

# **Alzheimer's Prevention Initiative**

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Banner Alzheimer's Institute · Banner Research · University of Arizona · Arizona State University  
Translational Genomics Research Institute · Arizona Alzheimer's Consortium

# **financial disclosures**

## **scientific advisor**

Alzheon, AstraZeneca, CereSpir, Eisai, Eli Lilly, Sanofi

## **industry-supported research grants & contracts**

Genentech/Roche, Avid/Eli Lilly, Novartis

## **NIH grants, foundation grants & philanthropy**

## **patent application**

biomarker strategy for the evaluation of preclinical AD treatments (pending)

**the problem**

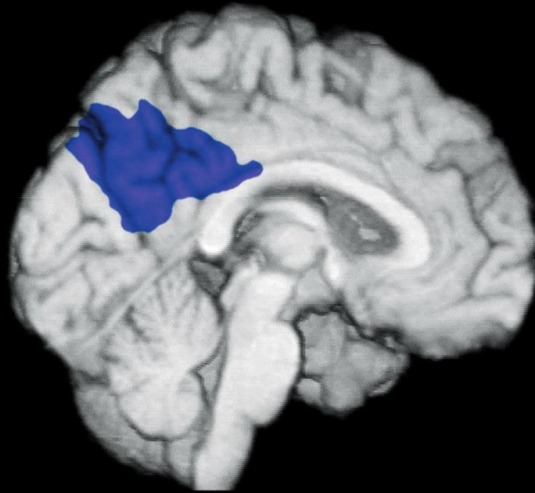
<i>APOE</i> $\epsilon 4$ copies	prevalence	AD risk	dementia onset
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0	73%	20%	84
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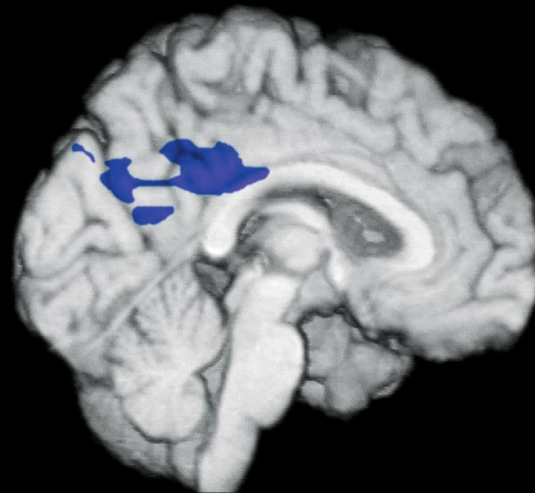
1	24%	47%	75
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2	3%	91%	68
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*clinically affected*

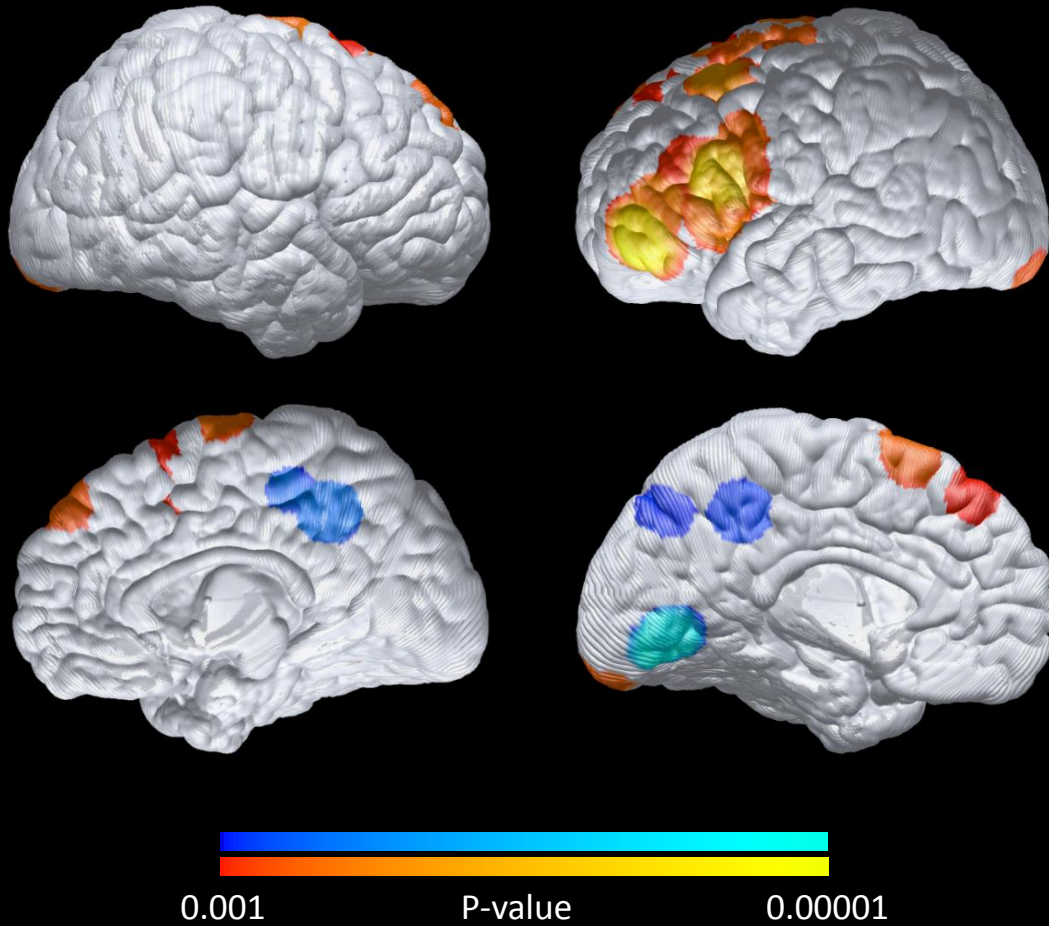


*at-risk*



Reiman, *New Engl J Med* 1996; *Ann Neurol* 1999; *Clin Neurosci Res* 2001, *PNAS* 2001, 2004, 2005, 2009; Chen, *Am J Psychiatry* 2007; Caselli, *New Engl J Med* 2010; Liang, *PNAS* 2008; Valla, *J Alzheimers Dis* 2010 ; Reiman, *Biomarkers Med* 2010; Fleisher, *Arch Neurol* 2011; Sperling, *Alzheimers Dementia* 2011; Reiman, Quiroz, *Lancet Neurol* 2012; Fleisher, *Lancet Neurol* 2012; Protas, *Arch Neurol* 2012; Dean, Jerskey, Chen, *JAMA Neurol* 2013; Langbaum, *Alzheimers Dementia* 2014; Ayutyanont, *J Clin Psychiatry* 2014; Fleisher, *JAMA Neurol* 2015; Chen, *J Nucl Med* 2015

gray matter volume differences in 59  
6-22 mo-old *APOE*  $\epsilon 4$  carriers & non-carriers



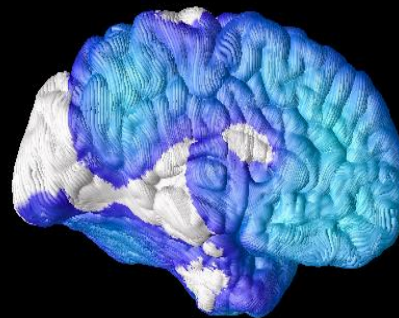
no APOE4 genes



1 APOE4 gene



2 APOE4 genes

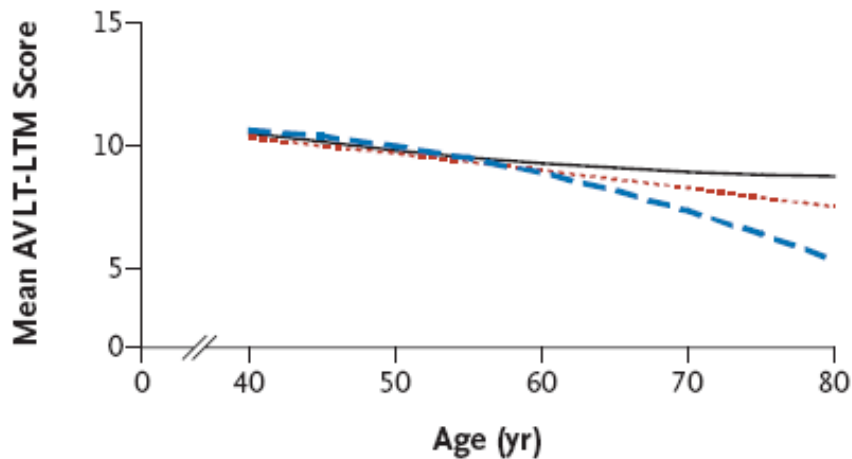


clinical AD

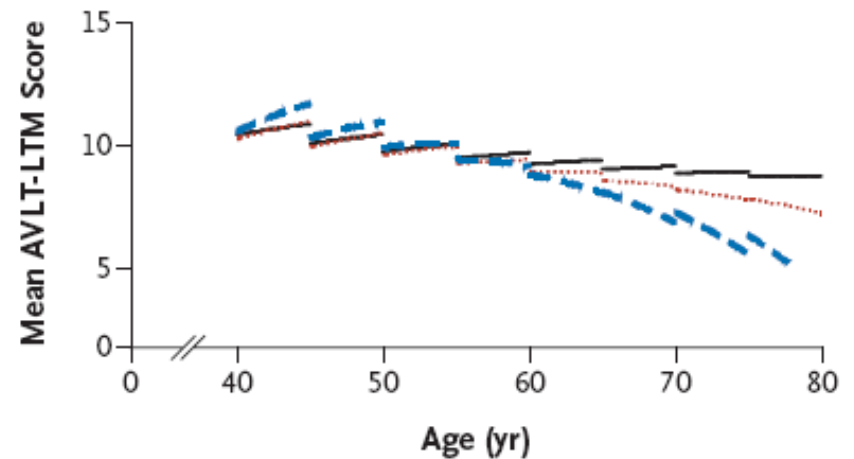


age-related memory decline in 815 cognitively unimpaired 21-97 yo adults  
(79 *APOE*  $\epsilon 4$  homozygotes, 238  $\epsilon 4$  heterozygotes & 498  $\epsilon 4$  non-carriers)

A Cross-Sectional Analysis



B 5-Yr Longitudinal Analysis



# new data analysis methods

Fox et al, *J Cereb Blood Flow Metab* 1988;

Chen et al, *J Cereb Blood Flow Metab* 1998, *Phys Biomed* 2007; *NeuroImage* 2004, 2009, 2010, 2011, *J Nucl Med* 2015;

Langbaum et al, *Alzheimers Dementia* 2014; Ayutyanont et al, *J Clin Psychiatry* 2014;

**catch-22**



ALZHEIMER'S  
**PREVENTION**  
INITIATIVE

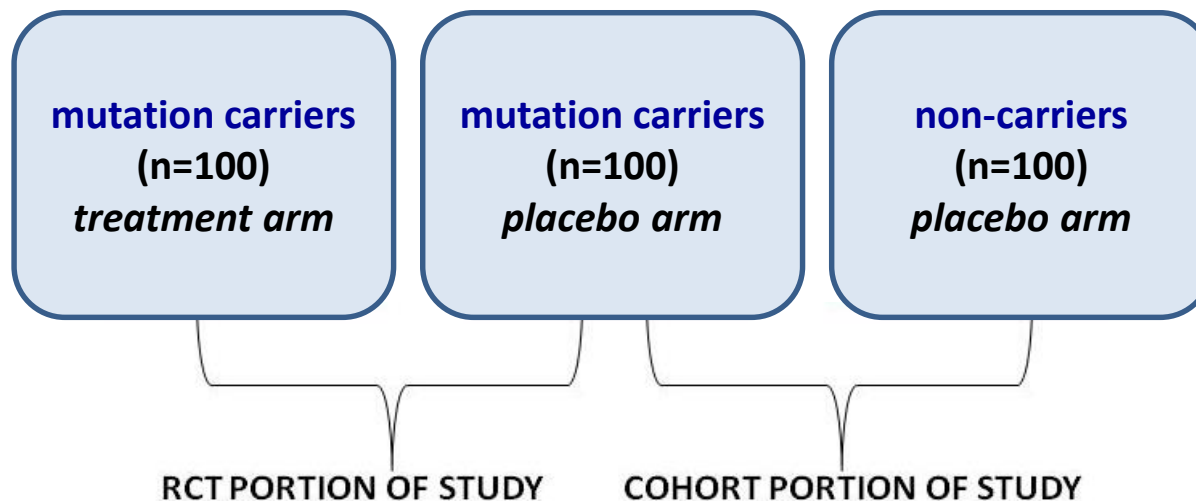
## a program to accelerate the evaluation of AD prevention therapies

- prevention / theragnostic biomarker development trials
  - 30-60 yo *PSEN1* E280A mutation carriers
  - 60-75 yo *APOE4* homozygotes
- registries to support these & other trials
  - Colombian API PSEN1 E280A Registry
  - Alzheimer's Prevention Registry ([www.endALZnow.org](http://www.endALZnow.org))
- other prevention trials (TBD)

## API trial goals

1. Evaluate anti-A $\beta$  therapies in potentially license-enabling prevention trials
2. Provide a better test of the amyloid hypothesis
3. Help qualify biomarkers for use as reasonably likely surrogate endpoints
4. Provide a foundation for other AD prevention trials
5. Complement, support & benefit from other prevention programs
6. Provide a public resource of data & samples after each trial is over
7. Determine the initial & longer-term impact of APOE genetic test disclosure
8. Help empower persons at imminent risk in the fight against AD

## API ADAD Trial



**60-mo double-blind, placebo-controlled trial of an anti-A $\beta$  agent**

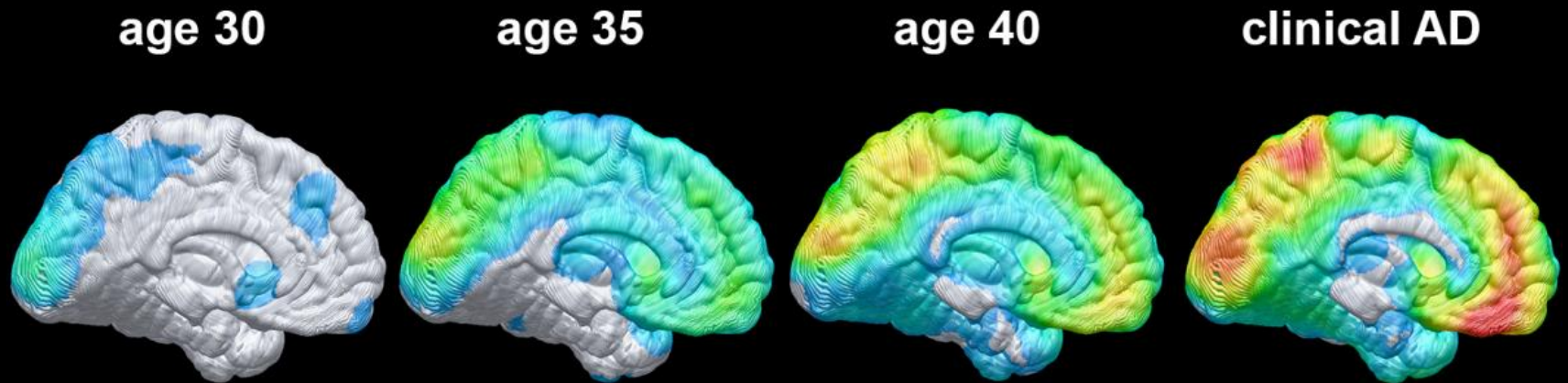
crenezumab SC every 2 weeks in members of the *PSEN1 E280A* kindred

Primary endpoint: change in the API composite cognitive score

24-mo interim analysis: florbetapir PET, FDG PET, MRI, CSF & cognitive/clinical endpoints

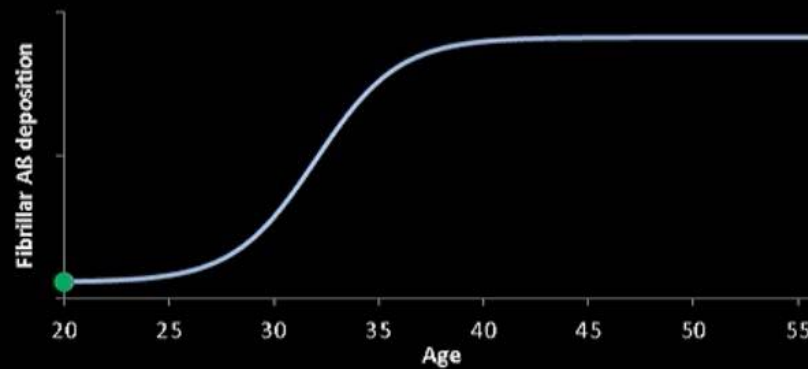
in collaboration with Genentech & the University of Antioquia

**increases in fibrillar amyloid deposition  
in *PSEN1 E280A* mutation carriers**



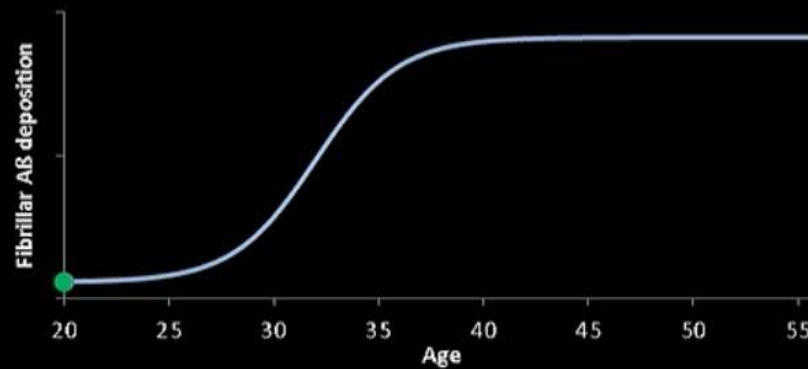


25 years before kindred's median age at clinical onset  
mutation carriers, healthy

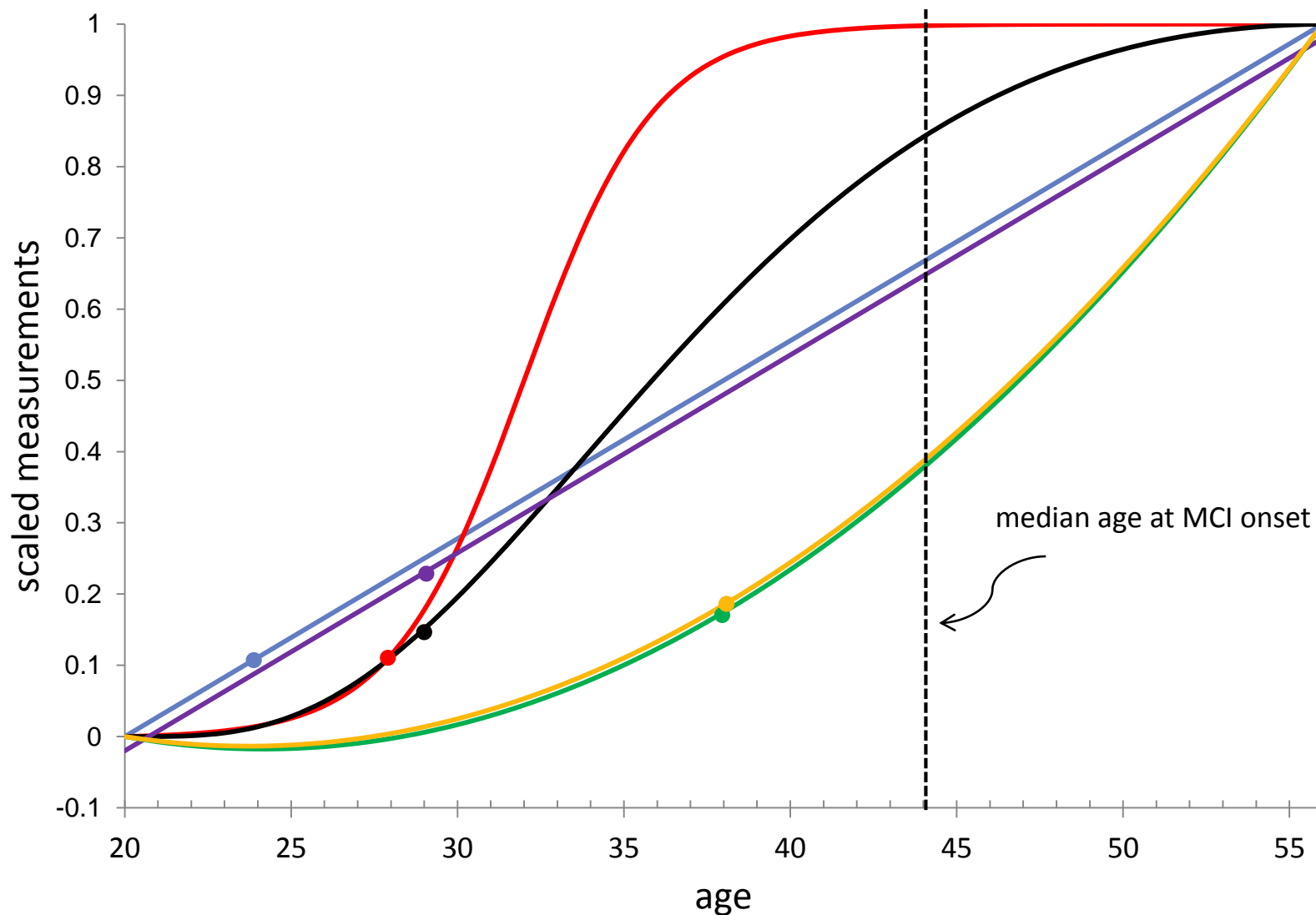




25 years before kindred's median age at clinical onset  
mutation carriers, healthy



## relationships between AD measures & age in *PSEN1* E280A mutation carriers





## finding composite cognitive test scores that predict clinical progression

- exhaustive searches to identify the optimal combination of cognitive tests in multiple longitudinal cohorts
- similar composite test scores in ADAD & LOAD cohorts
- power estimates for our API ADAD & APOE4 trials

## development of the API ADAD composite cognitive test score

### **Rush ADC Cohorts**

1. CERAD Word List Delayed Recall
2. Logical Memory Delayed Recall
3. MMSE Orientation to Place
4. MMSE Orientation to Time
5. Raven's Progressive Matrices

### ***PSEN1 E280A Cohort***

1. CERAD Word List Delayed Recall
2. Constructional Praxis
3. Boston Naming\*
4. MMSE Orientation to Time
5. Raven's Progressive Matrices

## estimated treatment effects in 100 unimpaired *PSEN1* E280A carriers per group\*

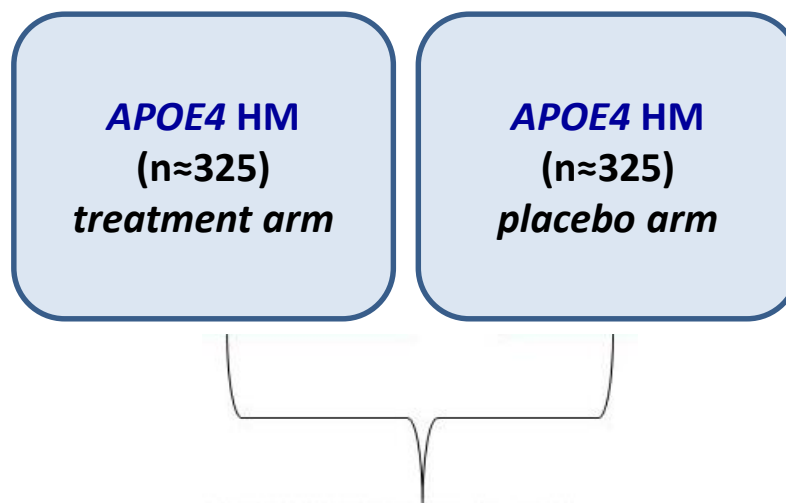
endpoint	24-mo treatment effect	60-mo treatment effect
API composite cognitive test score	44% <sup>1</sup>	29% <sup>1</sup>
sROI CMRgl decline	23% <sup>2</sup>	--
whole brain shrinkage	18% <sup>2</sup>	--
fibrillar A $\beta$ accumulation	27% <sup>2</sup>	--

\*assumes 80% power, two-tailed p=0.05 & 5% annual attrition

<sup>1</sup>estimated in *PSEN1* E280A mutation carriers

<sup>2</sup>estimated in *APOE4* homozygotes

## Original API APOE4 Trial Design



**60-mo double-blind, placebo-controlled trial of an investigational anti-A $\beta$  agent**

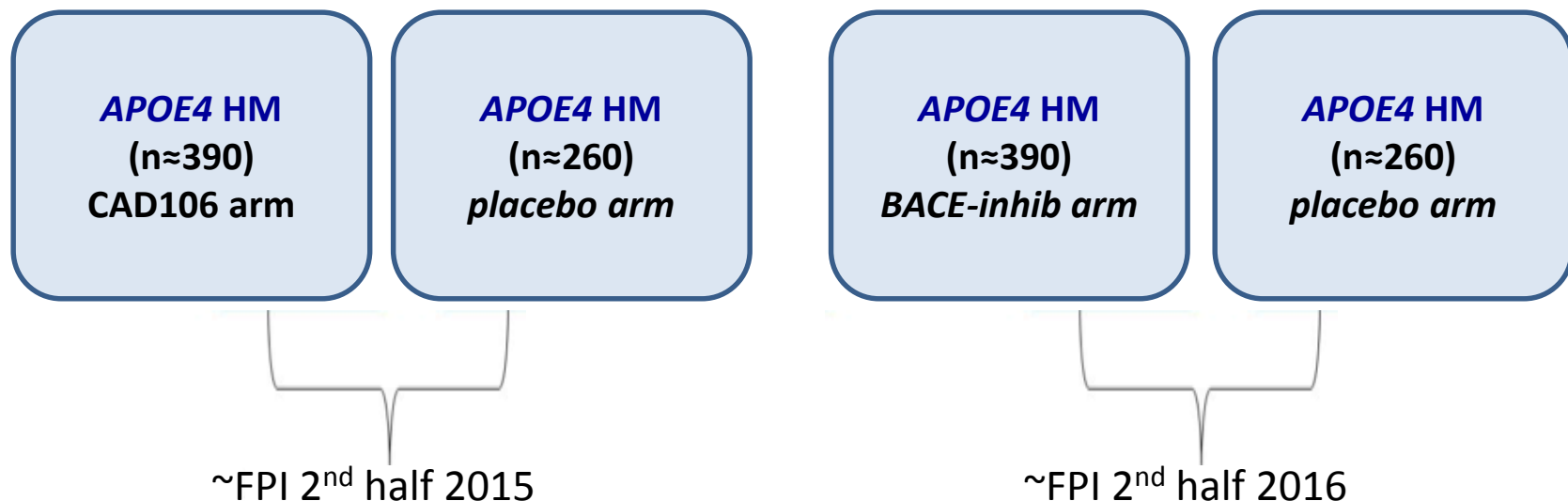
Primary endpoint: change in the API composite cognitive score

24-mo interim analysis: florbetapir PET, FDG PET, MRI, CSF & cognitive/clinical endpoints

Tau PET to be added (with AMP support)

*APOE* genetic test disclosure, assessment of short- & longer-term impact

## Current API APOE4 Trial Design



**60-mo double-blind, placebo-controlled trial of two investigational anti-A $\beta$  agents**

Primary endpoint: change in the API composite cognitive score

24-mo interim analysis: A $\beta$ , tau, & FDG PET, MRI; CSF, cognitive, & clinical endpoints

APOE genetic test disclosure, assessment of short- & longer-term impact

~60 sites in North America & Europe

in collaboration with Novartis

## API Preclinical Composite Cognitive Test Scores

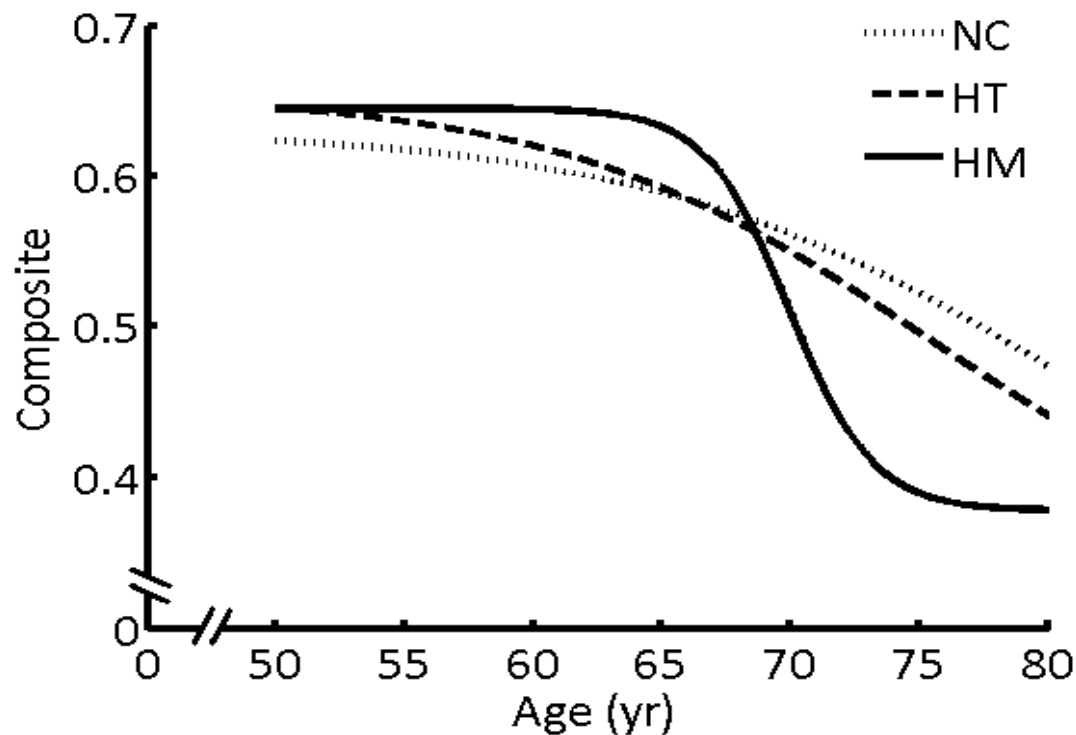
### API ADAD Composite Tests

1. Word List Delayed Recall
2. Ravens Prog. Matrices – Subset A
3. Multilingual Naming Test
4. CERAD Constructional Praxis
5. MMSE Orientation to Time

### API APOE4 Composite Tests

1. Word List Delayed Recall
2. Ravens Prog. Matrices – Subset A
3. Logical Memory Delayed Recall
4. Symbol Digit Modalities
5. Judgment of Line Orientation
6. MMSE Orientation to Time
7. MMSE Orientation to Place

## UDS-based composite cognitive test scores in unimpaired APOE4 HMs, HTs & NCs



optimal ages to track preclinical cognitive decline:  
60-75 in HMs, 70-80 in HTs

## estimated treatment effects in 325 unimpaired 60-75 yo *APOE4* HM per group\*

endpoint	24-mo treatment effect	60-mo treatment effect
API composite cognitive test score	65%	29%
sROI CMRgl decline	12%	--
whole brain shrinkage	9%	--
fibrillar A $\beta$ accumulation	14%	--

\*assumes 80% power, two-tailed  $p=0.05$  & 5% annual attrition  
estimated in *APOE4* homozygotes

# Alzheimer's Prevention Registry

**[www.endAlZnow.org](http://www.endAlZnow.org)**

## **Executive Committee**

Jessica Langbaum • Marilyn Albert • Kyle Brown • Meryl Comer • Jeff Cummings • Jennifer Manly • Ron Petersen  
Reisa Sperling • Gabrielle Strobel • Michael Weiner • Pierre Tariot • Eric Reiman • Maria Carillo (ex officio)

**what about our clinically affected patients?**

# Collaboration for Alzheimer's Prevention (CAP)

Stacie Weninger · Maria Carrillo · Neil Buckholtz · Lori Ryan · Russell Katz · Randy Bateman · John Morris

Reisa Sperling · Paul Aisen · Kathleen Welsh-Bohmer · Jessica Langbaum · Pierre Tariot · Eric Reiman

**Fidelity Biosciences Research Initiative · Alzheimer's Association · NIA · DIAN · A4 · TOMMORROW · API**

**new ways to work together**



New York Times, with permission



## acknowledgements: my API partners





## our API ADAD & APOE4 trial partners



# acknowledgements

## **National Institute on Aging**

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## **Colciencias**

1115-408-20512, 1115-408-20543

## **State of Arizona**

Arizona Alzheimer's Consortium

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**Francisco Lopera** & our University of Antioquia colleagues

Shehnaaz Suliman, Carole Ho & our Genentech/Roche colleagues

Michael Ryan, Ana Graf & our Novartis Colleagues

**Richard Caselli, Kewei Chen** & our Arizona APOE Cohort colleagues

Our BAI & Arizona Alzheimer's Consortium colleagues