



# **Alzheimer's Disease: Research Challenges and Opportunities**

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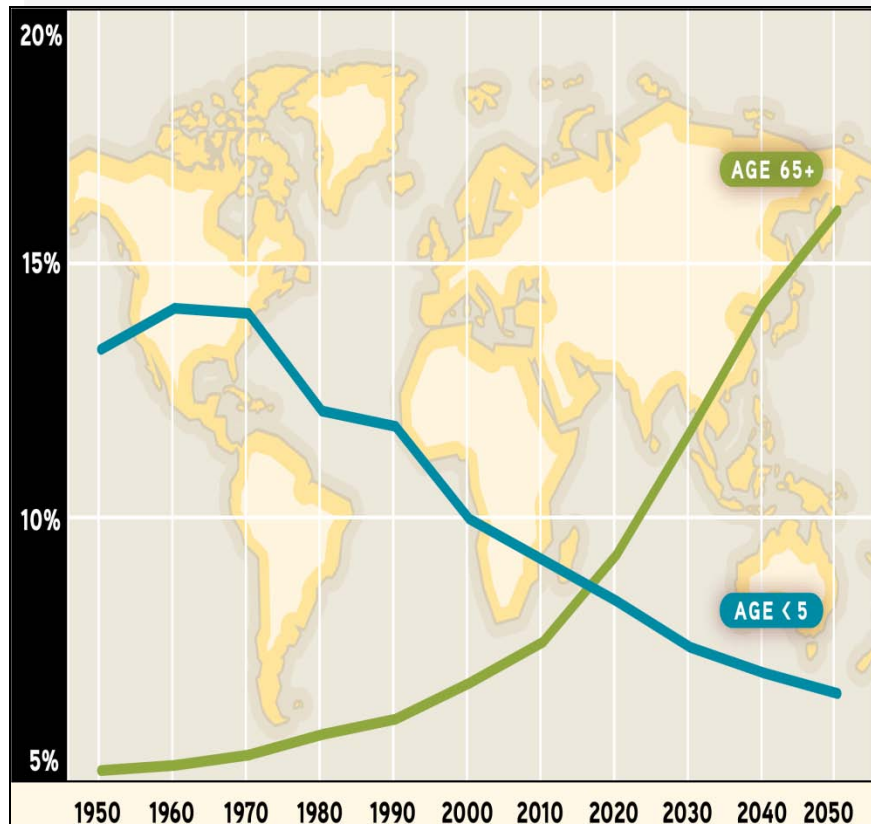
**104th Meeting of the Advisory Committee to the Director  
National Institutes of Health  
NIH Campus, Bethesda**

**Richard J. Hodes, M.D.  
Director  
National Institute on Aging**

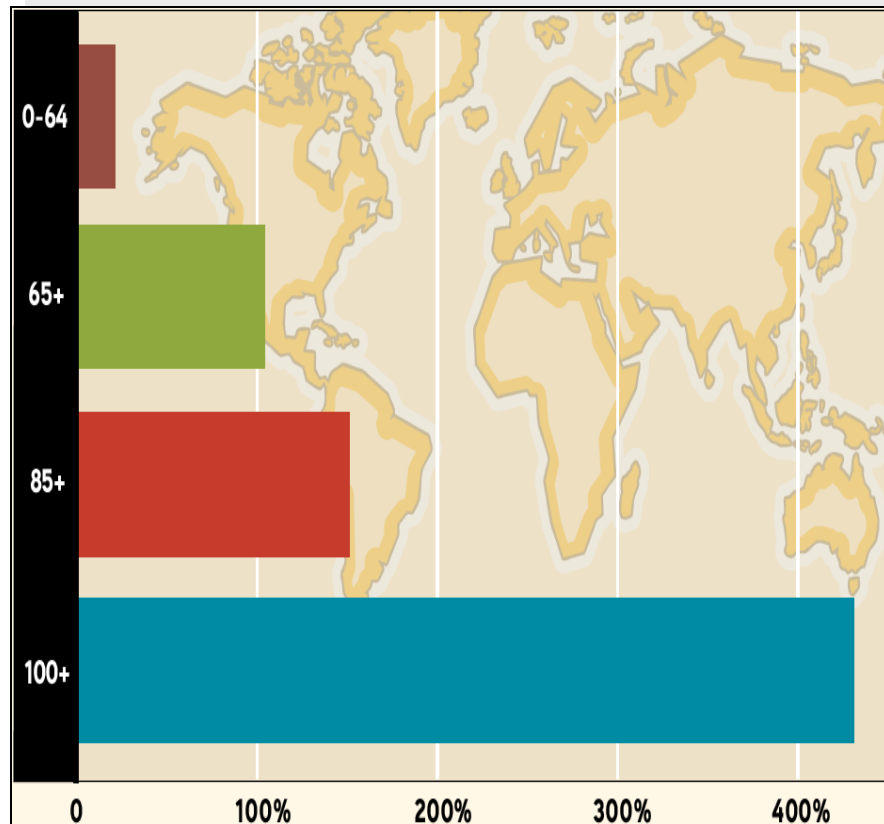
June 15 , 2012



## YOUNG CHILDREN AND OLDER PEOPLE AS A PERCENTAGE OF GLOBAL POPULATION



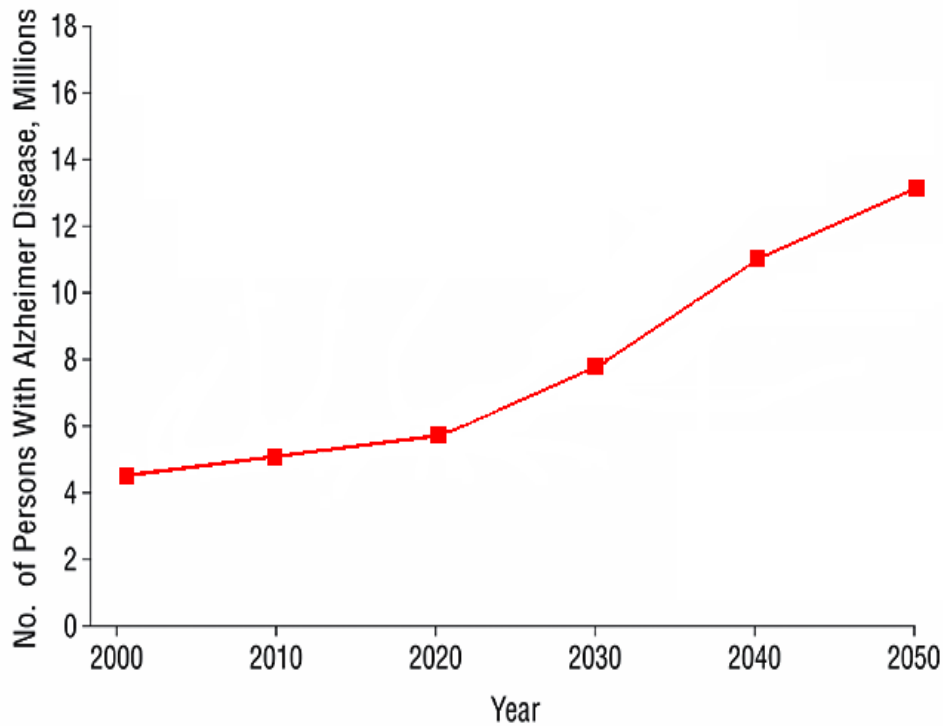
## PROJECTED INCREASE IN GLOBAL POPULATION BETWEEN 2005 and 2030, BY AGE



United Nation Department of Economic and Social Affairs, Population Division. *World Population Prospects. The 2004 Revision*. New York: United Nations, 2005 in *Why Population Aging Matters: A Global Perspective* at [www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/BehavioralAndSocialResearch/GlobalAging.htm](http://www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/BehavioralAndSocialResearch/GlobalAging.htm)

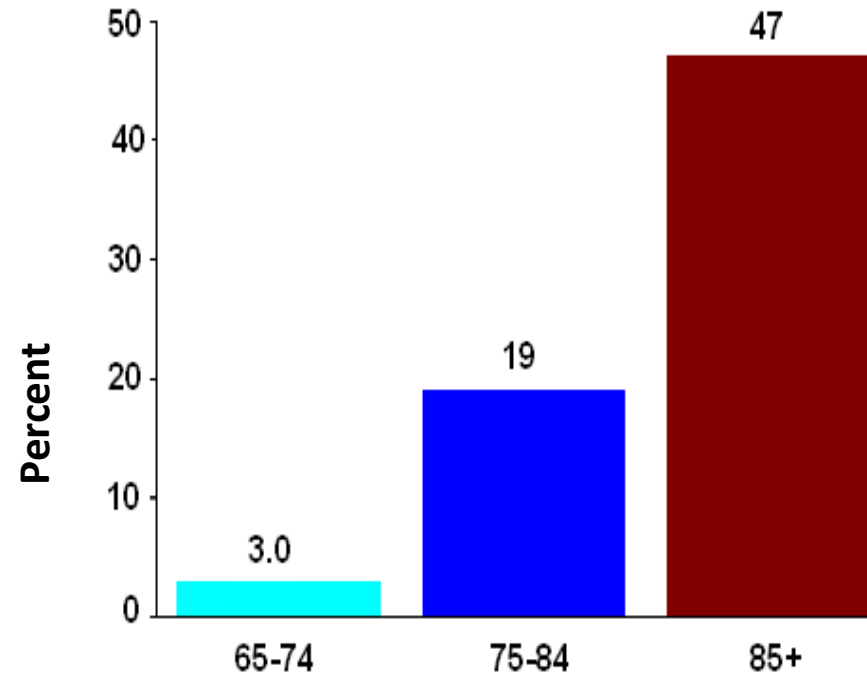
# Prevalence of Probable Alzheimer's Disease

Number of Persons with AD in Millions



Evans, et al. Arch Neurol, Vol. 60, 2003.

Percent of Persons with AD by Age



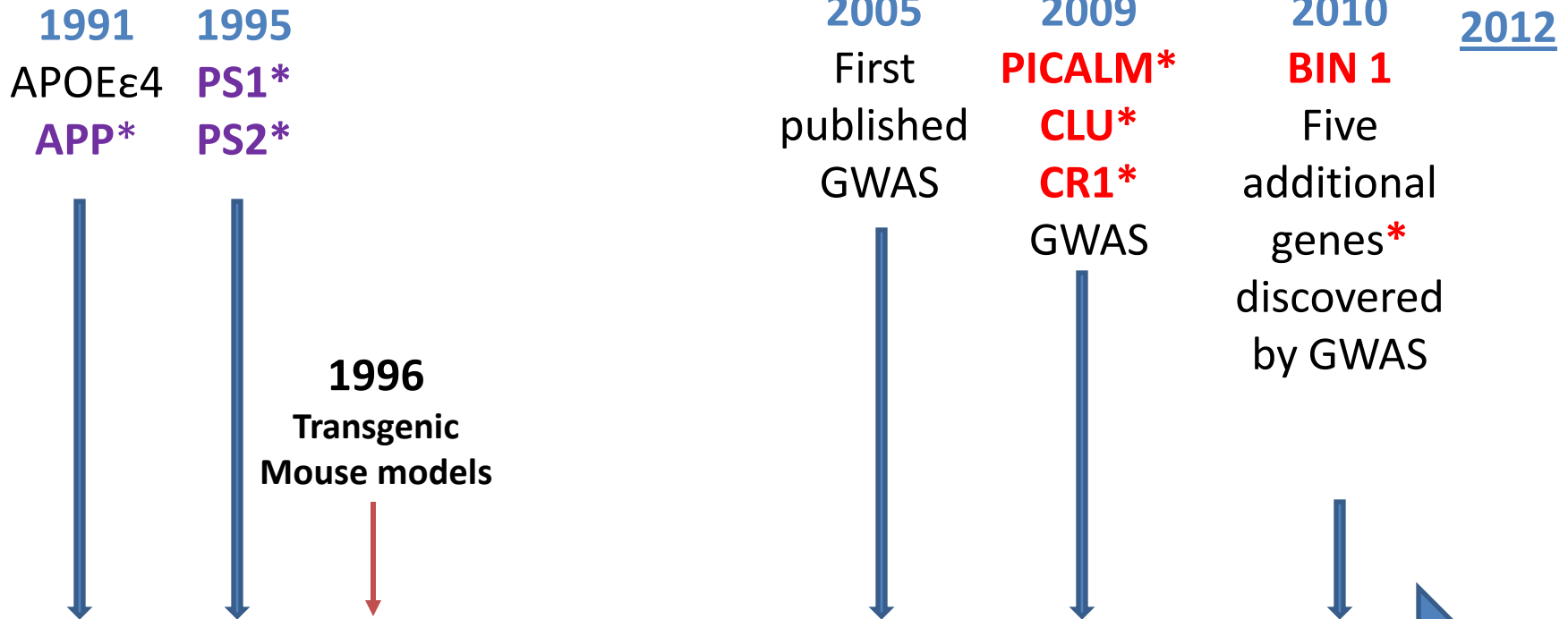
Evans D , et al. JAMA , Vol. 262, No. 18, 1989

# Possible Environmental and Lifestyle Factors Affecting Alzheimer's Disease

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- Age
- Head Injury
- High Blood Pressure
- Cholesterol
- Homocysteine
- Diabetes
- Education/Brain Reserve/Occupation
- Exercise
- Social Contacts

# Alzheimer's Disease Gene Discovery



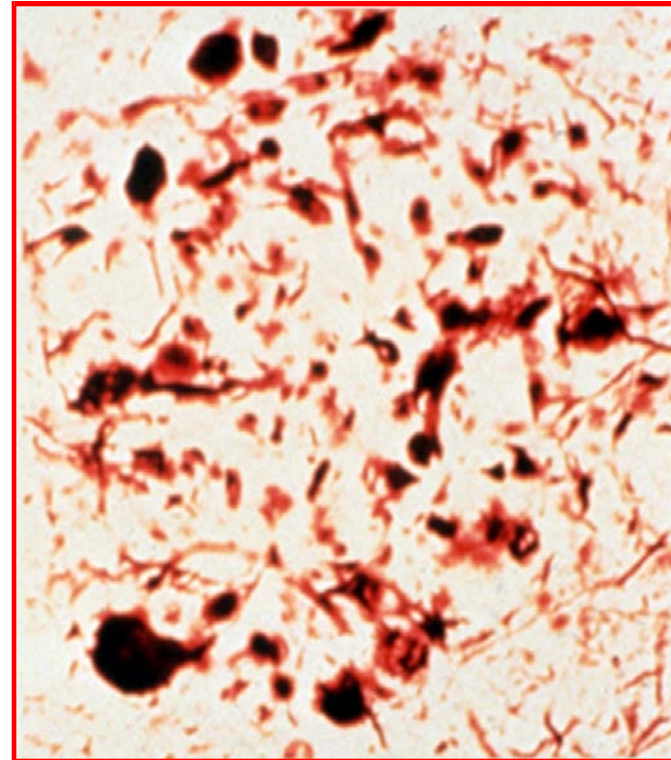
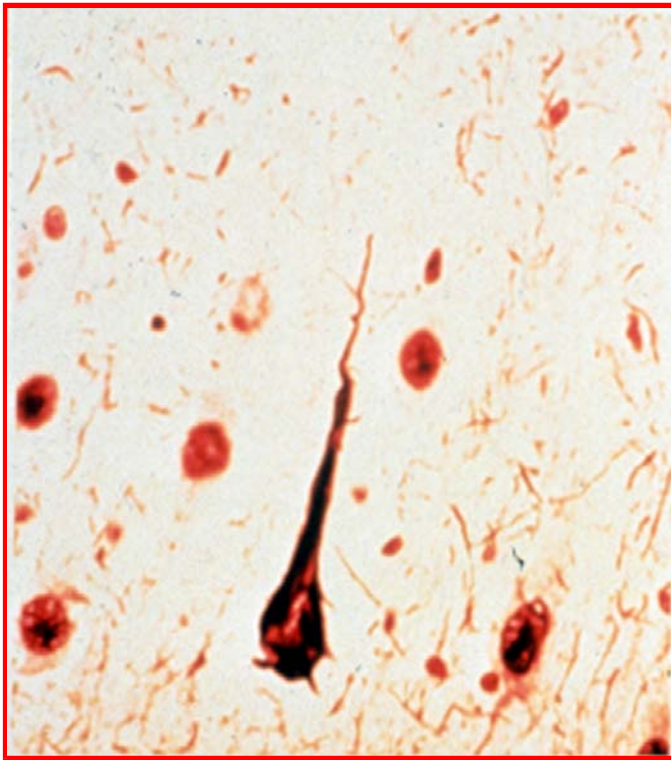
\* Early onset Alzheimer's Disease- family based studies

\* Late onset Alzheimer's Disease- case control studies

Range needed to identify genes: 3,000 – 27,000 cases and 11,000 – 41,000 controls

# Neurofibrillary Tangles

# Senile Plaques

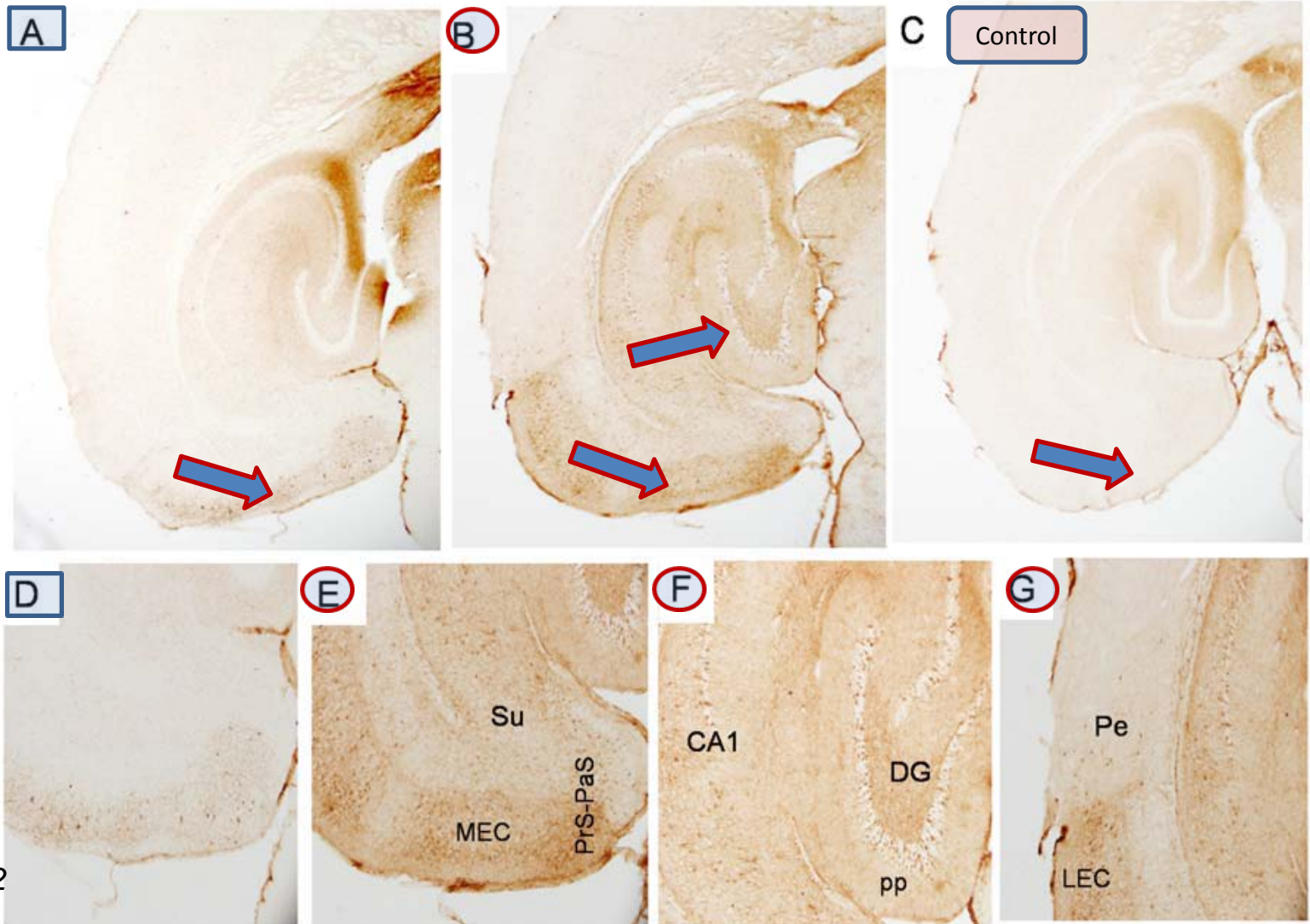




# The Spread of Tau in Transgenic Mice

□ Neuropsin-*Tau* mice, 10-11 months of age

○ Neuropsin-*Tau* mice, >22 months of age



Liu et al.,  
*PLOS one*, 2012

Progressive spread of taupathology in NT mice with antibody AT8

# Tau Pathology Spread in Hippocampus

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**Entorhinal Cortex transgene-expressing neurons to neurons without detectable transgene expression**

First to Entorhinal Cortex neighboring cells



Migration to neurons downstream in the synaptic circuit



Dentate Gyrus



Cornu Ammonis – all 4 fields



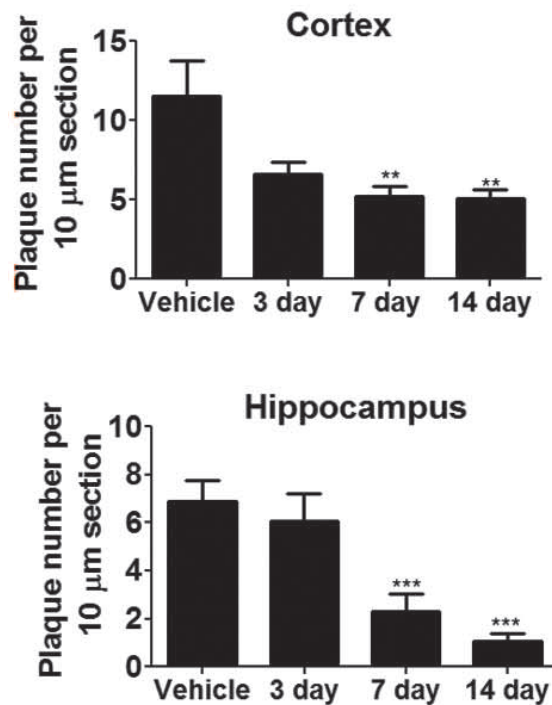
Cingulate Cortex



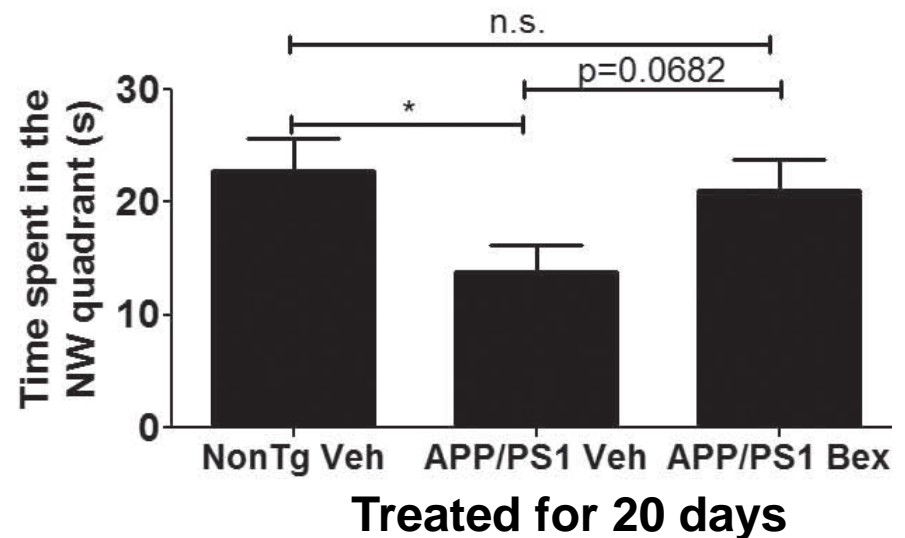
# ApoE-Directed Therapeutics Rapidly Clear $\beta$ -Amyloid and Reverse Deficits in AD Mouse Models

## Bexarotene treatment of $\beta$ -amyloid transgenic mice

### Decrease in plaques



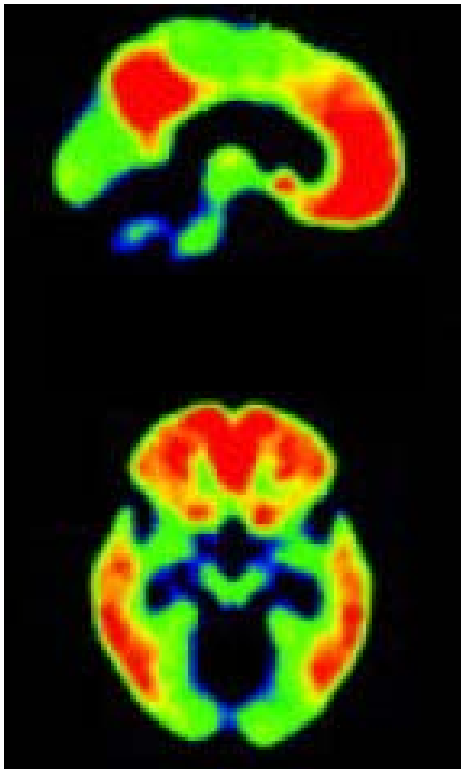
### Improved memory



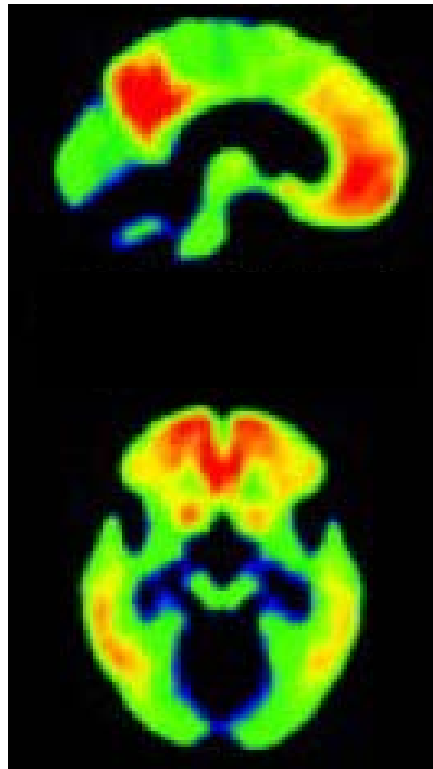
# Imaging Amyloid Plaques in Living People

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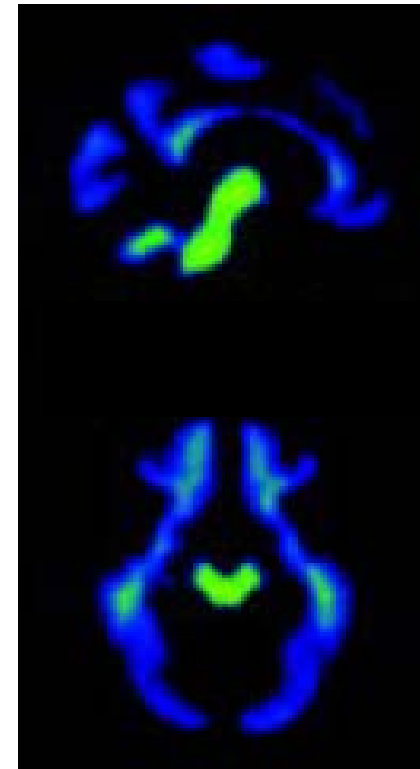
Alzheimer's  
Disease



Mild Cognitive  
Impairment

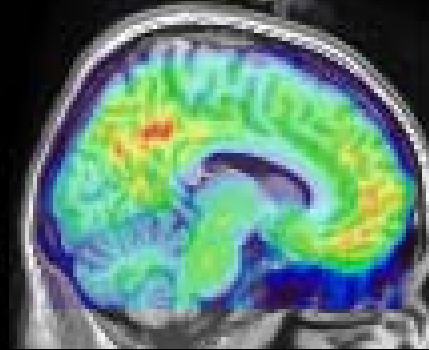
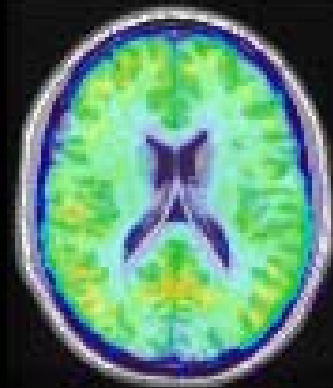


Normal

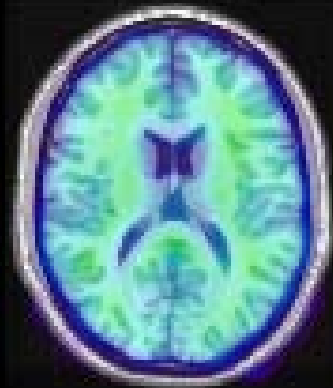


# Amyloid Plaques Precede Memory Problems

- Memory Problems 4 Years Later

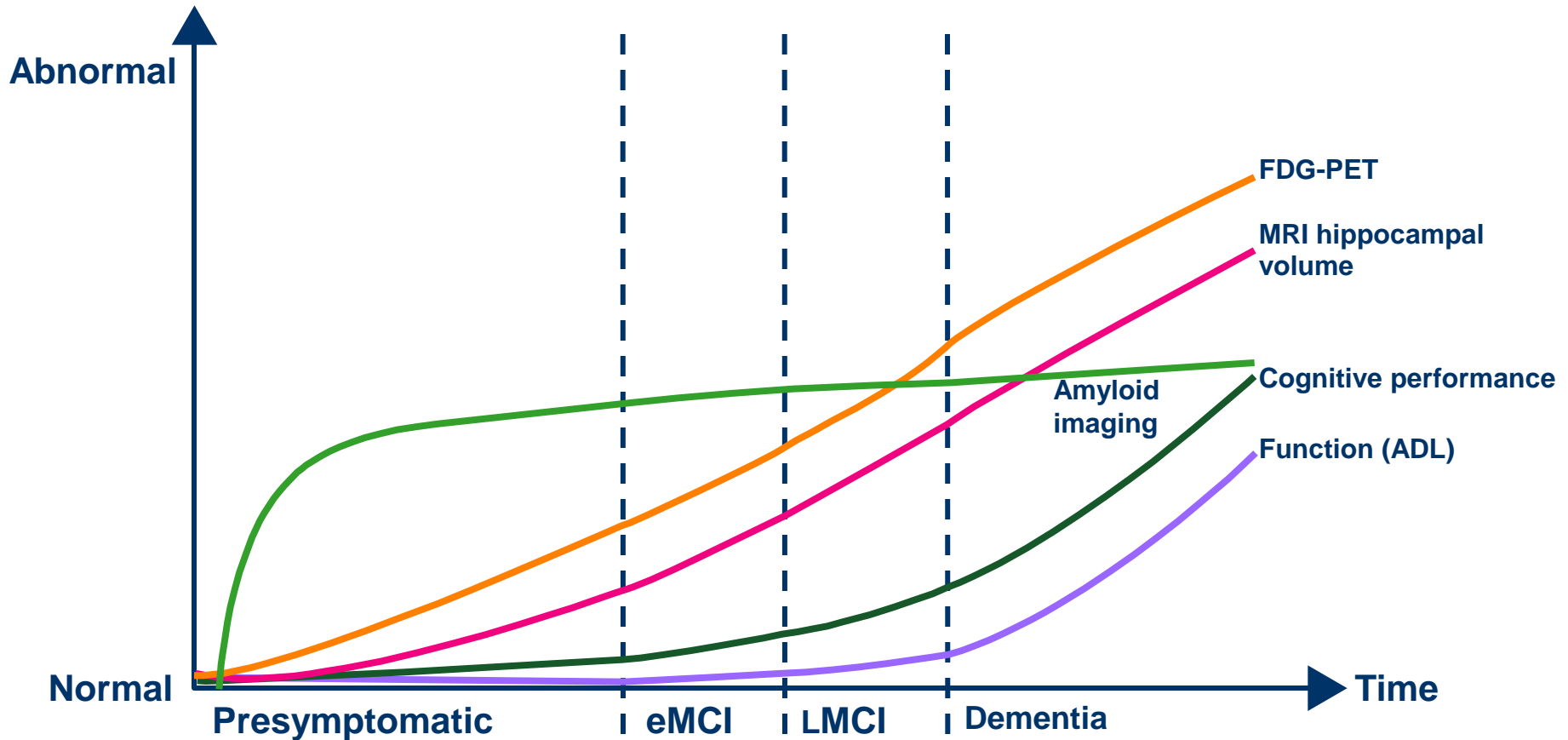


- Stable Memory



Baltimore Longitudinal Study of Aging

# AD Progression: ADNI Model



# New Diagnostic Guidelines for Alzheimer's Disease

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The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on workgroups on diagnostic guidelines for Alzheimer's disease.

McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH.

Alzheimers Dement. 2011 May;7(3):263-9.

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.

Albert MS, Dekosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH.

Alzheimers Dement. 2011 May;7(3):270-9.

Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR Jr, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH.

Alzheimers Dement. 2011 May;7(3):280-92.

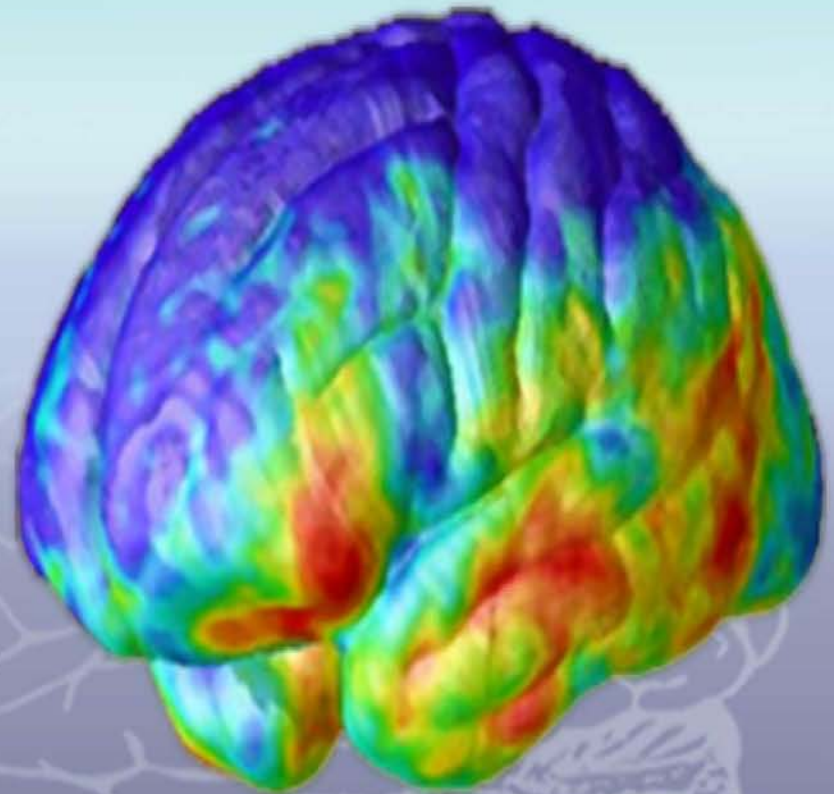
# Alzheimer's Disease Research Summit 2012: Path to Treatment and Prevention

May 14-15, 2012

National Institutes of Health

U.S. Department of Health & Human Services

Bethesda, MD



<http://www.nia.nih.gov/newsroom/alzheimers-disease-research-summit-2012-recommendations>

# NIH Alzheimer's Disease Research Summit 2012

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- Approximately 500 attended both days
- Almost 500 watched nationally and internationally by webcast
- Representatives from 38 states and 8 countries attended
- HHS Secretary Kathleen Sebelius presented the National Plan and NIH Director, Dr. Francis Collins announced two AD Clinical Trials
- Summit webcast is archived at:  
<http://videocast.nih.gov>



# Alzheimer's Disease Research Summit

## Path to Treatment and Prevention

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- Overarching issues transcended many of the sessions:
  - Heterogeneity of the disease
  - New research paradigms, e.g., systems biology needed
  - Rapid and extensive data/specimen sharing
  - Multidisciplinary translational teams
  - Strategies to overcome IP barriers
  - Public-private partnerships
  - National IRB

<http://www.nia.nih.gov/newsroom/alzheimers-disease-research-summit-2012-recommendations>

# Alzheimer's Disease Research Summit

## Recommendations

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- **Session 1:** Interdisciplinary Approach to Discovering and Validating the Next Generation of Therapeutic Targets for AD
- **Session 2:** Challenges in Preclinical Therapy Development
- **Session 3:** Whom to Treat, When to Treat, and What Outcomes to Measure
- **Session 4:** Drug Repurposing and Combination Therapy
- **Session 5:** Nonpharmacological Interventions
- **Session 6:** New Models of Public Private Partnerships
- <http://www.nia.nih.gov/newsroom/announcements/2012/05/alzheimers-disease-research-summit-offers-research-recommendations>

# Alzheimer's Disease Research Inventory

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- Information about Alzheimer's disease research available to the public online:  
<http://www.nia.nih.gov/research/dn/international-alzheimers-disease-research-portfolio>
- NIA has posted a preliminary list of projects coded using the **Common Alzheimer's Disease Research Ontology** developed jointly by NIA and the Alzheimer's Association
- Other funding organizations are invited to join the effort and list their research projects



# Alzheimer's Disease Projects Funded by FY 2012 NIH Additional \$50 million

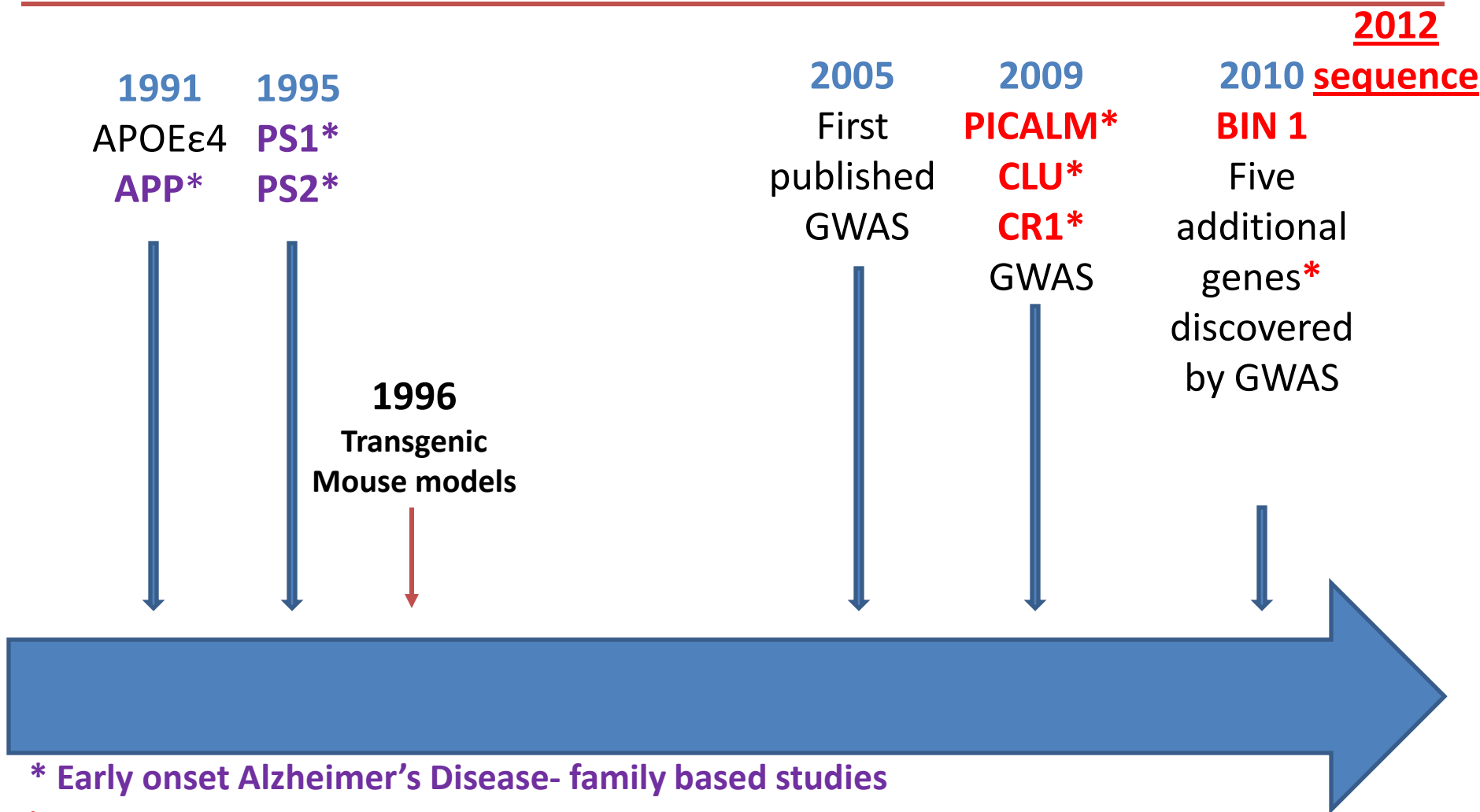
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On February 7, 2012, Secretary of Health and Human Services Kathleen Sebelius announced that \$50 million would be directed immediately to boost Alzheimer's research in FY2012 in response to President Obama signing the National Alzheimer's Project Act.

The following research projects will be funded:

- AD genome sequencing by NHGRI Genome Centers
- Use of new induced pluripotent stem cell methods to obtain insights into the cellular processes of Alzheimer's
- Small Business Alzheimer's Disease Research (STTR)R41/R42 -Phase I, Phase II, and Fast-Track /Small Business Innovation Research (SBIR) R43/R44 Grant - Phase I, Phase II, and Fast-Track
- Two AD Clinical Trials - one treatment and one prevention

# Alzheimer's Disease Gene Discovery

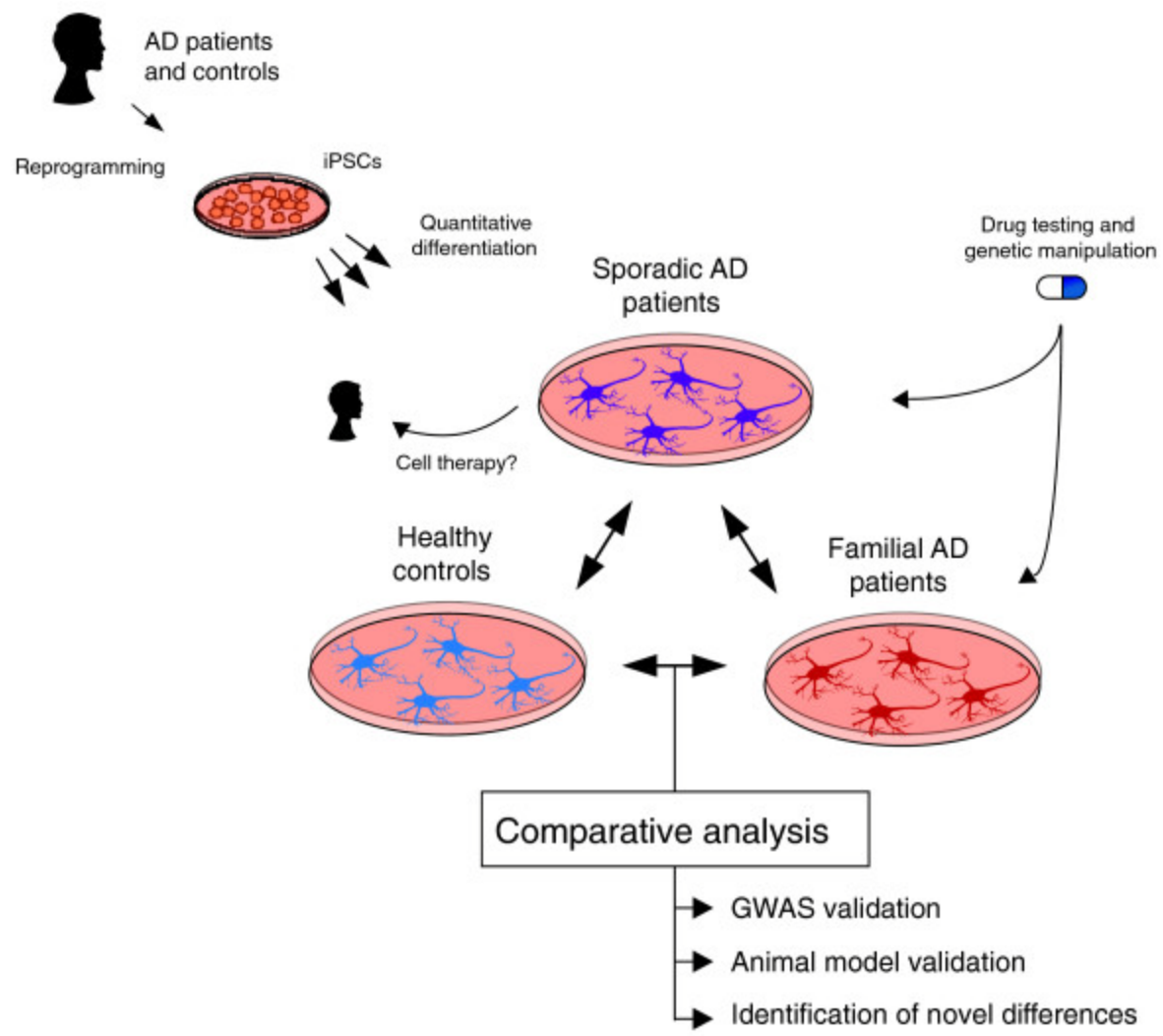


\* Early onset Alzheimer's Disease- family based studies

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Range needed to identify genes: 3,000 – 27,000 cases and 11,000 – 41,000 controls

# A General Approach for the Use of iPSCs to Model AD



# Pilot Trial of Intranasal Insulin for Alzheimer's and MCI

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- **Pilot:** 104 adults with MCI and mild to moderate Alzheimer's; placebo, 20 IU insulin, 40 IU insulin for 4 months, administered with nasal drug delivery device
- **Results:**
  - improved delayed memory in 20 IU group compared with placebo
  - preserved general cognition, activities of daily living for younger participants in both insulin groups
  - caregivers for both insulin groups rated participant functional status higher
  - changes in some biomarkers ( $A\beta 42$  and tau to  $A\beta 42$  ratio) associated with changes in memory and function

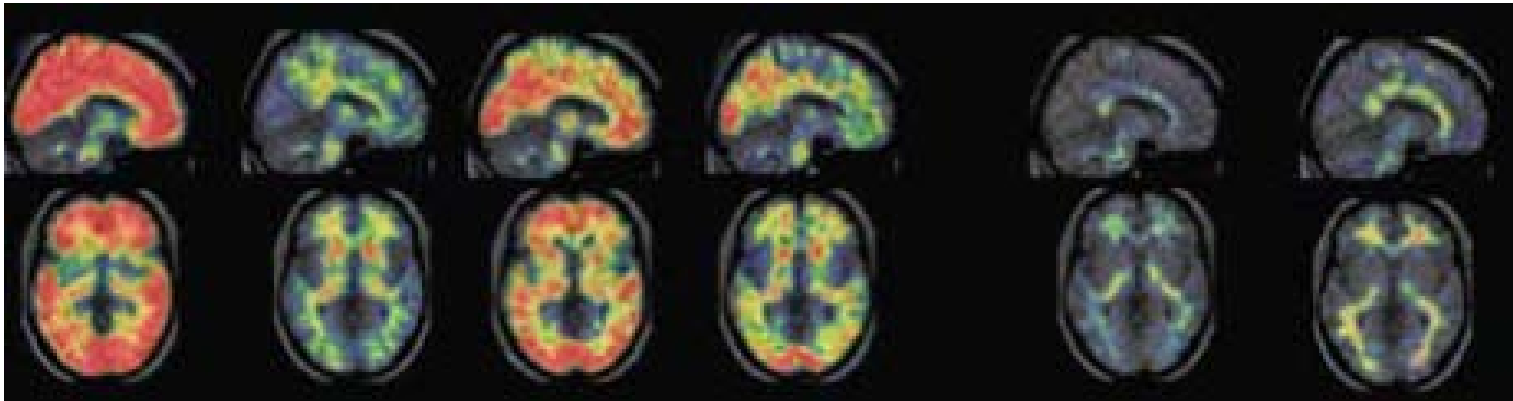


# Amyloid PET Scans in *Presymptomatic* Early-Onset Alzheimer's Disease

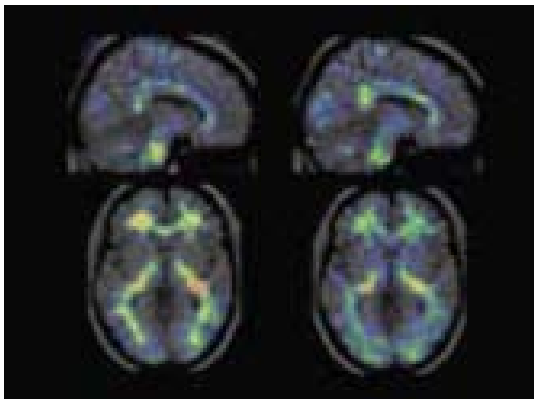
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**Gene Carriers**

**Non-Carriers**



**Age 35-39 Years**



**Age 25-29 Years**

## **Colombian Kindred**

- N = 5000 living individuals from ~ 25 families
- 1000 with the *E280A (Glu280Ala) Presenilin1* mutation
- Autosomal dominant, 100% penetrance
- Median age of MCI = 44 years, dementia = 49 years

# National Plan to Address Alzheimer's Disease

<http://aspe.hhs.gov/daltcp/napa/NatIPlan.pdf>



U.S. Department of Health and Human Services  
Office of Assistant Secretary for Planning and Evaluation

# National Plan to Address Alzheimer's Disease

**Goal 1: Prevent and Effectively Treat Alzheimer's Disease by 2025**

**Goal 2: Enhance Care Quality and Efficiency**

**Goal 3: Expand Supports for People with Alzheimer's Disease and Their Families**

**Goal 4: Enhance Public Awareness and Engagement**

**Goal 5: Improve Data to Track Progress**



# Session 1: Interdisciplinary Approach to Discovering and Validating Next Generation Therapeutic Targets

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- Understand complex pathobiology
- Systems-level understanding
- Genetic info to inform mechanistic insights
- New experimental models
- New *in vivo* imaging agents
- Robust biomarkers, large cohorts
- Peripheral biochemical changes
- Rapid sharing of new data/collaborative efforts
- Maximize existing infrastructure
- New translational teams

## Session 2: Challenges in Preclinical Therapy Development

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- Create infrastructure and resources to increase likelihood that preclinical therapeutic development will be successful
  - Expert advisory committees
  - Network of AD preclinical therapy centers
  - Open-access resource for negative data
- Develop broad capabilities in quantitative and systems pharmacology
- Increase predictive power in animal models
  - Standardized processes for animal models
  - Align features of AD animal models with clinical disease-biomarkers
  - Rigor and reporting of positive and negative data
- Expedited review track for applications

## Session 3: Whom to Treat, When to Treat, and What Outcomes to Measure

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- Initiate treatment trials in asymptomatic, at-risk individuals using biomarkers
- Collect DNA and biomarkers
- Expand large-scale registries, pop-based
- Neuropsychological/behavioral characterization of early changes
- Optimize biomarkers, standardization
- Treatment for symptomatic patients
- Stratify and individualize treatments
- Infrastructure for prevention initiatives



# Session 4: Drug Repurposing and Combination Therapy

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- Expand libraries of drugs, tissues for different stages of AD
- Maintain rigor in repurposed drug development
- Combination therapy may be necessary
- Evaluate drugs with multiple targets
- Develop translational groups across institutions

# Session 5: Non-pharmacological Interventions

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- Epidemiological data with mechanisms
- Identify molecular mechanisms, systems approach
- Rigorous clinical trials in asymptomatic and impaired subjects to establish effectiveness
- Combine non-pharmacological with pharmacological
- Standardize outcome measures
- Science of behavioral change
- Invest in technologies

## Session 6: New Models of Public Private Partnerships

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- Promote partnerships across all sectors
- Increase awareness of the value
- Enable partnerships for
  - Data sharing
  - Sharing tools for translational research
- Expand precompetitive space using new models
- Develop National IRB accessible to both public and private organizations