Use of amyloid PET on dementia diagnosis

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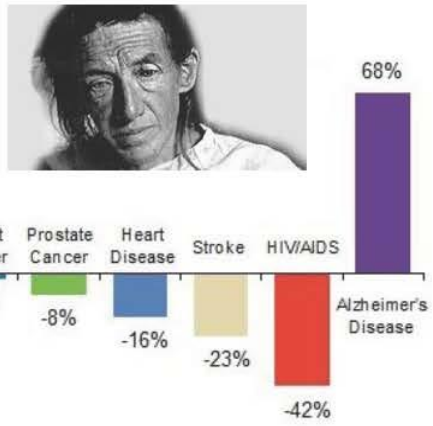
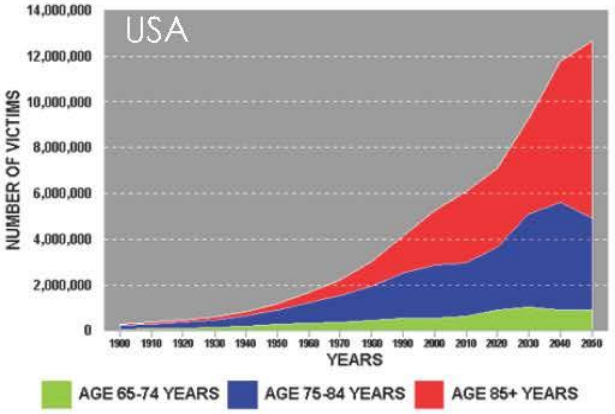
Problem to Solve :
Alzheimer's disease is a global crisis

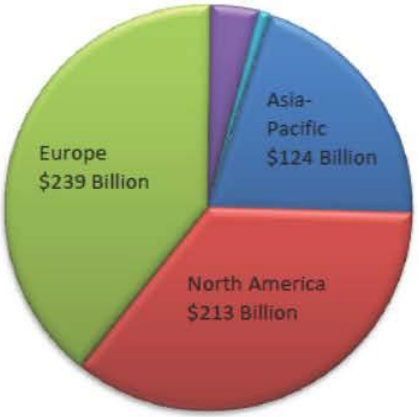
- As of 2013, there are 44.4 million people with dementia worldwide. This number will increase to 75.6 million in 2030, and 135.5 million in 2050.



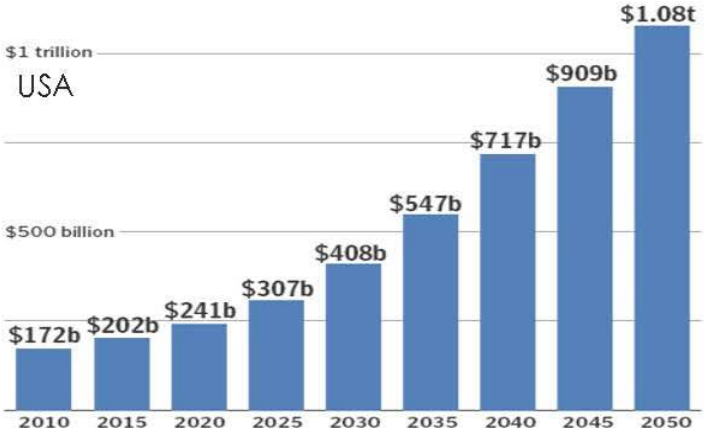
- The death rate due to Alzheimer's is increasing; while other diseases are under control



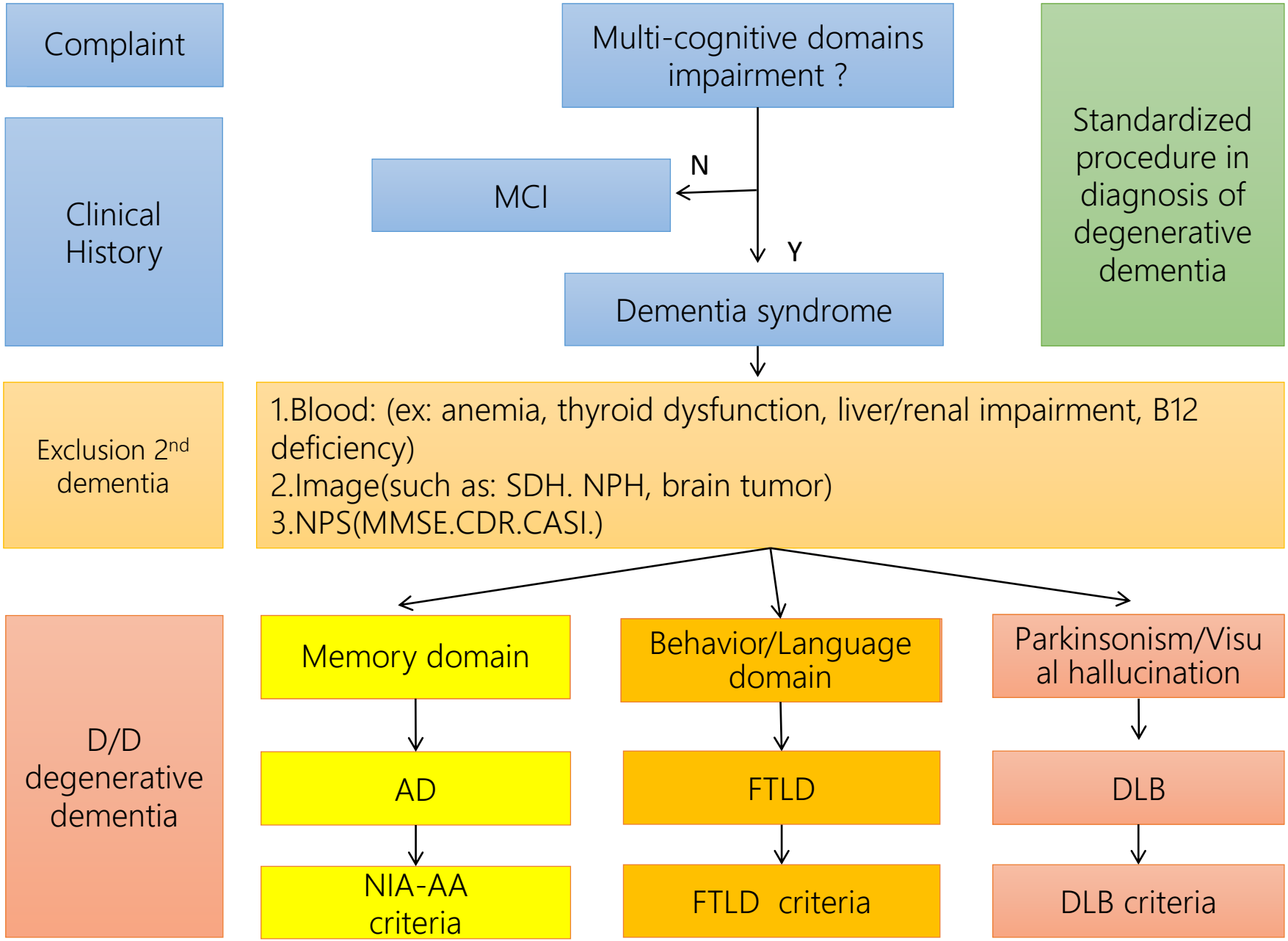
- Age is the biggest risk factor. After age of 60, the risk is increased by one fold every 5 years. The aged population continues to enlarge.



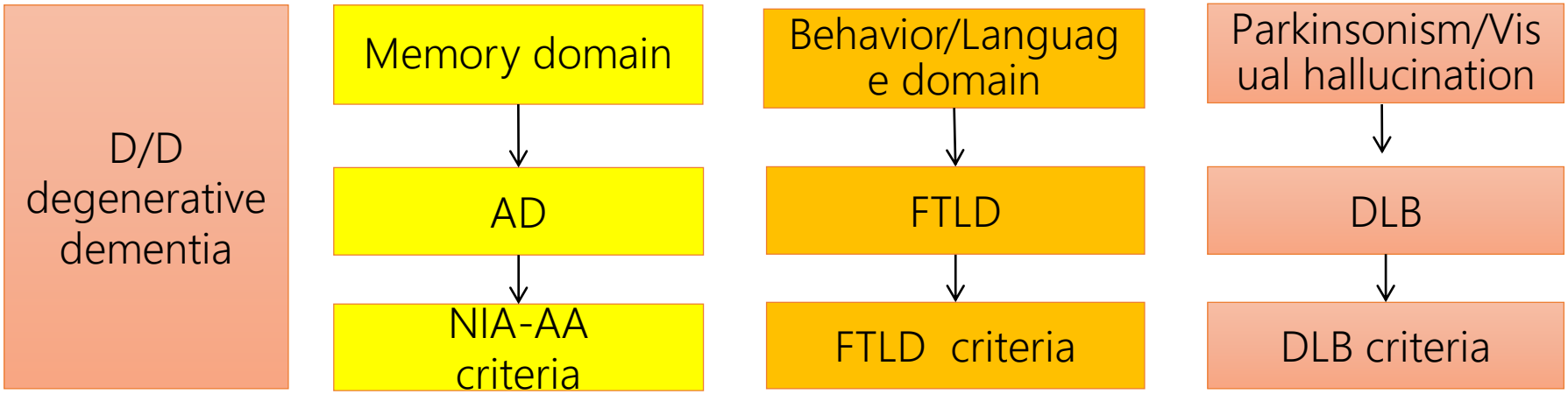
- The worldwide cost is 604 billion currently and will increase at least by 85% by 2030.



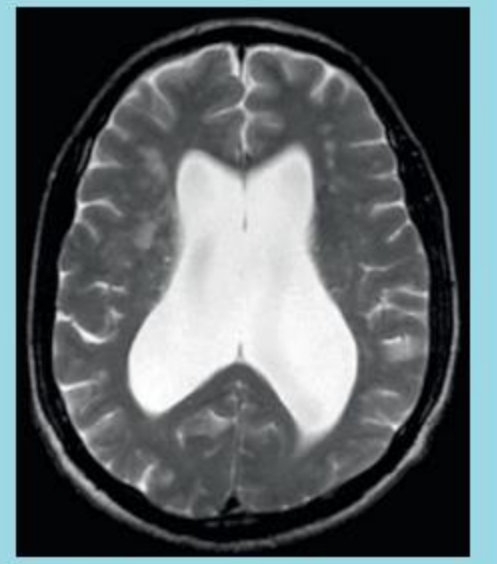
- The cost of dementia care is 214 billion USD in the US in 2014 and will be an estimated 1.2 trillion in 2050. The worldwide cost is 604 billion currently and will increase at least by 85% by 2030.


Complaint
Clinical History
Multi-cognitive domains impairment ?
N
MCI
Y
Dementia syndrome
Standardized procedure in diagnosis of degenerative dementia
Exclusion 2nd dementia
1.Blood: (ex: anemia, thyroid dysfunction, liver/renal impairment, B12 deficiency)
2.Image(such as: SDH. NPH, brain tumor)
3.NPS(MMSE.CDR.CASI.)
D/D degenerative dementia
Memory domain
AD
NIA-AA criteria
Behavior/Language domain
FTLD
FTLD criteria
Parkinsonism/Visual hallucination
DLB
DLB criteria

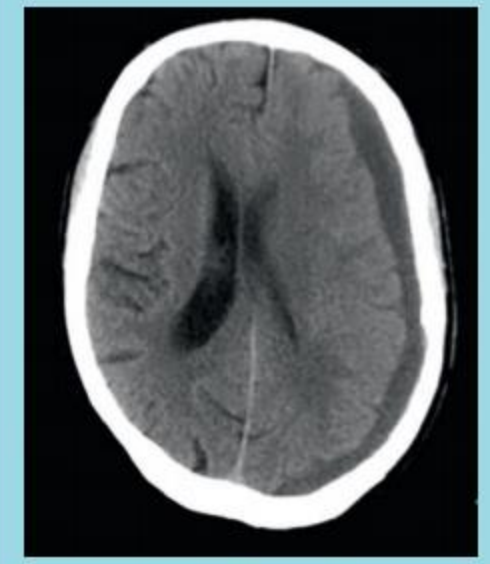
Biomarkers improve diagnostic accuracy



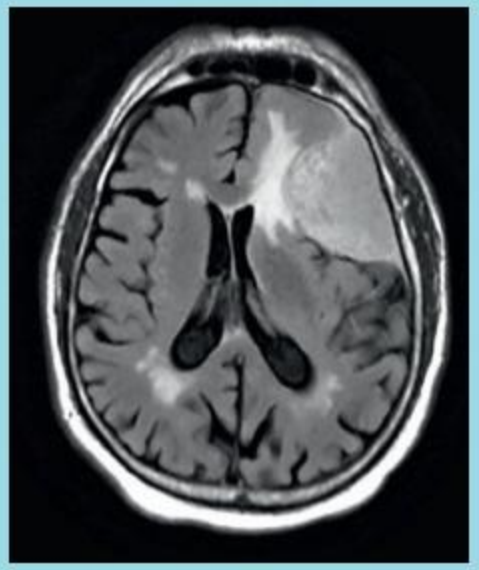
Biomarkers support clinical diagnosis	Biomarkers (use NIA-AA criteria as example): **Aβ deposition**: CSF $A\beta_{42}$, amyloid PET imaging **Neuronal injury**: CSF tau, hippocampus volume or medial temporal atrophy by MR, FDG-PET imaging
Gold standard	Neuropathological diagnosis for degenerative dementia AD: A β plaque, neurofibrillary tangle FTLD: TDP-43, tau, etc DLB: lewy body



Axial MRI (T2): Grossly enlarged ventricles in normal pressure hydrocephalus.
Case courtesy of Dr G Balachandran, Radiopaedia.org, rID: 15942

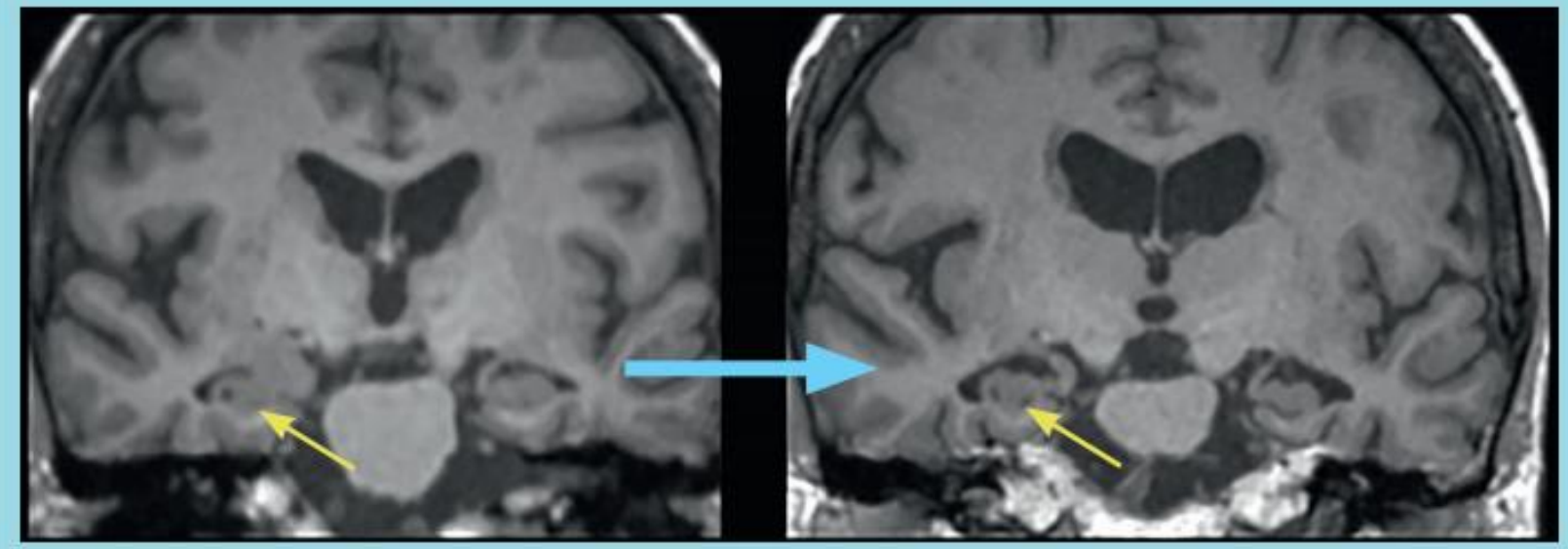


Axial CT: Chronic left subdural haemorrhage.
Case courtesy of Dr Jeremy Jones, Radiopaedia.org, rID: 6136



Axial MRI (FLAIR): Large left frontotemporal meningioma.
Case courtesy of Dr Frank Gaillard, Radiopaedia.org, rID: 30745

Box 1. Imaging can be used to rule out treatable causes of progressive cognitive impairment



Serial coronal MRI scans (T1) demonstrating five-month progression in bilateral hippocampal atrophy characteristic of early Alzheimer's disease. Right hippocampus highlighted.

Case courtesy of Dr Bruno Di Muzio, Radiopaedia.org, rID: 37720

Box 2. Typical imaging findings in Alzheimer's disease

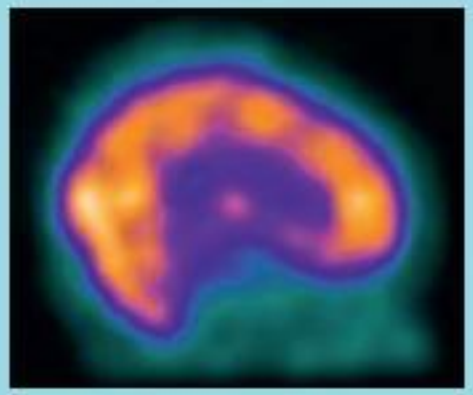
Statement on Positron Emission Tomography

January 2004

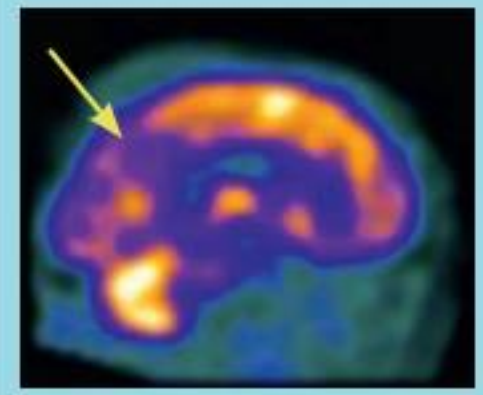
The Alzheimer's Association believes that Fluorodeoxyglucose positron emission tomography (FDG PET) may provide helpful information for the diagnosis and differential diagnosis of progressive cognitive impairment and dementia when used in conjunction with a thorough assessment conducted by an experienced and knowledgeable practitioner. However, FDG PET alone is not diagnostic for cognitive decline or dementia diagnosis. The Association supports the use of FDG PET for patients with dementia or patients with mild or moderate cognitive impairment of at least 6 months duration, when:

1) Dementia diagnosis, or cause for progressive cognitive impairment, remains uncertain after a comprehensive clinical evaluation, including review of the medical history, physical and neurological examinations, mental status testing, assessment of activities of daily living, laboratory tests, and structural imaging (MRI or CT), has been conducted by a physician experienced in the diagnosis and assessment of dementia, and

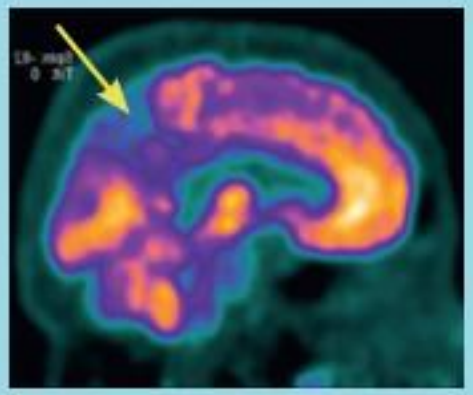
2) The information available through PET reasonably is expected to help clarify the diagnosis and/or help guide future treatment.



Sagittal HMPAO-SPECT image of healthy brain .
Case courtesy of Dr Frank Gaillard, Radiopaedia.org, rID: 10896



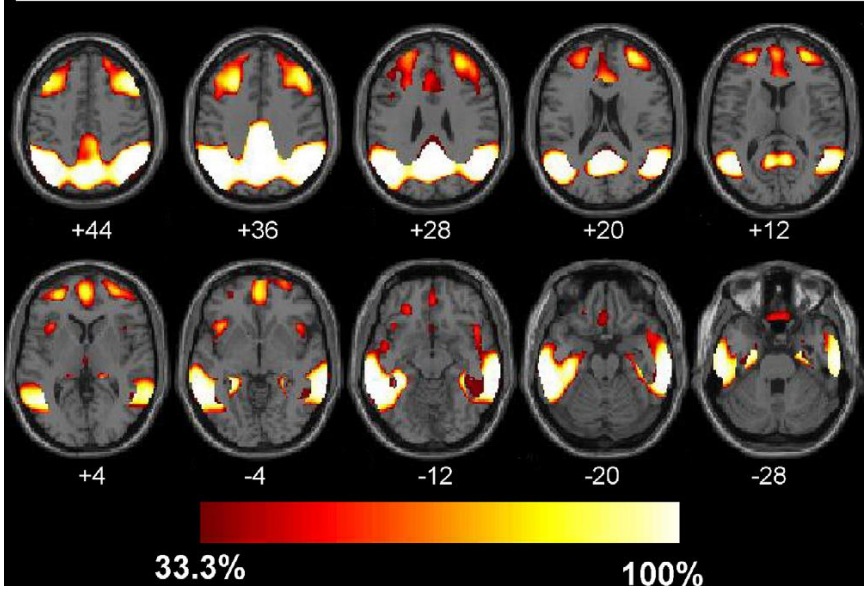
Sagittal HMPAO-SPECT image of a patient with Alzheimer's disease: Hypoperfusion in temporoparietal region.
Case courtesy of Dr Bruno Di Muzio, Radiopaedia.org, rID: 30090



Sagittal FDG-PET image of a patient with Alzheimer's disease: Hypometabolism in the temporoparietal region.
Case courtesy of Dr Bruno Di Muzio, Radiopaedia.org, rID: 22715

Box 4. HMPAO-SPECT and FDG-PET in Alzheimer's disease

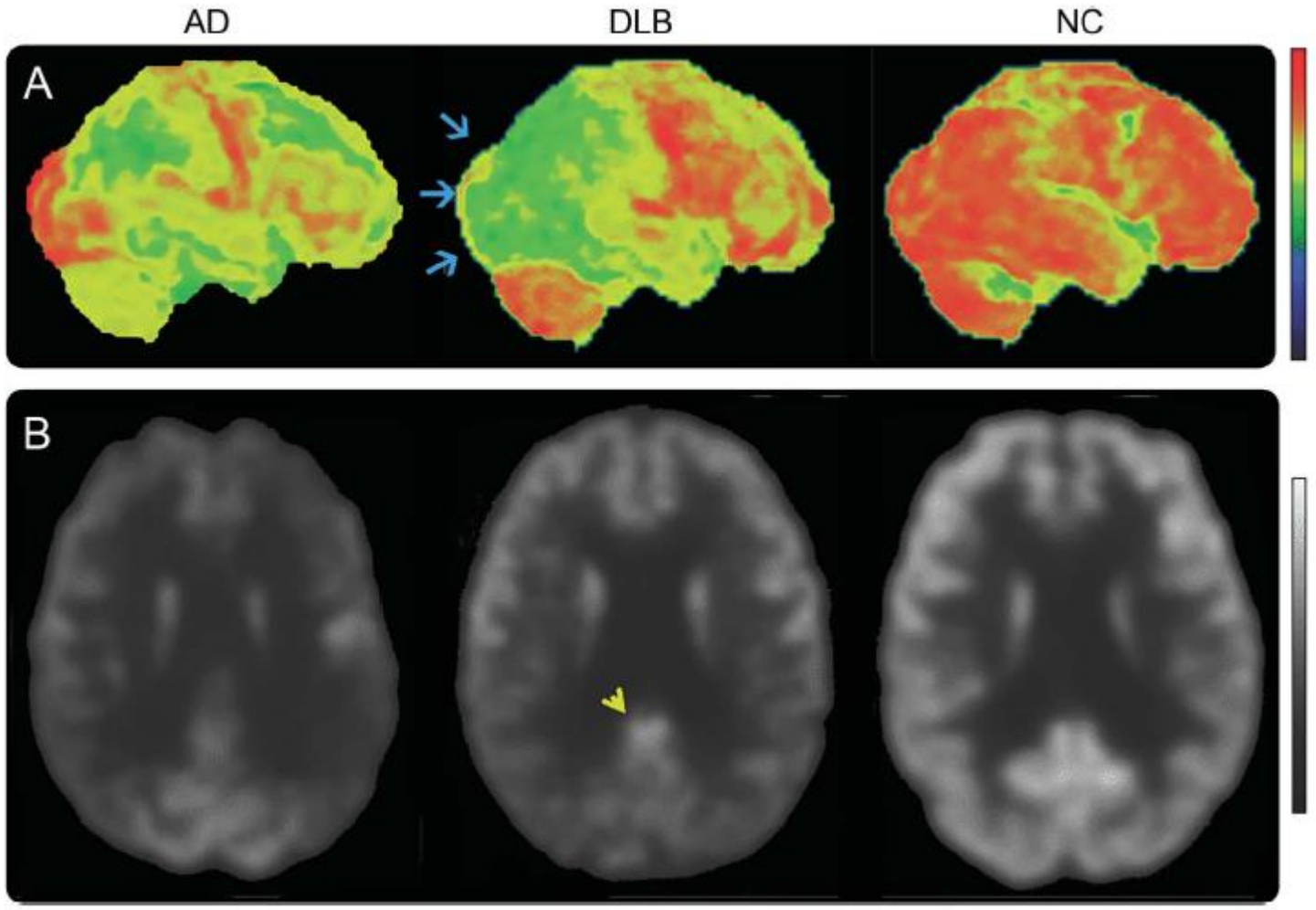
FDG-PET pattern in MCI/AD



- Probable Alzheimer's disease (pAD) :characteristic and progressive CMRgl reductions in posterior cingulate (PC), temporal (TE), parietal (PA), precuneus (PCu), occipital (OC).
- A meta-analysis including 27 studies evaluating FDG-PET in the diagnosis of AD resulted in a pooled sensitivity (SN) of 91% and specificity (SP) of 86%.
  - AD v.s Control: SN and SP of 99% and 98%.
  - AD v.s. DLB: SN and SP of 99% and 71%.
  - AD v.s. FTD: SN and SP of 99% and 65%.

Clinical Nuclear Medicine & Volume 39, Number 10, October 2014
Journal of Neuroscience Methods *192 (2010) 277–285*

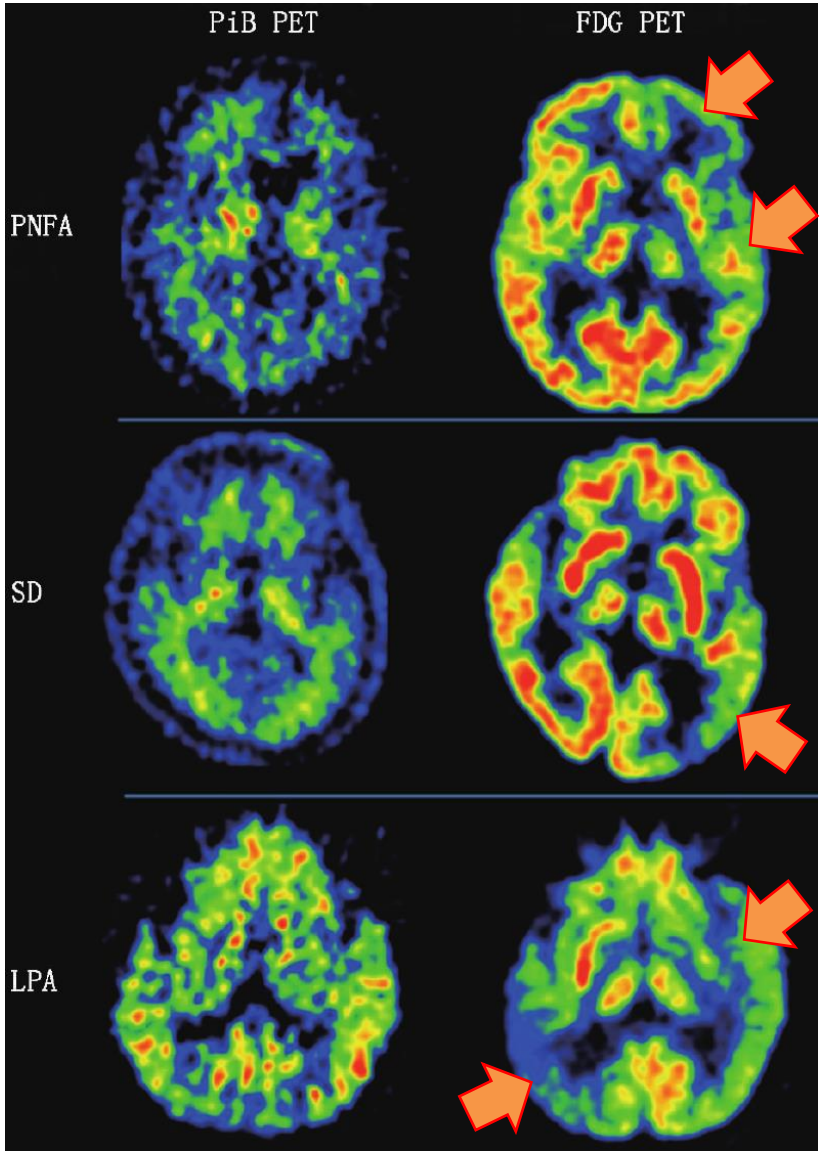
Figure 4 ^{18}F-FDG-PET images in Alzheimer disease (AD), dementia with Lewy bodies (DLB), and normal controls (NC)



FDG-PET in FTLD (2)

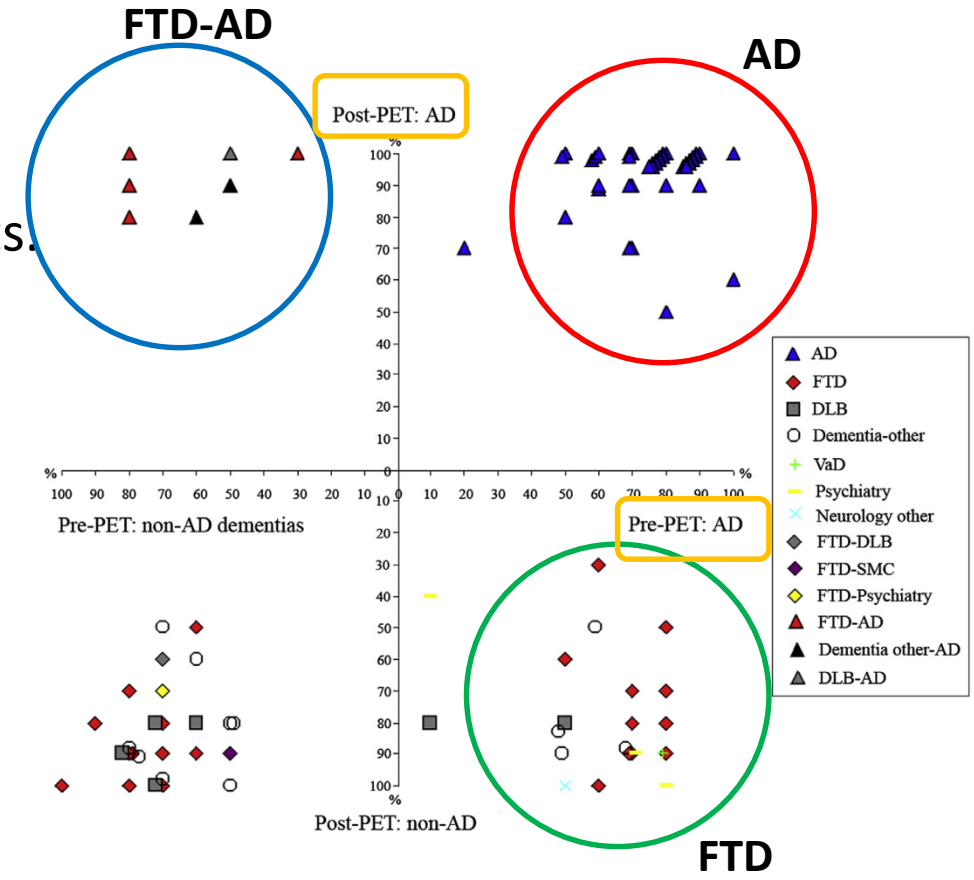
Language variant of FTLD

- Progressive nonfluent aphasia
  - Left posterior frontal and insular region atrophy.
  - Tau-positive pathology.
- Semantic aphasia
  - Anterior temporal region atrophy.
  - Ubiquitin-positive TDP-43 positive pathology.
- Logopanic aphasia
  - Left temporo-parietal region atrophy.
  - AD pathology.



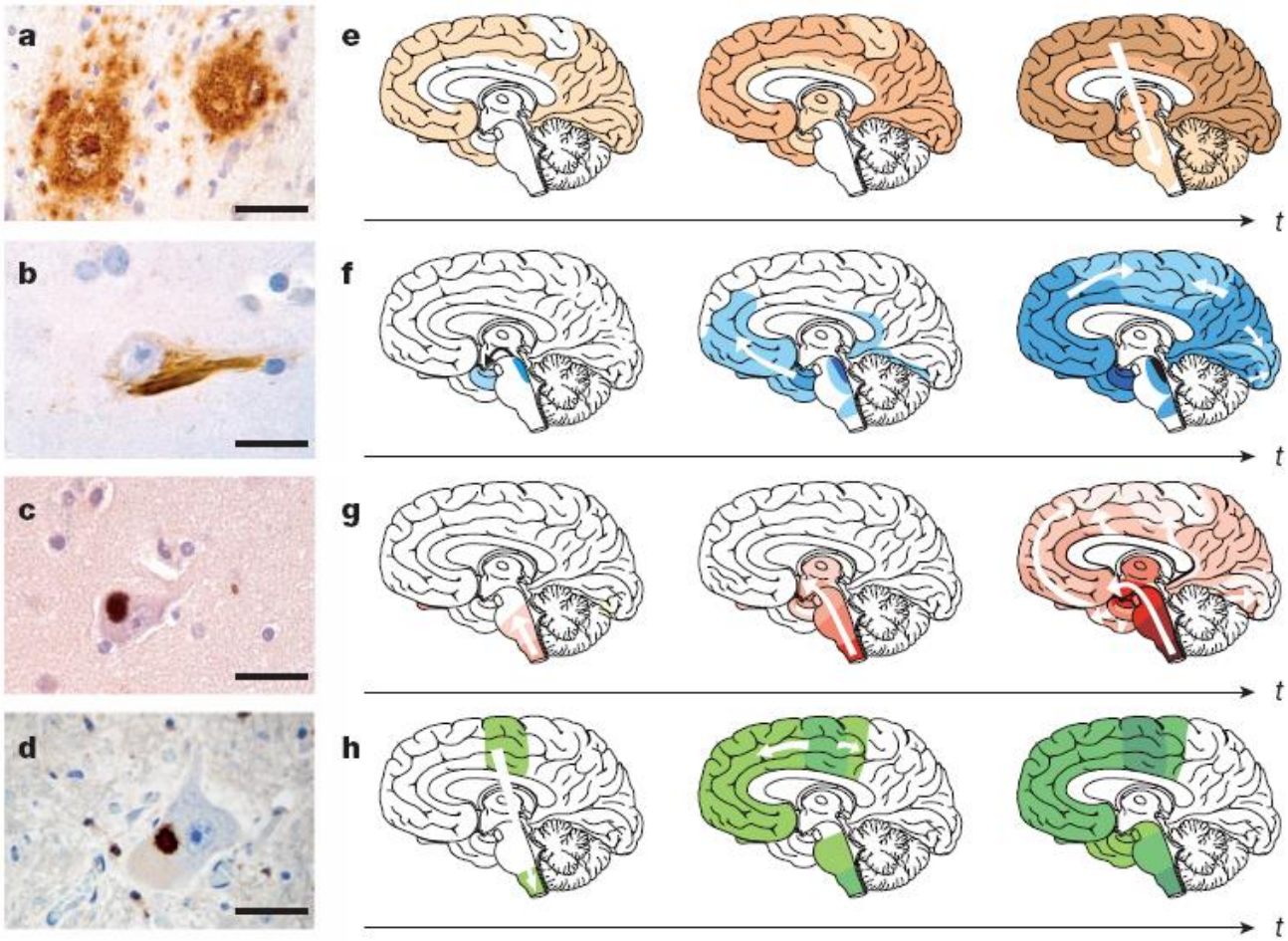
Management Impact of FDG-PET in Dementia: Results from a Tertiary Center Memory Clinic

- FDG-PET had moderate to high impact on the diagnosis and management in 44% participants.
- PET changed the type of dementia in 15% participants and prescription of cholinesterase inhibitors in 17% patients.
- Number of uncertain diagnoses reduced 11%, decreased differential diagnosis 37% and increase very probable diagnose 19%.



Alzheimer's & Dementia 9 (2013) 414–421
Journal of Alzheimer's Disease 42 (2014) 885–892

Self-propagation of pathogenic protein aggregates in neurodegenerative diseases



Amyloid: AD

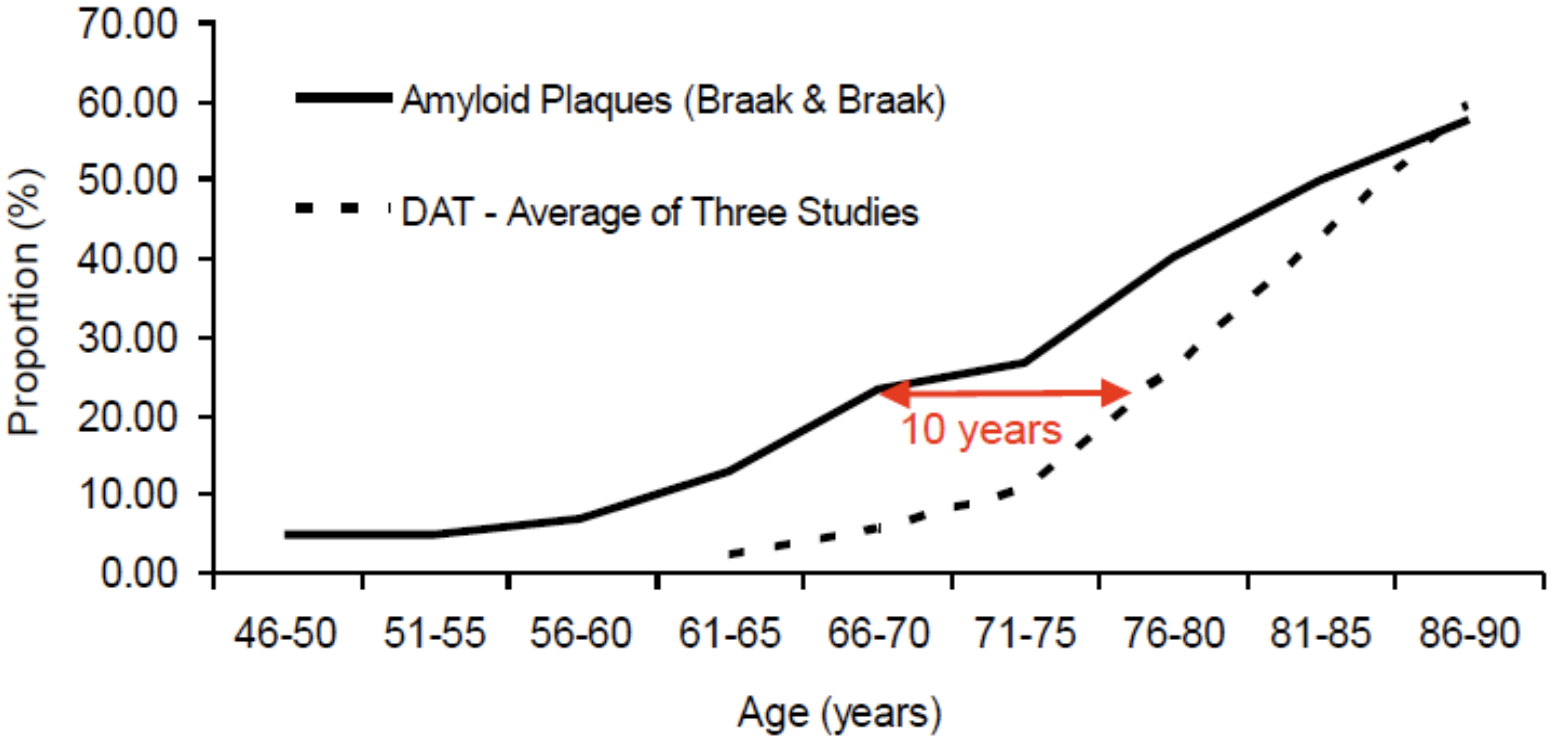
Tau: AD & others

a-Synuclein inclusion: DLB, PD

TDP-43 inclusion: MND

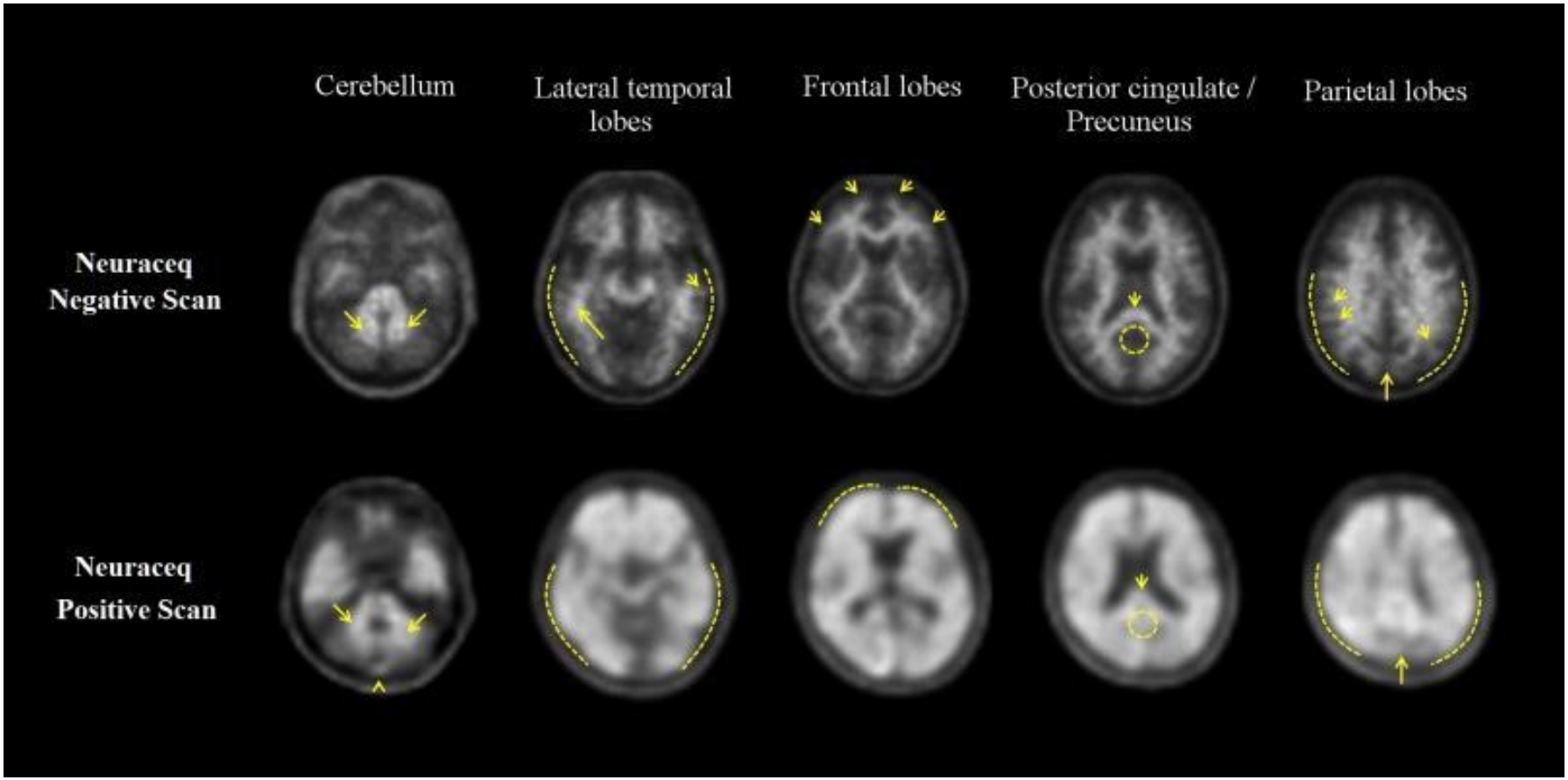
NATURE | VOL 501 | 5 SEPTEMBER 2013

Therefore we expect to see amyloid positivity in subjects before they have Alzheimer's disease

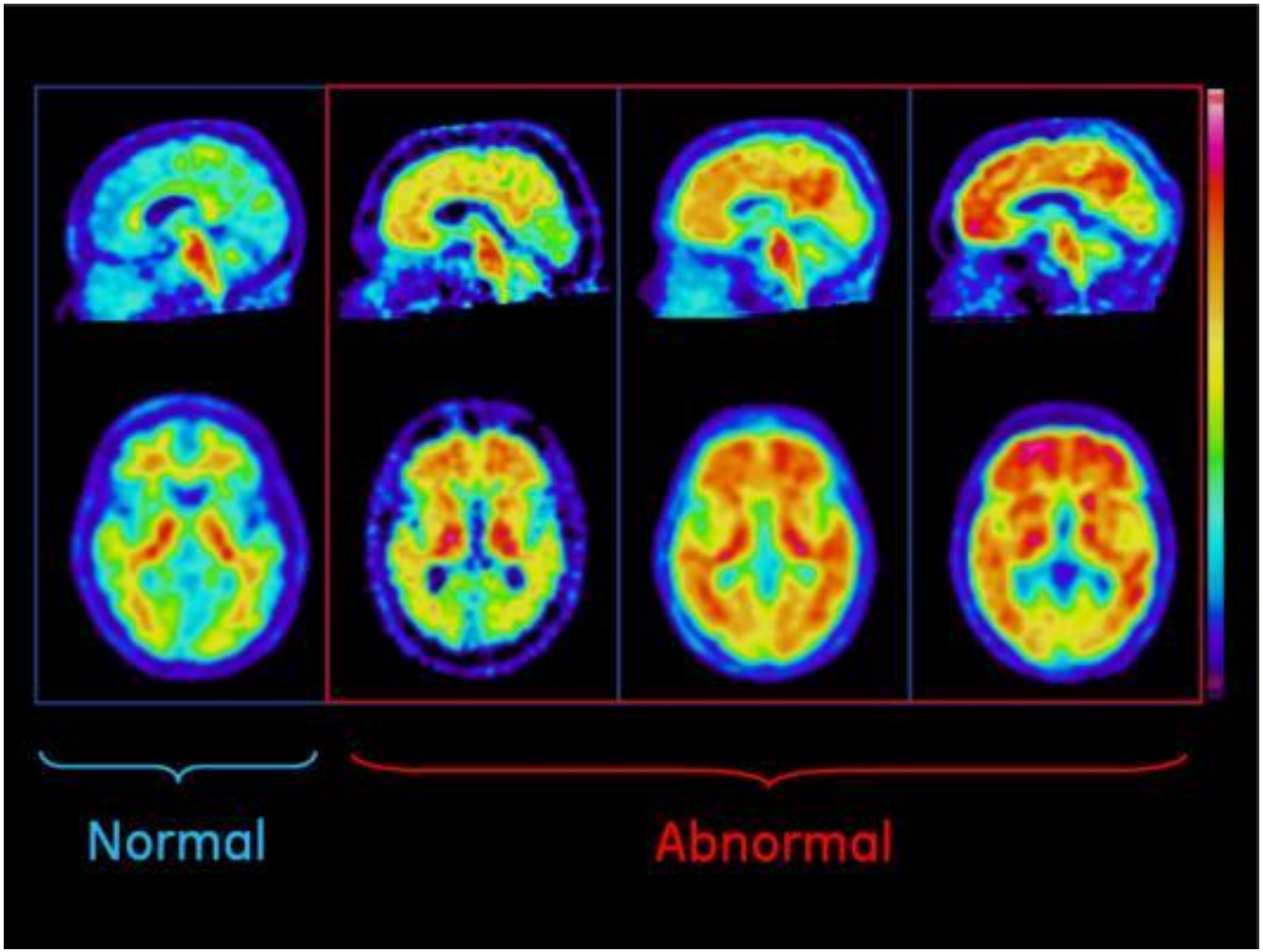


Hebert et al, 1995; Ganguli et al, 2000; Kukull, et al, 2002; Braak & Braak, 1991

FDA Approves Piramal Imaging's PET Imaging Tracer for Beta-Amyloid Plaques



GE amyloid imaging agent, F-18 flutemetamol,



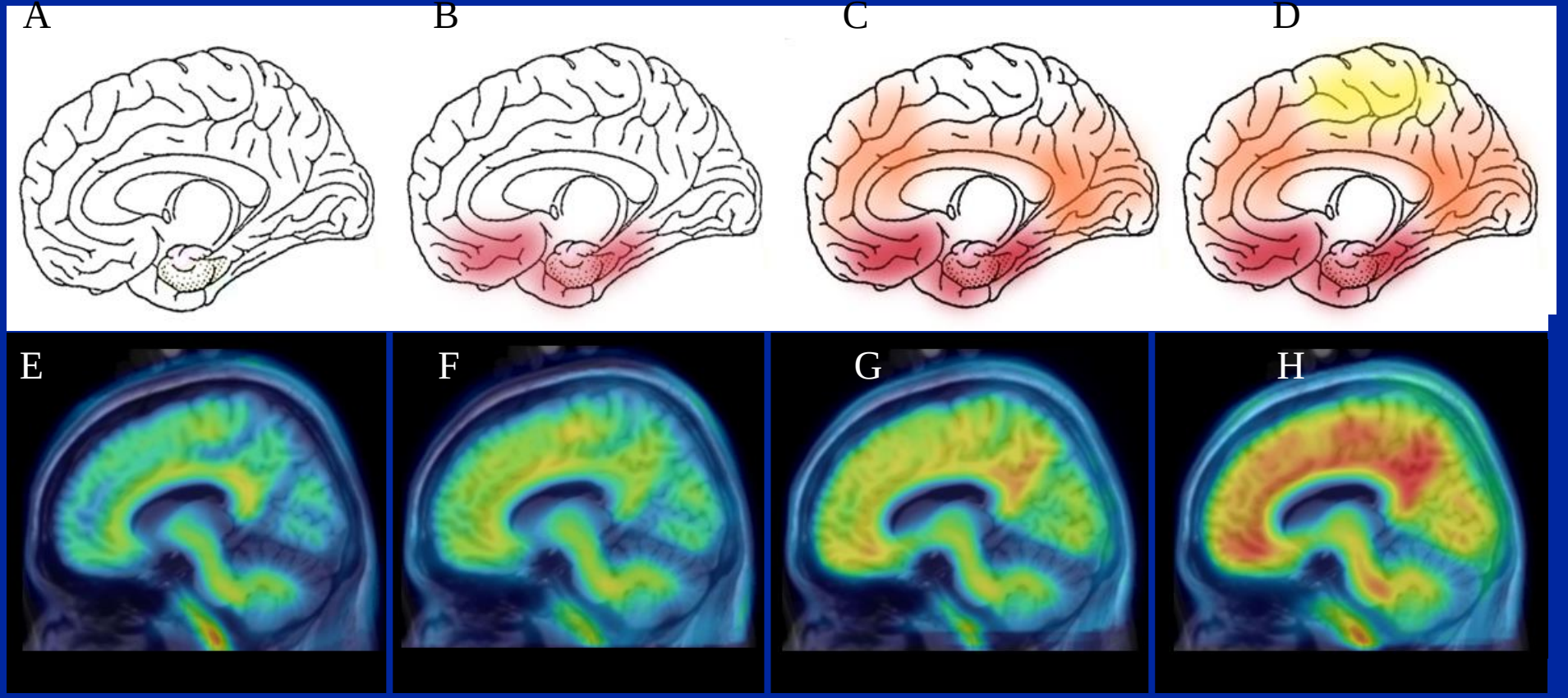
2010 kick out project for TADNI

Characteristics of subjects

Planed		Screened	Enrollment	Screen Failure	Screen	Baseline	6 month	1 years	2 years	completed	withdraw	AE	SAE	Ratio of accomplishment (%)
CGMH (Linkou)	60	82	72	10	0	0	23	4	31	8	6	0	1	120%
CGMH (Kaoshiung)	20	14	14	0	0	0	9	1	0	2	2	0	0	70%
TVGH	20	9	9	0	1	7	1	0	0	0	0	0	0	45%
TMU-SHH	20	1	1	0	0	0	0	0	0	0	1	0	0	5%
Total	120	106	96	10	1	7	33	5	31	10	9	0	1	88%

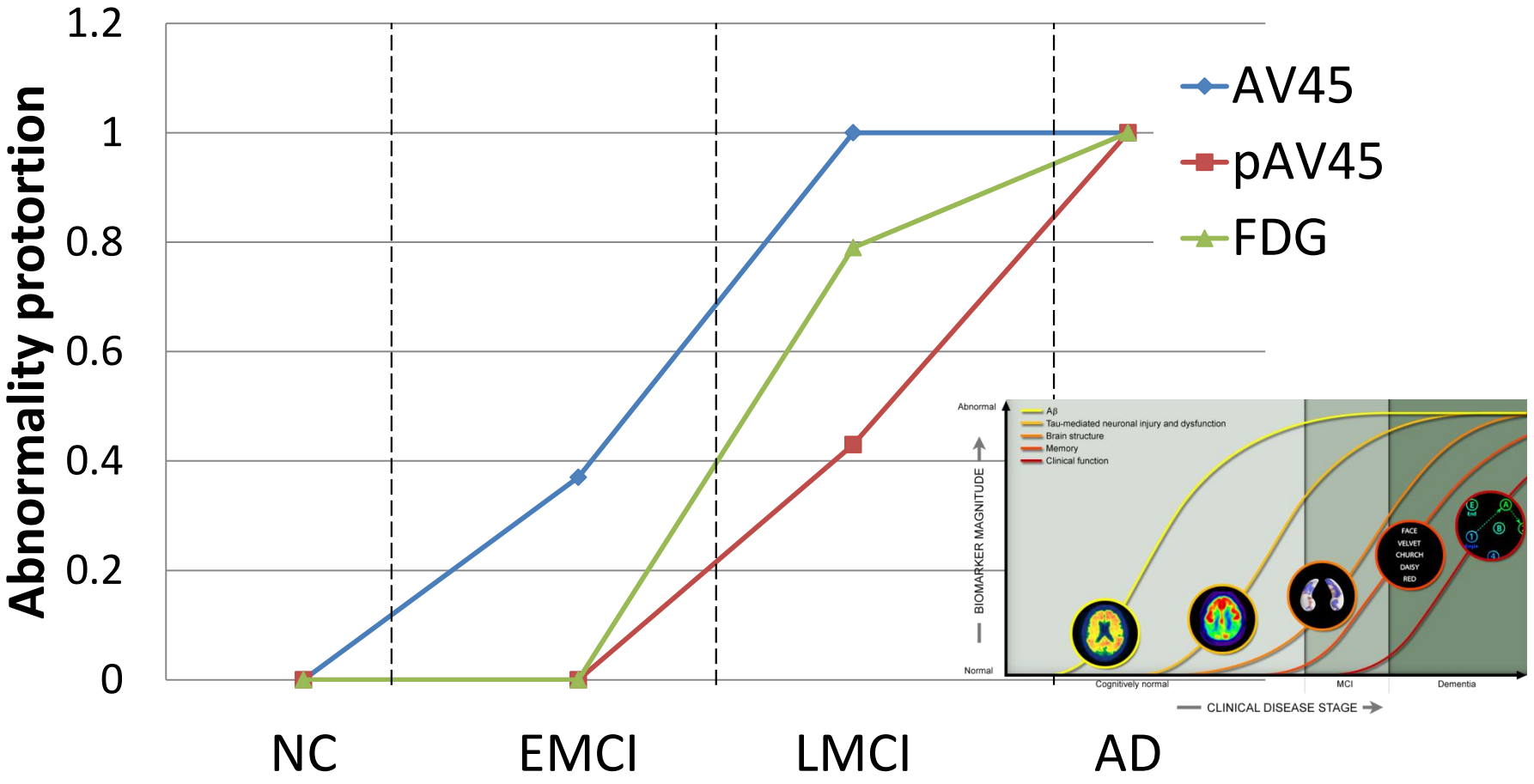
- Screen Failure : 1:claustrophobia 3:stroke 1:withdraw consent 1: GDS>6
- SAE: head and neck tumor, unrelated to Investigational product.

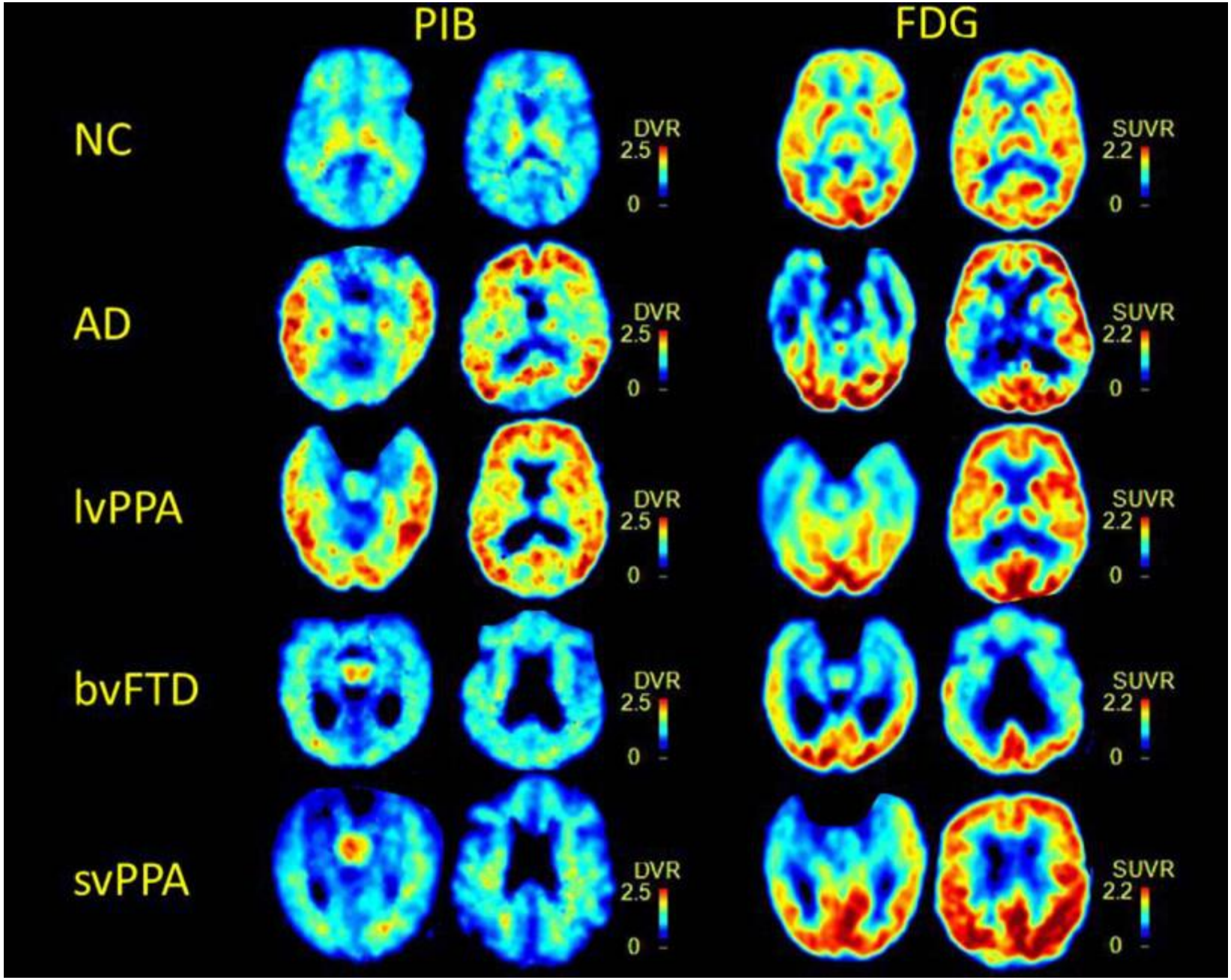
Regional Amyloid Deposition in Amnestic Mild Cognitive Impairment and Alzheimer's Disease Evaluated by [18F]AV-45 Positron Emission Tomography in Chinese Population.



PLoS One. 2013;8(3):e58974. Epub 2013 Mar 14.

Multimodality image information for disease staging





Alzheimers Res Ther. 2011 Nov 10;3(6):31.

Potential clinical utility

1. Determine whether MCI is due to AD
2. Diff erentiate AD from non-AD dementia (for example, frontotemporal lobar degeneration), particularly in early age-at-onset patients
3. Determine whether AD copathology is present in patients with cognitive impairment and other known neurologic disease (for example, Parkinson's disease, stroke/vascular disease, multiple sclerosis, epilepsy, HIV)
4. Differentiate AD from nondegenerative cognitive decline (for example, depression, substance abuse)
5. Determine whether AD is present in patients with advanced dementia and no reliable history
6. Identify whether AD is present in focal cortical syndromes (for example, posterior cortical atrophy, primary progressive aphasia, corticobasal syndrome)
7. Differentiate cerebral amyloid angiopathy from intracranial hemorrhage due to small-vessel vasculopathy

Laforce and Rabinovici Alzheimer's Research & Therapy 2011, 3:31

Unlikely to have clinical utility

1. Initial investigation of cognitive complaints (in the absence of a detailed neurologic evaluation and cognitive testing)
2. Differentiate AD from other amyloid-beta-associated dementia (for example, dementia with Lewy bodies, cerebral amyloid angiopathy)
3. Differentiate between AD clinical variants (for example, classic amnestic AD vs. posterior cortical atrophy or logopenic variant primary progressive aphasia)
4. Differentiate between non-AD causes of dementia (for example, molecular subtypes of frontotemporal lobar degeneration)

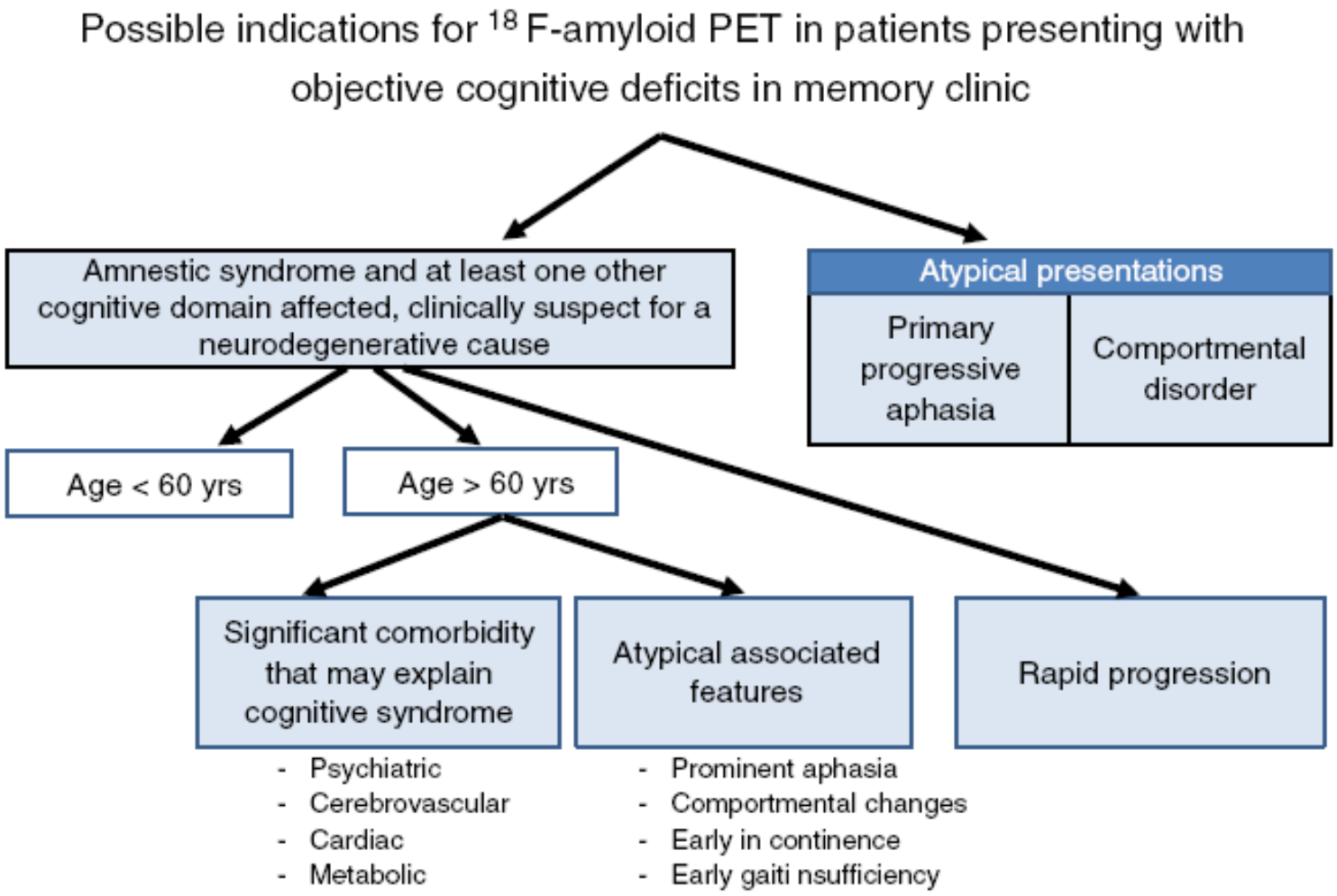
Laforce and Rabinovici Alzheimer's Research & Therapy 2011, 3:31

Utility for research only

1. Testing and longitudinal follow-up of asymptomatic or subjective cognitive impairments not meeting MCI criteria or at-risk individuals (for example, gene mutation carriers, family history of AD, apolipoprotein E ε4 allele)
2. Selection of candidates for anti-amyloid treatment trials (AD, MCI, preclinical)
3. Study of the natural evolution of amyloid burden and its role in the pathophysiology of AD and other dementias
4. Potential surrogate marker for anti-amyloid therapies

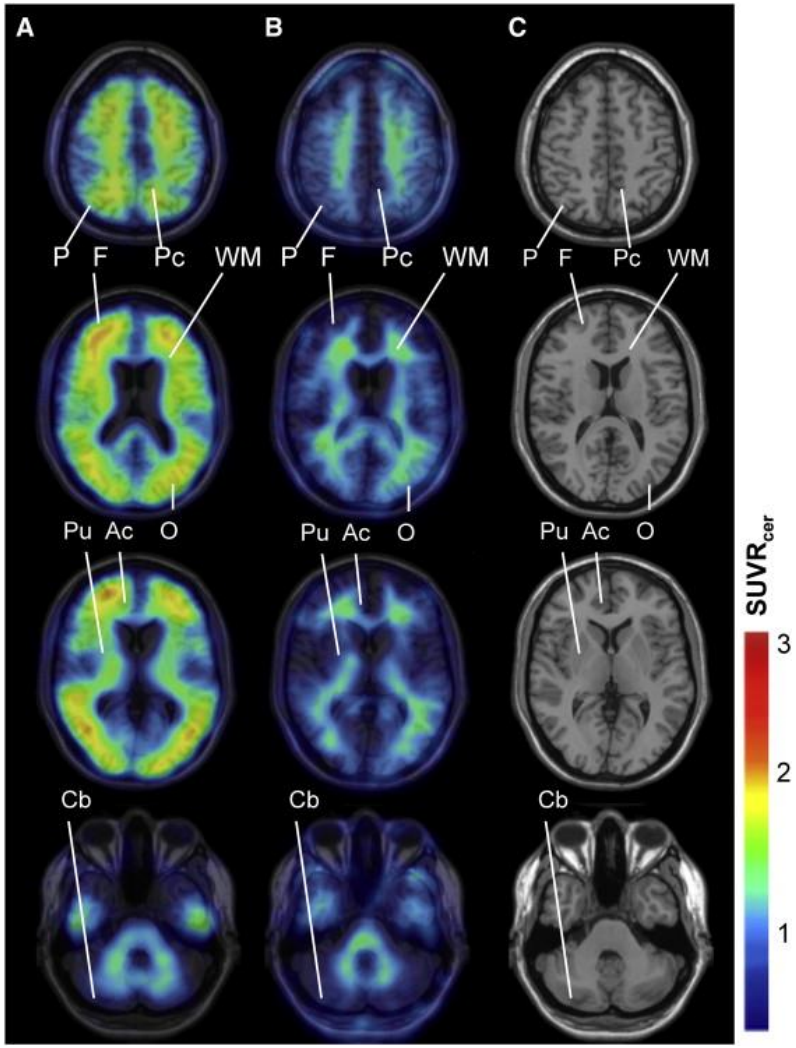
Laforce and Rabinovici Alzheimer's Research & Therapy 2011, 3:31

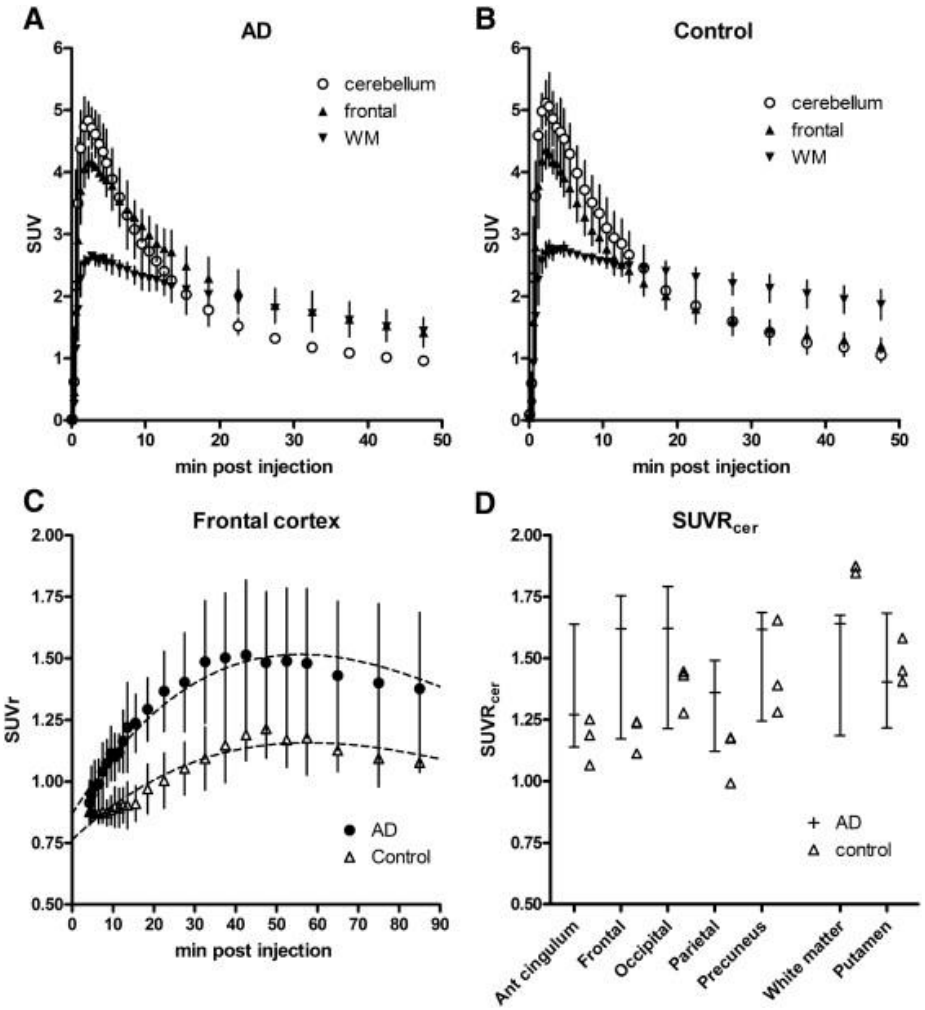
Tentative clinical algorithm for the utility of amyloid imaging



http://dx.doi.org/10.1016/j.nicl.2013.03.014

Whole-body biodistribution and brain PET



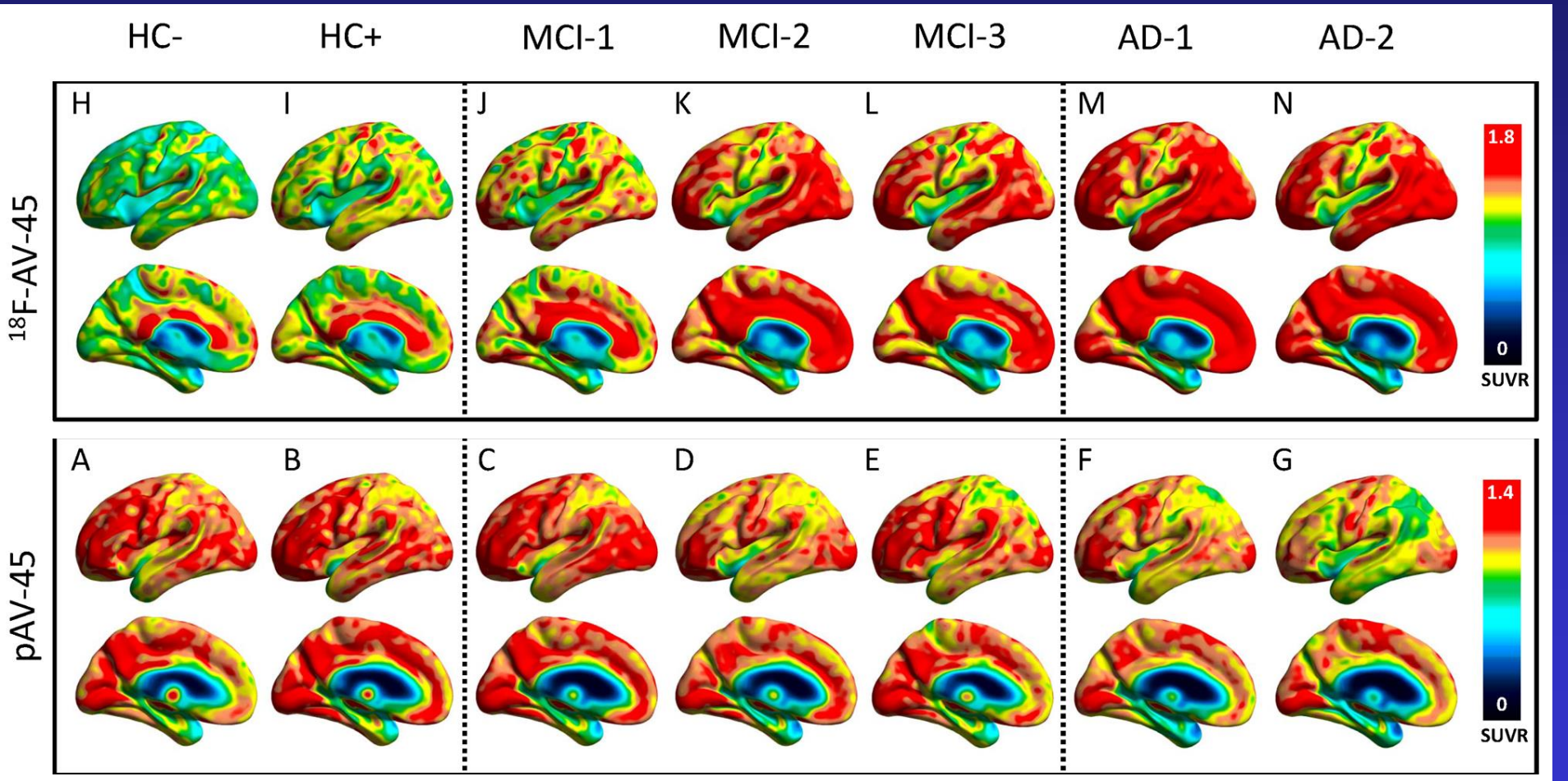


Nucl Med Biol. 2010;37:497-508

Lin *et al*, EJNM 2016

^{18}F-AV45 Imaging in disease severity

Amyloid



Perfusion

Society of Nuclear Medicine and Molecular Imaging (SNMMI) is an international scientific and professional organization founded in 1954 to promote the science, technology and practical application of nuclear medicine. The European Association of Nuclear Medicine (EANM) is a professional non-profit medical association that facilitates communication worldwide between individuals pursuing clinical and research excellence in nuclear medicine. The EANM was founded in 1985. SNMMI and EANM members are physicians, technologists, and scientists specializing in the research and practice of nuclear medicine. The SNMMI and EANM will periodically define new guidelines for nuclear medicine practice to help advance the science of nuclear medicine and to improve the quality of service to patients throughout the world. Existing practice guidelines will be reviewed for revision or renewal, as appropriate, on their fifth anniversary or sooner, if indicated.

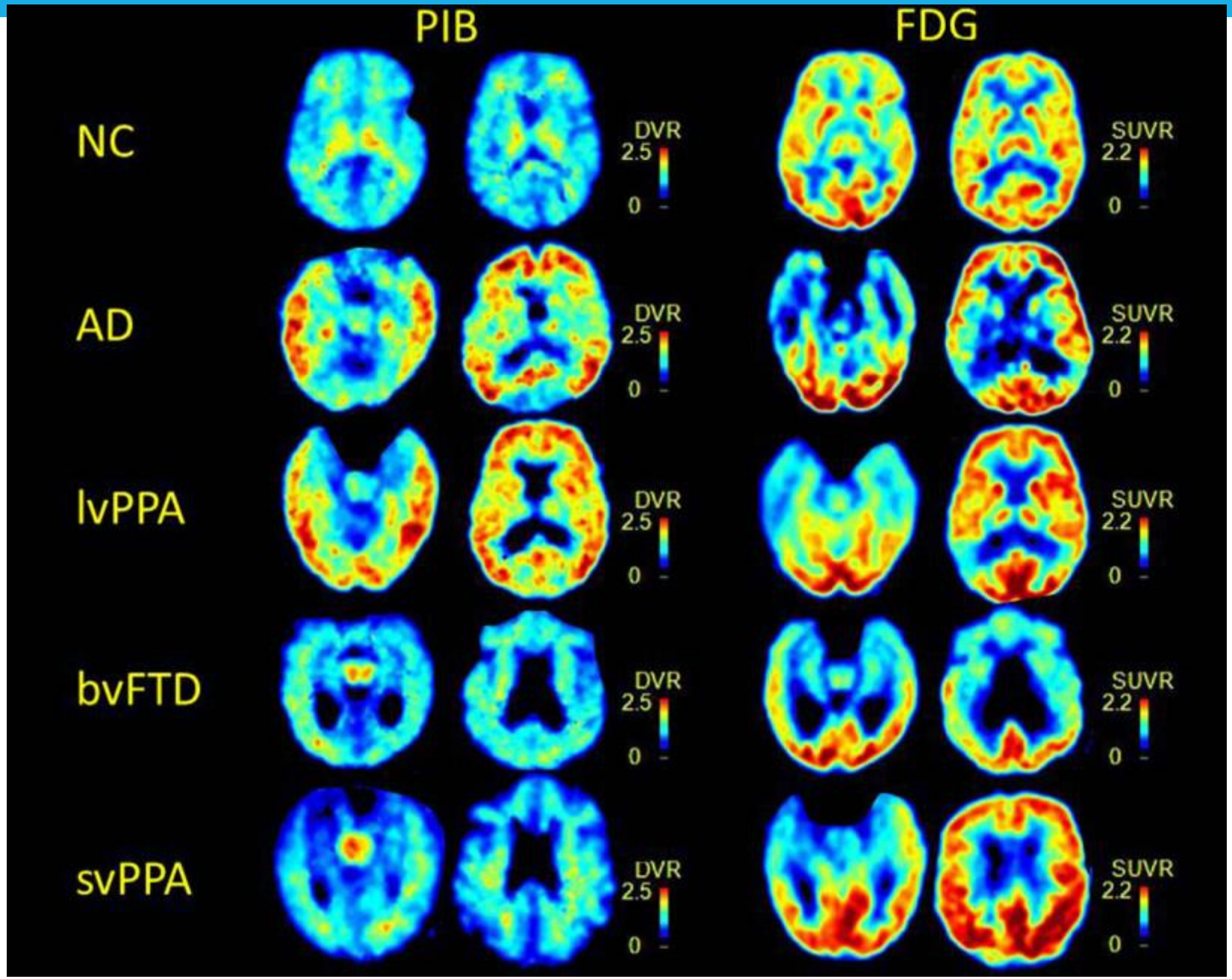
Each practice guideline, representing a policy statement by the SNMMI/EANM, has undergone a thorough consensus process in which it has been subjected to extensive review. The SNMMI and EANM recognize that the safe and effective use of diagnostic nuclear medicine imaging requires specific training, skills, and techniques, as described in each document. Reproduction or modification of the published practice guideline by those entities not providing these services is not authorized.

5. Image acquisition should be performed in 3D data acquisition mode with appropriate data corrections.

6. Image reconstruction should include attenuation correction with typical transaxial pixel sizes between 2-3 mm and slice thickness between 2-4 mm.

7. Advise the patient to hydrate and void after the scanning session to diminish radiation exposure.

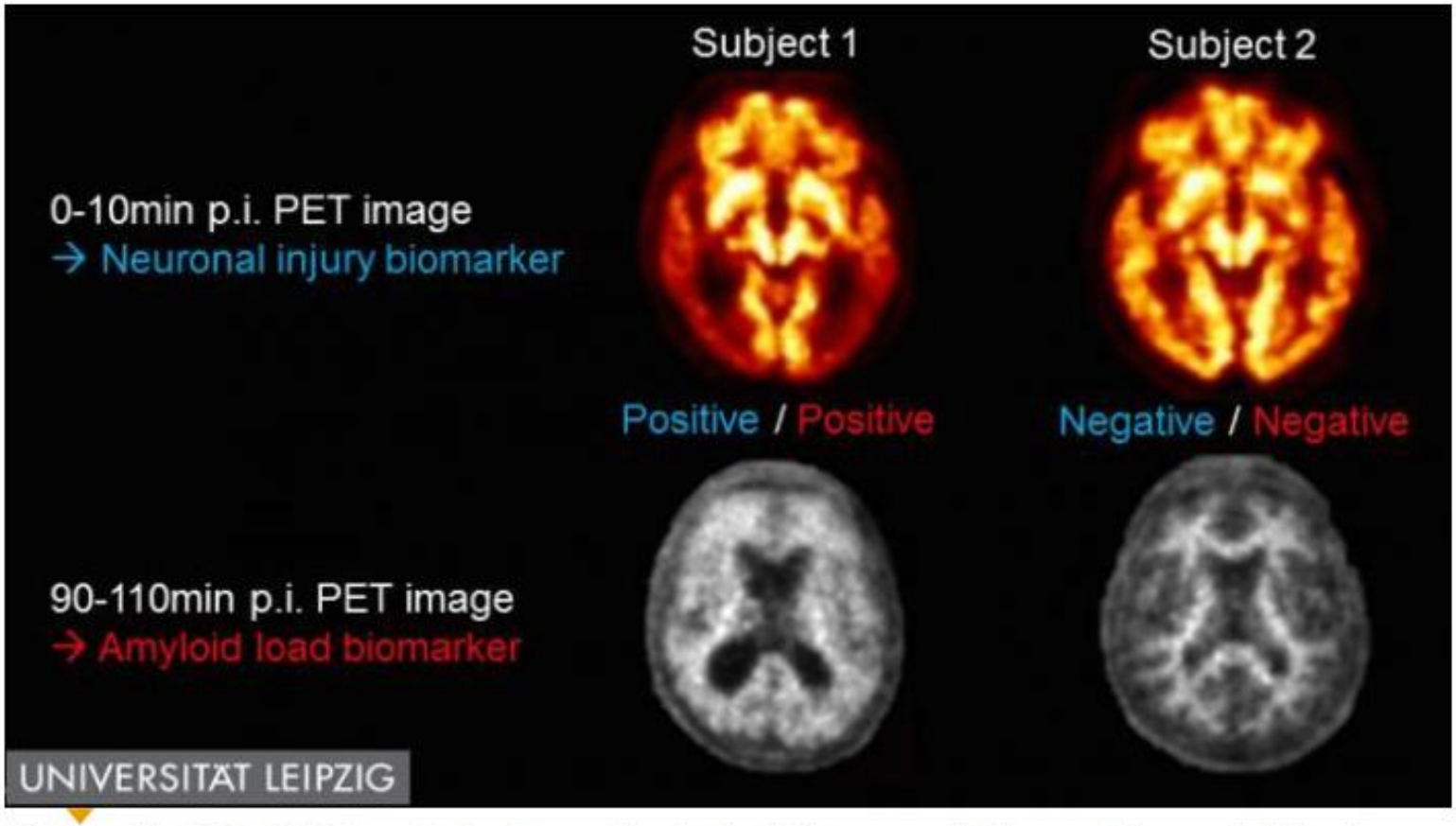
Note: Early post-injection images reflecting cerebral blood flow have been described as an aid for better image interpretation and improved accuracy for ^{18}F-Florbetapir[xiv]. Such methods and their diagnostic values are currently under investigation.



Alzheimers Res Ther. 2011 Nov 10;3(6):31.

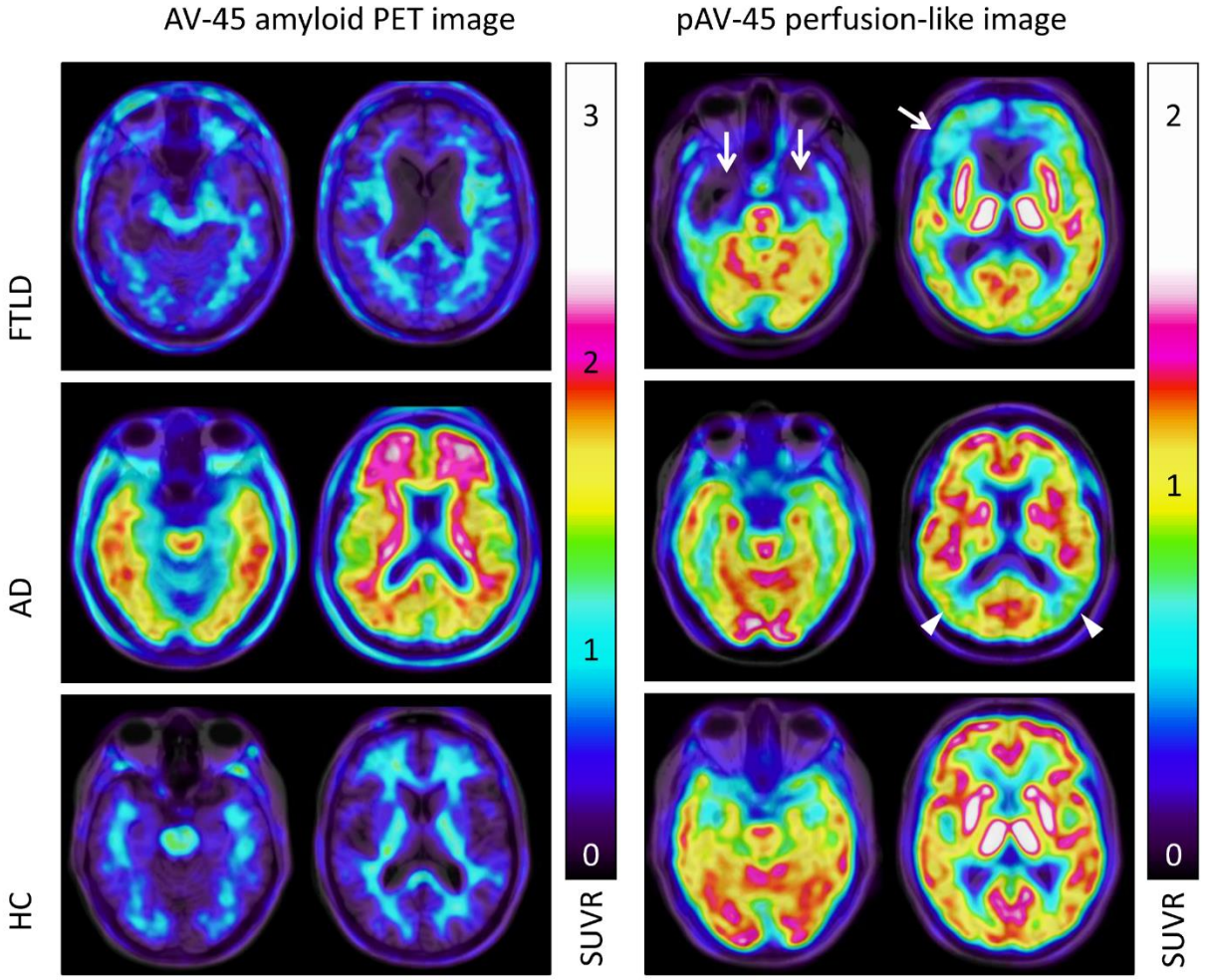
NEWS | PET IMAGING | JUNE 14, 2017

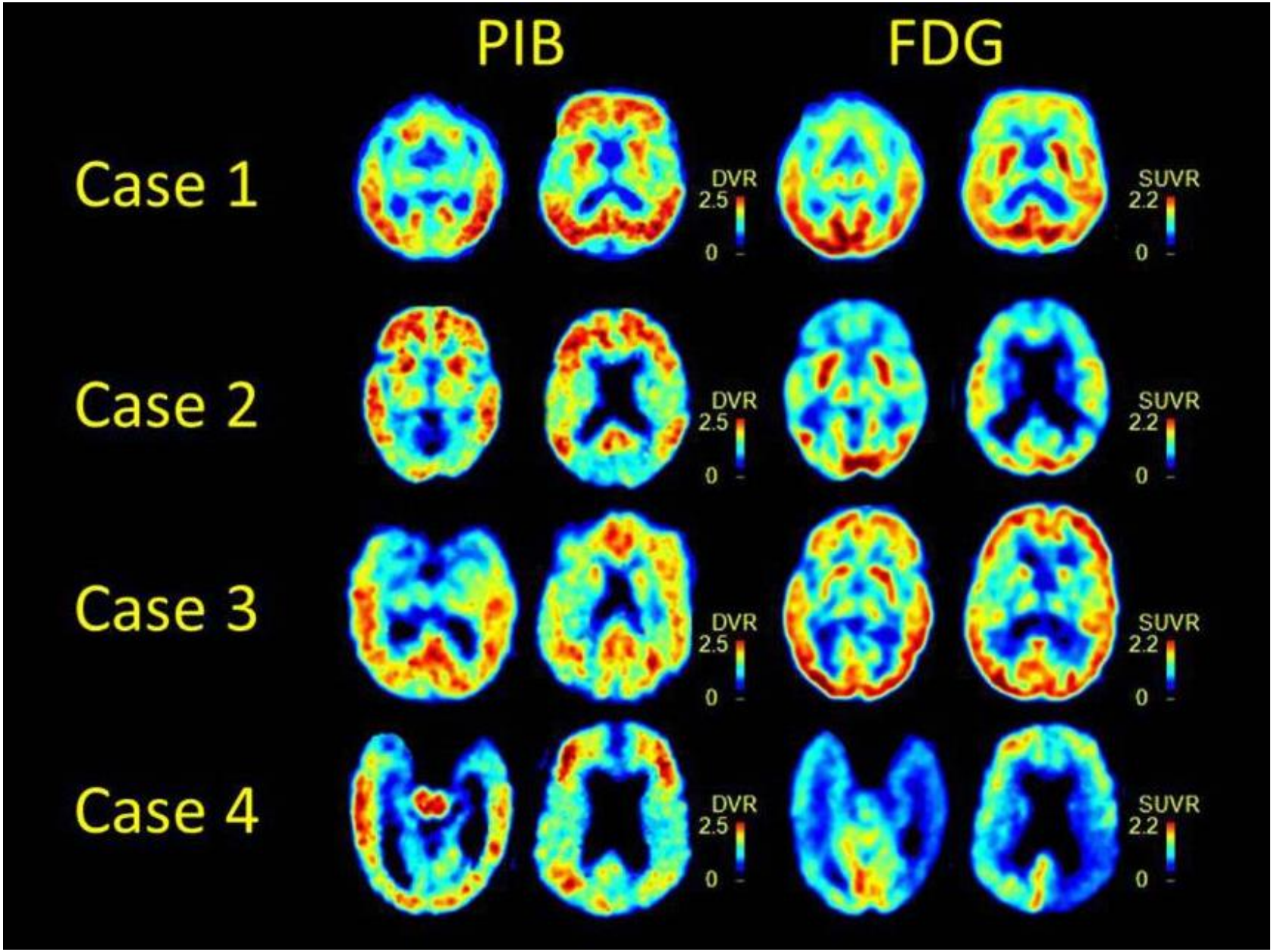
Single Dual Time-point PET Scan Identifies Dual Alzheimer's Biomarkers



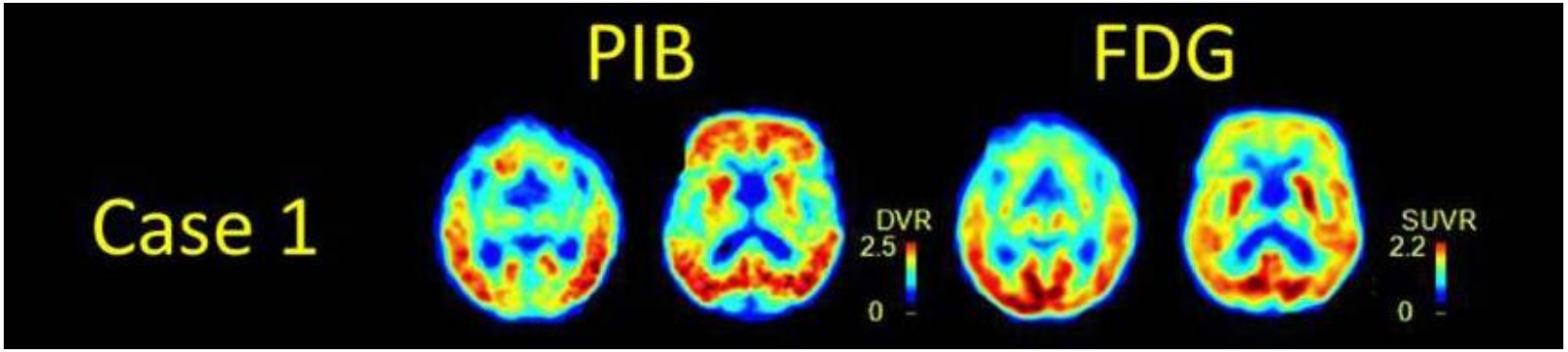
While subject No. 1 (left) was judged as positive for both the neuronal injury and the amyloid load biomarker, both Alzheimer's disease biomarkers were negative in subject No. 2 (right). Image courtesy of Henryk Barthel et al., University Hospital Leipzig, Leipzig, Germany

Dual phase [^{18}F]florbetapir PET among Patients with FTD, AD, and Healthy Controls in Chinese Population



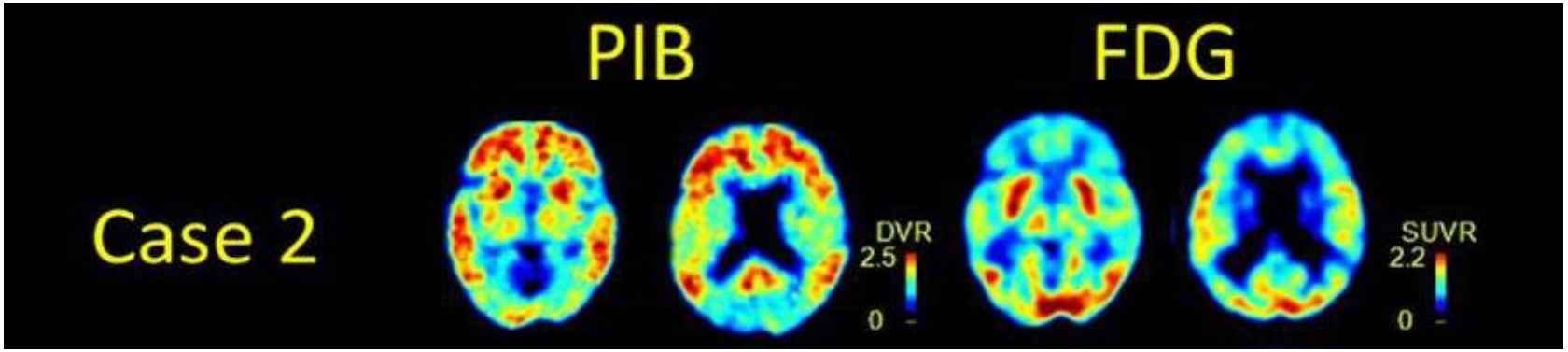


Alzheimers Res Ther. 2011; 3(6): 31.



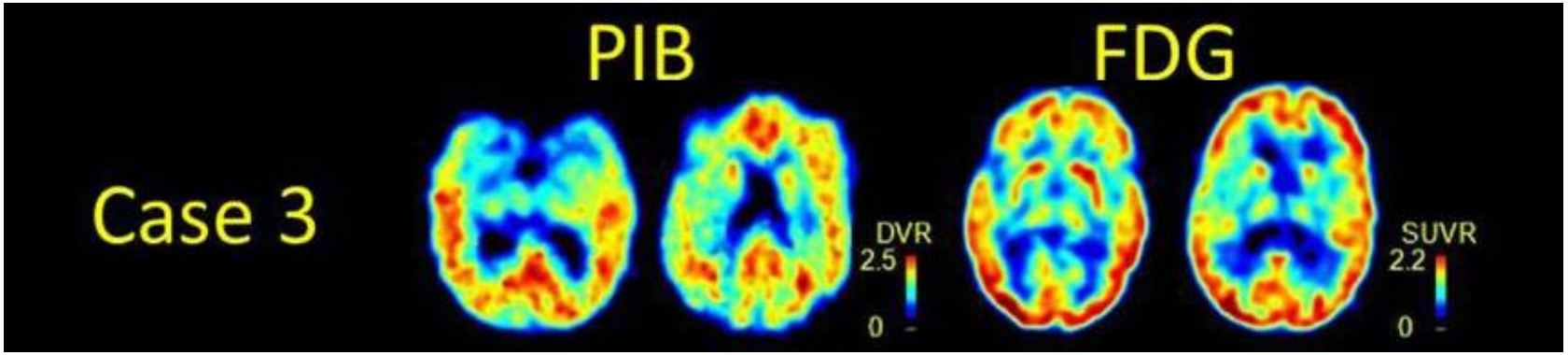
- Case 1 is an 89-year-old man with 8 years of progressive memory loss, executive dysfunction, behavioral changes, and an MMSE of 29. MRI showed severe hippocampal atrophy as well as significant subcortical white matter disease and a number of lacunes. Clinical diagnosis was mixed AD/vascular dementia. FDG showed bifrontal hypometabolism sparing the temporo-parietal cortex, while PIB revealed diffuse cortical binding.

Alzheimers Res Ther. 2011; 3(6): 31.



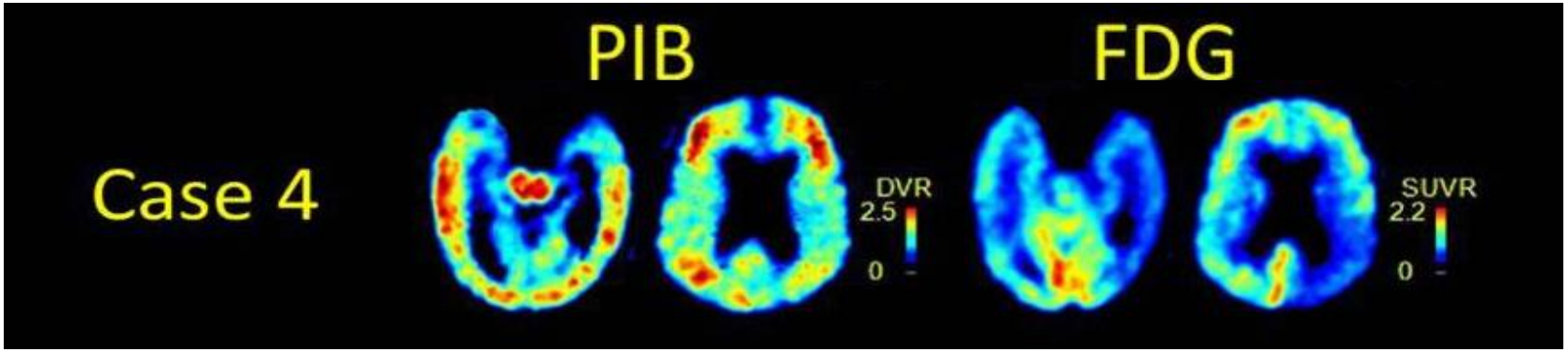
- Case 2 is a 55-year-old man with 9 years of profound behavioral changes including compulsive behaviors, disinhibition, socially inappropriate behavior, and impairment in executive, memory, and visuospatial functions (MMSE = 16). He was clinically diagnosed with bvFTD. FDG showed bilateral frontal and temporo-parietal hypometabolism, while PIB revealed diffuse cortical binding. Pathology is not available.

Alzheimers Res Ther. 2011; 3(6): 31.



- Case 3 is a 70-year-old woman presenting with non-fluent variant PPA (MMSE = 28). FDG showed focal left frontal hypometabolism, while PIB was unexpectedly positive.

Alzheimers Res Ther. 2011; 3(6): 31.



- Case 4 is a 68-year-old man with 6 years of progressive asymmetric left-sided apraxia, Parkinsonism, dystonia, tremor, and myoclonus. Levodopa treatment was unhelpful. Cognitive decline was characterized by deficits in executive and visuospatial functions, episodic memory and language (MMSE = 19). Visual hallucinations emerged later in the course. Clinical diagnosis was CBS. FDG revealed asymmetric right posterior frontal and temporo-parietal hypometabolism.

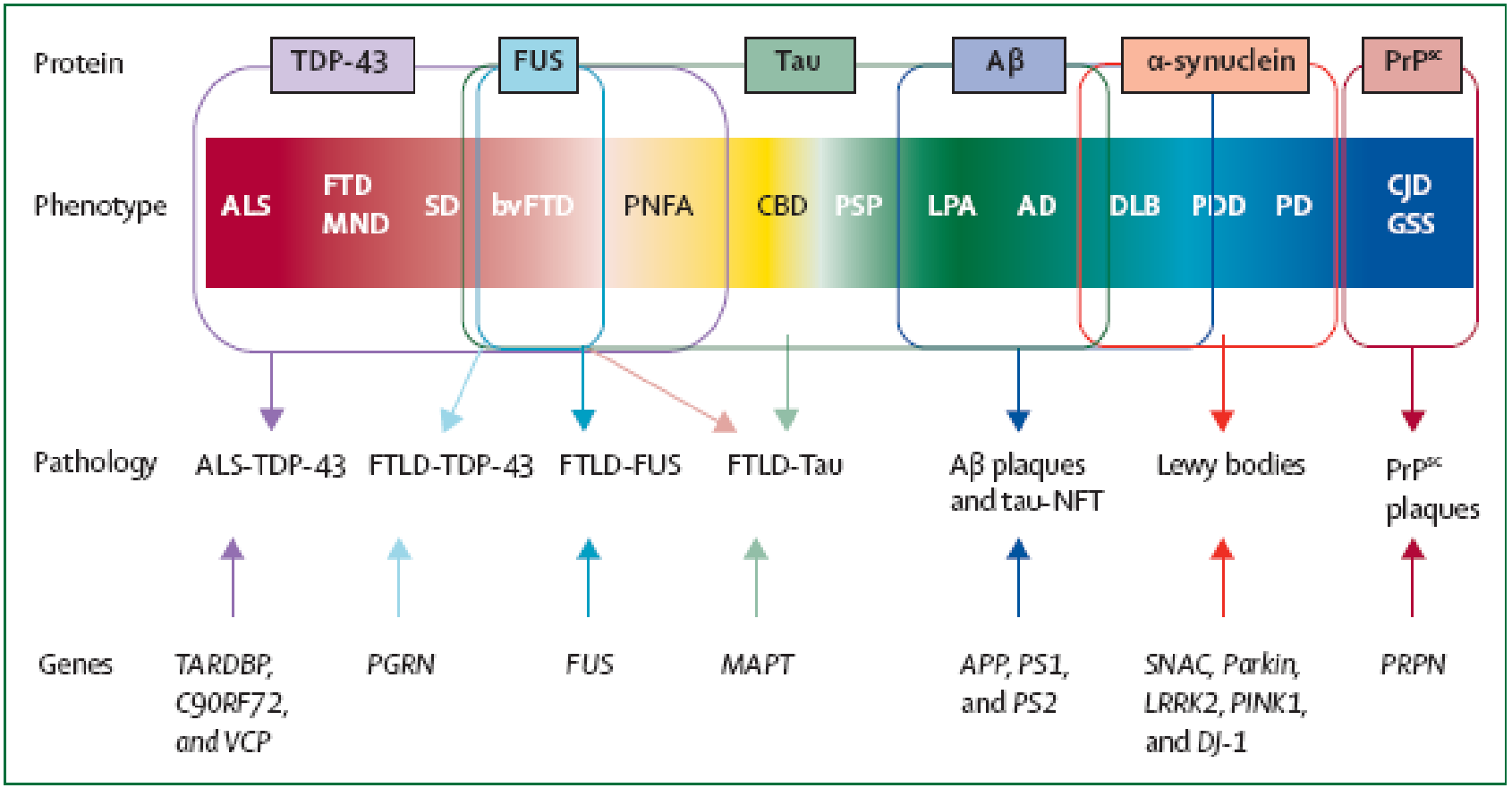
Alzheimers Res Ther. 2011; 3(6): 31.

Suspected non-Alzheimer pathophysiology (SNAP)

- Suspected non-Alzheimer disease pathophysiology (SNAP) is a biomarker-based concept that applies to individuals with **normal levels of amyloid-β biomarkers** in the brain, but in whom biomarkers of **neurodegeneration** are abnormal.
- SNAP is present in **~23%** of clinically normal individuals aged >65 years and in ~25% of mildly cognitively impaired individuals.

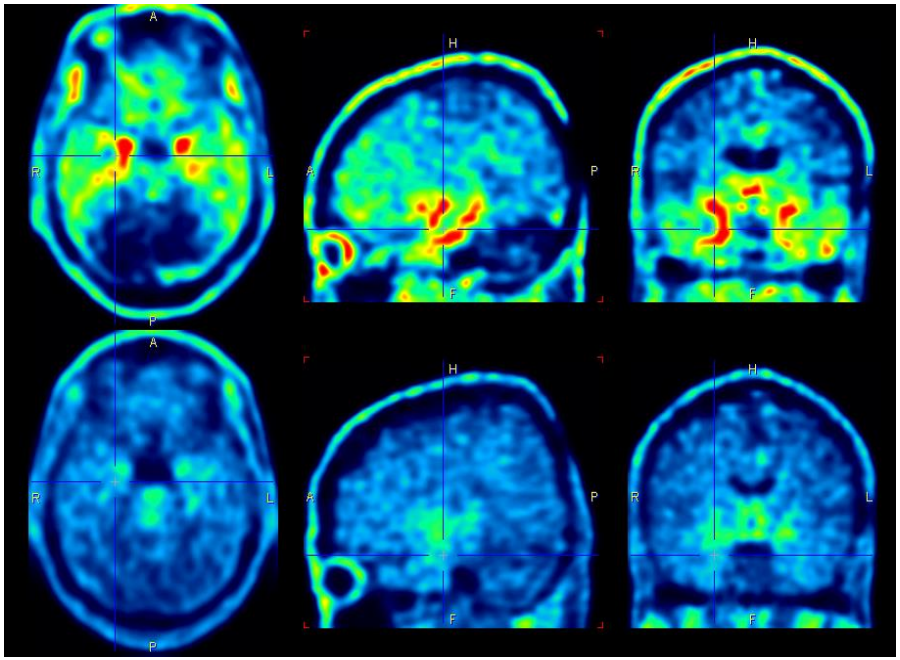
Nat Rev Neurol. 2016 Feb; 12(2): 117–124.

Clinical, genetic, and pathological spectrum of misfolded proteins in neurodegenerative disease

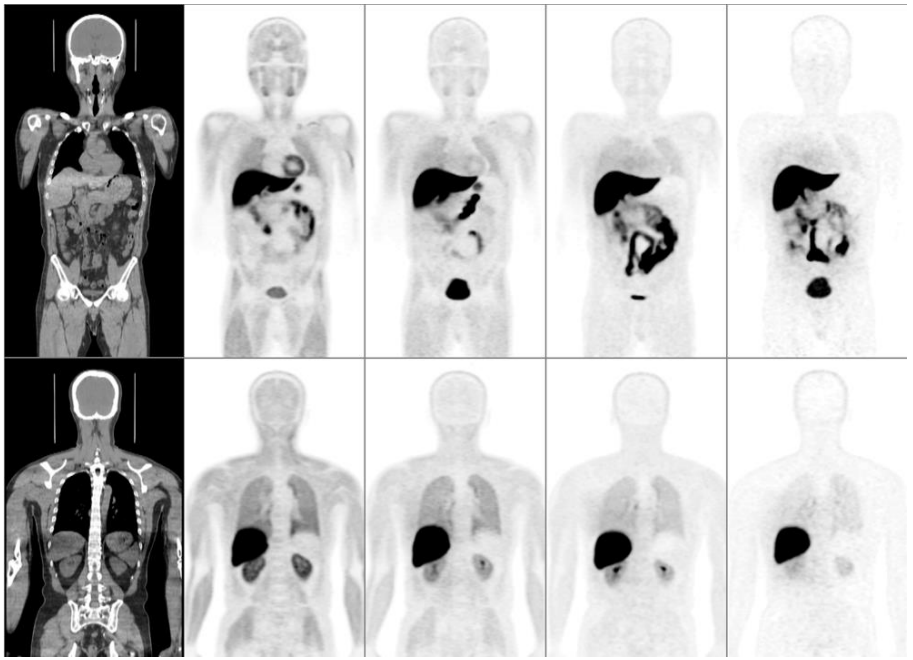


Lancet Neurol 2015; 14: 114–24

THK-5351 for Targeting Tau



This new tau PET tracer shows low uptake in controls, and intense tau pathology spreading across the frontal and temporal cortex in Alzheimer's disease



Coronal images (75 mm thick) of sequential whole body PET images (10, 60, 120, and 240 min after injection of ^{18}F-THK-5351) from one subject. Images are displayed on SUV scale.

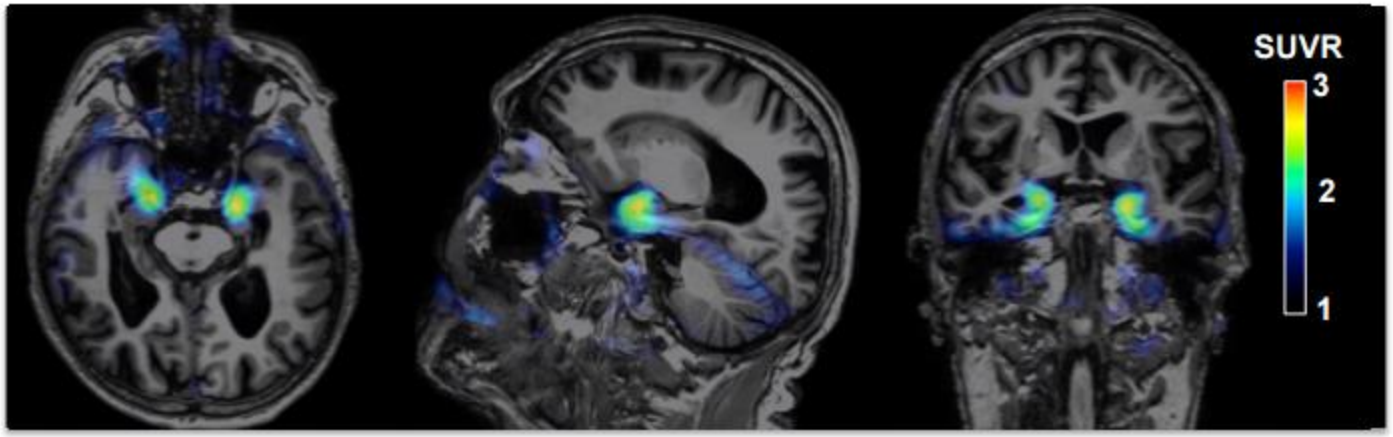
J Nucl Med. 2017 Mar 23

Suspected non-Alzheimer pathophysiology (SNAP)

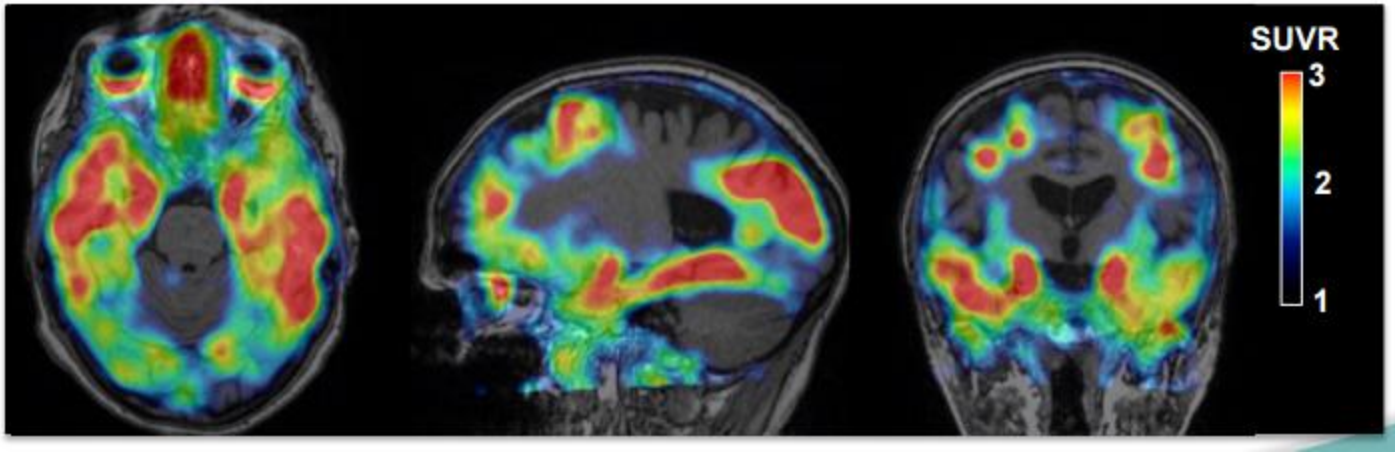
- Same low proportion (14% to 17%) of those with SNAP and those with no pathology at baseline went on to have amyloid accumulation in their brains. (Brian Gordon, PhD, *JAMA Neurology*.)
- People with SNAP didn't have greater levels of tau in Alzheimer's brain regions than those without any pathology (Elizabeth Mormino, *JAMA Neurology*.)
- This argues against SNAP being some sort of accelerated Alzheimer's pathology, and instead it's more likely that this is **some other form of neurodegeneration**.

[^{18}F]MK-6240: Alzheimer's Disease patients Imaging

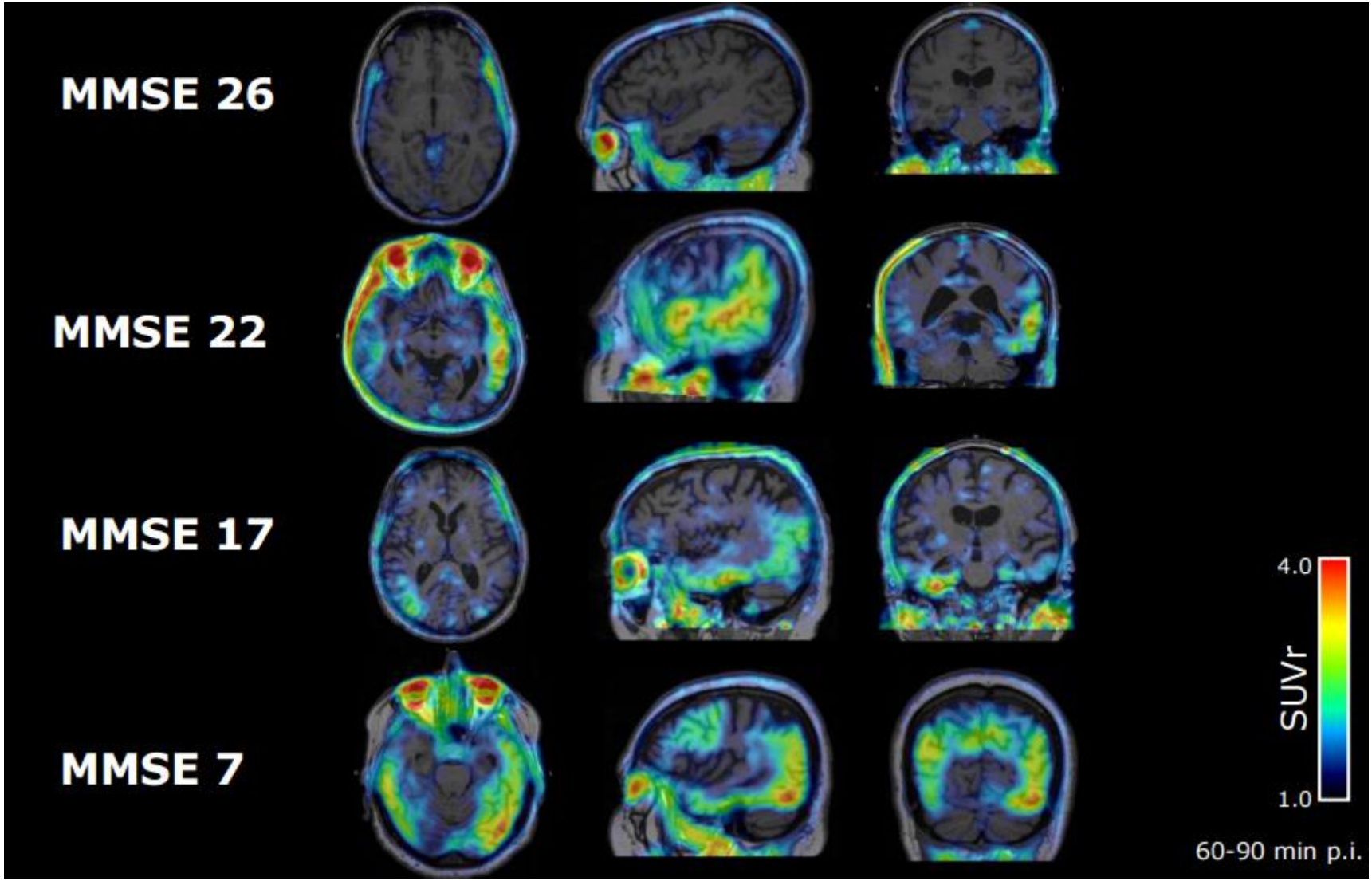
AD subject:
Age: 74 yo
MMSE: 28
Aβ status: NA



AD subject:
Age: 72 yo
MMSE: 18
Aβ status: +ve

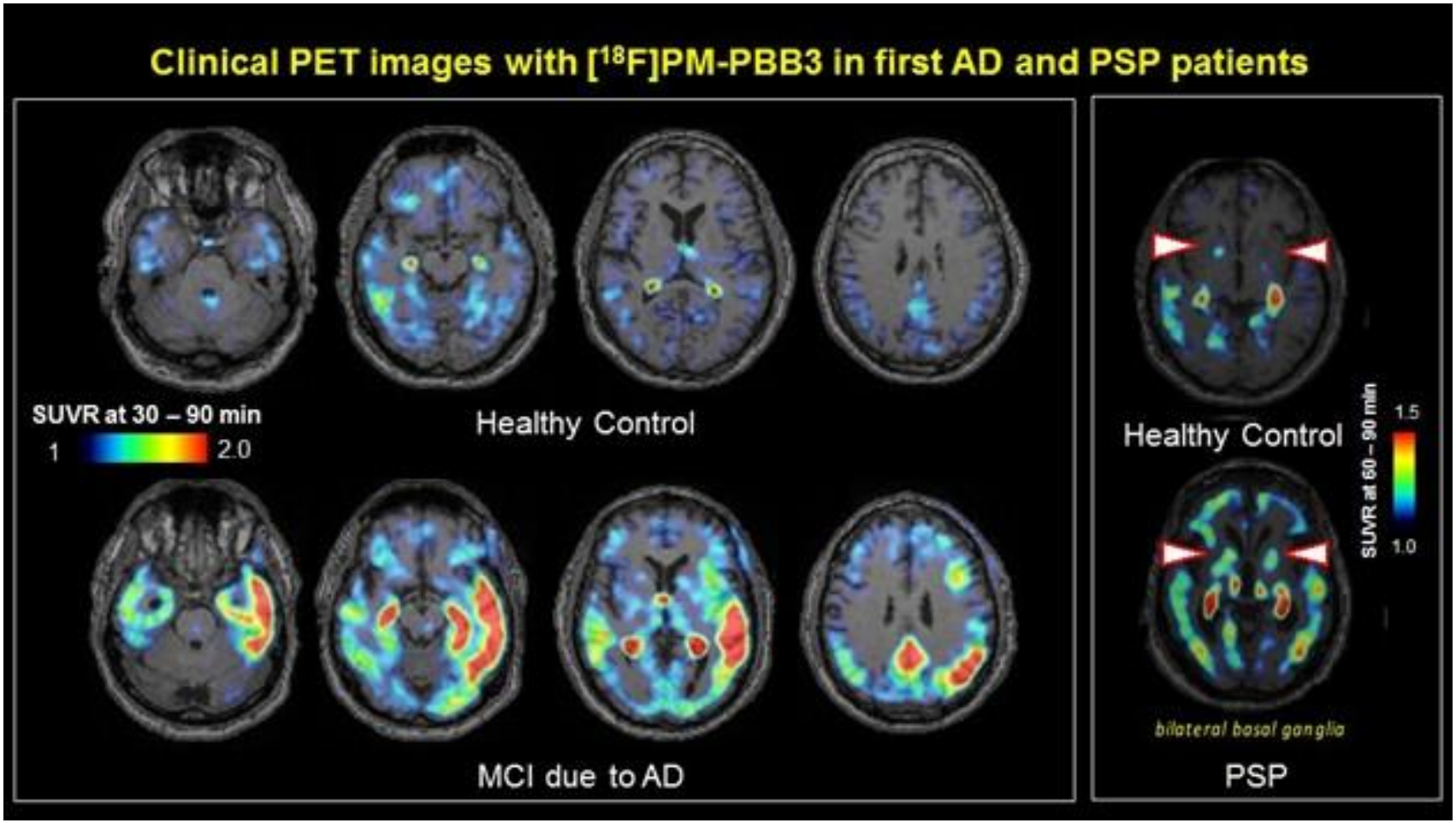


Cyrille Sur, Merck & Co., Inc. (Also known as MSD outside the US and Canada)



Andrew Stephens, MD, PhD
Piramal Imaging and AC Immune April 3, 2017

Next-Generation Tau PET Tracers



APRINOIA Therapeutics Inc.

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….and members from all groups