

**strategies for the accelerated evaluation of preclinical AD treatments
in *APOE* $\epsilon 4$ and autosomal dominant mutation carriers**

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scientific advisor

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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!



“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

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

what' s been holding us back?

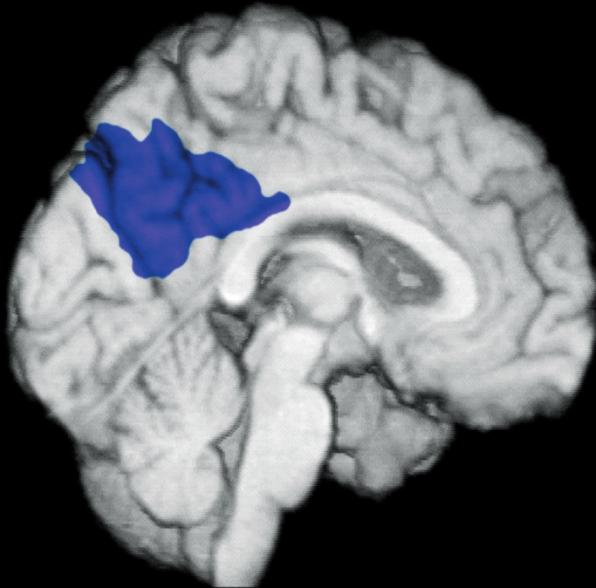
1. too many research participants, too much time & too much money
2. insufficient evidence to qualify AD biomarkers for use as surrogate endpoints
3. investigational AD-modifying treatment safety & tolerability data

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

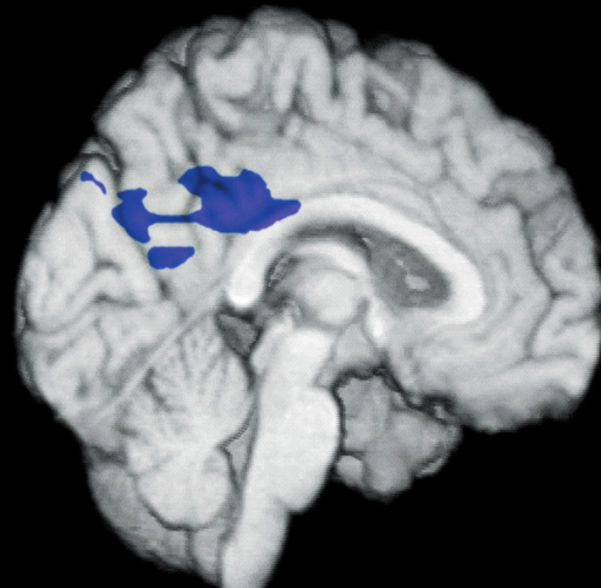
adapted from Corder et al, *Science* 1993

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

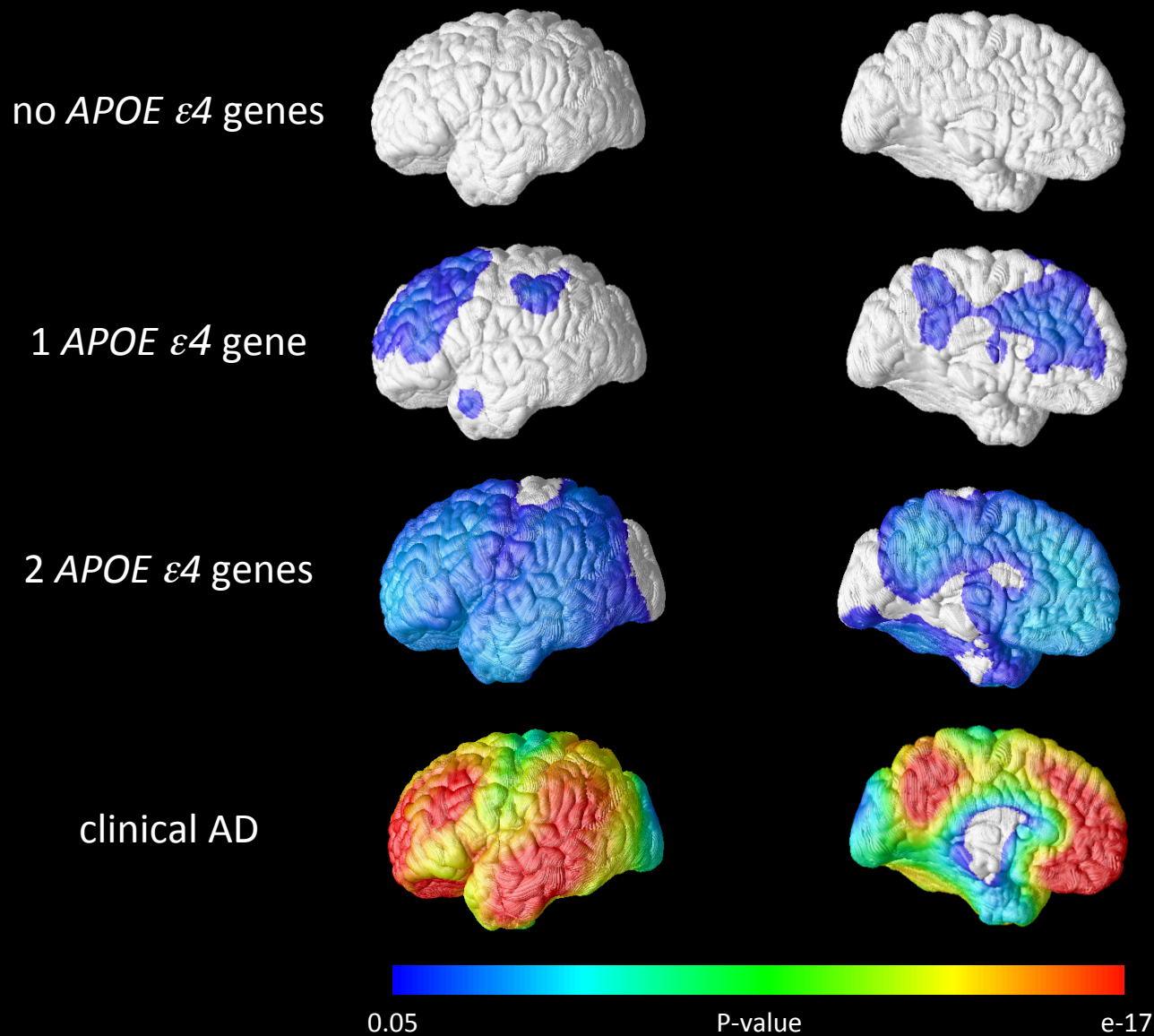
clinically affected



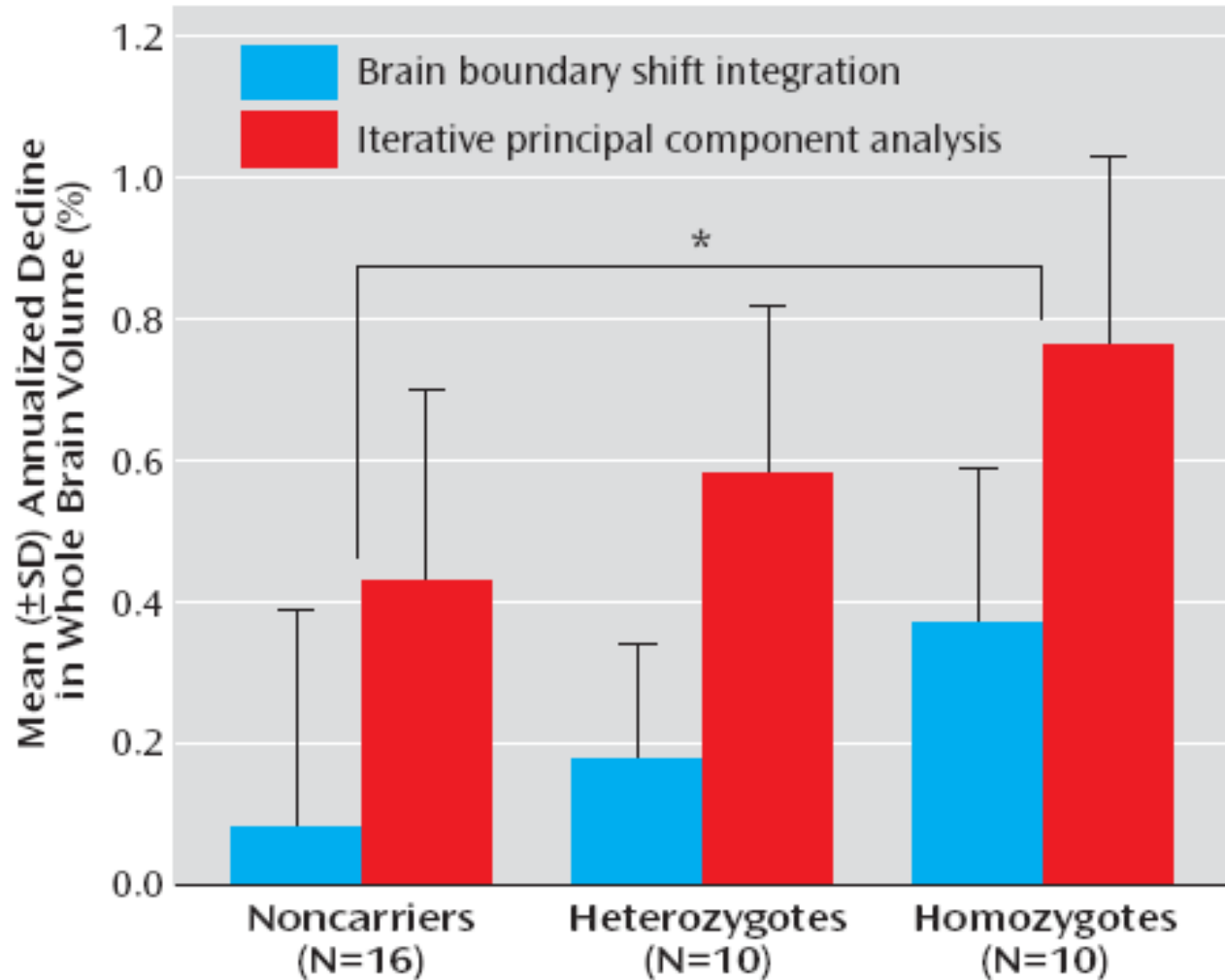
at-risk



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



whole brain shrinkage in cognitively normal *APOE* $\epsilon 4$ homozygotes, heterozygotes & noncarriers



but...

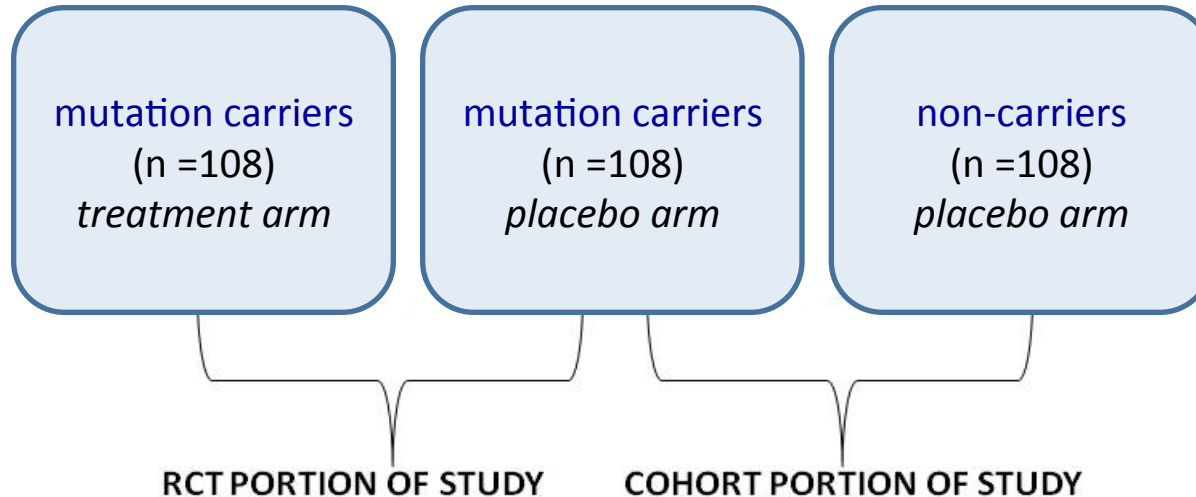
- **AD biomarkers need to be further characterized & compared in RCTs**
 - to determine the extent to which they can be budged by effective treatments
 - to identify confounding treatment effects unrelated to AD modification
 - to determine the extent to which a treatment's effects on biomarkers, alone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

“catch-22?”

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

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
~24 other autosomal dominant EOAD kindred participants from the USA

anticipated start date: 2nd quarter 2013

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

“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

cognitive & biomarker treatment effects that may be detected in 75 cognitively normal *PSEN1 E280A* mutation carriers per group, \geq 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

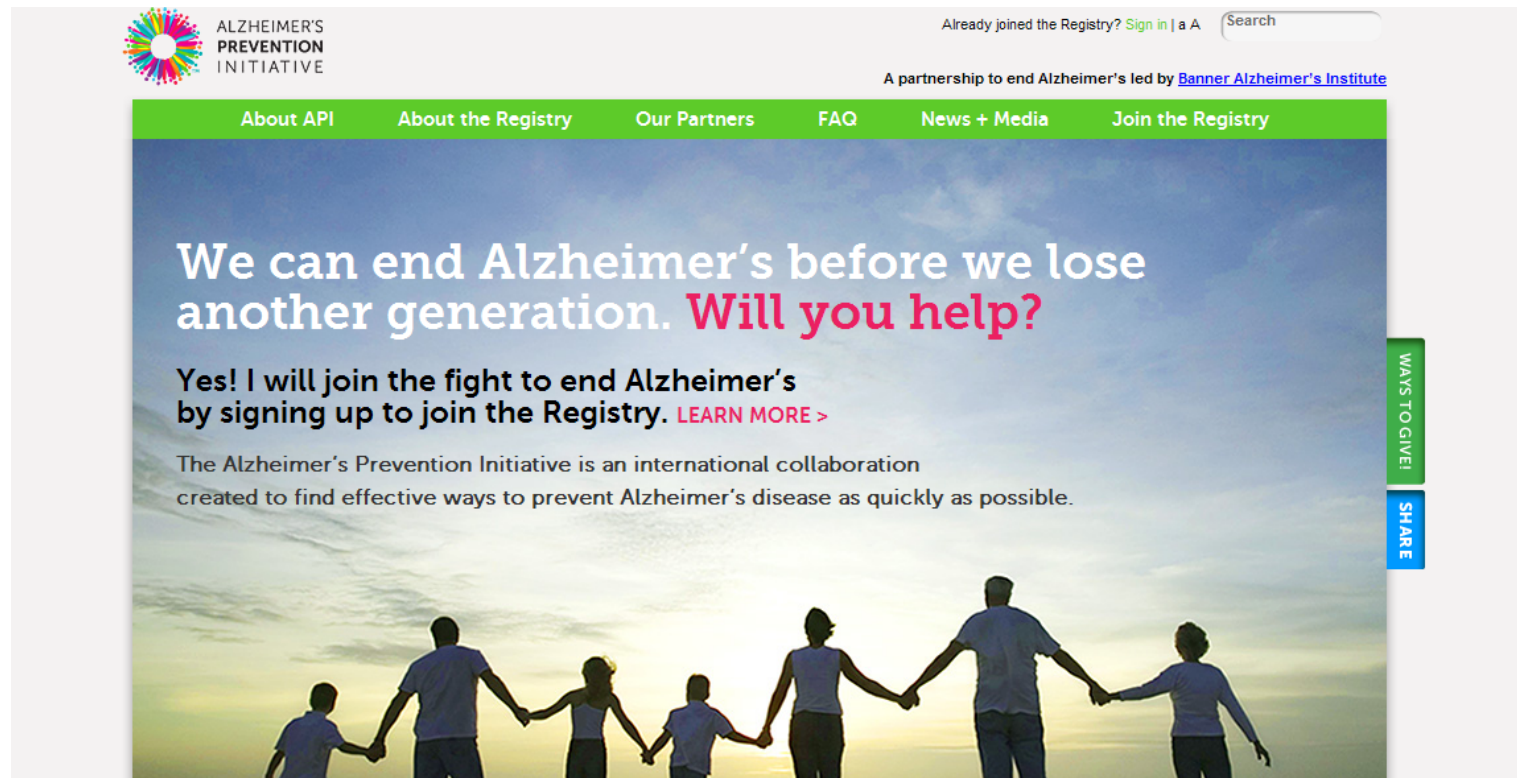
*assumes 80% power & two-tailed $p=0.05$

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

²estimated in *APOE $\epsilon 4$* homozygotes

Alzheimer's Prevention Registry

www.endAlznow.org



The screenshot shows the homepage of the Alzheimer's Prevention Registry. At the top left is the Alzheimer's Prevention Initiative logo. To its right, the text reads "ALZHEIMER'S PREVENTION INITIATIVE". Further right, there is a search bar and a link: "Already joined the Registry? [Sign in](#) | a A". Below this is a navigation bar with links: "About API", "About the Registry", "Our Partners", "FAQ", "News + Media", and "Join the Registry". The main content area features a large blue and white background with the text: "We can end Alzheimer's before we lose another generation. **Will you help?**" Below this is a call to action: "Yes! I will join the fight to end Alzheimer's by signing up to join the Registry. [LEARN MORE >](#)". A secondary line of text states: "The Alzheimer's Prevention Initiative is an international collaboration created to find effective ways to prevent Alzheimer's disease as quickly as possible." On the right side of the main content area, there are two vertical buttons: "WAYS TO GIVE!" and "SHARE". The background image shows silhouettes of a family holding hands against a sunset sky.

Executive Committee

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ADAD prevention trials: a few considerations

- enrichment strategy pros & cons
- approval pathway
- age criteria
- safety considerations
- generalizability
- risk disclosure
- other ethical & social issues

***APOE ε4* AD prevention trials: a few considerations**

- enrichment strategy pros & cons
- approval pathway
- age criteria
- safety considerations
- generalizability / differential treatment effects
- risk disclosure
- other ethical & social issues

“Don’ t Forget Our Families”



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

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