The Role of Amyloid Imaging in the Diagnosis of Mild Cognitive Impairment

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Disclosure

- Consultant for AVID, Eli Lilly, Grifols, and Quintiles; is an invited speaker for AVID, Quintiles, and Siemens; has DSMB membership with Merck, NIA, and Pfizer; and receives grant funding from Eli Lilly and NIA. Has been a site PI for sponsored studies with Avanir, Avid, Baxter, BMS, Genentech, Eli Lilly, Merck, Neuroptix, Pfizer, Roche, Takeda, and Wyeth

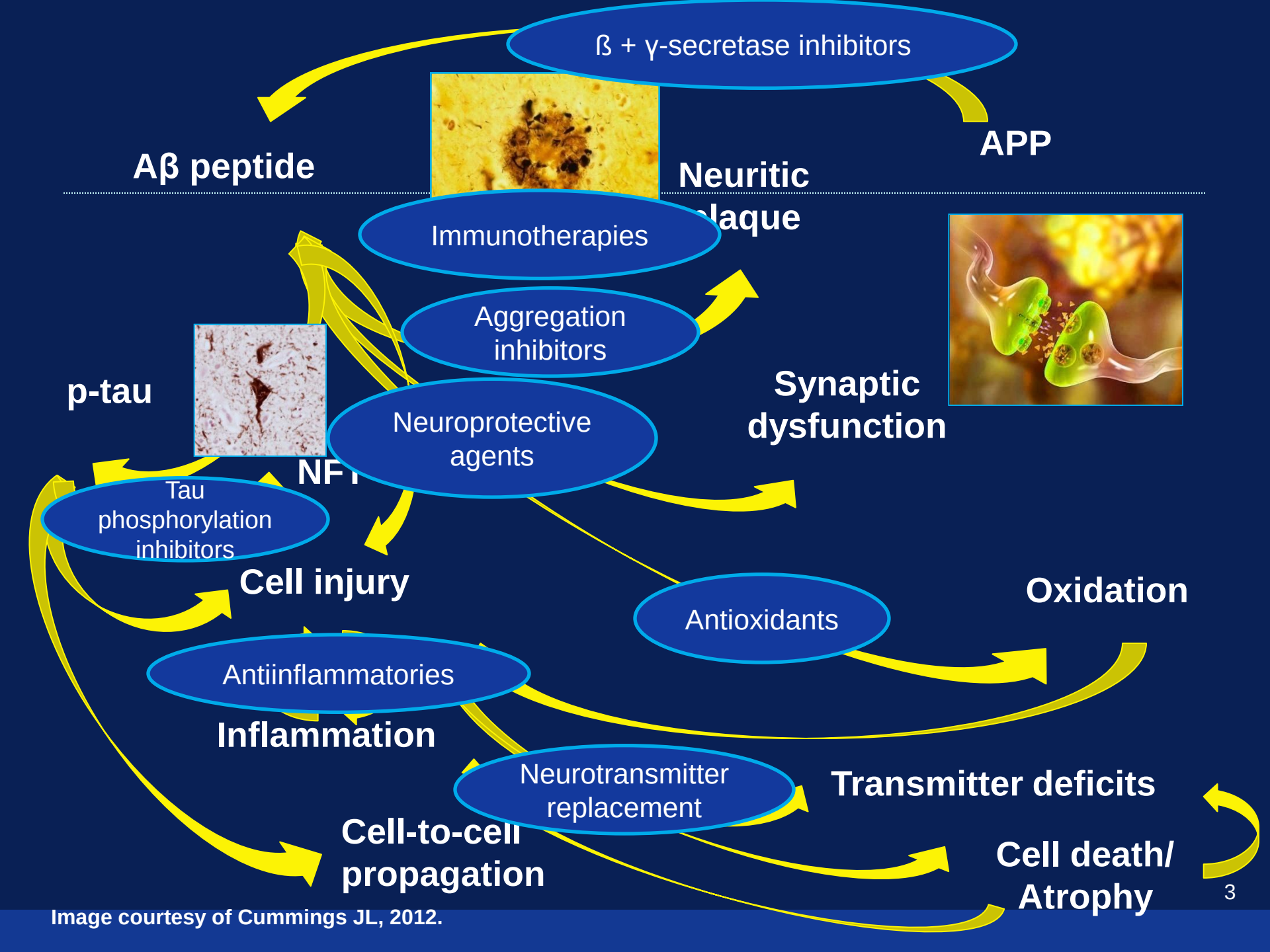


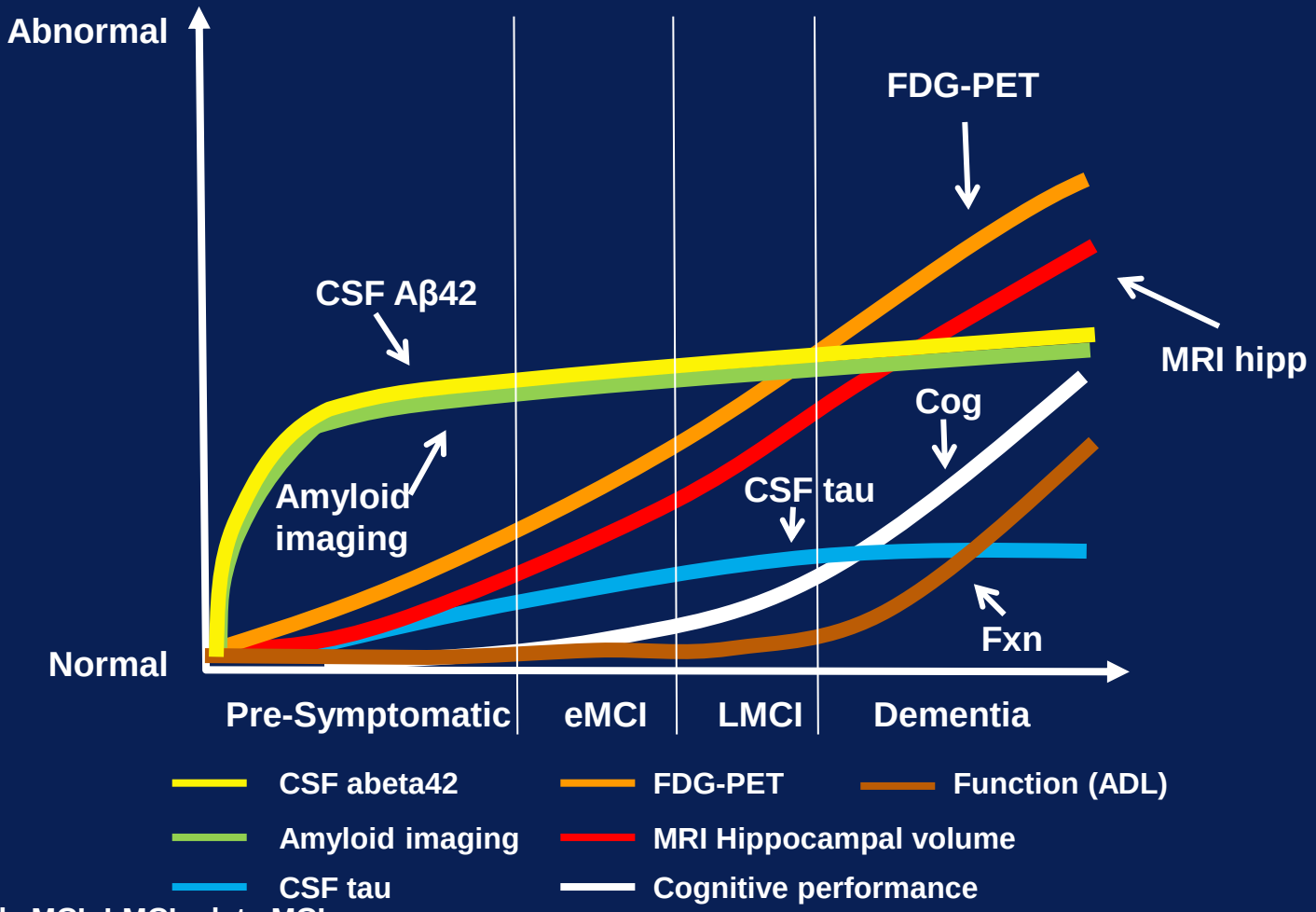
Image courtesy of Cummings JL, 2012.

Biomarkers of AD

Any identifiable marker that accurately represents underlying pathology associated with disease

- Blood or CSF
- Imaging

Alzheimer's Disease Progression

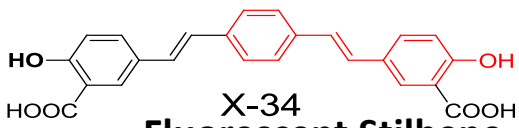


eMCI = early MCI; LMCI = late MCI.

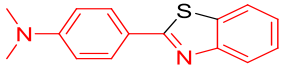
Aisen PS et al. *Neurology*. 2011;76:280-286.

Amyloid Imaging development

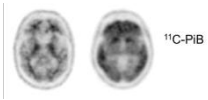
18F-labeled Amyloid Imaging Compounds

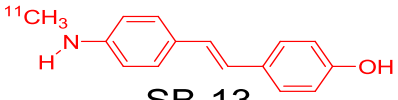


X-34
Fluorescent Stilbene

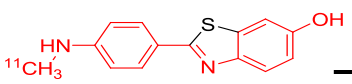


Neutral Thioflavin Derivatives

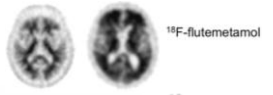


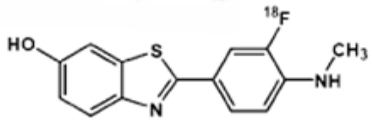


SB-13

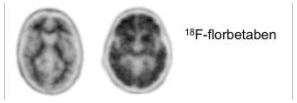


11C-PIB

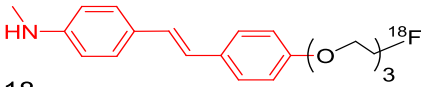




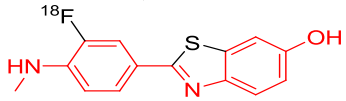
Flutametamol
GE/Vizamyl



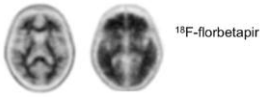
Florbetaben
Piramel



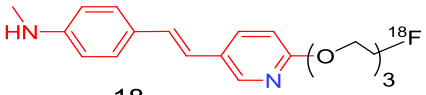
18F-AV-1 (BAY 94-9172)



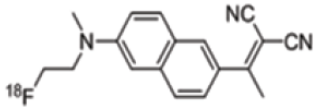
18F-PIB



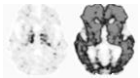
Florbetapir
Lilly/Amyvid

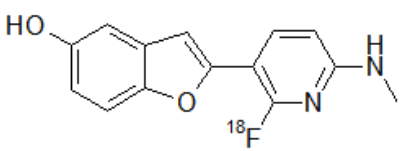


18F-AV-45



18F-FDDNP





NAV 4694
Navidea

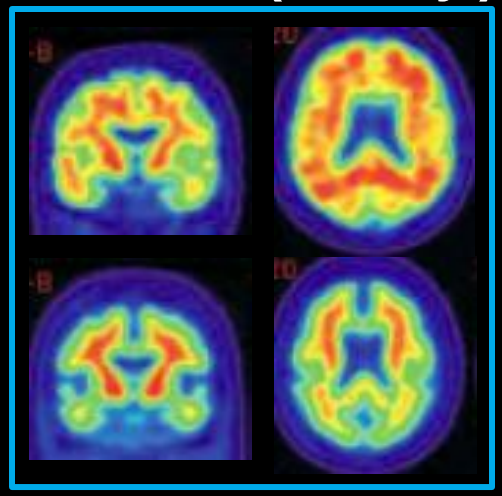
Imaging protocols vary between compounds.
Injection, 50-90 minutes uptake time, 10-20min scans.

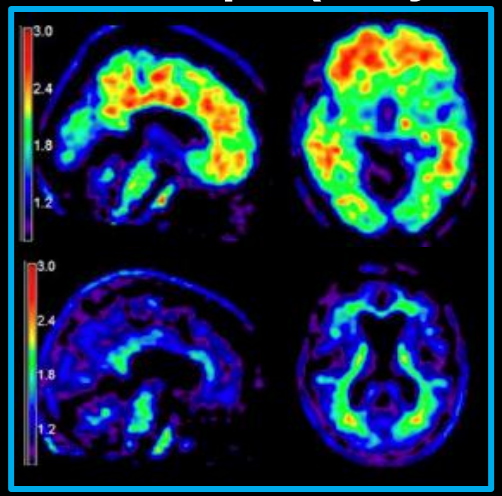
F18 Amyloid Imaging Tracers

Flutemetamol (Vizamyl)[1] **Florbetapir (Amyvid)[2]**

AD

NL

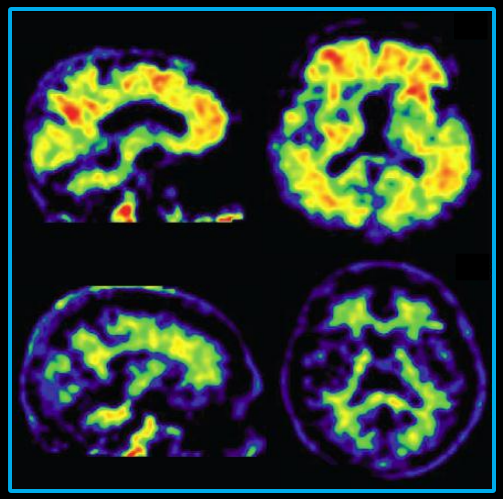


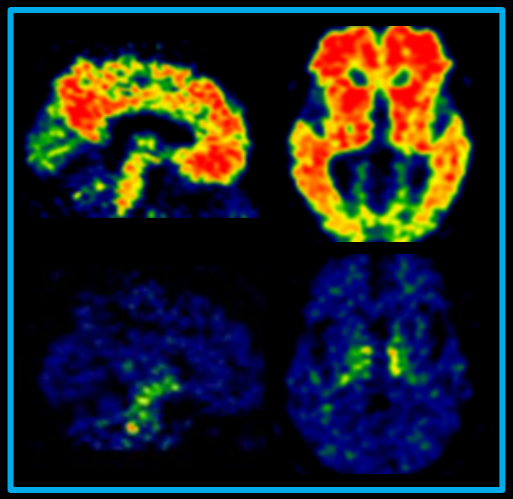


Florbetaben[3] **Navidea NAV4694[4]**

AD

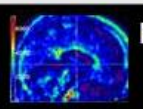
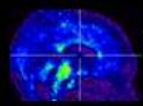
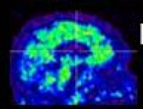
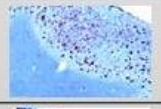
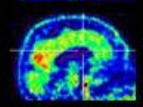
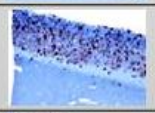
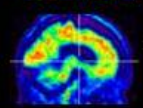
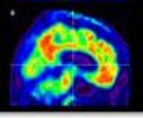
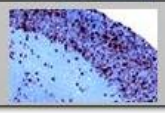
NL





1. Vandenberghe R et al. *Ann Neurol*. 2010;68:319-329. 2. Wong DF et al. *J Nuc Med.* 2010;51:913-920.
3. Barthel H et al. *Lancet Neurol.* 2011;10:424-435. 4. Chen K et al. AAIC 2012.

Amyloid Imaging Correlates With Amyloid Pathology

^{18}F-AV-45 PET	Visual Read	AV45 SUVr	Amyloid Staining (4G8 antibody)	Amyloid Burden (Quant IHC) (%)	Neuropathologic Diagnosis
 MCI	1	1.08		0.0	Normal brain
 AD	0	0.87		0.2	Tangle only
 PDD	3	1.15		3.6	AD with cortical Lewy bodies
 AD	4	1.42		5.4	AD
 AD	4	1.33		7.9	AD
 AD	4	1.67		8.6	AD

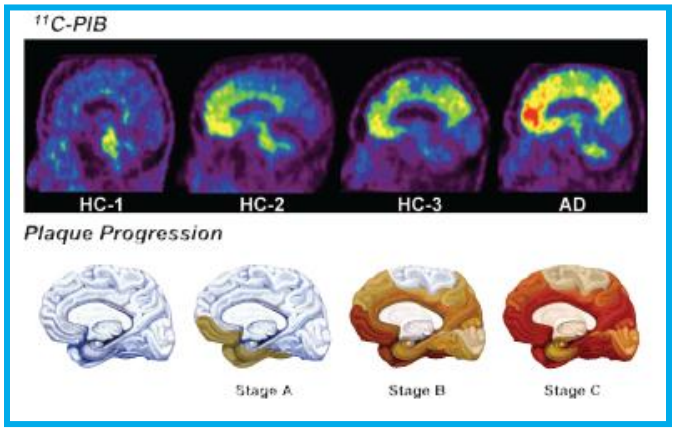
59 AUTOPSIES: Compared to Pathologic diagnosis

SUVR, cut point of ≥ 1.1,
sensitivity of 97%
specificity of 100%

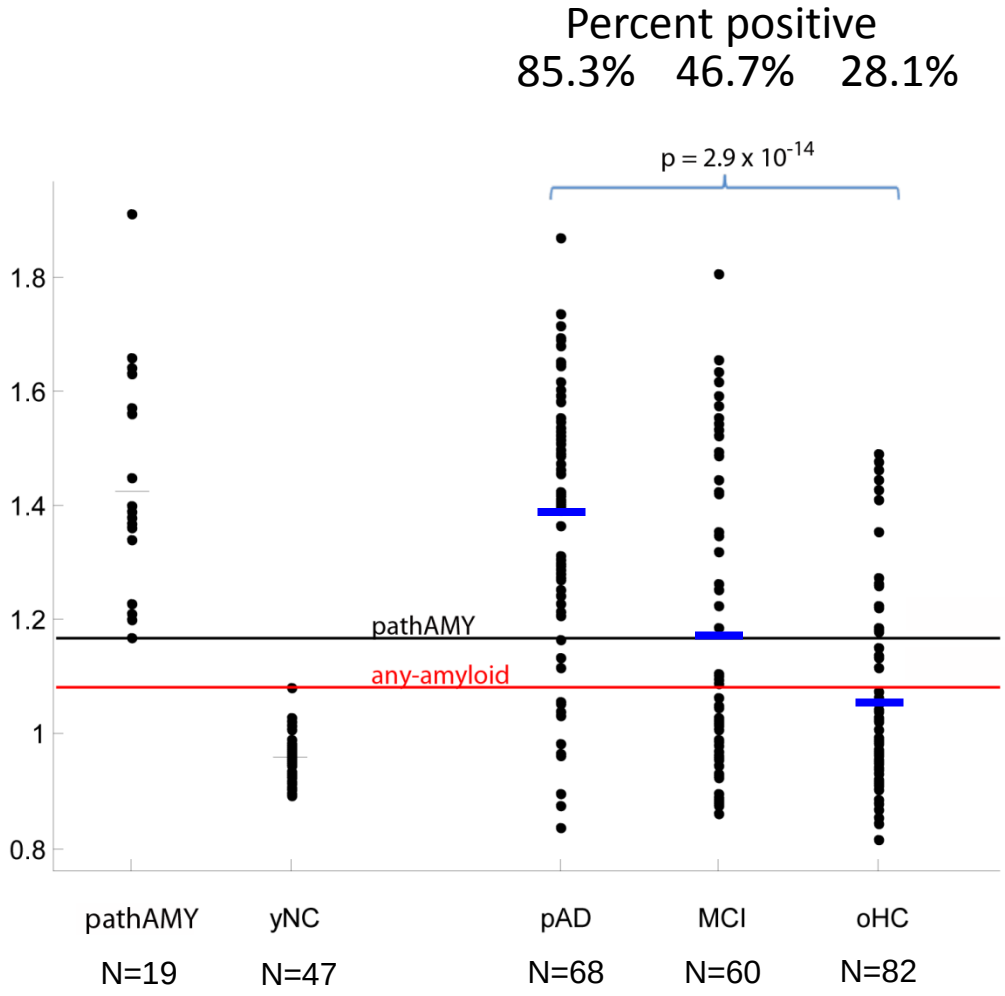
Fleisher AS. AAN Annual Meeting 2010. Abstract 1165AAN10D1.
Clark CM. *JAMA*. 2011;305:275-283; Clark CM et al. *Lancet Neurol*. 2012;11:669-678.

Amyloid Imaging in Alzheimer’s progression

Amyloid PET Measurements of Fibrillar Aβ Burden: AD spectrum

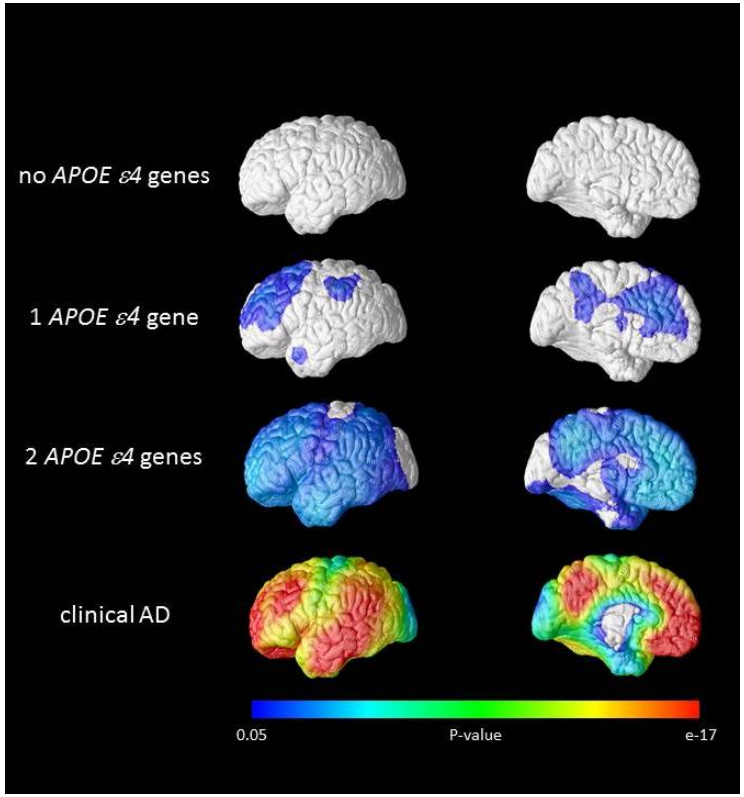


CC Rowe, NBA 2007

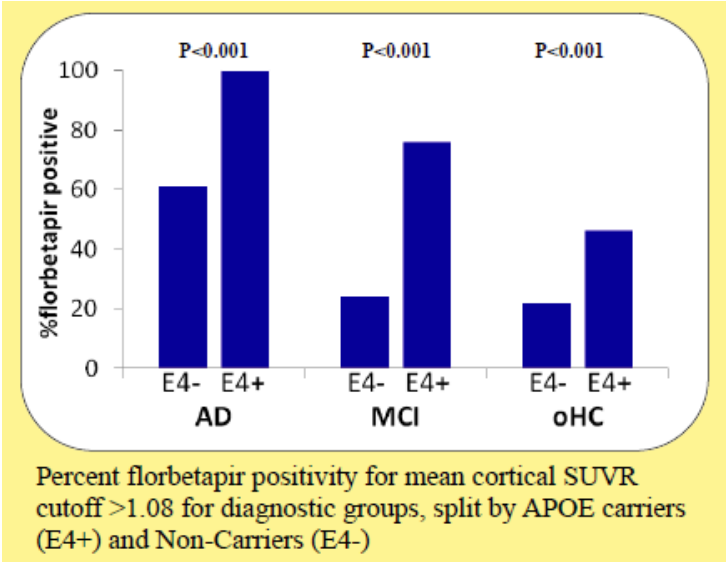


Rowe CC. *Neurology*. 2007;68:1718-1725.
Fleisher AS. *Arch Neurol*. 2011;68:1404-1411.

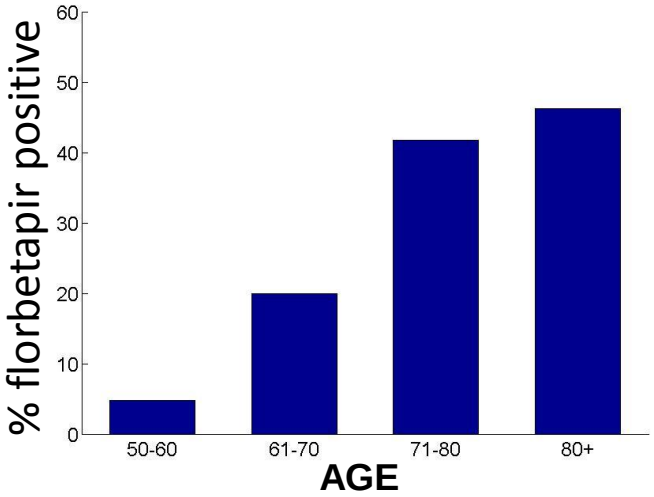
APOE4, Age and Amyloid PET



EM Reiman, *PNAS* 2009.



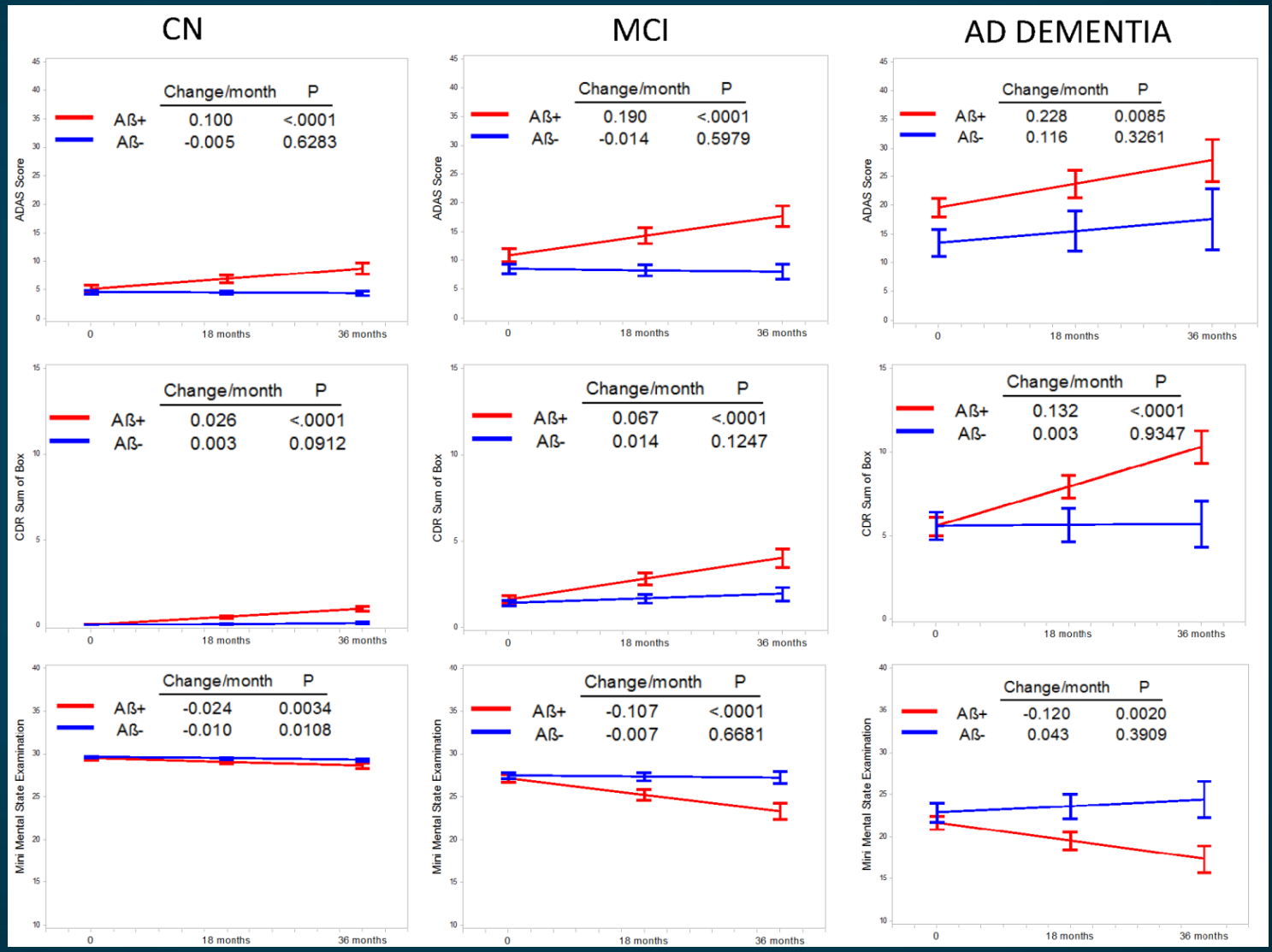
Percent florbetapir positivity for mean cortical SUVR cutoff >1.08 for diagnostic groups, split by APOE carriers (E4+) and Non-Carriers (E4-)



Fleisher AS et al. *Neurobiol Aging*. 2013;34:822-831.

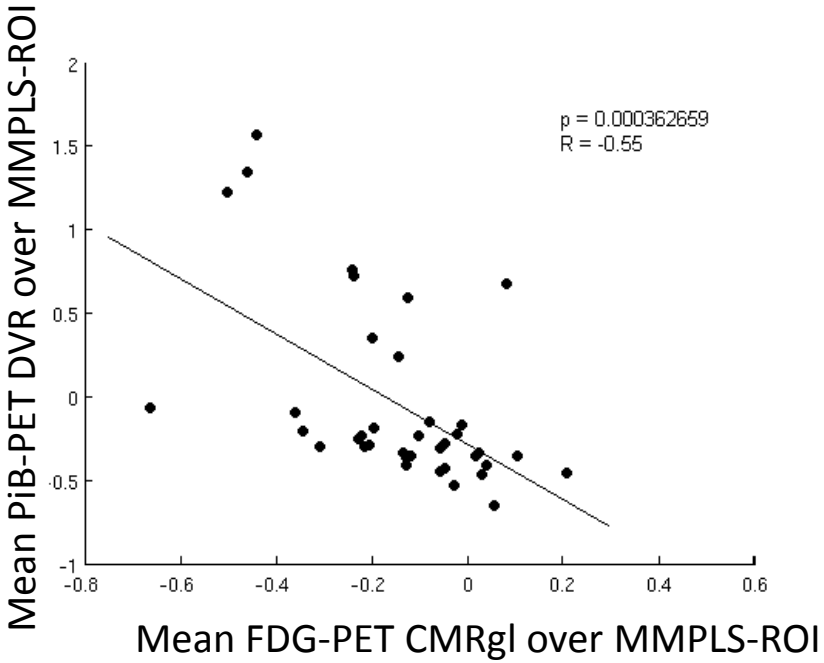
Cortical Amyloid Predicts 36 Month Cognitive Decline, MCI, and Dementia Due to AD in Normal Older Controls

NL 69, MCI 51, dAD 31

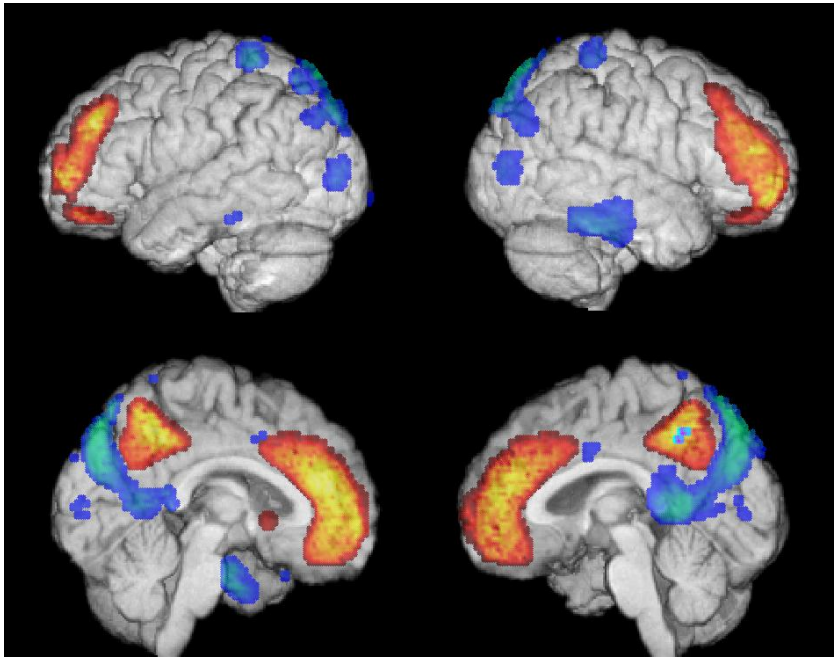


Doraiswamy PM, et al, in press, Molecular Psychiatry, 2014.

Increased cortical Amyloid is Associated with reduced parieto-temporal Glucose metabolism in cognitively normal APOE4 carriers

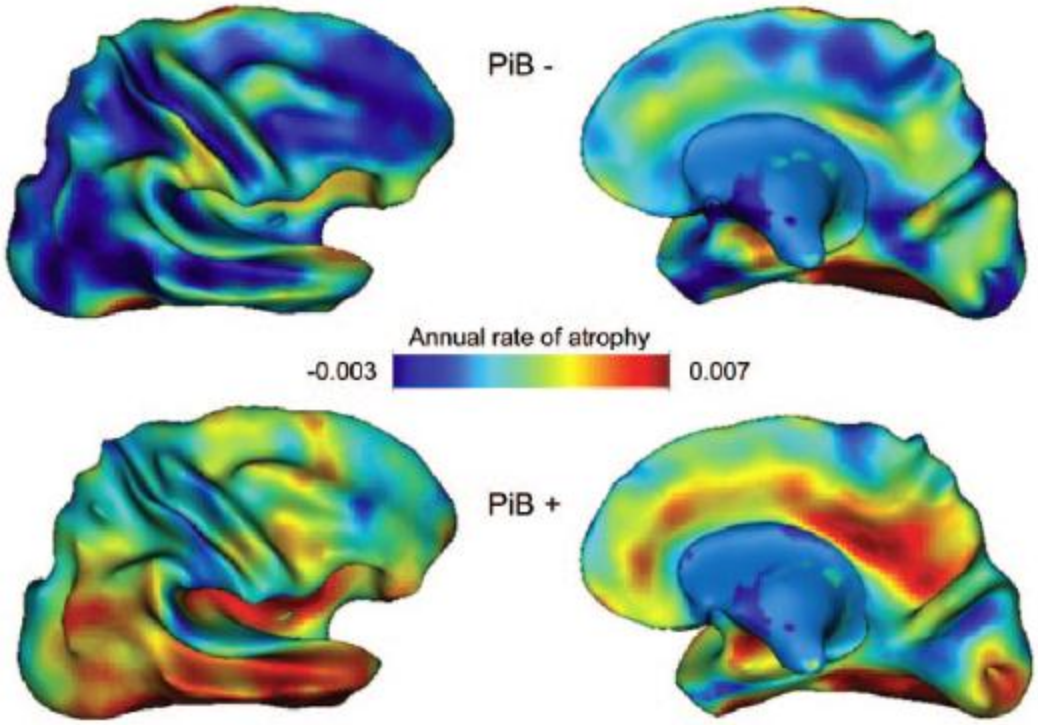


MMPLS - Dual modality brain maps of PiB PET DVR (HOT) and FDG PET CMRgl (COLD) patterns associated with APOE ε4 gene dose



Fleisher AS. HAI 2010.

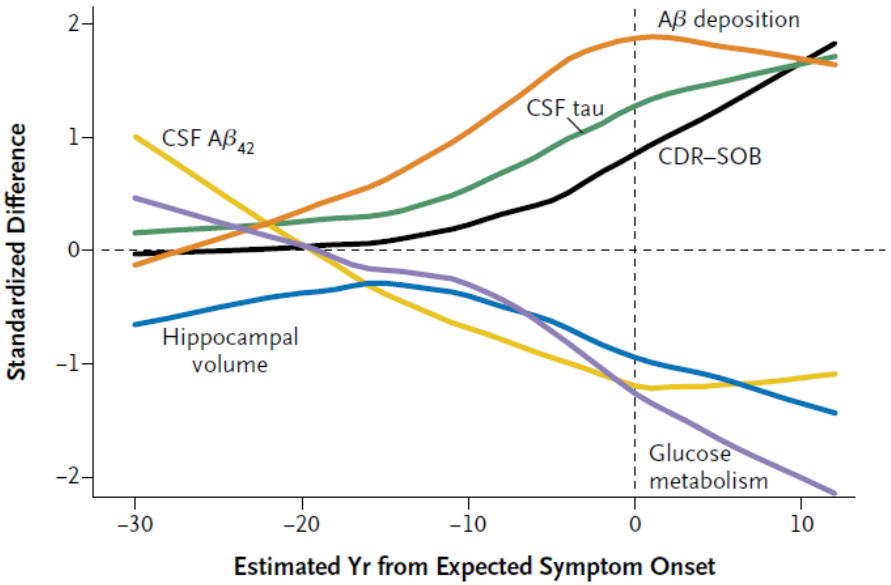
Cortical amyloid is associated with increased annual rate of global atrophy in cognitively normal individuals

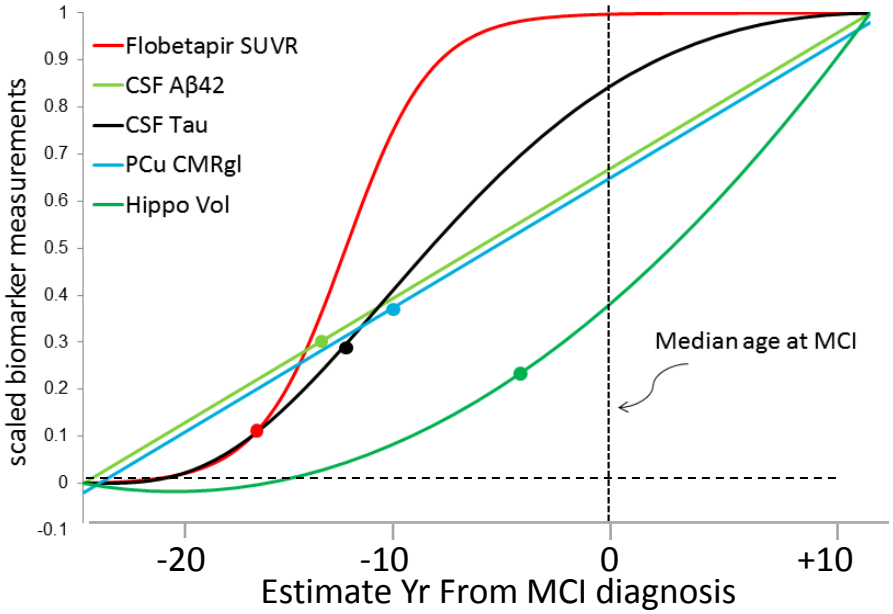


Chetelat G et al. *Neurology*. 2012;78:477-485.

Predicting Progression to MCI and Dementia

Biomarker changes in relation to the estimated age at clinical onset: ADAD studies



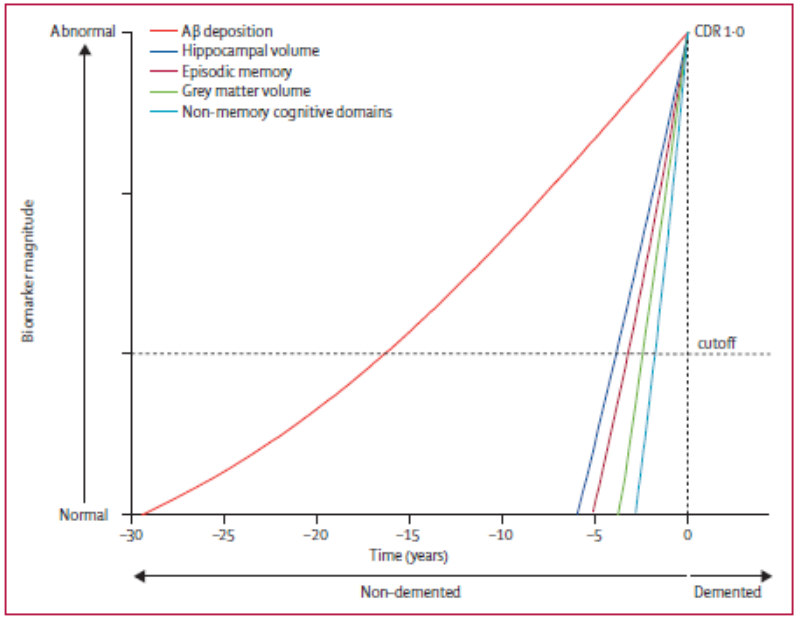


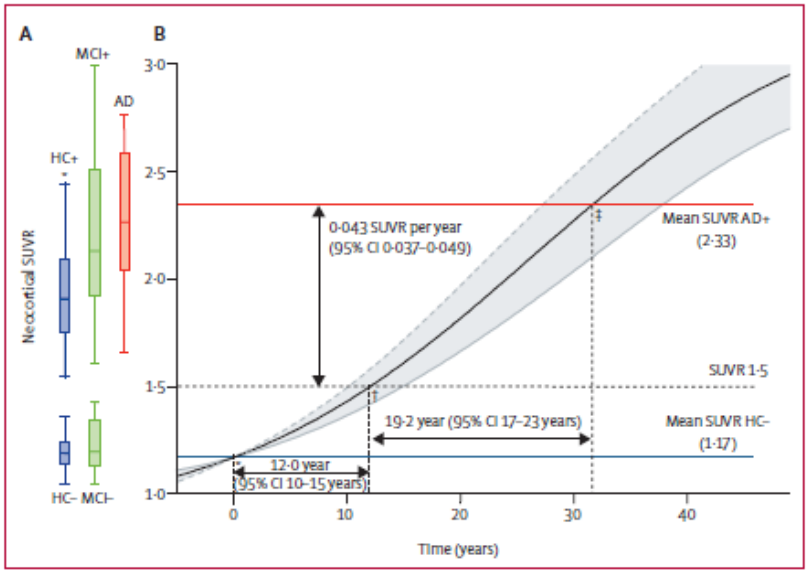
Fleisher AS, et al, Lancet Neurol, 2012
Fleisher AS, AAIC, 2013

Bateman R et al. *N Engl J Med*. 2012;367:795-804.

Biomarker changes in relation to age of dementia diagnosis: Australian Imaging Biomarker and Lifestyle study

NL, MCI, AD = 200
3-5 year f/u

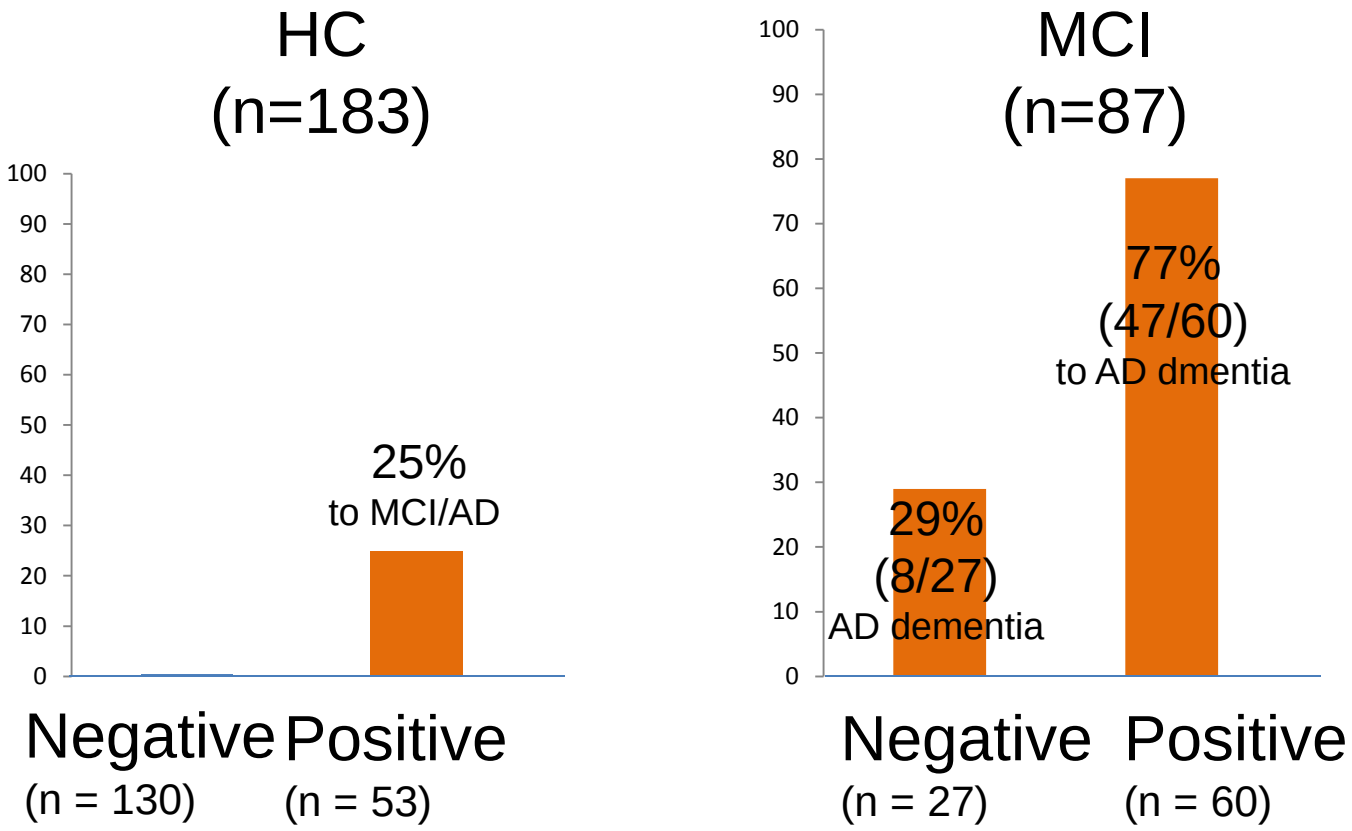




Villemagne VL et al. *Lancet Neurol*. 2013;12:357-367.

Australian ADNI (AIBL)

3-year risk of progression:
Positive versus Negative Amyloid PET scan



Rowe CC. AAIC 2013.

What we now know

Amyloid on PET is:

- Associated with fibrillar amyloid on pathology
- It distinguishes clinical stages of AD
- Influenced by age and APOE gene
- Associated with degree of lifetime cognitive activity
- Associated with increased rate of memory decline in “cognitively intact” elderly.
- Associated with increased rate of brain atrophy and brain metabolism
- It is associated with progression to MCI and Dementia
- More is worse

Amyloid PET Use Impacts Clinician Decision Making

- 229 patients with progressive cognitive decline and an uncertain diagnosis
- **After Amyloid PET physicians changed their diagnosis in 54.6% (125/229) of cases**
- **Diagnostic confidence increased by an average of 21.6%**
  - **86.9%** of cases had at least one change in their management plan
- **Cholinesterase inhibitor or memantine use increased by 17.7% among Amyloid positive cases and decreased by 23.3% among those with negative scans**
  - Planned brain structural imaging **decreased by 24.4%**
  - Planned neuropsychological testing **decreased by 32.8%**

Siderowf A et al. Human Amyloid Imaging Conference, 2013. Grundman M et al. *Alzheimer Dis Assoc Disord.* 2013;27:4-15.

"The Role of Amyloid imaging" in the Clinic - FDA Indication for Amyloid Imaging

Amyloid PET

Indication

- To estimate beta-amyloid neuritic plaque density
- In adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline
- A negative Amyloid scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition
- A negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD
- A positive Amyloid scan indicates moderate to frequent amyloid neuritic plaques
  - Neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition.
- Amyloid is an adjunct to other diagnostic evaluations

Amyloid [prescribing information]. Indianapolis, MN; Eli Lilly and Company; 2013.
GEHealthcare, 2013.

Suggested Use of Amyloid Imaging

Amyloid Imaging Taskforce: Appropriate USE Criteria

Amyloid imaging is appropriate in the following situations:

1. A cognitive complaint with objectively confirmed impairment
2. Performed only after full standard w/u is completed:
   - Structured clinical evaluation with objective neurocognitive testing
   - Structural brain imaging
   - Relevant laboratory tests
3. AD as a possible diagnosis, but uncertain
4. Knowledge of Aβ pathology would increase diagnostic certainty and alter management
5. Should only be ordered by dementia experts:
   - Specialty training, ≥25% dementia care practice
   - Geriatric/behavioral Psychiatry and Neurology

Johnson KA et al. *Alzheimers Dement*. 2013 Jan;9(1):e-1-16; Johnson KA et al. *J Nucl Med*. 2013; 54:1–3.

Who Pays for Amyloid Imaging

- Amyloid Imaging is now available in the clinic
  - Jan 30th, 2013:
    - Medicare Evidence Development Coverage Advisory Committee (MEDCAC)
      - "not sufficient evidence to support current Medicare reimbursement at this time"
  - July 3, 2013
    - Centers for Medicare & Medicaid Services (CMS)
      - Draft decision- "Coverage with Evidence Development"
- **Therefore: Amyloid imaging is only available to those who can afford it ($3-4k)**

Value of Amyloid Imaging in the clinic

- Earlier diagnosis
  - Care planning
  - Reduced hospitalization
  - Reduced cost of lifetime care

- Improve accuracy of diagnosis
  - Near 50% of patients with clinically diagnosed MCI, and 20% of Dementia are miss diagnosed with Alzheimer's Disease
    - Leads to excess diagnostic testing
    - Inappropriate treatments given
    - Inappropriate long term planning and use of resources
    - Missing true diagnosis
      - Untreated underlying disease – leading to future complications and cost of care
    - INCREASED COST

Conclusion

- There is a need for diagnostic biomarkers in AD, for both clinical and research application.
  - Amyloid PET as an important tool for better understanding AD stage
  - Important tool in symptomatic & pre-symptomatic therapy development
- Amyloid imaging can be a valuable tool to supplement clinical diagnosis and prognosis decisions.
  - It can identify cortical amyloid, and *rule out* Alzheimer's disease.
  - Cannot entirely *rule in* AD in isolation, but is a strong indicator given the appropriate clinical setting.
- Amyloid Imaging is now available in the clinic
  - Indications and guidelines for use have been defined
  - Who will have access and how broadly this tool will be used is yet to be seen.