Biomarkers and the future Diagnosis of Alzheimer's Disease

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Disclosure Statement

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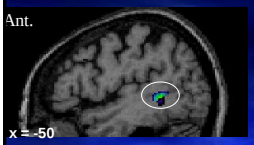
Pfizer, Bristol-Myers Squibb,
Janssen, and Lundbeck.

What we do in the Chertkow lab

- 1.Studying brain/behaviour correlations using AD subjects (and others, including normals), focussing on semantic memory.
- 2. Defining biomarkers for early diagnosis of AD

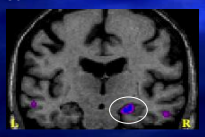
Picture Naming - Normal elderly

↓Accuracy & ↑ CBF



More difficult picture naming was associated with increased CBF to the **left lateral temporal cortex.**

x = -50



↑Accuracy & ↑ CBF

Easier picture naming was associated with increased CBF to the **right hippocampus.**

Whatmough, Verret. et al. (2004). *Journal of Cognitive Neuroscience. 16 (7).* 1211-1226

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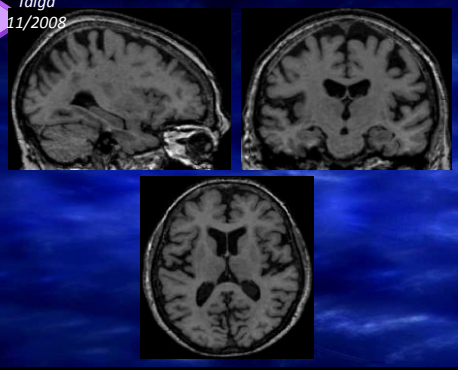
Px: Taiga - History

- Age 70 (1998) , no memory complaints,
- Volunteered as normal control in 1998
- Still normal 2007. Involved in many research projects
- No complaints, on ASA
- Mild diabetes, no meds
- Normal physical exam

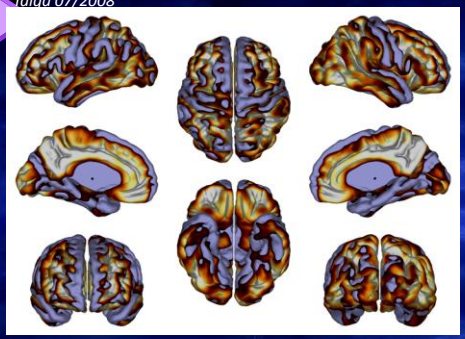
Px: Taiga - Imaging

- MRI:
  - Normal 1998
  - Mild atrophy 2008
- PIB:
  - +ve 2008!
  - SUVR high, 2.06

Taiga
11/2008



Taiga 07/2008



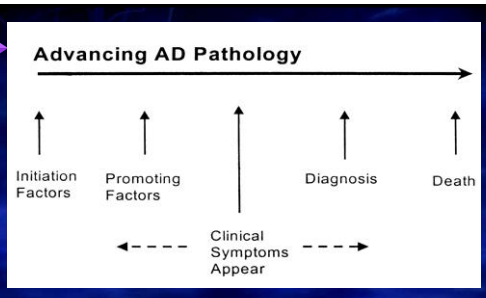
Px: Taiga – Follow up
Mild Progression of Memory Complaints and Memory Loss

	2006	2008	2010	2011
Shmandt [SMCS>6]	2	6	7	9
MMSE	28	27	25	25
MoCA	27	26	24	20

Shmandt scale >6= subjective memory complaints.
MoCA <26 = objective cognitive impairment

Px: Taiga - Diagnosis

- Changed to MCI in 2010
- No limitations in ADL, IADL
- 2012: Beginning to have impairment of finances, medications, instrumental activities of daily living. Deemed to have "mild dementia", probable AD.



There is converging evidence from both genetic at-risk and age at-risk cohorts that the pathophysiology of AD begins years, likely more than a decade, prior to the diagnosis of dementia

What is dementia? {2011}

- Definition: a)Decline in intellectual abilities (memory plus one other domain)..from previous level
- b)Interfering with social or occupational life and day to day function. - same
- In addition…..
- Not delirium- same
- There may be little insight and reporting is done by family
- There may be concomitant depression
- Changes in affect and personality
- Psychiatric abnormalities
- Downhill course, fatal illnesses

Cognitive Continuum

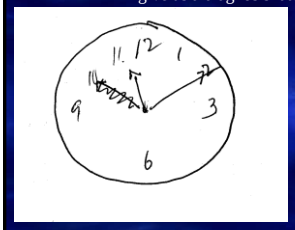
Normal

Mild Cognitive Impairment

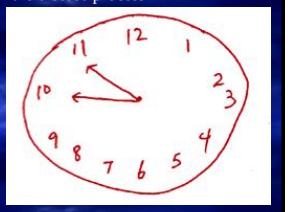
Dementia

How do we diagnose AD dementia now?

Our tools for diagnosis – clinical, neuropsychological – give us a diagnosis late in the disease process



2003- AH, 72 years old, MCI

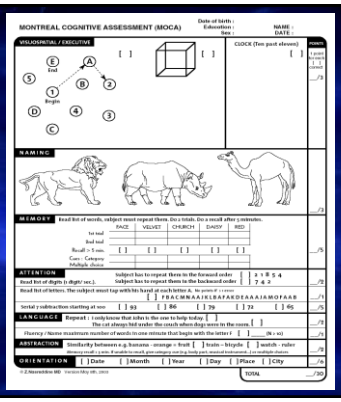


2006 – AH, 75 years old, mild AD

MoCA Montreal Cognitive Assessment -a cognitive screening tool for detection of MCI

Ziad S Nasreddine, Howard Chertkow, Natalie A Phillips **J.Am Geriatr Soc 53:695–699,2005**

- 30-point scale
- 10 minutes to administer
- French/English+17 languages
- Tests 8 domains
- Available at www.mocatest.org
- Score<26 abnormal



Clinical categories

ADNI STUDIES

Normal function:
- No complaints of cognitive loss — YES
- Testing is within normal limits

Subjective complaints only: — YES
- Patient or family complains of loss
- Testing is within normal limits

Mild Cognitive Impairment:
- Patient or family complains of loss
- Objective very mild impairment (early) or mild impairment (late) in cognition — YES YES
- Not sufficient to be dementia

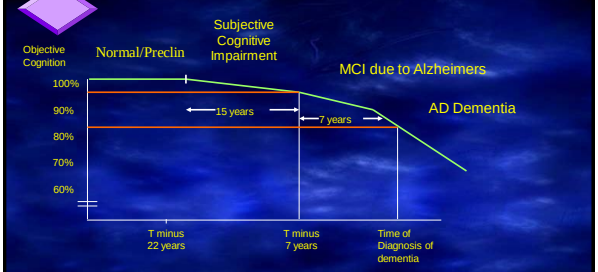
Dementia:
- Significant decline in two or more cognitive domains — YES
- Sufficient to impair day to day function

The Alzheimer's Disease Neuroimaging Initiative

Design:

Natural history non-treatment study in which a total of 1200 subjects (including 200 normal controls, 600 MCIs, and 400 mild ADs) being recruited at 53 sites in the US and Canada for longitudinal follow up.

ADNI



When does AD begin?
B. Reisberg, IPA meeting, 2009

Delineating the predementia stages of AD may be pivotal in finding new therapies! (Vellas et al, 2011, Progress in Neurobiology, 95; 594-600)

- **Interventions at "dementia" stage of AD may be too late to show effects.**
- **Study early MCI and late MCI (as in ADNI)**
- **Study "MCI due to AD" (Albert, 2011)**
- **Study Cognitively normal with positive amyloid biomarkers**
- **Use high risk populations defined by genetics (APoE) and imaging (FDG PET)**
- **Study earlier age groups, and follow longer**

Can Biomarkers supplement clinical diagnosis?

Role of Biomarkers

- Diagnosis and differential diagnosis
- Predicting future disease risk
- Predicting prognosis when memory loss
- Measuring disease severity
- Monitoring progression
- Predicting/monitoring response to therapy

$ Ease of Use

Classes of Alzheimer's Disease Biomarkers
[NIH Working Group, 2010]

- A) B/M of molecular neuropathology
  - CSF A-beta, CSF tau, PET amyloid imaging
- B) Downstream measures of structural change
  - Brain atrophy, hippocampal volumes, DTI, VBM.
- C) Downstream measures of functional change.
  - FDG PET, fMRI activation, fMRI resting state connectivity.
- D) Associated biochemical changes.
  - Inflammation, oxidative stress(isoprostane), NDD measures.

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Categories of Biomarkers used in the new lexicon

- **Biomarkers of Aß deposition**
  - **CSF $Aß_{42}$**
  - **PET amyloid Imaging**
- **Biomarkers of Neuronal Injury**
  - **CSF tau/p-tau**
  - **Hippocampal or medial temporal volume**
  - **Rate of brain atrophy**
  - **FDG-PET**
  - **SPECT perfusion imaging**
  - **Less well validated: fMRI, diffusion tensor, MRI perfusion, MR spectroscopy**
- **Associated biochemical change**
  - **Inflammatory biomarkers (cytokines)**
  - **Oxidative Stress**

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup
Guy M. McKhann, David S. Knopman, Howard Chertkow, et al., Alzheimer's & Dementia, 2011

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup
Marilyn S. Albert, Steven T. DeKosky, et al., Alzheimer's & Dementia, 2011

Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup
Reisa A. Sperling, Paul S. Aisen, *et al.*, Alzheimer's & Dementia, 2011

"Introduction to the recommendations from the NIA and the AA Workgroups on diagnostic guidelines for AD". Cliff Jack, M. Albert, David S. Knopman, G. McKhann et al., Alzheimer's & Dementia, 2011

• • IN MCI and AD…
- clinical diagnoses are paramount and biomarkers are complimentary
- "The core clinical diagnostic criteria for MCI and AD dementia are completely operational in a setting where no access to biomarkers exists".

""The core clinical diagnostic criteria for MCI and AD dementia are intended to guide diagnosis in the clinical setting".

Biomarkers are currently for research, and for special cases.
….but in the future they may play a central role.

"The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup"-Guy M. McKhann, David S. Knopman, Howard Chertkow, et al., Alzheimer's & Dementia, 2011

•Revision of clinical criteria

1. Criteria for dementia of all causes
2. Probable AD – core clinical criteria: AD-Clinical = amnestic, BUT ALSO. non-amnestic presentations such as logopenic Primary Progressive Aphasia , Posterior Cortical Atrophy, dementia with prominent frontal/executive dysfunction.
   - - increased level of certainty with causative genes, documented decline
3. Possible AD core clinical criteria
   - Atypical course or
   - Etiologically mixed (Vascular, extrapyramidal, other neuro illness)
4. Probable/ possible AD with biomarkers ("evidence of the AD pathophys").

Px: Scytale

- 77 year old female in 2007
- 9 years education
- +ve family history of dementia (mother, in 60s)

Px: Scytale - Presentation

- Progressive anxiety, irritability-referred to geriatric psychiatry –
- Disinhibited, unable to plan
- Functional impairment IADL's
- Is it "organic" frontal brain damage, or is it "functional"?

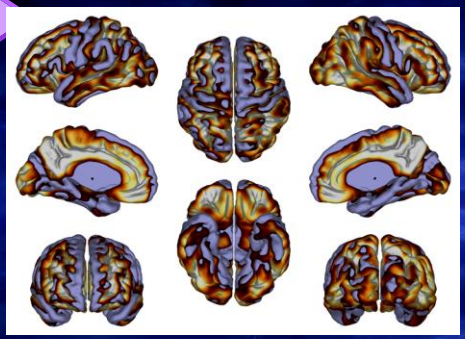
Px: Scytale - Neuropsych (2007)

- Memory impairment
- Language impairment
- Poor attention and concentration
- Marked executive function/frontal deficits
- Non-verbal skills better than verbal skills

Px: Scytale - Imaging

- PIB:
  - +ve amyloid, generalized, typical distribution
  - SUVR 1.99
- MRI:
  - Moderate global atrophy
  - Left more than right atrophy
  - Hippocampal atrophy left severe, right mild
- FDG:
  - Severe metabolic loss left temporal and parietal lobe
  - Moderate decrease left frontal lobe
  - Mild decrease right temporal and parietal lobe

Scytale 07/2009



Px: Scytale - Impression

- AD, probable
- Cognitive, MRI, FDG, PET deficits in parallel
- Use of biomarkers in patients with prominent neuropsychiatric/frontal features will allow more definitive diagnosis of AD

McKhann et al.: Biomarkers in AD

Clinical diagnosis category Probable AD	BoM probability Intermediate	Abeta (CSF or PET) Indeterminate or unavailable	Neuronal injury (MRI, FDG PET, CSF tau) Positive	
	Intermediate	Positive	Unavailable or indeterminate	
	High BoM probability	Positive	Positive	
Possible AD	High but does not rule out other etiology	Positive	Positive	

"Probable/ possible AD with evidence of the AD pathophysiological process"

Px: Aragorn

- Presented onset age 72 of short term memory loss, irritability
- Lacking initiative, apathetic
- Decline in language skills, reading, writing
- Word finding problems
- Can't recall family names
- Misplacing items
- Impaired function

Px: Aragorn - History

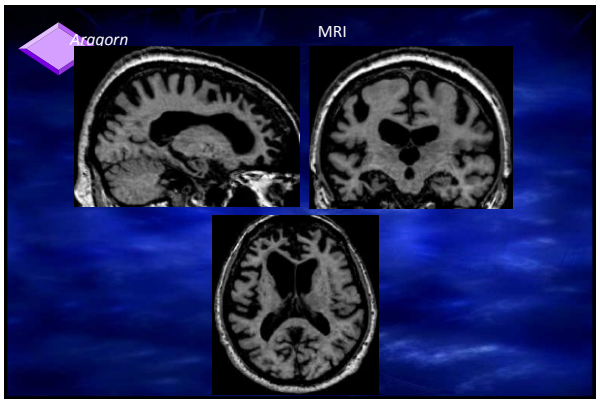
- 8 years education
- Worked as barber
- No family history dementia
- No family history dementia
- No vascular risk factors

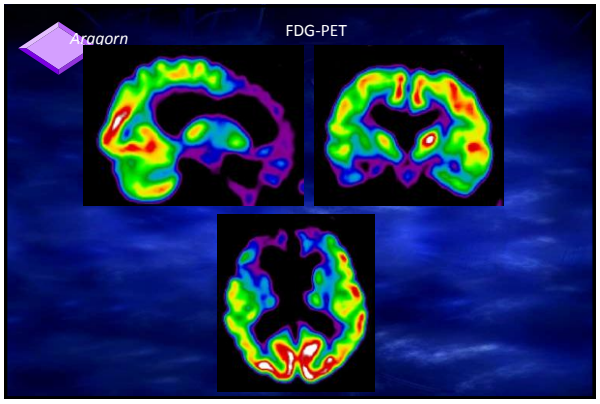
Px: Aragorn - Exam

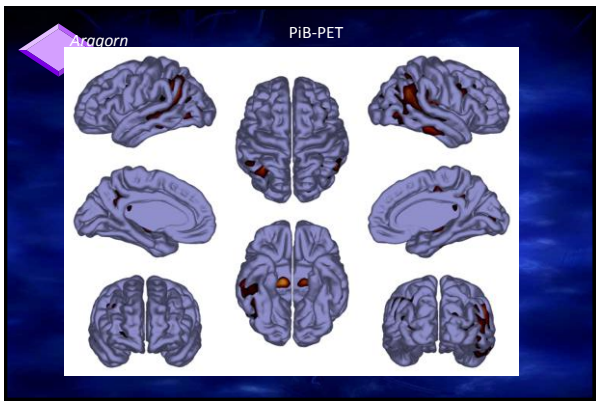
- Normal general exam
- Non focal neurologic exam
- +ve grasps
- Mental status: poor attention and concentration, disoriented, anomic, MMSE=16, slow, poor delayed verbal memory
- Similar results on neuropsychology
- Diagnosis – severe dementia, Probable AD

Px: Aragorn - Imaging

- MRI (2008):
  - Moderate atrophy, more frontal and temporal
- FDG PET:
  - Severe decrease entire left frontal lobe
  - Mild decrease right frontal support FTD
- PIB PET:
  - Negative, SUVR 1.1


Aragorn
MRI


Aragorn
FDG-PET

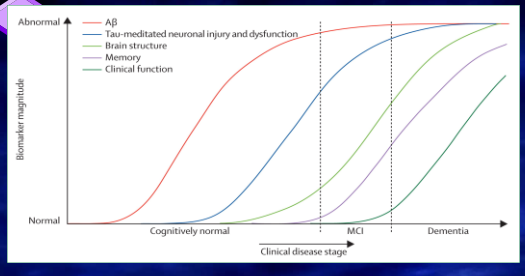

Aragorn
PiB-PET

Px: Aragorn – Revised Diagnosis

- AD is excluded by negative biomarkers!
- FTD is likeliest diagnosis

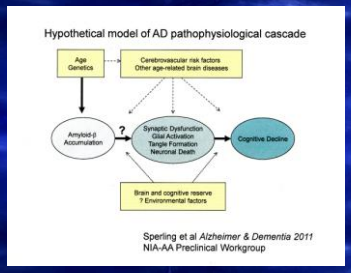
- **New Criteria:** Cllnicians can exclude "dementia due to AD" if subject meets the clinical criteria for possible AD, but BOTH BIOMARKER GROUPS ARE NEGATIVE

Lets talk about imaging biomarkers



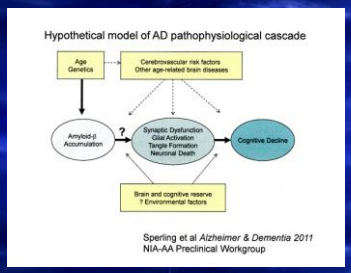
Dynamic biomarkers of the Alzheimer's pathological cascadeAβ is identified by CSF Aβ42 or PET amyloid imaging. Tau mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment. *From Jack et al. 2010, Lancet Neurology.*

Underlying model

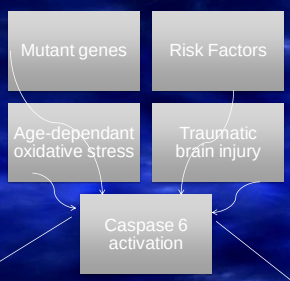


Underlying model

This model Assumes That amyloid Is The primary Cause!

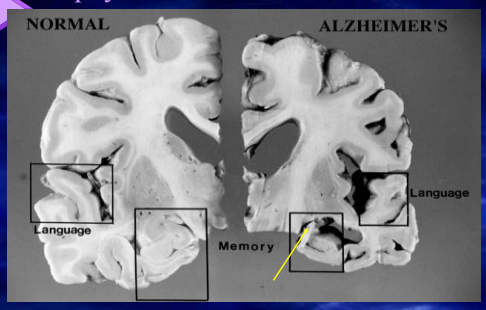


LeBlanc, 2010: Caspase 6 activation is likely firsts stage



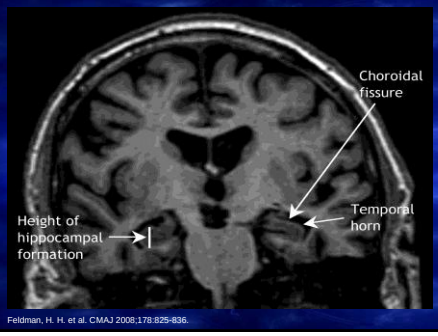
Neuritic damage……Amyloid deposition……Inflammation……
synaptic damage…..tau hyperphosphorylation

Atrophy in Alzheimer's disease



Atrophy of the brain in AD: Medial temporal lobes are affected first and most severely

T1-weighted coronal magnetic resonance imaging scan showing extensive hippocampal atrophy (arrows).



Feldman, H. H. et al. CMAJ 2008;178:825-836.

Medial Temporal Atrophy Rating Algorithm

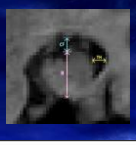
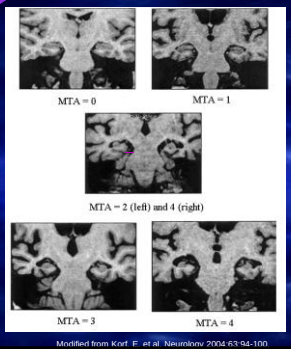


Table 1. Medial Temporal Atrophy Rating Algorithm

Score	Width of Choroidal Fissure	Width of Temporal Horn	Height of Hippocampus
0	Normal	Normal	Normal
1	Mildly widened	Normal	Normal
2	Moderately widened	Mildly widened	Mildly reduced
3	Markedly widened	Moderately widened	Moderately reduced
4	Markedly widened	Markedly widened	Markedly reduced

DeCarli, C. et al. Arch Neurol 2007;64:108-115.

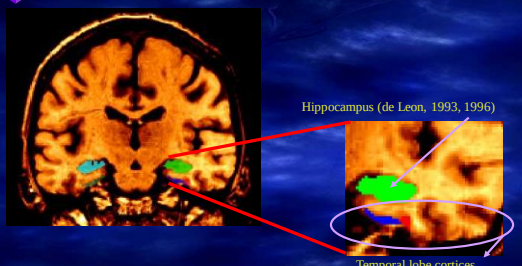
Medial temporal lobe atrophy (MTA) scale.



Modified from Korf, E. et al. Neurology 2004;63:94-100

The rating from 0 to 4 is displayed; higher scores indicate more atrophy. When one score is given, left = right.

Volumetric Studies

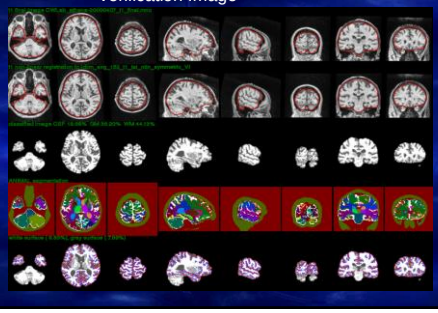


MRI variables to look at

- Hippocampal volume most validated in AD, but not validated in any therapy trial……
- Brain volumes- -less valid (see immuno.trial)
- Voxel based morphometry
- Ventricular volume
- Cortical thickness
- White matter changes MT, VBM
- DTI, ASL, etc…..
- Functional MRI variables..resting and activity

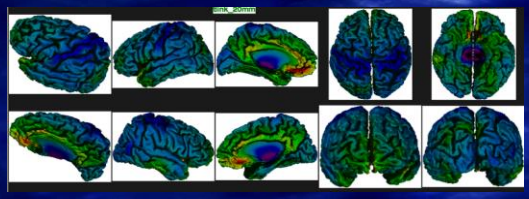
MNI Pipeline - Civet

Verification Image

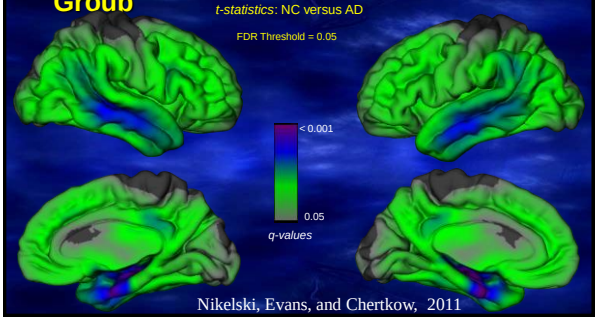


MNI Pipeline – Civet (and "Beagle")

Cortical Thickness Superimposed onto Mid-Surface



ADNI AD vs Normal brain Cortical Thickness - Effects of Diagnostic Group



Nikelski, Evans, and Chertkow, 2011

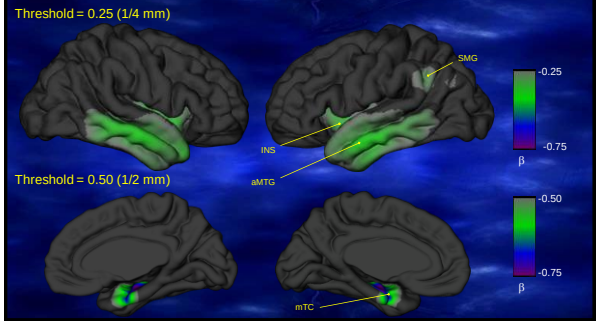
Percentage decrease in cortical thickness between AD, Normals

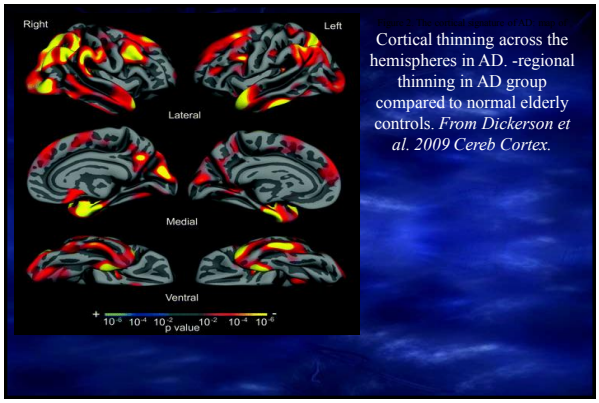
Region	*t*	*β*	NC mean (mm)	% ⇓
L. Insula	-6.0	-0.35	4.89	7
L. ant. MTG	-11.7	-0.36	3.63	10
L. ant. med. TC	-15.1	-0.75	3.32	23
R. Insula	-6.7	-0.37	4.86	8
R. ant. MTG	-11.7	-0.36	3.46	10
R. ant. med. TC	-15.0	-0.76	3.39	22

Nikelski, Evans, and Chertkow, 2011

Effects of Diagnostic Group

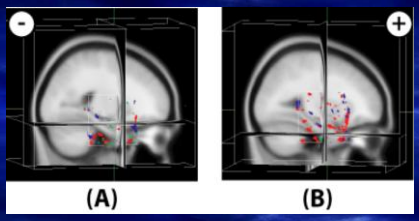
Nikelski, Evans, and Chertkow, 2011





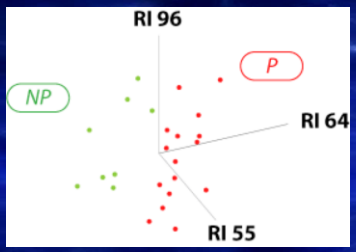
Cortical thinning across the hemispheres in AD. -regional thinning in AD group compared to normal elderly controls. *From Dickerson et al. 2009 Cereb Cortex.*

Duchesne, S., Bocti, C., De Sousa, K., Frisoni, G.B., Chertkow, H., & Collins, D. L. (2010).. *Neurobiology of Aging, 31(9),* 1606-17.



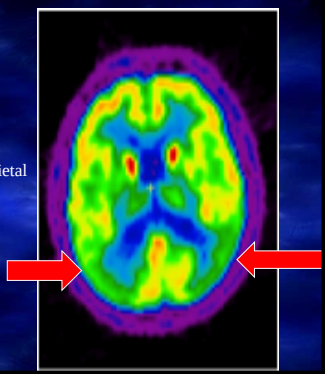
Areas of discriminating intensity covariances in right medial temporal lobe.

Duchesne, S., Bocti, C., De Sousa, K., Frisoni, G.B., Chertkow, H., & Collins, D. L. (2010).. *Neurobiology of Aging, 31(9),* 1606-17.



Patients data plotted along most discriminat eigenvectors. The NP (green) and P (red) patients data are shown here plotted along the three most discriminating eigenvectors in the multidimensional reference space of cross-sectional MR intensity and shape information

FDG PET in Alzheimer's Disease:
Decreased glucose metabolism
In bilateral posterior temporal-parietal region



Evaluating Early Dementia With and Without Assessment of Regional Cerebral Metabolism by PET: A Comparison of Predicted Costs and Benefits

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Evaluating dementia in patients with early symptoms of cognitive decline is clinically challenging. Growing evidence indicates that appropriate incorporation of PET into the clinical work-up can improve diagnostic and prognostic accuracy with respect to Alzheimer's disease (AD), the most common cause of dementia in the geriatric population. The precise diagnostic role of PET and its economic impact in this context, however, have not been systematically examined previously. **Methods:** We compared the relative value of 2 strategies for assessing whether early AD is responsible for cognitive symptoms in geriatric pts: (*a*) a conventional approach, based largely on established clinical criteria for the presence of dementia and excluding non-AD etiologies that could contribute to the patient's symptoms, and (*b*) a proposed approach using PET to examine regional cerebral metabolism and look for characteristic patterns of abnormal metabolism. The total costs (measured in $/diary) and benefits (measured in number of accurate diagnoses) of diagnostic testing and clinical outcomes accruing to each strategy were calculated using formalized tools of decision analysis. The primary outcome measure by which the strategies were compared was the ratio of costs to benefits obtained following each approach. **Results:** Following the proposed approach led to improved accuracy in identifying early AD, without adding to the overall costs of diagnosis and treatment ($3,439 vs. $3,064 per patient approached by the proposed or conventional algorithm, respectively). The strategy making use of PET was associated with a reduced rate of false-negative and false-positive findings compared with the conventional approach (5.1% vs. 8.2% and 12.0% vs. 33.0%, respectively, at a prevalence of 01.6% in the studied symptomatic population) and a cost savings of $1,138 per correct diagnosis rendered ($4,047 vs. $5,185). The lower cost per unit benefit for the proposed strategy was maintained over a wide range of tested values for variables of sensitivity, specificity, costs of PET and long-term care, and varying approaches to the use of structural neuroimaging. **Conclusions:** Appropriate use of PET for evaluating early dementia in geriatric patients can add valuable information to the clinical work-up, without adding to the overall costs of evaluation and management, resulting in a greater number of patients being accurately diagnosed for the same level of financial expenditure. Thus, the opportunity exists for diminishing the morbidity of dementia economically, with earlier institution of more appropriate management in evaluated patients.

Key Words: Alzheimer's disease; dementia; PET; FDG; functional brain imaging; cost-to-benefit ratio; cost-effectiveness; decision tree; decision analysis

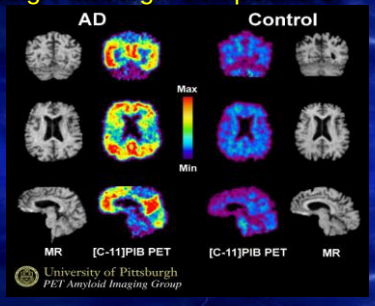
J Nucl Med 2002; 43:253–266

Dementia exacts a huge toll on our health and welfare and, as mean life expectancy continues to rise, the magnitude of this problem is growing. It is estimated that 8% of people who are ≥65 y old suffer from the most common form of dementia, Alzheimer's disease (AD) (*1,2*). Disease prevalence climbs rapidly with age, and at least 30% of

Human Amyloid Imaging in AD Using Pittsburgh Compound-B

Appearance in expected gray matter areas

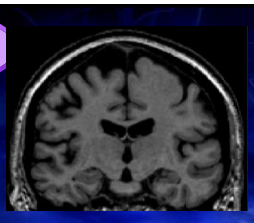
Absence in areas where there is no amyloid

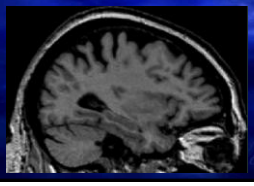


Very little retention

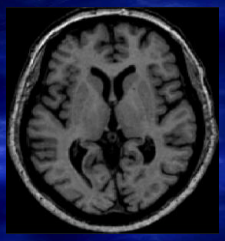
Absence of retention in gray matter

Klunk et al., Annals of Neurology 2004

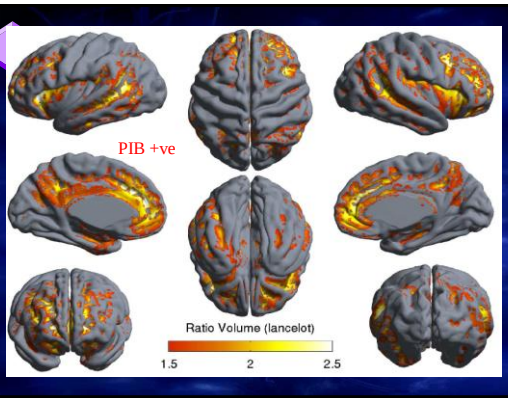


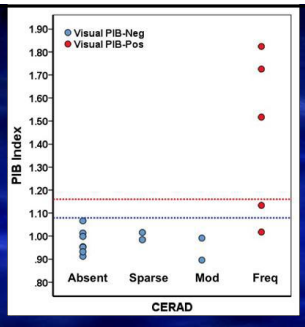


Lancelot- mild MCI, was normal last year



No hippocampal atrophy!

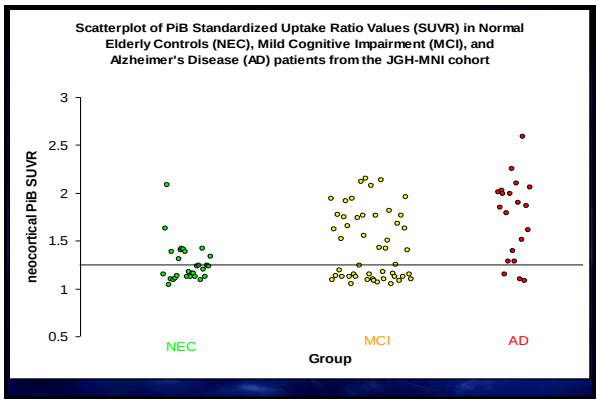




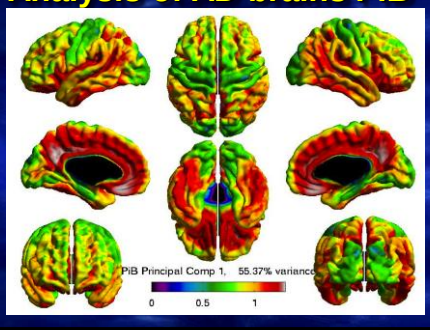
Relationships among postmortem CERAD diagnosis, quantitative PIB threshold (blue line = liberal, red line = conservative), and visual reads. All scans read as positive showed frequent CERAD plaques. *Gil Ravinovici, William Jagust*

JGH-MNI PiB cohort demographics

	NEC	MCI	AD	Atypicals
N (% female)	29 (67)	49 (40)	20 (30)	40 (35)
Age	76.5 +/- 5.6 (68-86)	76.6 +/- 6.7 (62-90)	76.7 +/- 6.1 (65-86)	68.5 +/- 9.3 (48-83)
Education	14.6 +/- 2.6 (9-19)	14.1 +/- 3.5 (9-25)	12.8 +/- 4.4 (6-20)	12.8 +/- 3.1 (6-20)
MMSE	28.6 +/- 1.6 (24-30)	27.5 +/- 2.1 (21-30)	23 +/- 4.5 (12-29)	23 +/- 6.4 (6-30)
MoCA	27.1 +/- 2.3 (21-30)	23.2 +/- 2.7 (17-29)	18.7 +/- 5.5 (5-26)	19 +/- 6.3 (2-28)
% ApoE4	27	14	82	/
%PiB+	30	50	85	55



Principle Componenets Analysis of AD brains PIB

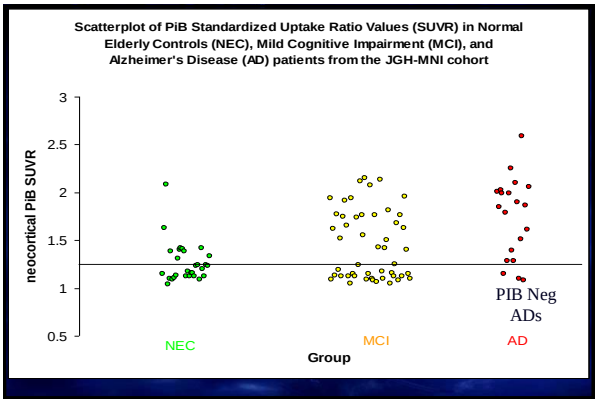


Rowe,C. et al "Amyloid imaging results from the Australian Imaging (AIBL) study of aging." Neurobiology of Aging, 31,(2010), 1275-83

- PIB, cognitive measures in 177 NEC, 57 MCI, and 53 mild AD subjects.
- PIB was "positive" in 33% of NECs:
  - 18% age 60-69
  - 65% in those over age 80
- PIB +ves were even greater in ApoE4+ves.
- S. Vaitekunis: "Is PIB a test like positive bacteria in urine? Only definitely requires treatment (ie., pathological) in younger subjects?"

Who has amyloid in the brain? (PIB results)

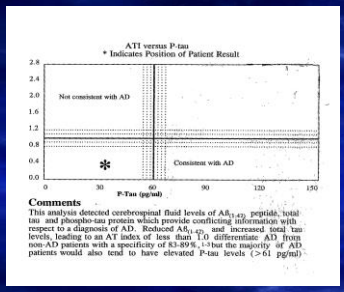
- Alzheimer's subjects - 95% +ve
- Mild Cognitive Impairment - 60% +ve
- Mintun (2007), Rowe (2007) : MCI with +ve PIB have high rate of progression to AD at 2, 3 years.



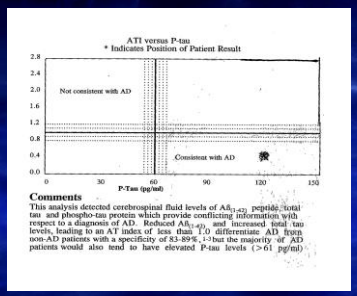
PIB negative AD?

- **Variably in studies – 10% (Morris), 15% (De Carli).**
- **Misdiagnosis? Eg., frontotemporal dementia**
- **AD due to soluble A-beta? PIB labels only fibrillar A-beta in compact plaques.**
- **Cairns et al, 2009: AD, altered CSF, +pathology, with negative PIB(Arch. Neurology, 66;1557-62)**
- **Tangle – only AD (Nordberg)**

CSF amyloid beta and phospho tau measures



ATI is abeta/tau ratio (index)



NOTE: CSF amyloid and tau levels can currently be obtained clinically in Canada via Athena Inc. private

"Probable/ possible AD with evidence of the AD pathophysiological process"

Biomarkers of Amyloid (a-beta) accumulation

Biomarkers of neuronal degenereation or injury

"We do not advocate the use of AD biomarker tests for routine diagnostic purposes at the present time"

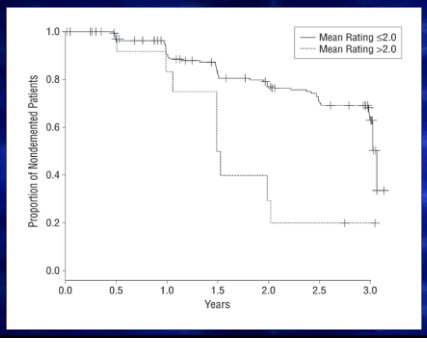
- not standardized
- clinical criteria are good
- need more research
- access is limited

-but useful in clinical trials, research, and where available and "deemed appropriate by the clinician"

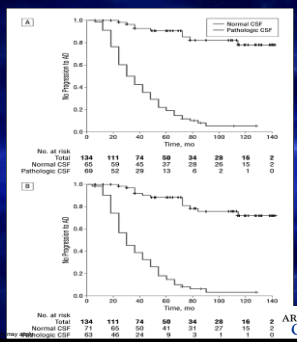
Predicting which MCI individuals will progress- "MCI due to AD"

Some MCI individuals progress to dementia (usually AD), but some do not

Qualitative Estimates of Medial Temporal Atrophy, DeCarli et al., 2007



Kaplan-Meier estimates of the rate of progression to Alzheimer disease (AD) in patients with mild cognitive impairment with either normal or pathologic cerebrospinal fluid (CSF) biomarker levels at baseline



Buchhave, P. et al.
Arch Gen Psychiatry
2012;69:98-106

ARCHIVES OF GENERAL PSYCHIATRY

Predicting which MCI individuals will progress to Alzheimer's dementia- we are almost there!

- Hippocampal atrophy common in MCI, strongly predicts progression
- Dubois et al, 2008:Proposal- MCI plus "abnormal biomarker" [PET, CSF, MRI] = "prodromal AD"
- Rowe, 2010: All MCI with +ve PIB AND MRI hippocampal atrophy will progress to AD.

2011-NIH committee: "MCI due to Alzheimer's".

ie.: these individuals HAVE AD already

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

Marilyn S. Albert, Steven T. DeKosky, et al., Alzheimer's & Dementia, 2011

- **Proposes term "MCI of the Alzheimer's type":**
- **"MCI- Research criteria incorporating biomarkers"-biomarker evidence of AD (imaging and/or CSF= amyloid).**
- **Recognition that MCI is frequently AD**

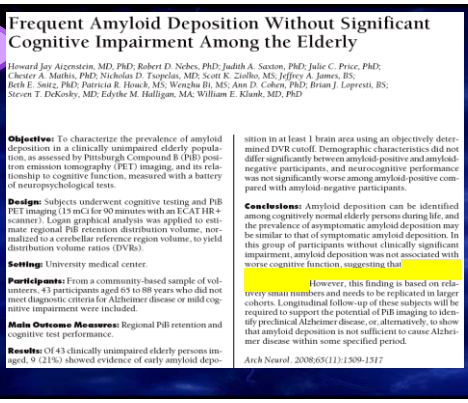
Albert et al.: Biomarkers in MCI

Clinical diagnosis category MCI due to AD Core clinical criteria	BoM probability of AD etiology Uninformative	Abeta (CSF or PET) Unavailable or conflicting or indeterminate	Neuronal injury (MRI, FDG PET, CSF tau) Unavailable or conflicting or indeterminate	
MCI due to AD Intermediate likelihood	Intermediate	Positive Unavailable	Unavailable Positive	
MCI due to AD High likelihood	Highest	Positive	Positive	
MCI –unlikely due to AD	Lowest	Negative	Negative	

A few caveats..clinical vs. research use of "MCI due to AD"

- Even MCI patients who test negative for amyloid can go on to dementia!
- The biomarkers are not yet standardized, validated, or available generally.
- Their predictive ability remains to be tested clinically (ie., do we need more than one positive biomarker to be 100% accurate in prediction?
- Prediction WITHIN A SET TIME FRAME is essential

The new challenge: normal individuals who have abnormal biomarkers



Frequent Amyloid Deposition Without Significant Cognitive Impairment Among the Elderly

Howard Jay Aizenstein, MD, PhD; Robert D. Nebes, PhD; Judith A. Saxton, PhD; Julie C. Price, PhD; Chester A. Mathis, PhD; Nicholas D. Tsopelas, MD; Scott K. Ziolko, MS; Jeffrey A. James, BS; Beth E. Snitz, PhD; Patricia R. Houck, MS; Wenzha Bi, MS; Ann D. Cohen, PhD; Brian J. Lopresti, BS; Steven T. DeKosky, MD; Edythe M. Halligan, MA; William E. Klunk, MD, PhD

Objective: To characterize the prevalence of amyloid deposition in a clinically unimpaired elderly population, as assessed by Pittsburgh Compound B (PiB) positron emission tomography (PET) imaging, and its relationship to cognitive function, measured with a battery of neuropsychological tests.

Design: Subjects underwent cognitive testing and PiB PET imaging (15 mCi for 90 minutes with an ECAT HR+ scanner). Logan graphical analysis was applied to estimate regional PiB retention distribution volume, normalized to a cerebellar reference region volume, to yield distribution volume ratios (DVRs).

Setting: University medical center.

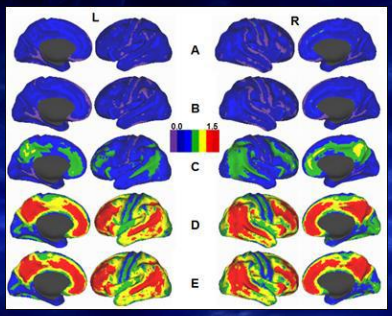
Participants: From a community-based sample of volunteers, 43 participants aged 65 to 88 years who did not meet diagnostic criteria for Alzheimer disease or mild cognitive impairment were included.

Main Outcome Measures: Regional PiB retention and cognitive test performance.

Results: Of 43 clinically unimpaired elderly persons imaged, 9 (21%) showed evidence of early amyloid deposition in at least 1 brain area using an objectively determined DVR cutoff. Demographic characteristics did not differ significantly between amyloid-positive and amyloid-negative participants, and neurocognitive performance was not significantly worse among amyloid-positive compared with amyloid-negative participants.

Conclusions: Amyloid deposition can be identified among cognitively normal elderly persons during life, and the prevalence of asymptomatic amyloid deposition may be similar to that of symptomatic amyloid deposition. In this group of participants without clinically significant impairment, amyloid deposition was not associated with worse cognitive function, suggesting that [redacted]. However, this finding is based on relatively small numbers and needs to be replicated in larger cohorts. Longitudinal follow-up of these subjects will be required to support the potential of PiB imaging to identify preclinical Alzheimer disease, or, alternatively, to show that amyloid deposition is not sufficient to cause Alzheimer disease within some specified period.

Arch Neurol. 2008;65(11):1509-1517



PIB distribution on lateral and medial surfaces of the cortex on the left and right hemispheres of the human brain. A, Healthy adults younger than 50 y; B-D, Cognitively normal adults older than 50 with low (B), moderate (C), and high (D) Aβ deposition; E, Individuals with Alzheimer's dementia. *Vlassenko et al., 2012*

Morris et al (2010), Ann Neuro, 67: 122-131-When normal controls have abnormal AD biomarkers

Normal Elderly Controls overall:

- Percentage with +ve biomarkers (in AD range):
  - PIB PET positive =15%
  - Abnormally low ABeta42 in CSF – 28%
  - Abnormally high total Tau in CSF – 6.6%
  - Abnormally high phospho tau 181 in CSF = 4.2%

*These numbers are influenced by age of cohort, APO-E4 gene, and other factors that affect % with brain amyloid

Religious Orders Study (Rush U.)

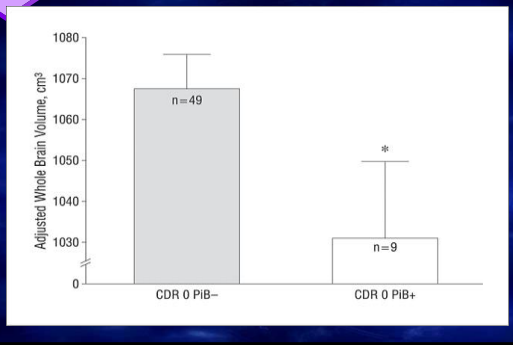
- ↗ Schneider et al, 2007 Neurology:
  - ↙ 50% of normals have some brain pathology
  - ↙ ½ of probably Alzheimer's Disease patients have another pathology in brain: infarcts, etc.

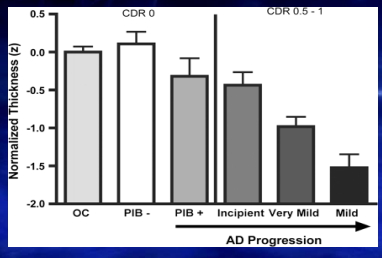
Bennet, 2006 (Neurology): "Neuropathology of normal aging"

-about 1/3 to ½ of NECs had post-mortem amyloid, especially mid-frontal. Also had neurofibrillary tangles.

- These subjects had mild decrease in episodic memory.

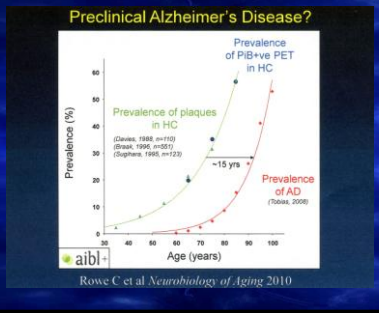
Brain amyloid is NOT innocuous: Brain Volume Decline in Aging, Fotenos et al. 2008



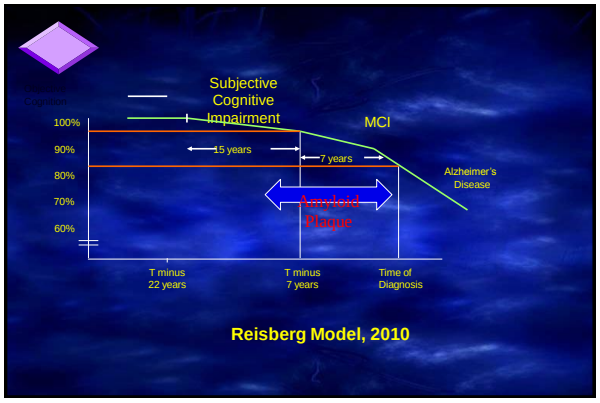


Mean thickness of AD cortical signature regions is decreased in amyloid (PIB)-positive Normal Elderly controls (CDR = 0), and demonstrates progressive thinning as the symptoms of AD dementia become progressively more prominent across the spectrum of Incipient, very mild, and mild AD dementia. (N = 115) *From Dickerson et al. 2009*

Modelling development of amyloid before dementia



Rowe C et al *Neurobiology of Aging* 2010



Reisberg Model, 2010

Earlier biomarkers being pursued?

- Measures of microglial inflammation: PET with *PK11195* –^{11}C, and astroglial with ^{11}C-DED (Deprenyl).
- Abnormalities of nerve growth factors: *tyrosine kinase A (TrKA)* in CSF.
- Abnormalities of oxidative stress: *HemeOxygenase-1* in CSF and blood; *Oxidative stress-mediated dehydroepiandrosterone formation* in serum and CSF.
- Caspase six activation in csf

Do all PiB positive normals progress to dementia? Does amyloid guarantee future dementia?

- Many researchers would answer "yes", but no empirical results yet
- Bennet – It depends on other pathology for expression (vascular lesions very important)
- Note: 50% of NEC have pathology, less than 1/5 get dementia.
- Some elderly appear able to "live at peace" with their amyloid! Why???

Role of cognitive reserve in cognitive decline

- Normal elderly have variable resistance to pathology burden=cognitive reserve
- To explain imperfect correspondence between AD pathology and cognitive changes.
- IQ [NART], education as proxies
- Brain/neural reserve [hardware] vs. cognitive reserve [software].

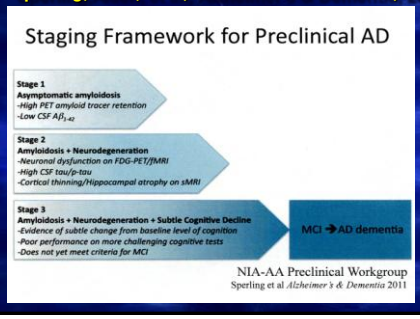
Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

Reisa A. Sperling, Paul S. Aisen, *et al.*, Alzheimer's & Dementia, 2011

- Preclinical AD: asymptomatic,cognitively normal subjects in high risk states (amyloid in brain, or auto. dominant genes)."Draft operational research framework for staging preclinical AD"
- Stage 1: Asymptomatic amyloidosis (PET, CSF)
- Stage 2: Amyloidosis plus neurodegeneration (also MRI cortical thinning, hippocampal atrophy, or FDG PET or CSF tau).
- Stage 3:Amyloidosis plus neurodegeneration plus subtle cognitive decline (not yet MCI).

"Toward defining the preclinical stages of Alzheimer's disease"

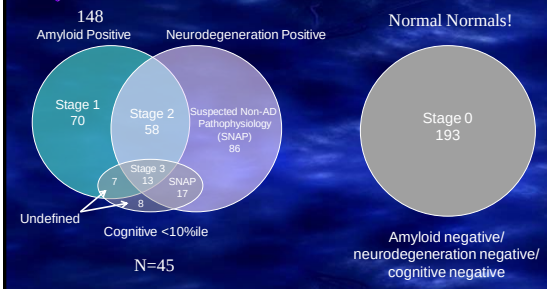
Sperling,Aisen, *et al.*, Alzheimer's & Dementia, 2011



"Toward defining the preclinical stages of Alzheimer's disease"
Sperling,Aisen, *et al.,* Alzheimer's & Dementia, 2011

- Not intended as clinical diagnostic criteria
- Prognostic utility of these biomarkers in individual subjects remains unclear
- Some individuals with evidence of AD neuropathological changes will not develop clinical symptoms during life
- Multiple examples in other diseases:
  - Carcinoma *in situ*
  - Heart disease detected on cardiac catheterization or stress test

Operationalizing Preclinical AD Criteria -435 elderly subjects (Jack et al, 2011)



Canadian Consensus Conference: (after Dubois): "Asymptomatic at-risk for AD"

Summary and Conclusions(1)-Future of biomarkers in cognitive aging, MCI, and dementia?

- New lexicon highlights biomarker concept.
- Currently research criteria for "MCI of the Alzheimer's type" – will be used for clinical trials
- Possible role in early detection and diagnosis clinically in the near future. - not yet clinical tools except in AD.
- Not clear if it will be 1 test, or algorithm of biomarkers plus age plus genetics plus reserve measures plus vascular risk…….

Summary and Conclusions(2)

- Biomarker studies will clarify when is MCI really "prodromal AD" [term of Dubois, Feldman et al International Working Group].
- We are hampered by lack of understanding of exact pathophysiology of early AD.
- Different imaging modalities tell you different things– the information is not redundant
- Pressure for earlier diagnosis will be driven by availability of new disease modifying drugs and preventive therapies

Funding Support

- Canadian Institutes for Health Research
  - MOP 10392
  - MOP 29342
  - KT grants
- FRSQ
  - Chercheur national award
  - Axe Cognition Aging Network award
- Alzheimer's Society of Canada
- C5R
- NIH ADNI network

Dr. Howard Chertkow's Cognitive Neuroscience Team

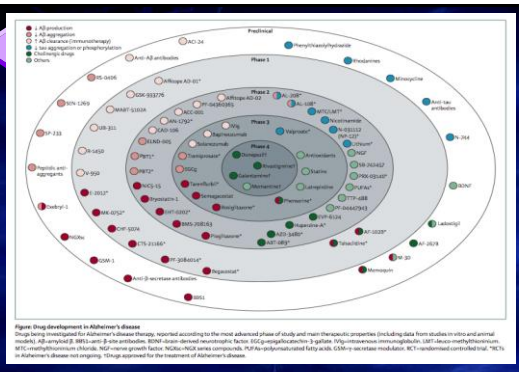


Figure: Drug development in Alzheimer's disease
Drugs being investigated for Alzheimer's disease therapy, reported according to the most advanced phase of study and main therapeutic properties (including data from studies in vitro and animal models). Aβ=amyloid β. BACE=anti-β-site antibodies. BDNF=brain-derived neurotrophic factor. EGCG=epigallocatechin-3-gallate. IVIg=intravenous immunoglobulin. LMT=leuco-methylthioninium. MTC=methylthioninium chloride. NGF=nerve growth factor. NGXs=NGX series compounds. PUFAs=polyunsaturated fatty acids. GSM=γ-secretase modulator. RCT=randomised controlled trial. *RCTs in Alzheimer's disease not ongoing. †Drugs approved for the treatment of Alzheimer's disease.

From Mangialasche et al. Lancet Neurol. 2010

What can be done to accelerate research on drugs to stop AD?-Use biomarkers to aid in population selection/assessment of progression.

- Extensive biomarker validation and standardization is a priority
- Develop validated surrogate endpoints for clinical outcomes, to shorten clinical trials
- Need biomarkers able to detect AD early in its course.
- Biomarkers should be reliable, minimally invasive, simple to perform, inexpensive ideally (Consensus report, Neurobiology of Aging, 1998; 19, 101-116)

Current role of biomarkers in AD clinical trials?

- No imaging or CSF biomarker has been accepted as a validated surrogate in any Alzheimer's Disease clinical trial.
- It is not clear, for instance, that successful anti-amyloid disease modifying immunotherapy, will lead to LESS brain shrinkage (it may lead to MORE atrophy!).

What can be done to accelerate research on drugs? - Treating earlier!

(Vellas et al, 2011, Progress in Neurobiology, 95; 594-600)

- Interventions at "dementia" stage of AD may be too late to show effects.
- Study early MCI and late MCI (as in ADNI)
- Study "MCI due to AD" (Albert, 2011)
- Study Cognitively Normal individuals with positive amyloid biomarkers
- Use high risk populations defined by genetics (APoE) and imaging (FDG PET)
- Study earlier age groups, and follow longer

Anti-Amyloid treatment in Asymptomatic AD (A4) Trial Proposal – (ADCS)

- Enrol older individual (>70 years) – who are amyloid positive
  - High tracer retention on PET amyloid imaging
  - Low CSF $A\beta_{1-42}$
- Clinically normal/asymptomatic*
- Treat with Solunezumab (anti-amyloid monoclonal) for 3 years
- Test the hypothesis that altering "upstream" amyloid accumulation will impact "downstream" neurodegeneration and rate of cognitive decline

Summary (1)-Future of biomarkers in cognitive aging, MCI, and dementia?

- New lexicon brings biomarker research to the forefront.
- New categories for AD with biomarker support
- Currently research criteria for "MCI of the Alzheimer's type" – used for clinical trials.
- Biomarker studies will clarify when is MCI really "prodromal AD".
- Possible role in early detection and diagnosis clinically in the near future. - not yet clinical tools except in AD.

Summary (2)

- Different imaging modalities tell you different things– the information is not redundant
- Pressure for earlier diagnosis will be driven by availability of new disease modifying drugs and preventive therapies
- There is still no proven effective AD prevention strategy! We are hampered by lack of understanding of exact pathophysiology of early AD.

Things the biomarkers will allow us to do (and associated problems): 5. Give us clues as to what treatments will cure AD

Px: Baal - HPI

- Presented age 52, immigrant
- Eleven years education, mechanic
- Onset visual confusion, visual agnosia, losing directions, insidious and progressive.
- +ve family history memory loss mother
- No vascular risks, no medications
- No change in mood, behavior, personality
- Unable to drive, manage garage

Px: Baal - Exam

- Memory loss mild on neuropsych
- Folstein 25
- Executive function acceptable
- Visual processing impaired
  - Impaired copying.
  - Impaired naming (28/60 BNT)
- Normal blood tests, APO-E E3/E4
- Normal neuro exam
- Diagnosis:Posterior cortical atrophy, atypical Alzheimer's Disease.

Px: Baal - Progression

- Progressive deterioration of AD dementia
- On Aricept. Little response Cis
- Folstein down to 21 by 2009
- Started on Double Blind Bapinuzamab Sept 2009. Started on Open Label study July 2011.
- Gradual worsening - personality intact, but more apathetic
- Disorientation, forgetting recent events
- Impaired IADL's, some ADLs
- Progressive memory loss

Px: Baal – Imaging

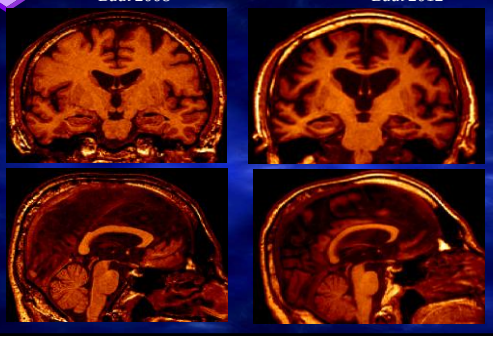
- MRI:
  - Virtually normal 2007/2008.
  - 2012: Moderate atrophy, Mild hippocampal atrophy (Schelten's 1,2)

  RESEARCH SCANS:
- FDG: 2008. 2012
- PIB:
  - 2008; 2012

MRI

Baal 2008

Baal 2012

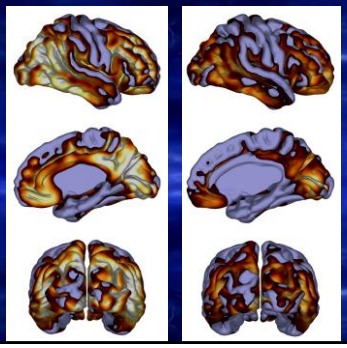


PiB-PET

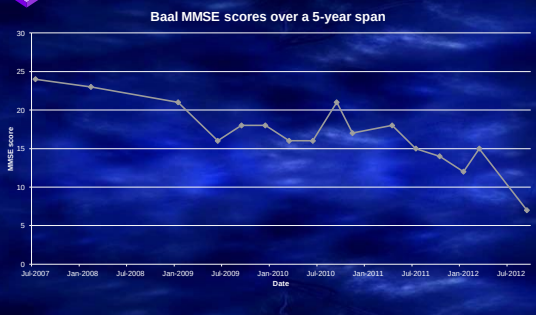
Baal 2008-PreBap

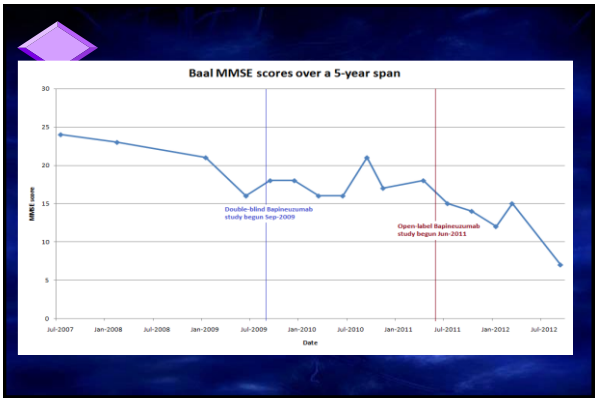
Baal 2012, Post-Bap

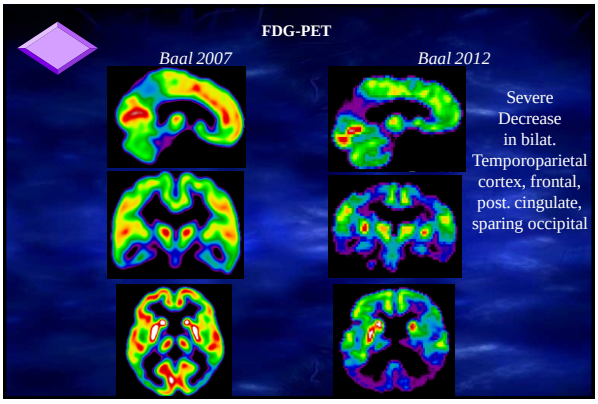
Positive PIB, SUVR 1.86 Large amyloid More occipital than usua.



Positive PIB SUVR 1.61 Less amyloid than 2008







Bapineuzumab Phase 3: Target Engagement, But No Benefit-

European Federation of Neurological Societies (EFNS) annual meeting 2012 in Stockholm, Sweden. Reisa Sperling, and Stephen Salloway,

- **Passive immunotherapy in 1,121 ApoE4 carriers and 1,331 non-carriers, respectively.**
- **Bapineuzumab prevents accumulation of Aβ in the brain of patients with mild to moderate Alzheimer's disease and lowers phospho-tau (p-tau) in their cerebrospinal fluid (CSF).**
- **Despite the positive biomarker results,clinical data showed the drug failed to protect patients in these trials from cognitive and functional decline.**

Conclusion

- Treatment with Bapineuzamab succeeded in decreasing brain amyloid in a man with AD.
- No evidence that the atrophy was less after therapy.
- No evidence that the metabolism was better (in fact it was worse)
- No evidence that cognition was better (it was worse).