launching a new era in Alzheimer's prevention research

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financial disclosures

scientific advisor

Amnestix/Sygnis, AstraZeneca, Baxter, Bayer, Chiesi, Eisai, Elan,
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patent application

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

our rallying cry

Now is the time
to launch the era of
Alzheimer's prevention research!

ALZHEIMER'S PREVENTION INITIATIVE

why now?

1. the urgent need
2. suggested but unproven "healthy lifestyle" interventions
3. investigational AD-modifying treatments
4. too little too late?
5. AD biomarkers

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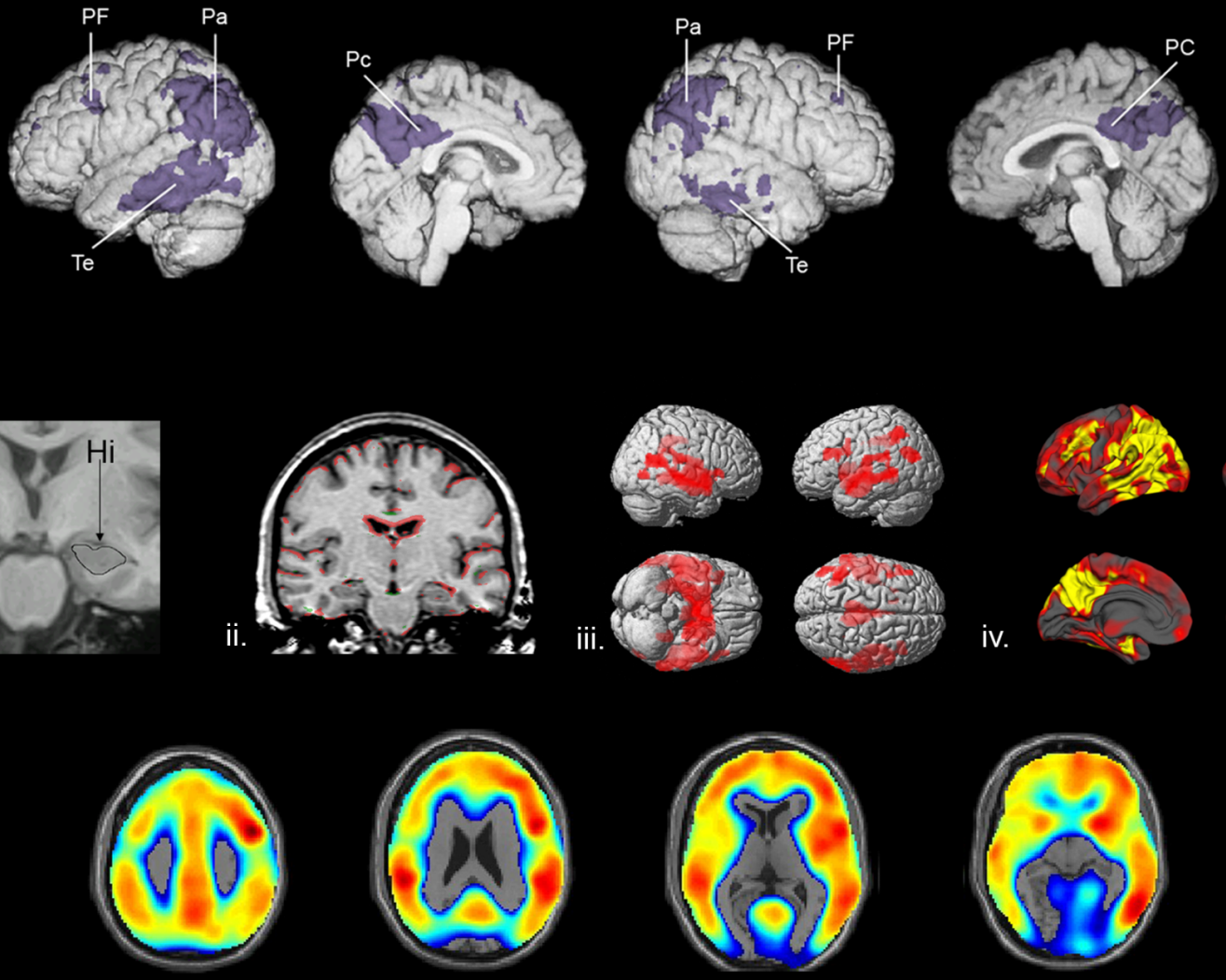
what's been holding us back?

1. too many research participants, too much time & too much money
2. insufficient evidence to qualify AD biomarkers for use as surrogate endpoints
3. investigational AD-modifying treatment safety & tolerability data

the best established brain imaging measurements in the detection & tracking of AD



From Reiman & Langbaum, in *Imaging in the Aging Brain*, 2009

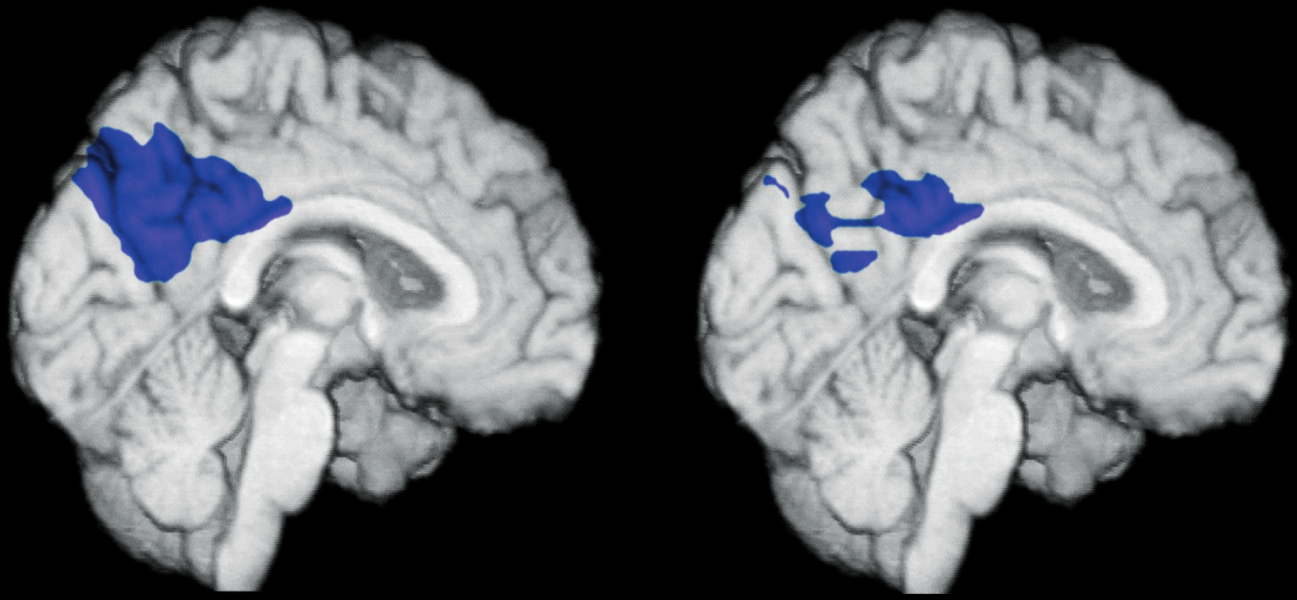
APOE ε4 Copies	prevalence	% with AD	onset age
0	73%	20%	84
1	24%	47%	75
2	3%	91%	68

adapted from Corder et al, *Science* 1993

detecting & tracking Alzheimer's disease biomarkers years before the onset of symptoms

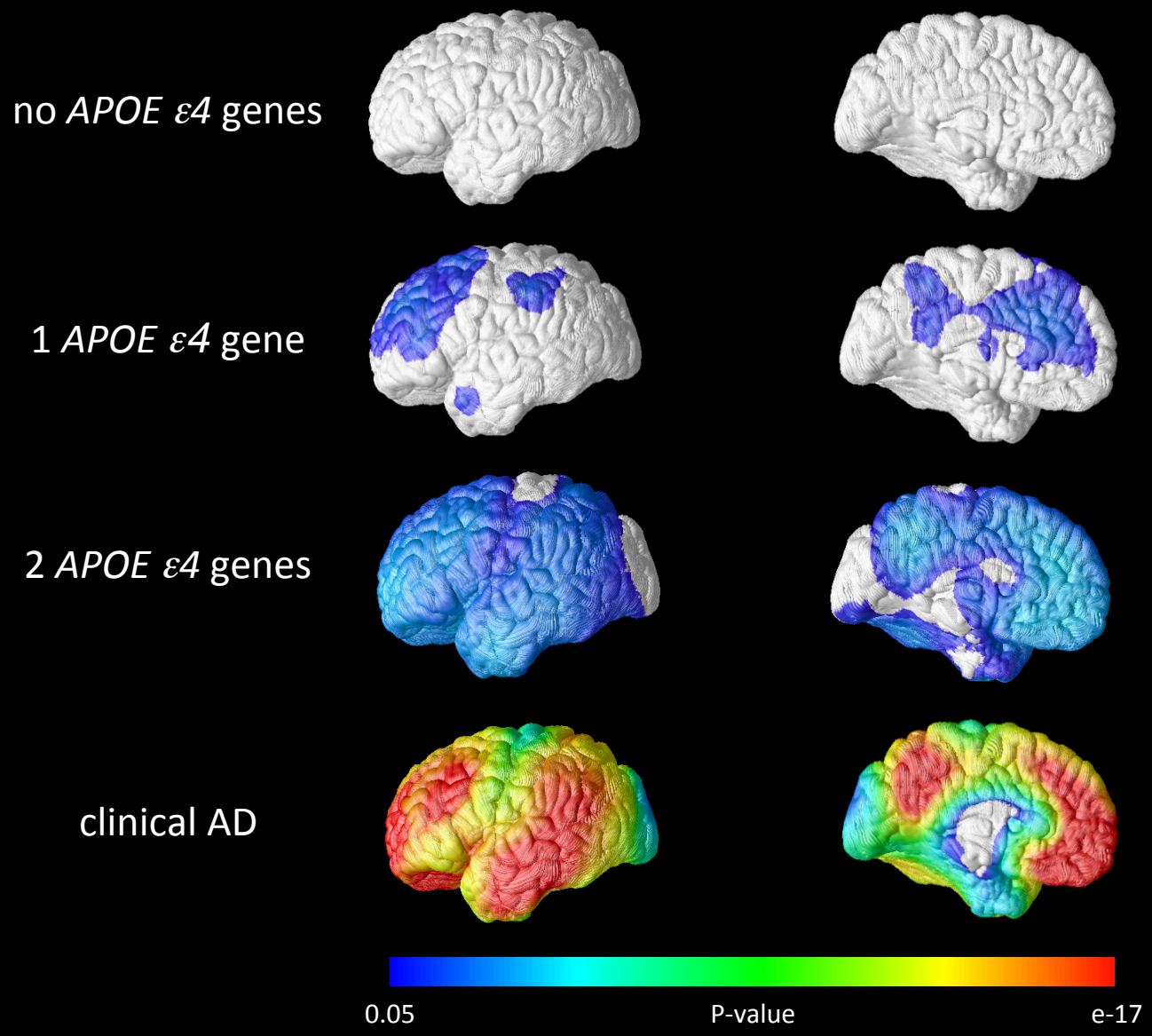
clinically affected

at-risk



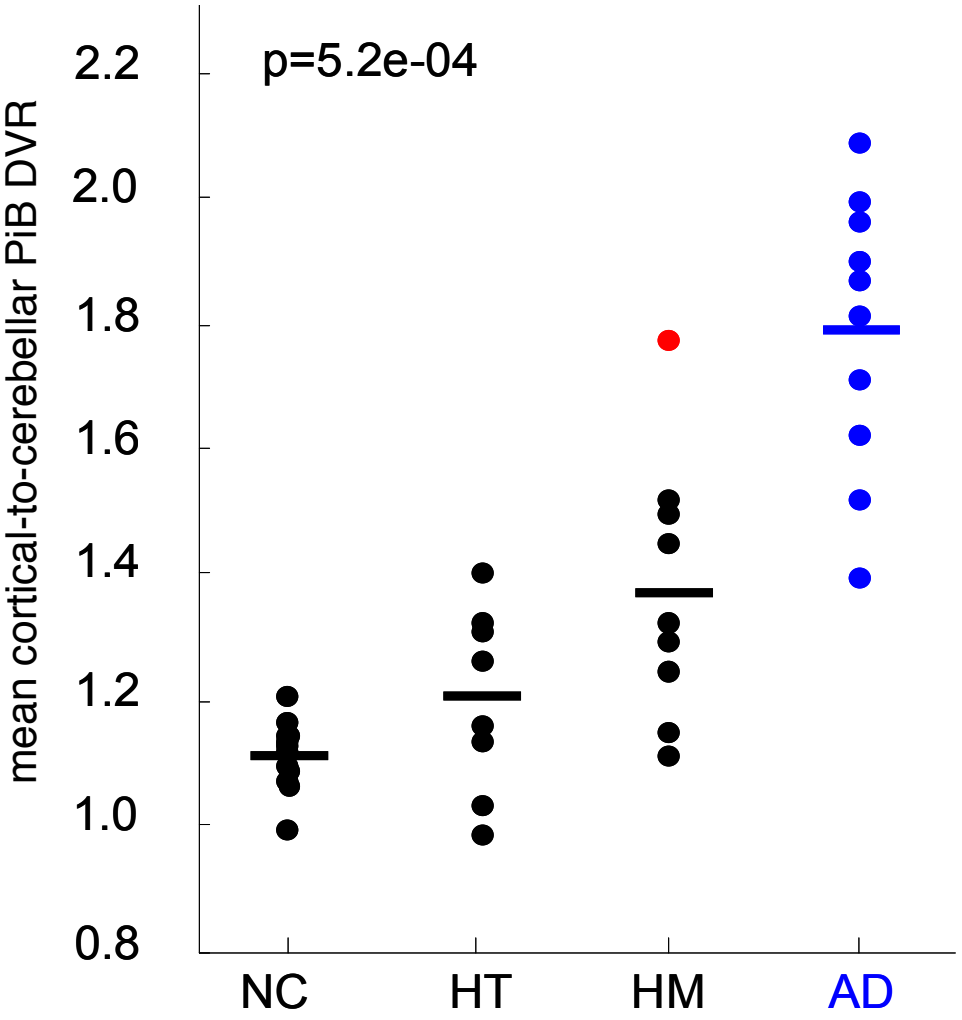
Reiman et al, *New Engl J Med* 1996 & *PNAS* 2001, 2004, 2005, 2009;
Chen et al, *Am J Psychiatry* 2007; Caselli et al, *New Engl J Med* 2009

PiB PET measurements of fibrillar Aβ burden in cognitively normal older adults at three levels of genetic risk for late-onset AD



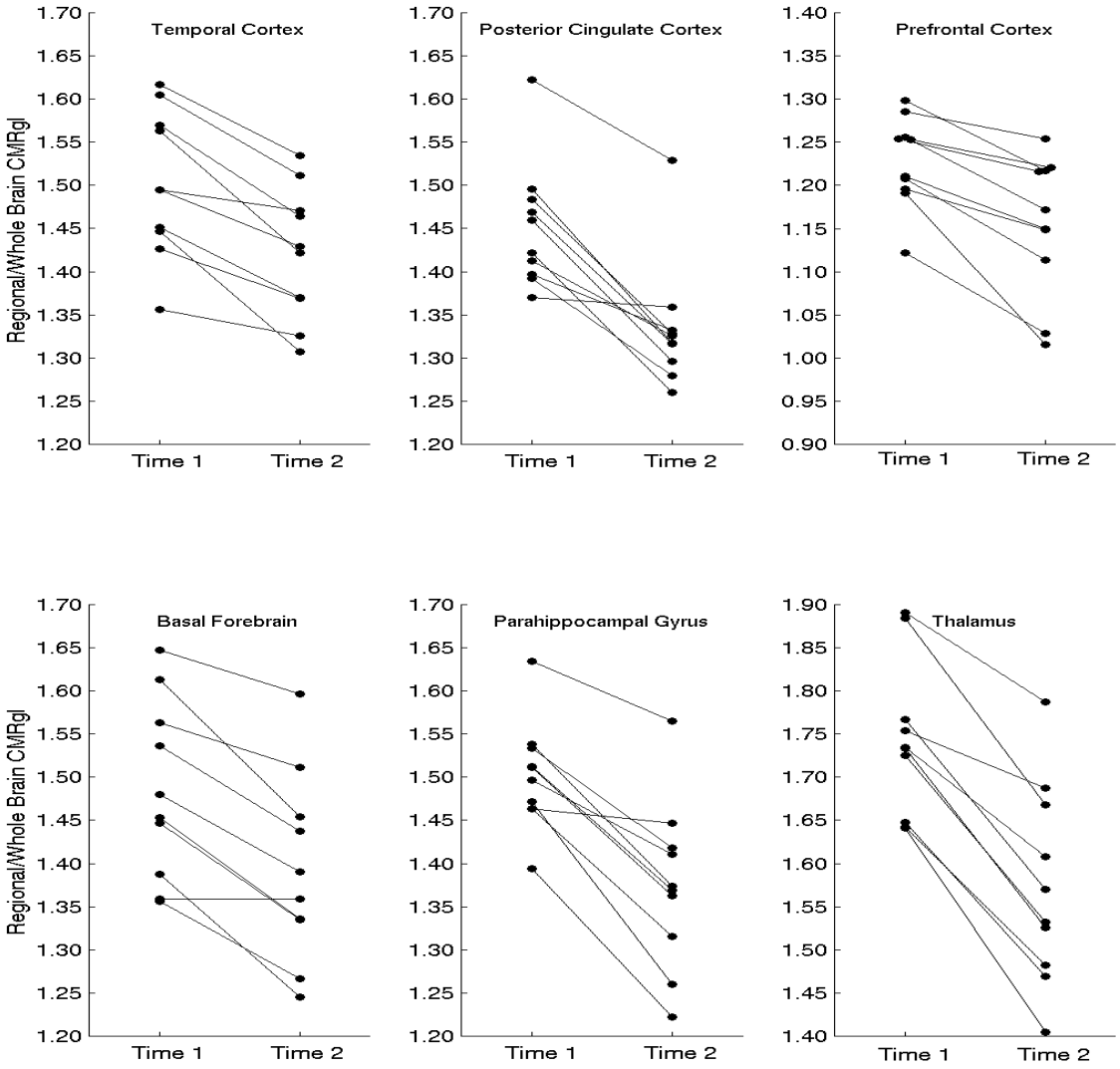
Reiman et al, *PNAS* 2009

PiB PET measurements of fibrillar Aβ deposition in cognitively normal older people at three levels of genetic risk for late-onset AD



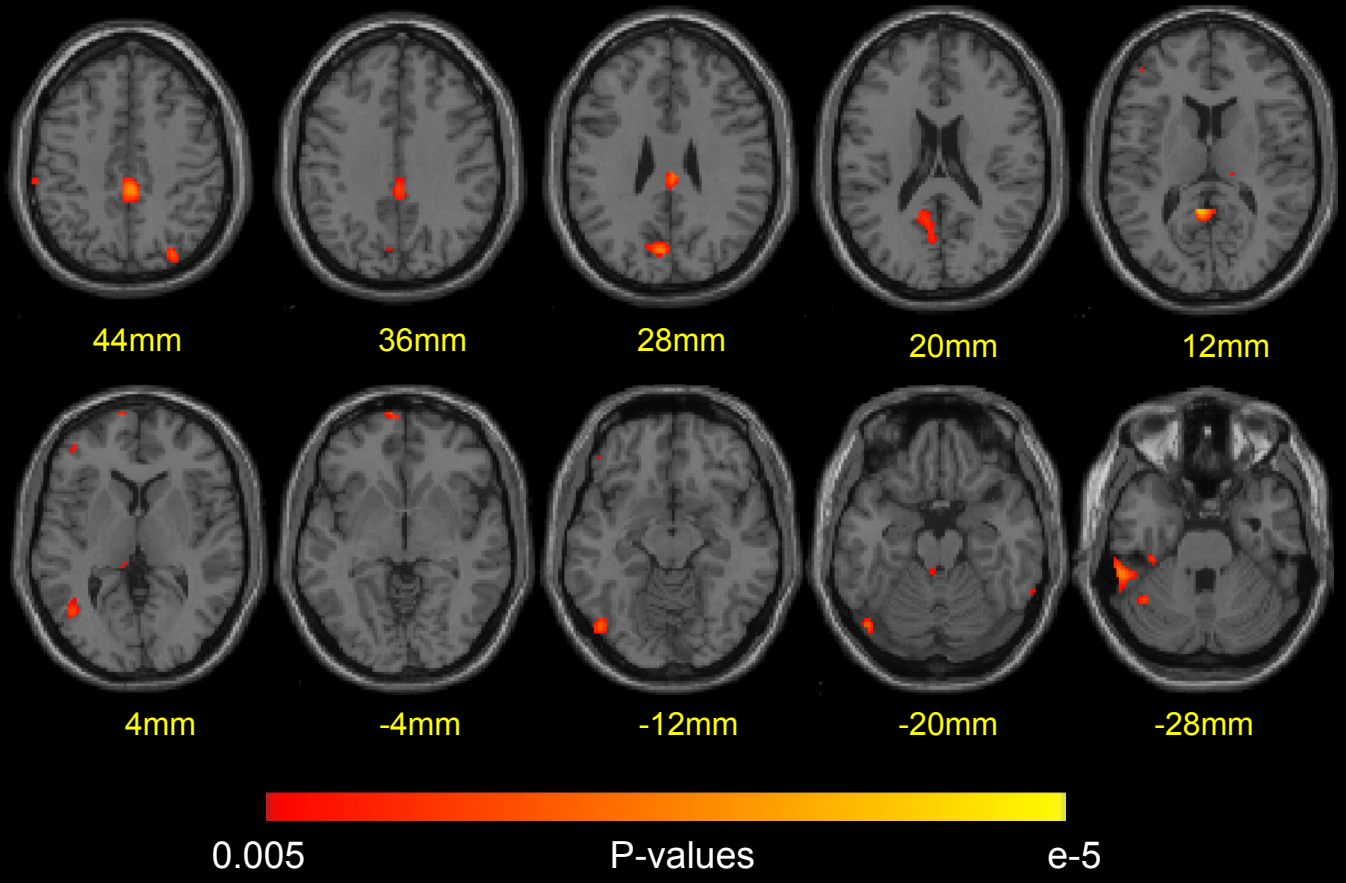
Reiman et al, *PNAS* 2009

two-year CMRgl declines in cognitively normal late middle-aged *APOE ε4* heterozygotes



Reiman et al, *PNAS* 2001

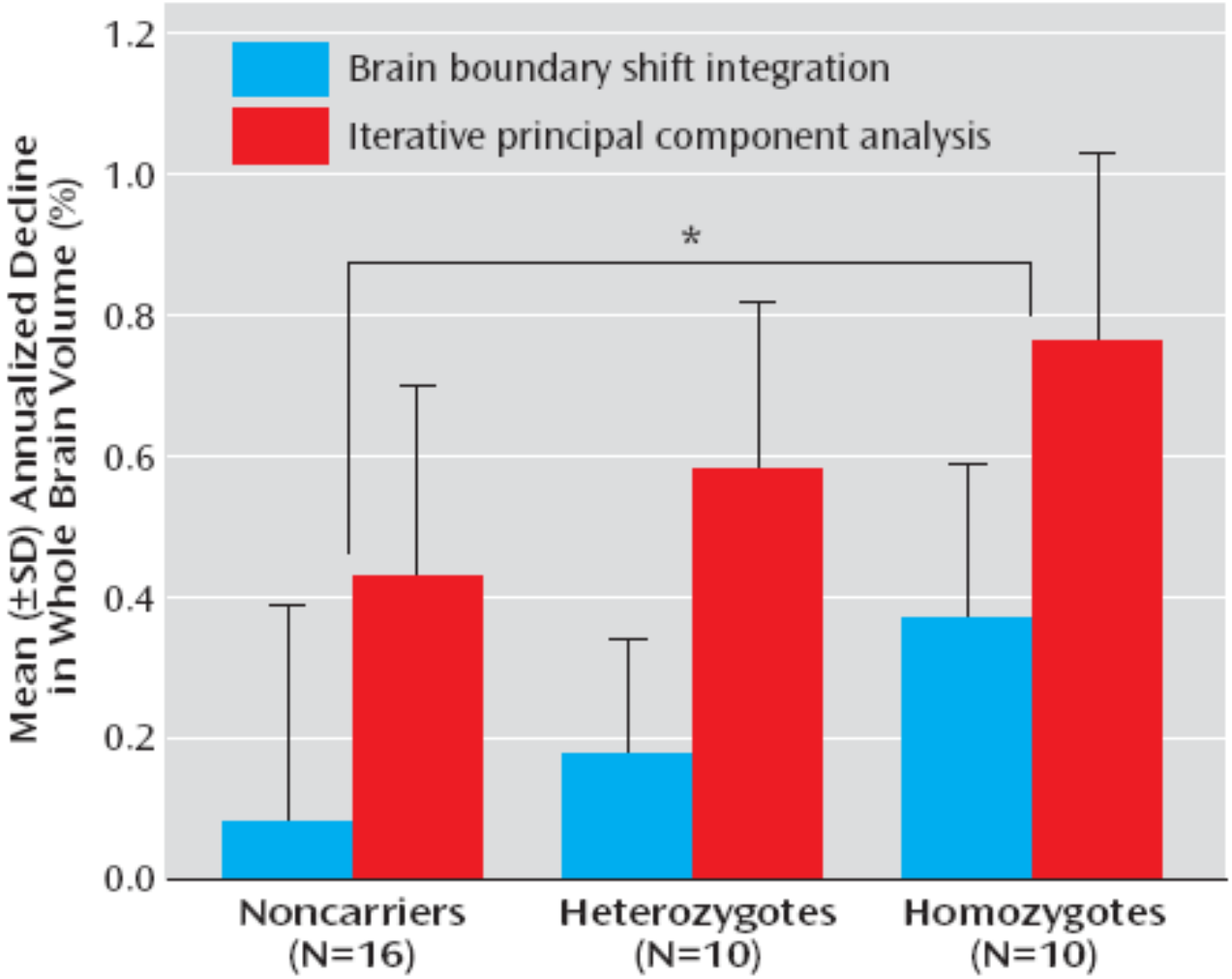
statistical ROI for the assessment of two-year CMRgl declines in cognitively normal APOE ε4 homozygotes



Number of homozygotes per group needed to detect a 25% treatment effect with 80% power (two-tailed P=0.05) in a 24-month prevention trial:

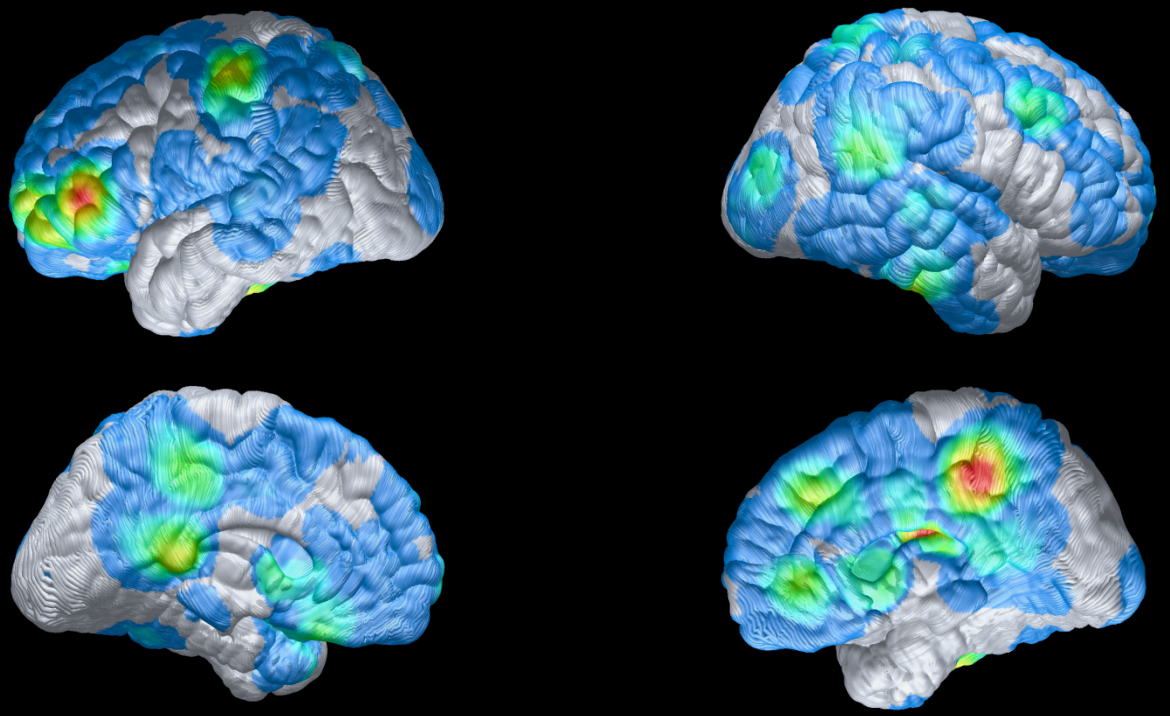
125

whole brain shrinkage in cognitively normal *APOE ε4* homozygotes, heterozygotes & noncarriers



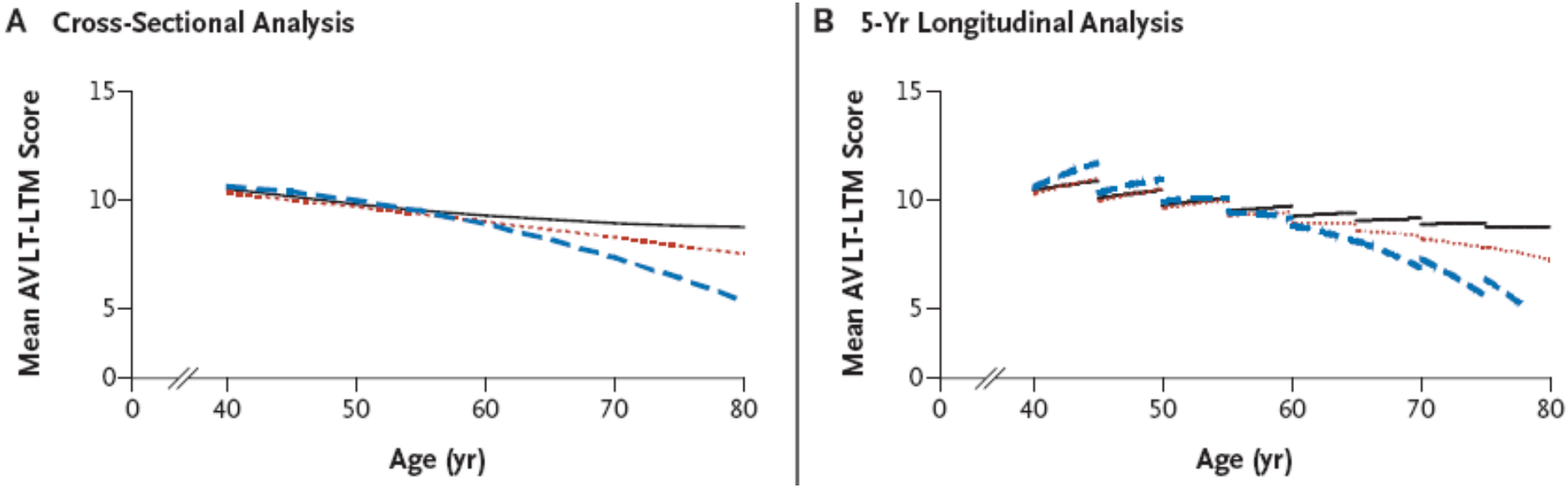
Chen et al, *Am J Psychiatry* 2007

associations between two-year fibrillar Aβ increases & *APOE ε4* gene dose in cognitively normal older adults



Reiman et al, unpublished data

age-related memory decline in 815 cognitively normal subjects, including 79 homozygotes, 238 heterozygotes & 498 *APOE* ε4 non-carriers, 21 to 97 years of age



Caselli et al, *New Engl J Med* 2009

but…

- **AD biomarkers need to be further characterized & compared in RCTs**
  - to determine the extent to which they can be budged by effective treatments
  - to identify confounding treatment effects unrelated to AD modification
  - to determine the extent to which a treatment's effects on biomarkers, alone or in combination, are "reasonably likely" to predict a clinical benefit*

"catch-22?"

"preclinical AD treatments:" a proposed definition

interventions started in the absence of MCI or dementia
& intended to postpone the onset, reduce the risk of,
or completely prevent the clinical stages of AD

adapted from Reiman et al, *Biomarkers Med* 2010

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API: a program to accelerate the evaluation of preclinical AD treatments

1. preclinical AD treatment/biomarker development trials in people who, based on their age & genetic background, are at the highest imminent risk of AD symptoms
   - autosomal dominant AD mutation carriers close to their estimated age at clinical onset
   - *APOE ε4* carriers close to their estimated age at clinical onset
2. prevention registries to support these & other trials
   - our goal: ~3,300 *E280A PSEN1* mutation kindred members in Antioquia, Colombia
   - our goal: ~250,000 persons in North America

Reiman et al, *Biomarkers Med* 2010; Reiman et al, *J Alzheimers Dis* 2011

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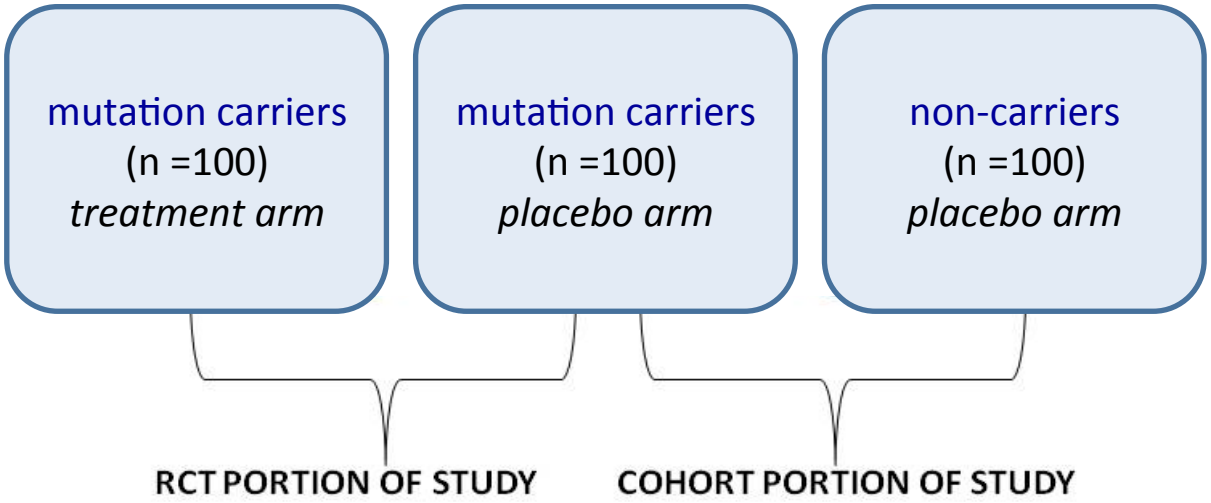
preclinical EOAD treatment/biomarker development trial



double-blind, placebo-controlled trial for up to 60 months
crenezumab 300 mg SC every 2 weeks

primary endpoint: change in the API composite cognitive score
24-month interim analysis using florbetapir & FDG PET, MRI, CSF & several cognitive/clinical endpoints

300 *PSEN1 E280A* kindred participants from Colombia
a small number of other autosomal dominant EOAD kindred participants from the USA

anticipated start date: 2nd quarter 2013

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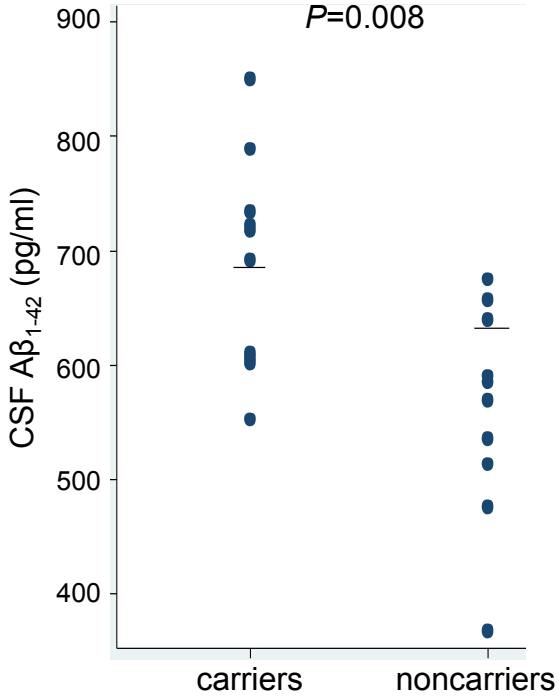
API trial goals

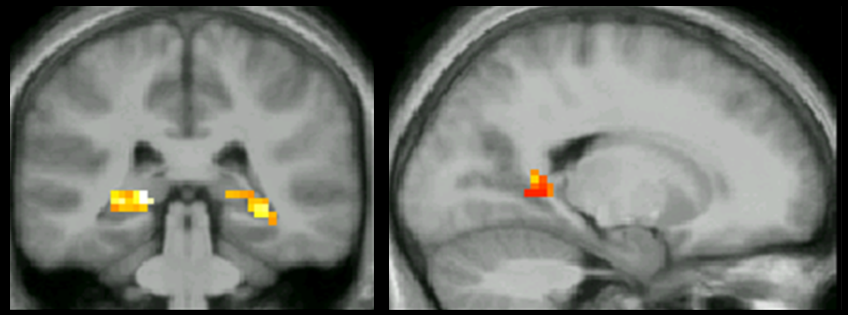
1. to evaluate an anti-amyloid therapy in the preclinical treatment of autosomal dominant AD
2. to provide a better test of the amyloid hypothesis
3. to help qualify biomarkers for use as reasonably likely surrogate endpoints in preclinical AD trials
4. to provide a foundation for other preclinical AD trials
5. to complement, support & benefit from other initiatives (including the planned DIAN & A4 trials)
6. to provide a resource of data & samples to the scientific community after the trial is over
7. to give persons at highest imminent risk for AD access to investigational treatments
8. …and more trials to come

functional & structural MRI abnormalities before measurable CSF evidence of fibrillar Aβ in young adult *PS1 E280A* mutation carriers

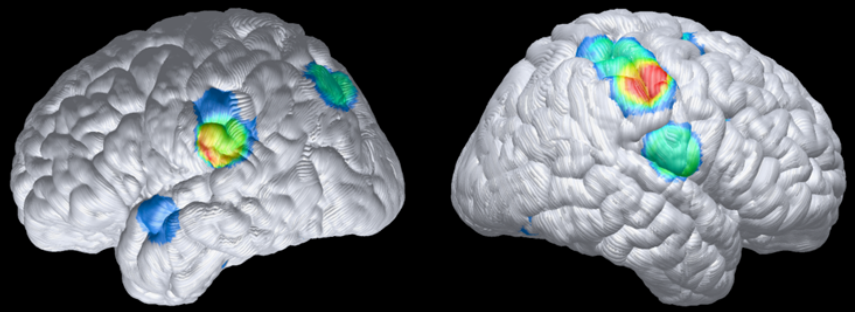
higher (not lower) CSF $A\beta_{1-42}$ levels



greater hippocampal activation & less precuneus deactivation during an associative memory encoding task

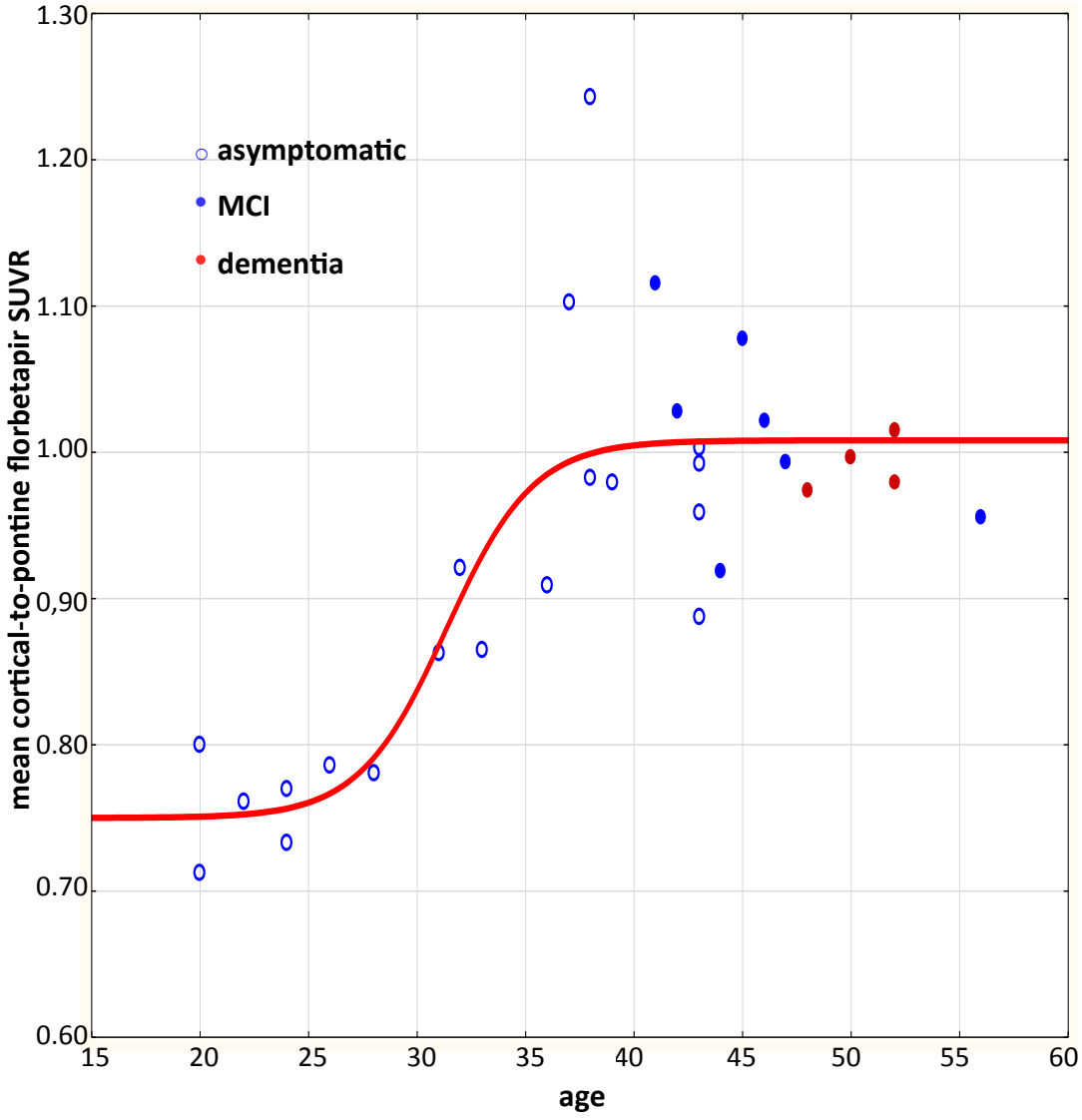


less parietal (& parahippocampal) gray matter



Reiman et al, *Lancet Neurol* 2012

ages associated with fibrillar Aβ accumulation in mutation carriers from the world's largest autosomal dominant early-onset AD kindred



Fleisher et al, *Human Amyloid Imaging Abstr* 2012; *Alzheimer's Assoc Internat Conf Abstr* 2012

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"API Composite Cognitive Test Score"

optimal cognitive test combination

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* Antioquia Cohort**

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

adapted from Langbaum et al., AAIC abstr 2011 & Ayutyanont et al., AAIC abstr 2011

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cognitive & biomarker treatment effects that may be detected in 75 cognitively normal *PSEN1 E280A* mutation carriers per group, ≥ age 30, completing a 24-mo RCT*

endpoint	treatment effect
API composite cognitive test score	44%[1]
sROI CMRgl decline	23%[2]
whole brain shrinkage	18%[2]
cerebral Aβ accumulation	27%[2]

*assumes 80% power & two-tailed p=0.05

[1]estimated in *PSEN1 E280A* carriers; 29% treatment effect in a 60-mo RCT

[2]estimated in *APOE ε4* homozygotes

upcoming preclinical AD trials

API

DIAN

A4

Opal

others

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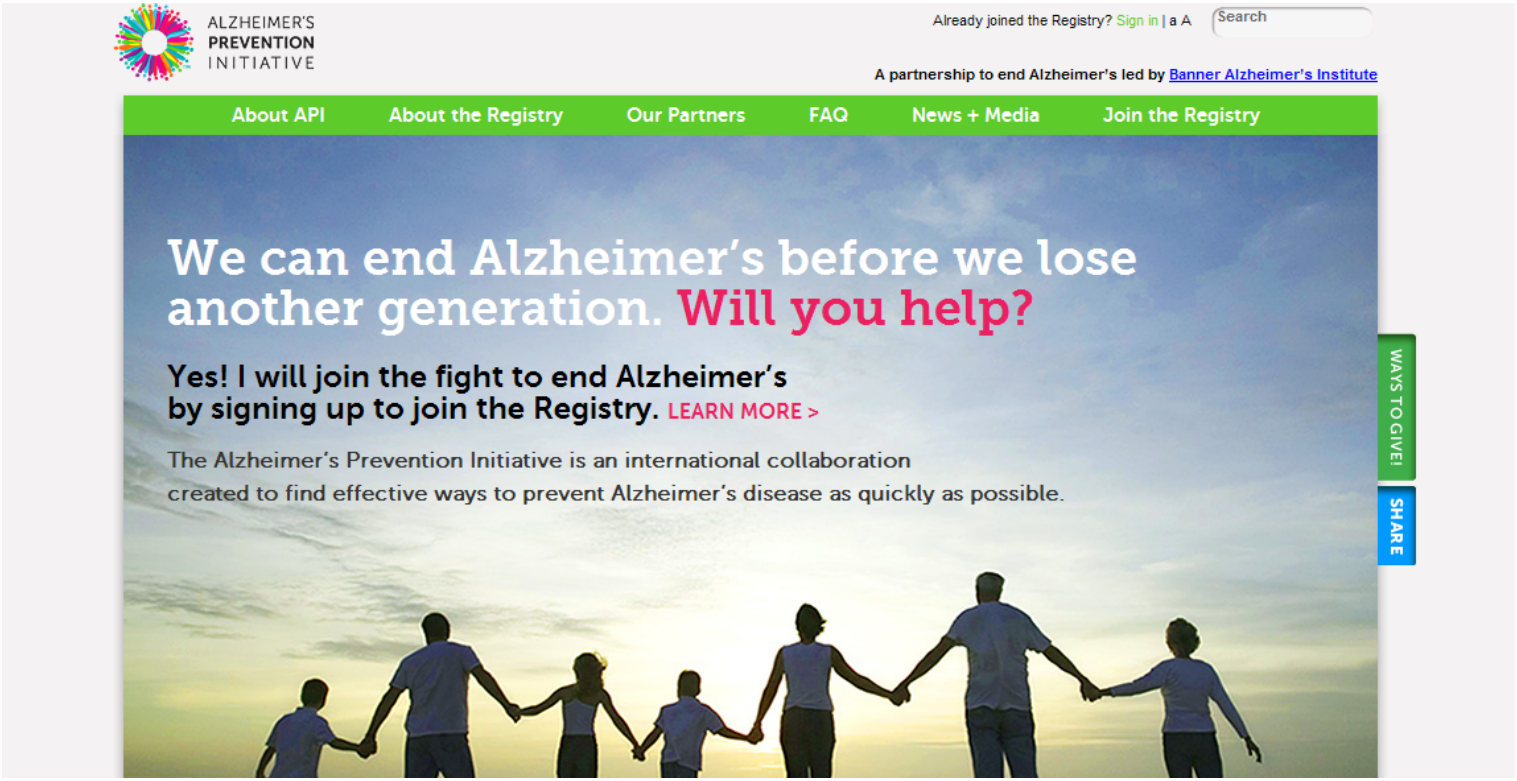
Alzheimer's Prevention Registry

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

Gloria cares for her sister Maria, age 61, who developed AD symptoms in her 40s

Photograph by Todd Heisler, February 2009, courtesy of the NY Times, with permission

colleagues, collaborators & advisors

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florbetapir PET

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