The Study of Alzheimer Disease Genetics Shifts the Paradigm to Dementia Prevention

24th Annual Simons Research Symposium

John C. Morris, MD

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Disclosure Statement (2013-2014)

- **Sources of Research Support**
  1. National Institute on Aging (P50 AG05681; P01 AG03991; P01 AG026276; U19 AG032438)
  2. Anonymous Foundation
  3. Alzheimer’s Association

- **Consulting Relationships**
  1. Lilly USA
  2. Charles Dana Foundation

- **Industry-Sponsored Trials**
  1. Janssen
  2. Pfizer
  3. Eli Lilly/Avid Radiopharmaceuticals

- **Fees > $10,000**
  - None

- **Stock Equity**
  - None

- **Speaker’s Bureaus**
  - None

- **Editorial Boards**
  - Annals of Neurology
Knight ADRC – Faculty and Staff
(with gratitude to our participants and families!)
“Alzheimer disease” (AD) refers to the neurodegenerative brain disorder, regardless of clinical status, representing a continuous process of synaptic and neuronal deterioration.

AD has two major stages:
- Preclinical (presymptomatic; asymptomatic), undetectable by current clinical methods
- Symptomatic (clinical)

Symptomatic AD is defined by intraindividual cognitive decline, from subtle to severe, that interferes with daily function, and can be subclassified on symptom severity:
- Incipient (prodromal; mild cognitive impairment)
- Dementia

AD Pathologic Hallmarks
- Plaques (diffuse, neuritic, CAA) (Aβ)
- Neurofilibrillary tangles (NFT) (tau)
- Neuronal and synaptic dysfunction and loss, Atrophy of the brain
- Inflammation
National Population: Notice the increase in the elderly as baby-boomers age

Source: U.S. Census Bureau
Spending on AD (to scale)

- For every $400 spent caring for those with AD, only $1 is spent on AD research.

- For heart disease, the ratio is 25:1
  - $100 billion in care
  - $4 billion in research

- For cancer, the ratio is 13:1
  - $75 billion in care
  - $6 billion in research
Confirmed Risk Factors for AD

- Age

- Genetics (family history)
  - Chromosomal disorder: All Down Syndrome individuals develop AD
  - Rare kindreds in which AD is caused by a single gene mutation (*APP, PSEN1, PSEN2*) with autosomal dominant inheritance
  - Complex: Most AD cases result from a mixture of genetic susceptibility (*APOE*) and environmental risk factors
Classification of Alzheimer Disease by Age at Onset

- Most common by far: “late onset” (after age 65 y)
  - Sometimes referred to as “sporadic”
  - >90% of persons with AD are 70 y or older

- Very rare (<1% of all persons with AD): “early onset” or “familial AD” (FAD)
  - AAO typically before age 60 y
  - Many (but not all) with an autosomal dominant inheritance pattern
Dementia

- Definition: An acquired syndrome of decline in memory and other cognitive domains sufficient to affect daily function

- Detection:
  - Intra-individual change: Informant observations about decline in previously established cognitive and functional abilities
  - Inter-individual differences: Cognitive test performance compared with age- and education-matched norms
Intraindividual Decline, Not Test Score, Marks Alzheimer Dementia
8-item Informant Interview to Differentiate Aging and Dementia*(PPV = 87% for CDR 0 vs CDR ≥ 0.5)

Report only a change caused by memory and thinking difficulties:

1. Is there repetition of questions, stories, or statements?
2. Are appointments forgotten?
3. Is there poor judgment (eg, buys inappropriate items, poor driving decisions)?
4. Is there difficulty with financial affairs (eg, paying bills, balancing checkbook)?
5. Is there difficulty in learning or operating appliances (eg, television remote control, microwave oven)?
6. Is the correct month or year forgotten?
7. Is there decreased interest in hobbies and usual activities?
8. Is there overall a problem with thinking and/or memory?

*Adapted from Galvin et al, “The AD8: A Brief Informant-Interview to Detect Dementia”, Neurology. 2005;65:559-564. Permission to use: contact denny@abraxas.wustl.edu
Clues to Differential Diagnosis

Alzheimer’s Disease

- Temporal profile + laboratory results
- Stroke, Focal Signs
- EPS, Visual Hallucinations
- Behavior, Language

Rapidly evolving dementias
Vascular dementia
Frontotemporal dementias
Lewy body dementia
NACC Accuracy Study

88 (16.7%) of 919 persons with clinical dx of AD did not merit neuropath dx of AD

<table>
<thead>
<tr>
<th>Primary findings in the 88:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropath AD (below criteria)</td>
<td>17</td>
</tr>
<tr>
<td>Tangle-predominant AD/AGD</td>
<td>15</td>
</tr>
<tr>
<td>Frontotemporal Dementia</td>
<td>15</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>10</td>
</tr>
<tr>
<td>Lewy body disease (with or without AD)</td>
<td>9</td>
</tr>
<tr>
<td>Hippocampal sclerosis (with or without AD)</td>
<td>9</td>
</tr>
</tbody>
</table>

Beach TG et al., J Neuropath Exp Neurol 2012;71:266-273
NIA-AA Diagnostic Guidelines for Dementia Due to AD
(McKhann G et al, Alzheimer’s & Dementia 2011; 7: 263-269)

- Enhance diagnostic confidence for AD
  - Molecular biomarkers of AD
    » Low levels of CSF Aβ42
    » Elevated levels of CSF tau and phospho-tau
    » Amyloid imaging (PET tracers: ¹¹C PIB, ¹⁸F Florbetapir, others)
  - “Downstream” indicators of neurodegeneration
    » Reduced temporoparietal metabolism with FDG-PET
    » Whole brain and/or regional atrophy on MRI
    » (Disrupted connectivity on fMRI)
  - Causative gene mutation *(PSEN1, PSEN2, APP)*
    » *APOE4* insufficiently specific to be a diagnostic biomarker
Presymptomatic Detection of AD: Biomarkers (PIB Imaging)

- Amyloid – Cognitively normal
- Amyloid + Alzheimer dementia
- Amyloid + Cognitively normal

3 years later, Alzheimer dementia

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Biomarker Vignettes

- Cases from my outpatient practice

- Commercial CSF assays from Athena Diagnostics
  - Cost about $1,500 - $1,800; nor radiation exposure
  - Medicare reimburses; some private insurers reimburse ~80%, but Athena will not run assay until patient/family pays remaining costs

- Florbetapir (Amyvid®) approved by FDA on April 2012 for persons being evaluated for cognitive decline; other commercial amyloid PET tracers now approved; at WUSM, with Avid/Lilly voucher costs ~$1,400 (non-reimbursed); without voucher, out-of-pocket costs ~$3,400
Caveats for AD Biomarkers

- Dichotomous biomarker test result (“positive” or “negative”), but AD is a continuous process
  - Ambiguous or indeterminant results will occur
- Standardization and validation (sensitivity and specificity) in practice settings is lacking
- Varying access to biomarkers in the community
- Reimbursement???
- Screening of cognitively normal persons???
Biomarker Vignettes

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The Anxious Professor

- 52 yo Spanish biomedical engineer with “memory problems”: mother had post-stroke dementia at age 68 y
  - Pt’s siblings (eldest 60 yo) w/o cognitive difficulties
- Husband reports pt has “always been high-strung and anxious”, attributes memory changes in last 3 y to menopausal Sx, recommends “behavior classes” for her
- Pt: “my memory always has been horrendous”
- No medical conditions except longstanding generalized anxiety disorder; Rx’ed with fluoxetine and clonazepam
**The Anxious Professor**

- **Lab chief**
  - Progressive memory prob × 1 y
    » Unable to “multi-task”; recent difficulty submitting manuscript online (had done so many times before)
    » Recommend medical leave

- **Husband**
  - For 2 y, progressive repetition and misplacement of items
  - Unable to operate new television, less fastidious housekeeping
  - Geographical disorientation when driving (missed appt)

- **Patient**
  - “I’m my own worst enemy because I’m such a worrier”
  - Denies anhedonia, weight change, or sleep difficulty
The Anxious Professor

- Neuropsychological assessment (age 52 y)
  - Anxious (late for appt as “I got lost”)
  - Circumlocution, dysnomia
  - Mod-severe deficits in memory, lesser deficits in naming and executive function
  - Normal attention and visuoperceptual abilities

- Routine EEG: mild generalized slowing

- $B_{12}$, TSH, RPR unremarkable
The Anxious Professor

- Wt 115 lb (height 5’ 3”)
- Anxious
- Unremarkable neurological exam
- Impaired in autobiographical memory

<table>
<thead>
<tr>
<th>Verbal Fluency (18)</th>
<th>Word List Recall (7)</th>
<th>Logical Memory (13)</th>
<th>Trails B (105 s)</th>
<th>MMSE (29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>2</td>
<td>4</td>
<td>180 s</td>
<td>29</td>
</tr>
</tbody>
</table>
Meet criteria for MCI? For dementia?

- Progressive intraindividual cognitive decline for 1-2 y
- Objective and subjective deficits in:
  » Episodic memory
  » Executive function
- General cognition “normal” (MMSE = 29)
- Interference with normal activities
  » Work performance
  » Missed appts
  » Decreased housework, operation of TV
The Anxious Professor – Biomarker Studies

- Structural MRI (age 52) - unremarkable
- FDG-PET (age 52) – biparietal hypometabolism

A) Sag FDG PET
B) Sag T1 MRI
C) Axial FDG PET
D) Axial FLAIR

Courtesy of T. Benzinger, MD, PhD
The Anxious Professor – Biomarker Studies

- Structural MRI (age 52) - unremarkable
- FDG-PET (age 52) – biparietal hypometabolism
- CSF (age 52)
  - 14-3-3: normal
  - Aβ/tau: “consistent with AD”

* Athena Diagnostics (Worcester, MA): ADmark®: Phospho-tau, Total-tau, Aβ42; cost of $1045 (not including LP); Medicare will reimburse
The Anxious Professor - Outcomes

- Patient: relief (need not return to work; know cause of her difficulties)

- Husband: initially stunned and distressed; soon after, more supportive of patient (he is taking early retirement), planning for wife’s future (exercise; Social Security disability) and their children (considering genetic testing)

- Families and patients overwhelmingly “want to know”

- Physicians are reluctant to deliver diagnosis of AD
A Physicist with Visual Phenomena: Initial Encounter – I.

- 74 yo LH retired (x 12y) PhD physicist; wife of 7 y serves as collateral source
- Multiple stable medical prob: asthma, HTN, ↑ chol., BPH, HOH bilaterally (amlodipine, atorvastatin, inhaler)
- No family hx of dementia: father died at 81y, mother at age 86y
- Hospitalized for empyema 8 mo ago, developed delirium (improved with quetiapine); brain MRI “normal”
A Physicist with Visual Phenomena: Initial Encounter – II.

- 2 y of gradually progressive memory problems
  - Relinquished role as an amateur thespian because he couldn’t remember his lines
  - Misplaces items; however, does not repeat

- Functional impairment
  - Relinquished driving 8 mo ago (fender benders)
  - Difficulty with calculations (wife pays restaurant bills)
  - Trouble operating appliances (computer, TV remote)

- Dysthymic affect, denies depressive features
For 3 y, visual illusions/misidentifications
- Living room sofa “undulates” or “changes its shape”
- Misinterprets shadows as animals (dog or cat), resolves when light turned on

Recently told wife that an “imposter” was masquerading as his rabbi

No vision changes
A Physicist with Visual Phenomena: Initial Encounter – Exam

- Neuro exam unremarkable except for mildly shuffling gait
- Language generally intact but unable to follow spoken 3-step command, mild dysgraphia
- Fully oriented
- Unable to draw a clock
Neuropsychological evaluation

- Difficulty grasping instructions
- “Saw” or sensed a person wearing green next to him but face not identifiable
- Mod–severe deficits in anterograde memory, semantic fluency, attention, and mental flexibility
- “Consistent with primary neurodegenerative dementia”
A Physicist with Visual Phenomena:
Capgras Syndrome

- Delusional misidentification: a familiar person is believed to be replaced by an imposter
- Misidentification syndromes (Capgras most frequent form) noted in ~16% of both clinically dx’ed AD dementia and DLB
  - Rarely if ever noted in FTD-bv, PPA, CBD, PSP, or PD¹
- In DLB, dysfunction of visual association cortex-amygdaloid pathways may underlie visual misidentifications and hallucinations²,³

²Yamamoto R et al., J Neurol Sci 2006; 246:95-101
³Kantarci K et al., Neurology 2010; 74:1814-1821
A Physicist with Visual Phenomena: My Differential Diagnosis

- AD dementia vs. DLB
  - Minor considerations
    - Absence of repetition uncharacteristic for AD dementia
    - Motor exam unremarkable except for mild shuffling
  - Other considerations
    - Visual misidentifications
    - Deficits in all cognitive domains, but clock draw disproportionately poor for early stage dementia

- CSF results
  - Aβ42: 646.8 pg/ml (cutoff <500 pg/ml)
  - Total tau: 229.9 pg/ml (cutoff >400 pg/ml)
  - P-tau: 43.8 pg/ml (cutoff >70 pg/ml)

* Indicates Position of Patient Result

ATI versus P-tau

Not consistent with AD

Consistent with AD

P-Tau (pg/ml)

0.0 0.4 0.8 1.2 1.6 2.0 2.4 2.8

0 30 60 90 120 150

P-tau 45.6 970
# Failure of AD Candidate Therapeutics

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target/Mechanism</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-(\text{A}\beta)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin; Simvastatin</td>
<td>Cholesterol (HMG CoA reductase inhibitor)</td>
<td>Negative</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Inflammation</td>
<td>Negative</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Insulin (PPAR gamma agonist)</td>
<td>Negative</td>
</tr>
<tr>
<td>Latrepirdine</td>
<td>Mitochondrial function</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>(\text{A}\beta)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AN1792</td>
<td>Amyloid immunoRx</td>
<td>Negative (AEs)</td>
</tr>
<tr>
<td>Tramiprosate</td>
<td>Amyloid aggregation</td>
<td>Negative</td>
</tr>
<tr>
<td>Tarenflurbil</td>
<td>Gamma secretase</td>
<td>Negative</td>
</tr>
<tr>
<td>Semagacestat; Avagacestat</td>
<td>Gamma secretase</td>
<td>Negative</td>
</tr>
<tr>
<td>Bapineuzumab</td>
<td>Amyloid immunoRx</td>
<td>Negative</td>
</tr>
<tr>
<td>Solanezumab</td>
<td>Amyloid immunoRx</td>
<td>Negative (+/-)</td>
</tr>
<tr>
<td>IVIG</td>
<td>Nonselective immunoRx</td>
<td>Negative</td>
</tr>
<tr>
<td>LY2886721</td>
<td>Beta secretase</td>
<td>AEs</td>
</tr>
<tr>
<td>ACC-001</td>
<td>Amyloid immunoRx</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Preclinical and Symptomatic AD

Preclinical AD

~20 y

No AD

Symptomatic AD

~7-10 y

Synaptic/Neuronal Integrity

↓

Hippocampal Volume

↑

CSF tau

+ Amyloid Imaging

↓

CSF Aβ

Transition Period

~5 y

0.5 → 1 → 2 → 3

Cognitively Normal

↓

Cognition, ↓

Metabolism, and Other Potential Indicators

Death

Tau

Microglia

Inflammation

Oxidative stress

Other

Neuronal loss

CDR

Other

Symptomatic AD

~7-10 y
Presymptomatic Detection of AD: Biomarkers (PIB Imaging)

Amyloid –
Cognitively normal

Amyloid +
Alzheimer dementia

Amyloid +
Cognitively normal
3 years later, Alzheimer dementia

Courtesy of Mark A. Mintun and John C. Morris.
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Percent of Cognitively Normal Participants with Amyloid Plaques

Courtesy of Mark Mintun, MD, and Andrei Vlasenko, PhD
Preclinical Alzheimer Disease

- ~30% of cognitively normal older adults have biomarker evidence of preclinical AD
- Biomarker-positive CN persons are at increased risk of developing symptomatic AD compared with biomarker-negative CN older adults
- However, individual level prediction not currently possible
  - Is symptomatic AD inevitable?
  - If so, when will it develop?
- Asymptomatic AD mutation carriers are destined to develop symptomatic AD, and at about the same age as their affected parent
Autosomal Dominant Alzheimer’s Disease (ADAD)

- <1% of AD cases result from autosomal dominant mutations in 3 genes directly involved in amyloid beta (Aβ) production
  - Amyloid precursor protein (APP)
  - Presenilin 1 (PSEN1)
  - Presenilin 2 (PSEN2)

- Auguste D., the first AD patient described by Dr. Alois Alzheimer, was found to carry an ADAD mutation in Presenilin 1 (F176L)
## Comparison of Autosomal Dominant and Sporadic AD

<table>
<thead>
<tr>
<th>Measure</th>
<th>Autosomal Dominant AD</th>
<th>Sporadic AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical presentation</td>
<td>Amnestic</td>
<td>Amnestic</td>
</tr>
<tr>
<td>Cognitive deterioration</td>
<td>Memory, frontal/executive, generalized cognitive decline</td>
<td>Memory, frontal/executive, generalized cognitive decline</td>
</tr>
<tr>
<td>MRI</td>
<td>Hippocampal atrophy and whole brain atrophy</td>
<td>Hippocampal atrophy and whole brain atrophy</td>
</tr>
<tr>
<td>PiB PET</td>
<td>Cortex plus basal ganglia</td>
<td>Cortex</td>
</tr>
<tr>
<td>FDG PET</td>
<td>Parieto-occipital hypometabolism</td>
<td>Parieto-occipital hypometabolism</td>
</tr>
<tr>
<td>CSF Aβ 42</td>
<td>Decreased by 50%</td>
<td>Decreased by 50%</td>
</tr>
<tr>
<td>CSF tau</td>
<td>Increased by 2-fold</td>
<td>Increased by 2-fold</td>
</tr>
</tbody>
</table>
**DIAN Aims (2008-2014)**

- Determine WHEN the pathobiology of AD begins in asymptomatic mutation carriers (MCs) in relation to parental age of onset of dementia
- Determine the SEQUENCE and RATE of the pathobiological changes
- Compare the clinical and pathological phenotypes of dominantly inherited AD with late onset AD
- Establish an international, longitudinal registry of 400 persons (~200 MCs, ~200 NCs) from families with a known pathogenic mutation for AD
Dominantly Inherited Alzheimer Network (DIAN)*

Steering Committee
(Core & Site Leaders, FDA, Ethicist, Family Members, NIA, Other Key Personnel)

Sub-Committees
- Imaging Core Executive Committee
- Resource Allocation Review

DIAN Coordinating Center
Core A: Administration
Morris

External Advisory Committee

Core B: Clinical
Bateman

Core C: Biostatistics
Xiong

Core D: Neuropath
Cairns

Core E: Biomarker
Fagan

Core F: Genetics
Goate

Core G: Imaging
Benzinger

Core H: Informatics
Marcus

Clinical Coordinating Center
Aisen
ADCS

National Cell Repository For AD
Foroud (NCRAD)

PET Pre-Processing
U Mich
Koepppe (ADNI)

MRI Pre-Processing
Mayo
Jack (ADNI)

Univ of Pittsburgh
Pittsburgh
McDade

Inst of Neurology
Univ College
London
Rossor

Univ of Melbourne
Melbourne
Masters

Edith Cowan
Univ
Perth
Martin

Univ of New South Wales
Sydney
Schofield

Wash. Univ
St. Louis
Bateman

UCLA
Los Angeles
Ringman

Indiana Univ
Indianapolis
Ghetti

Columbia Univ
New York
Mayeux

B&W; MGH
Boston
Sperling

Butler Hosp
Brown Univ
Providence
Salloway

Univ of Pittsburgh
Pittsburgh
McDade

UC San Diego
Galasko

Mayo-Jacksonville
Graff-Radford

University of Tübingen
Jucker
DZNE

Ludwig-Maximilians-
Universität
Danek
DZNE

UC San Diego
Galasko

Mayo-Jacksonville
Graff-Radford

University of Tübingen
Jucker
DZNE

Ludwig-Maximilians-
Universität
Danek
DZNE

*U19 AG032438 (JC Morris, PI)
### Participant Entry Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic</th>
<th>Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>*<em>N = 402</em> (Target 80%</td>
<td>280 (71.4%)</td>
<td>112 (28.6%)</td>
</tr>
<tr>
<td>Asymptomatic, 20% Symptomatic)**</td>
<td>259 (71.4%)</td>
<td>108 (29.4%)</td>
</tr>
<tr>
<td>**(Table based on 367</td>
<td>125 (NC-)</td>
<td>12 (NC-)</td>
</tr>
<tr>
<td>participants. 35 Mutations</td>
<td>134 (MC+)</td>
<td>96 (MC+)</td>
</tr>
<tr>
<td>in Process)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>38.5 (SD 10.0)</td>
<td>34.9 (SD 9.0)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender (% Female)</strong></td>
<td>58.4%</td>
<td>56.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Parental Age of Onset</strong></td>
<td>46.6 (SD 6.8)</td>
<td>47.3 (SD 7.1)</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Education</strong></td>
<td>14.8 (SD 2.6)</td>
<td>14.5 (SD 2.9)</td>
</tr>
<tr>
<td></td>
<td>29.2 (SD 1.2)</td>
<td>29.1 (SD 1.2)</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ApoE4+</strong></td>
<td>1 E4</td>
<td>2 E4</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
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</tbody>
</table>

MC = Mutation Carrier; NC = Non-carrier

*Table statistics based on 367 participants with NCRAD-confirmed mutation data available as of 31 MAY 2014
## Procedure Completion Rates
(as of July 31, 2014)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Baseline N= 396</th>
<th>Follow-up N= 290</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive battery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- UDS</td>
<td>100%</td>
<td>98%</td>
</tr>
<tr>
<td>- Computerized</td>
<td>94%</td>
<td>86%</td>
</tr>
<tr>
<td>Nonfasted Blood (for genetics)</td>
<td>100%</td>
<td>N/A</td>
</tr>
<tr>
<td>Fasted blood</td>
<td>97%</td>
<td>98%</td>
</tr>
<tr>
<td>MRI</td>
<td>94%</td>
<td>90%</td>
</tr>
<tr>
<td>PET PIB</td>
<td>87%</td>
<td>83%</td>
</tr>
<tr>
<td>FDG PET</td>
<td>90%</td>
<td>88%</td>
</tr>
<tr>
<td>Lumbar Puncture</td>
<td>80%</td>
<td>69%</td>
</tr>
</tbody>
</table>
Alzheimer Biomarker Pathochronology in Autosomal Dominant AD

- CSF Aβ
- PIB Binding
- CSF Tau
- Hippocampal Volume
- Brain Metabolism
- Episodic Memory
- CDR-SB

Years
-25 to +5

Estimated Age at Onset of Symptoms

Morris et al., Clin Invest 2012; 2:975-984, based on Bateman et al, NEJM 2012
Through public/private support and partnership, the DIAN-TU has launched trials to provide advancement of treatments, scientific understanding and improvements in the approach to Alzheimer’s disease drug developments.

*Financial support has also been provided by anonymous sources.
DIAN Biomarker Trial Design

- Launched 2012 with two drugs each with a unique target to alter the disease course and full data and sample availability
- Multiple arms: 3:1 active:placebo (75% chance of active drug)
- Non-carriers assigned to placebo
- Maximum Biomarker duration = 2 years
- Extend study if positive results to cognitive endpoint registration trial
# First Drugs in the DIAN-TU Trial

<table>
<thead>
<tr>
<th>DRUG</th>
<th>TYPE</th>
<th>Mechanism of Action Biomarker</th>
<th>Downstream Biomarkers</th>
<th>EXPLORATORY Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solanezumab (LILLY)</td>
<td>Anti-Aβ antibody (soluble Aβ)</td>
<td>CSF Aβ42</td>
<td>CSF tau, ptau181, vMRI, Tau PET (NIH AMP)</td>
<td>FDG PET, fcMRI,Tau PET (NIH AMP)</td>
</tr>
<tr>
<td>Gantenerumab b (ROCHE)</td>
<td>Anti-Aβ antibody (aggregated Aβ)</td>
<td>PET PIB</td>
<td>CSF tau, ptau181, vMRI, Tau PET (NIH AMP)</td>
<td>FDG PET, fcMRI, Tau PET (NIH AMP)</td>
</tr>
<tr>
<td>TBD</td>
<td>TBD</td>
<td></td>
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</tr>
</tbody>
</table>
Biomarker Phase for parallel adaptive drug design. Enrollment of both mutation carriers and non-carriers. Option of non-disclosure of genetic status to participate in the DIAN-TU trial.
DIAN-TU Network

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Other Secondary Prevention Trials to Launch 2013-2014

- Alzheimer Prevention Initiative (conducted in Colombia and US); E Reiman, P Tariot
  - PSEN1 E280A family, 200 MC and 100 NC; began in late 2013
  - Crenezumab (Genentech), subcutaneous

- A4 (Anti-Amyloid in Asymptomatic AD); R Sperling, ADCS
  - In North America, clinically normal persons 65-85 y with elevated brain amyloid (PIB), 500 individuals per treatment arm
  - Solanezumab (Eli Lilly), IV infusion every 4 wks for 3 y

- TOMMORROW; Takeda and Zinfandel Pharmaceuticals
  - 5800 cognitively normal persons at increased AD risk based on APOE and TOMM40 genotypes, age 65-83 y worldwide
  - Pioglitazone (AD-4833, PPAR-γ), oral
Conclusions for Early Detection and Intervention in AD

- Once symptoms occur, even in prodromal/MCI stage, the brain already has been irreversibly damaged by AD
- Symptomatic AD may benefit from combination therapies
- AD biomarkers may be useful to support clinical diagnoses and now allow *in vivo* detection before symptoms occur
- Prevention trials with anti-amyloid monotherapies have begun in asymptomatic persons at great risk of symptomatic AD, but much work (timing, outcomes, etc.) remains