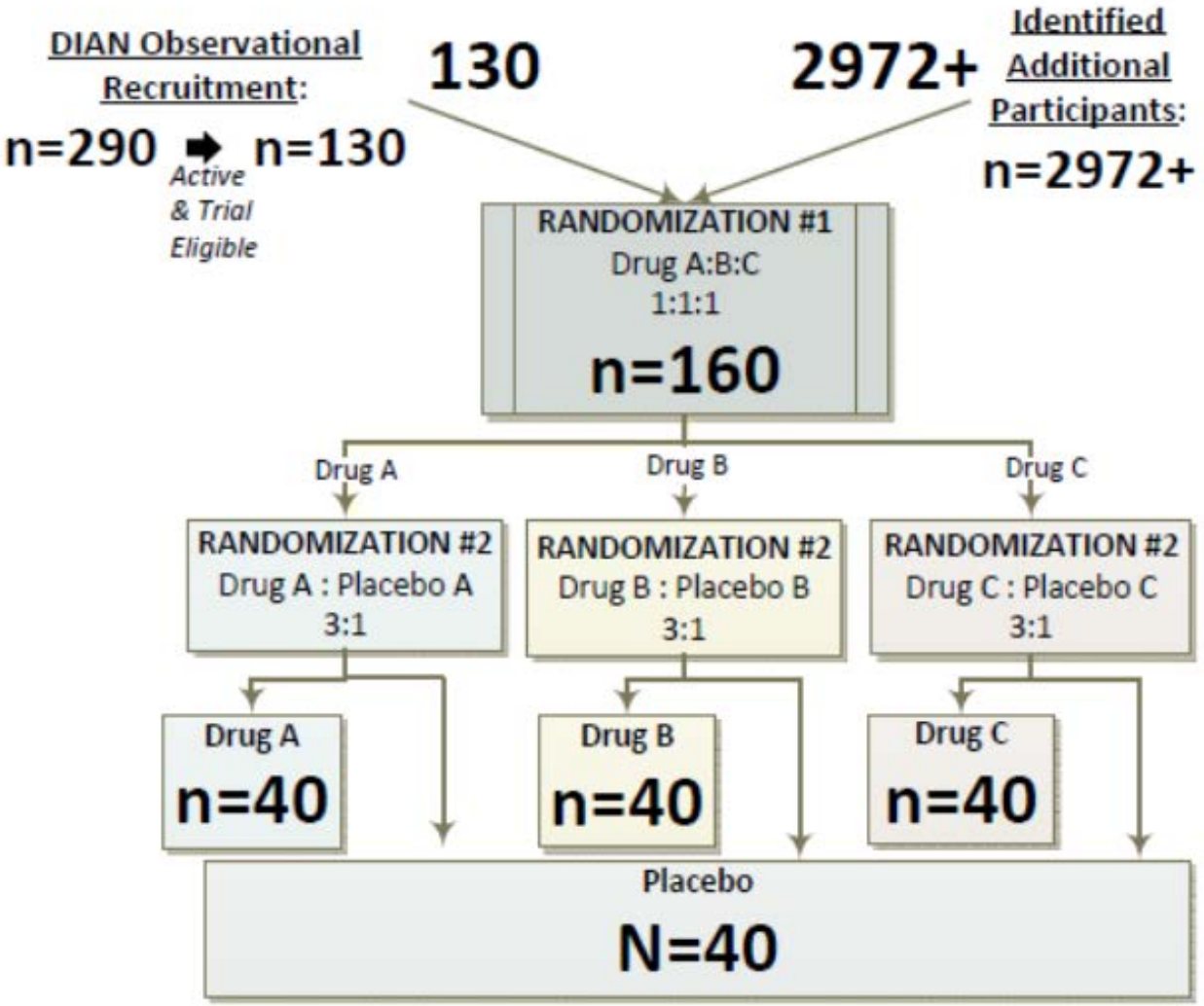
- CSF tau
- CSF p-tau
- volumetric MRI
- FDG PET
- Functional connectivity MRI

The first three drugs in the DIAN trial

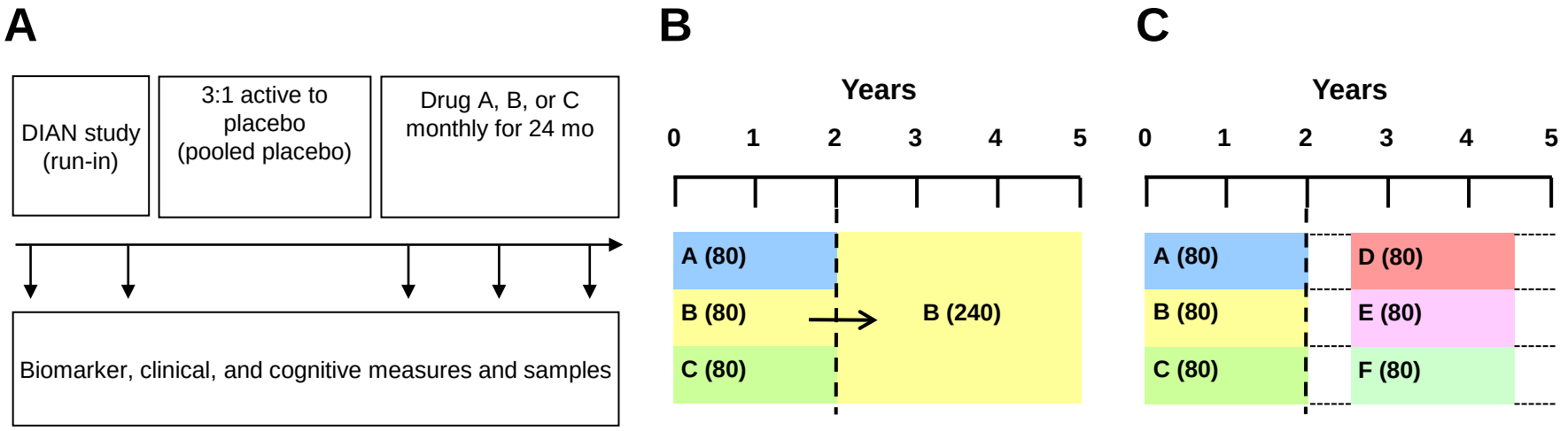
DRUG	TYPE	BM OUTCOME (TARGET)	BM OUTCOME (DOWNSTREAM)
Solanezumab (LILLY)	Anti-Aβ antibody (soluble Aβ)	Free CSF Aβ	CSF tau, ptau181, vMRI, amyloid PET, FDG PET, fcMRI
Gantenerumab (ROCHE)	Anti-Aβ antibody (fibrillar Aβ)	PIB PET	CSF tau, ptau181, vMRI, amyloid PET, FDG PET, fcMRI
BACE Inhibitor	Beta-Secretase Inhibitor	CSF Aβ	CSF tau, ptau181, vMRI, amyloid PET, FDG PET, fcMRI

- 2 yr treatment to BM outcome + 3 yr cognitive outcome for promising drug(s)
- ADAD from DIAN and DIAN Expanded Registry, N=240 (mixed mutations)
- N=240 (160 MC, 3 drug arms + pooled placebo, 40 each; ~80 NC, placebo)
- Age = -15 to +10 years compared to parental age of dementia onset

Subject Randomization from DIAN and DIAN Expanded Registry



Adaptive Design for drug(s) to continue to a Cognitive Endpoint Trial



Outcomes:

- If drug(s) demonstrate positive biomarker profiles, enrollment continues for a cognitive endpoint registration trial.
- If none of the three original drugs is successful, then new biomarker trials may be started.

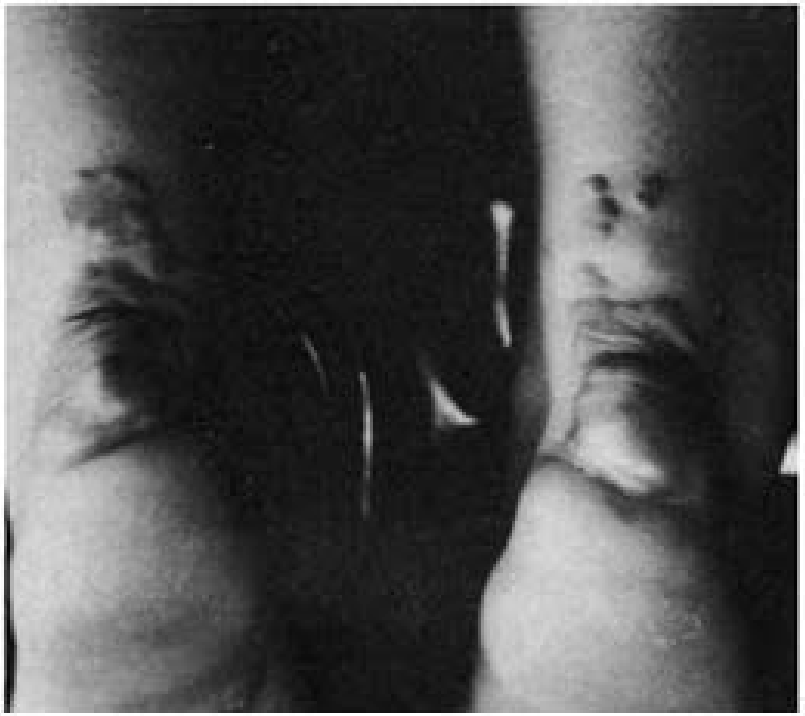
*Biomarker Power Analysis**

Efficacy outcome	Est'd power (n=32/arm)	2/3 redc'd effect size power (n=32/arm)	Reported effect size	Effect sizes @ 80% power	SD- rate of change/year
PIB SUVR	**99.6%**	**86.5%**	0.16 (p=0.003)	0.098	0.137
PIB SUVR	**>99.9%**	**>99.9%**	0.50 (p<0.05)	0.098	0.137
Unbound Free CSF $A\beta_{42}$	**>99.9%**	**>99.9%**	230 (p<0.001)	53.4	75
CSF tau	**>99.9%**	**>99.9%**	83.1 (p=0.09)	16.59	23.29
CSF ptau 181	**84.1%**	**50.6%**	9.0 (p=0.03)	8.52	11.94

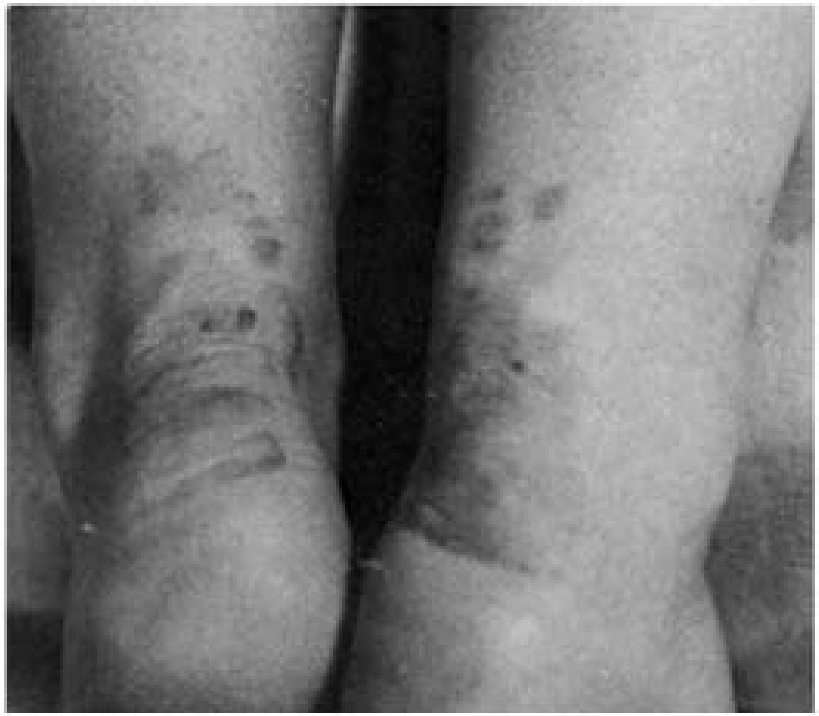
*Analysis performed on published data and DIAN longitudinal data (C. Xiong).
References: Rinne, 2010; Ostrowitzki, 2011; Farlow, 2011; Blennow, 2012

Historical Precedent:

Treatment of inherited high cholesterol with statin drug

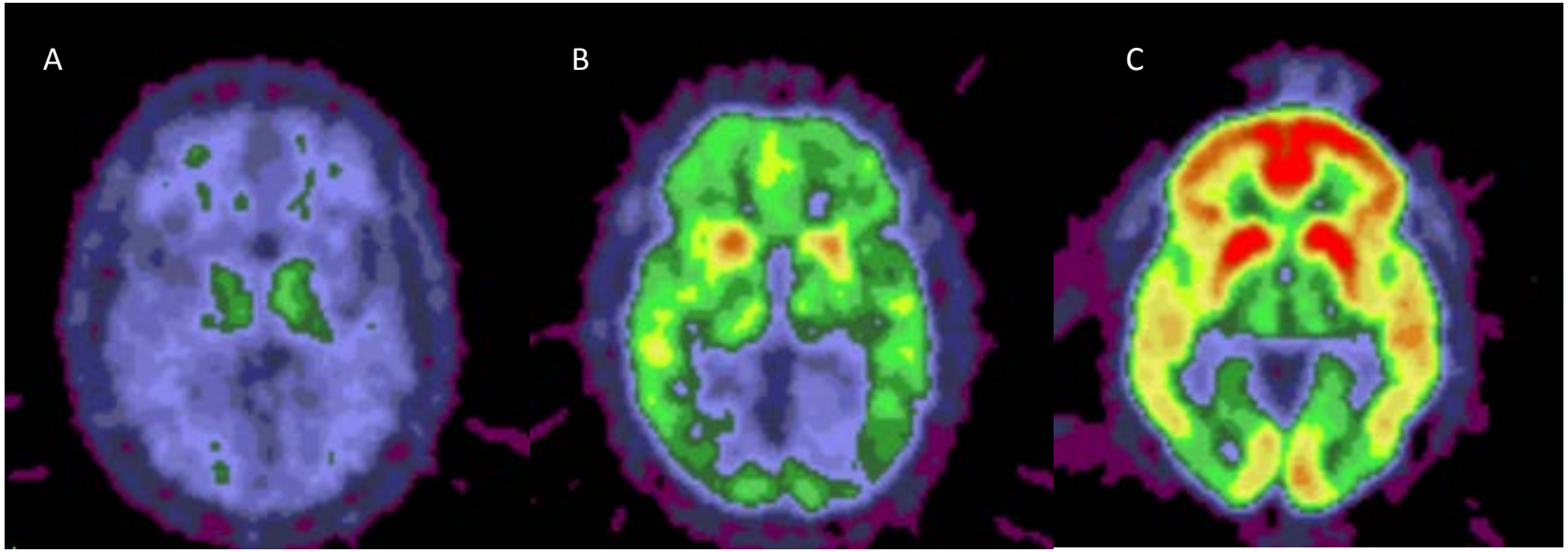


Pre-treatment



Post-treatment

Amyloid deposition in the 30's and 40's in people with ADAD Mutations



15 years prior to estimated symptoms

10 Years prior to estimated symptoms

~5 years after Alzheimer's disease symptoms

Courtesy of Mark Mintun and Randy Bateman

DIAN Trials Summary

- **Participants and patients eager for clinical trials.**
- **Strong scientific rationale for DIAN treatment trials.**
- **Regulatory agencies (FDA and EMA) supportive of autosomal dominant AD prevention trials.**
- **Fifteen DIAN therapeutic nomination packets have been received from Pharma.**
- **DIAN Pharma Consortium Formed to assist in clinical trial design – members currently include 10 pharmaceutical companies.**
- **DIAN Trials Unit established to design, implement and manage DIAN treatment trials.**
- **First studies targeted to start in early 2013**

The DIAN and the DIAN TU

The DIAN participants and family members

The Alzheimer's Association, ADAD Forum, DIAN Pharma Consortium

DIAN Principal Investigator
JC Morris

DIAN TU Principal Investigator
RJ Bateman

Coordinating Center Cores

Admin – JC Morris
Clinical – RJ Bateman
Biomarkers – AM Fagan
Biostatistics – C Xiong

Genetics – AM Goate
Imaging – T Benzinger
Informatics – D Marcus
Neuropathology – NJ Cairns

Performance Sites

- **United States:** Washington Univ (Bateman), MGH/BWH (Sperling), Butler Hosp/Brown Univ (Salloway), Columbia Univ (Mayeux), Indiana Univ (Ghetti), UCLA (Ringman), U of Pittsburgh (Klunk), Mayo Clinic, Jacksonville (Graff-Radford)
- **Europe:** Institute of Neurology, Univ College London (Rossor), Ludwig-Maximilians-Universität München (Danek), University of Tübingen (Jucker)
- **Australia:** Prince of Wales Medical Research Institutes, Sydney (Schofield), Mental Health Health Research Institute, Melbourne (Masters), Edith Cowan Univ , Perth (Martins)