UAB SCHOOL OF MEDICINE

Update on Molecular Imaging in Dementia

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ACCSI

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
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DISCLOSURE INFORMATION

ACOI 2016 ANNUAL CONVENTION, DESERT SPRINGS

- I HAVE THE FOLLOWING FINANCIAL RELATIONSHIPS TO DISCLOSE:

  CONSULTANT FOR:
  ELI LILLY/AVID
  GE HEALTHCARE
  BLUE EARTH DIAGNOSTICS
  ALPHA SOURCE (SPOUSE)

  GRANT/RESEARCH SUPPORT FROM:
  ELI LILLY/AVID
  ABBVIE (SPOUSE)

- I WILL DISCUSS THE FOLLOWING OFF LABEL USE AND/OR INVESTIGATIONAL USE IN MY PRESENTATION:
  INVESTIGATIONAL TAU-PET TRACERS
  OFF-LABEL USE OF [^{123}I]IOFLUPANE

ACOI 75

75 YEARS OF DEDICATION TO OUR MEMBERS

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JMCCONATHY@UABMC.EDU

Outline of presentation

- Overview
- FDG-PET
- Amyloid-PET
- Future directions
- Cases

About a peculiar disease of the cerebral cortex…

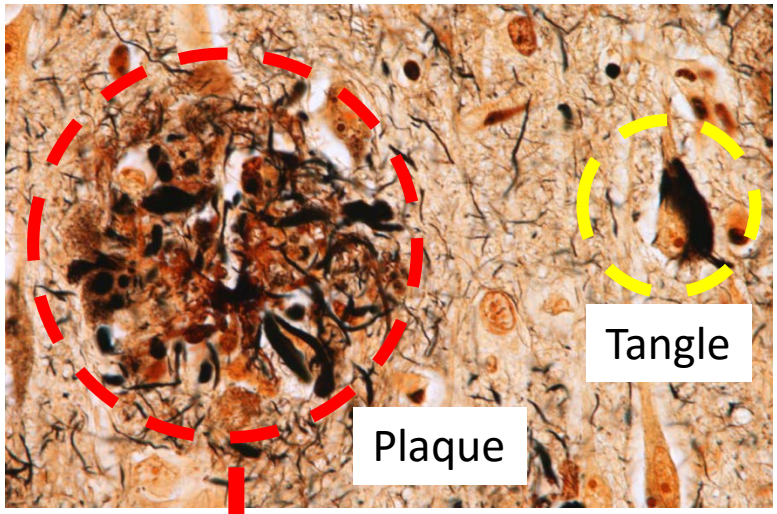
“There are without any doubt many more psychic illnesses than listed in our textbooks. In some of these instances a later histological examination will subsequently reveal peculiarities of the specific case. Then, we will gradually arrive at a stage, when we will be able to separate out individual disease from the large illness categories of our textbooks; to delineate them clinically more accurately.”

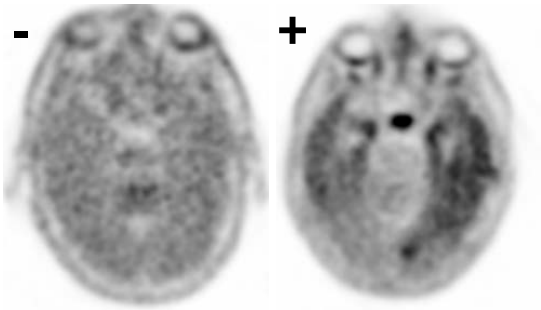
- from the first case report of Alzheimer‘s dementia in 1907 by Dr. Alois Alzheimer

Alois Alzheimer

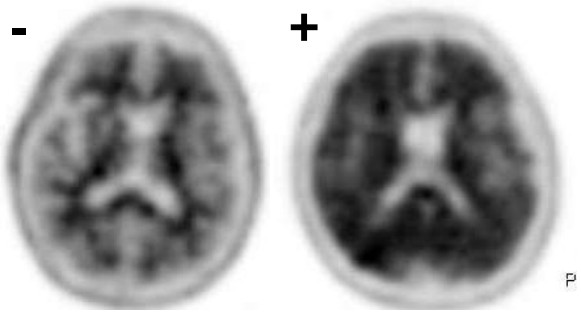
Strassnig M et al., 2005. About a peculiar disease of the cerebral cortex: Alzheimer's original case revisited, Psychiatry (Edgmont).

Neuritic plaques containing amyloid and neurofibrillary tangles containing tau are key features of Alzheimer's disease





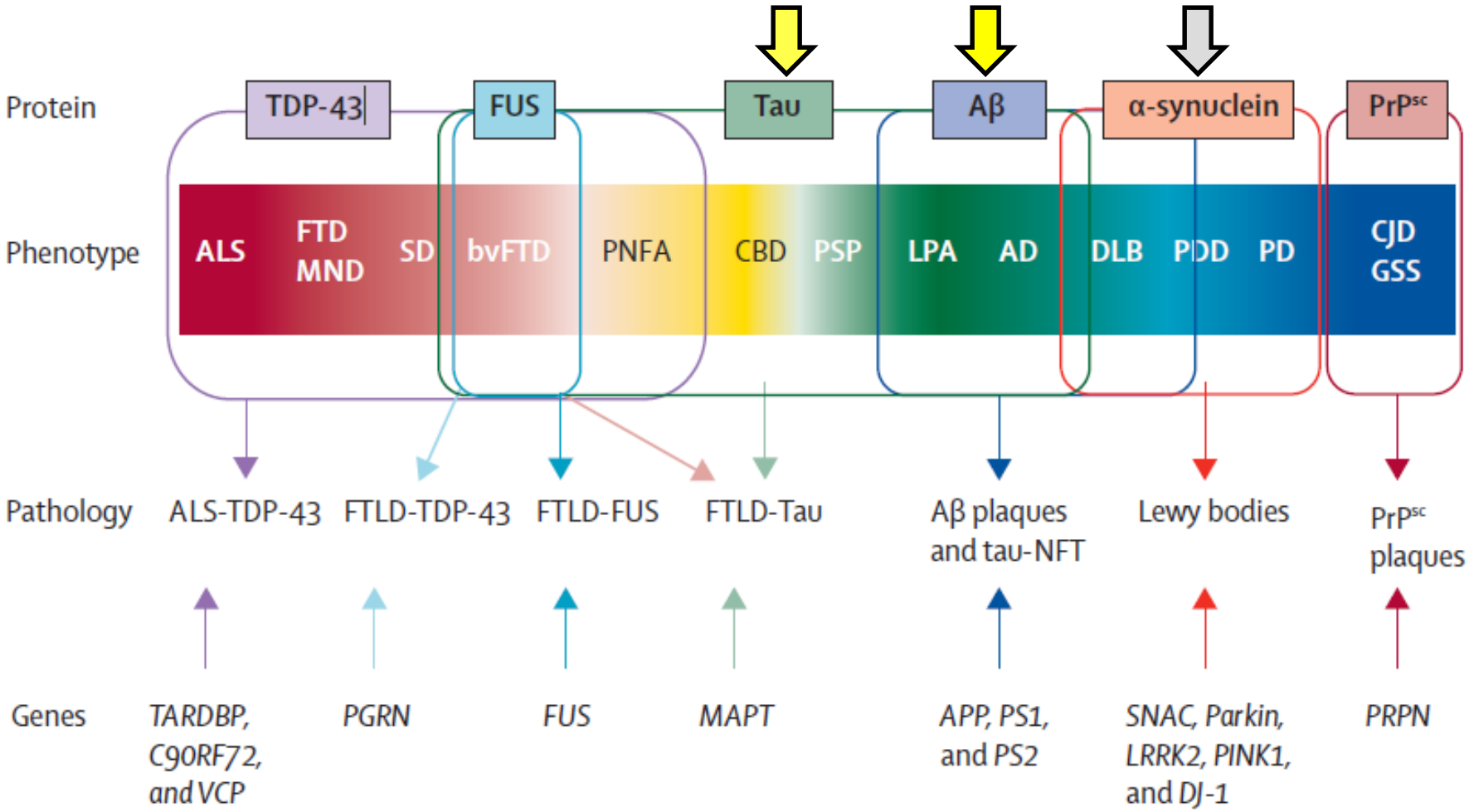
Tau-PET



Amyloid-PET

Braak, H. et al., 1995. Staging of Alzheimer's disease-related neurofibrillary changes, Neurobiol Aging. 16: 271-278; discussion 278-284.
Chien, D. T. et al., 2013. Early clinical PET imaging results with the novel PHF-tau radioligand [F-18]-T807, J Alzheimers Dis. 34: 457-468.

Proteinopathies in neurodegenerative diseases



VL Villemagne, et al., 2015. Tau imaging: early progress and future directions. 14: 114-24.

Core clinical criteria for dementia

- Based on cognitive or behavioral symptoms that:
  - Interfere with ability to function
  - Represent a decline from previous level of function
  - Not explained by delirium or psychiatric disorder
- Typically insidious onset
- Impairment is detected and diagnosed through history-taking from the patient and an informant and objective cognitive assessment

McKhann GM et al., 2011. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, Alzheimers Dement. 7:263-9.

Mild cognitive impairment (MCI)

- Same clinical criteria as dementia except there is no interference with usual activities
  - often comes to clinical attention through self-reporting
  - can be detected on neuropsychological testing

- Prognosis of MCI is variable and depends on the etiology
  - may be the beginning of dementia
  - may be stable for years
  - may resolve (e.g. depression, medication related)

Key clinical features of dementia due to AD

- Initial and most prominent cognitive deficits are typically in one of the two following categories:
  - amnestic presentation including learning and recall of recently learned information (most common)
  - non-amnestic presentations
    - language (esp. word finding)
    - visuospatial
    - executive dysfunction

McKhann GM et al., 2011. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, Alzheimers Dement. 7:263-9.

Accuracy of clinical diagnosis of AD dementia

- Clinical diagnosis of probable AD dementia is approximately 80% concordant with pathology
  - may be better at dementia centers (~90%)
  - may be challenging in first patient encounters
- Diagnostic accuracy for other causes of dementia may be substantially lower
  - Dementia with Lewy bodies (DLB)
  - Frontotemporal dementia (FTD)
- Neurodegeneration is advanced at the time of clinical diagnosis
  - may not be adequate for selecting patients for clinical trials
  - important implications for therapy

Diagnostic considerations in patients with cognitive impairment

- Relatively common types of dementia:

  1) Alzheimer's dementia (AD)
  2) Dementia with Lewy bodies (DLB)
  3) Frontotemporal dementia (FTD)
  4) Vascular dementia (VaD)
  5) Parkinson's disease (PD)

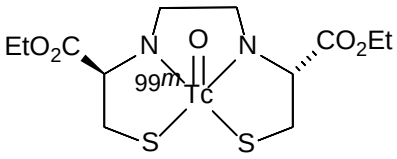
- Rare types of dementia
- Mild cognitive impairment (MCI)
- Non-degenerative etiologies

Goals of biomarkers in dementia

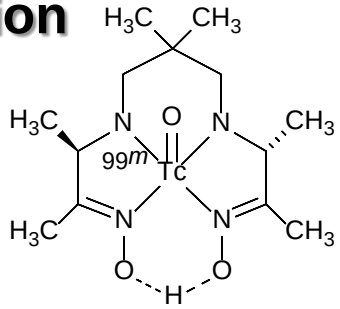
- Increase specificity and certainty in the diagnosis of dementing diseases
- Understand the time course of the pathophysiology of dementing diseases
- Select appropriate individuals at high risk for dementia for clinical trials and therapy
- Monitor response to therapies
- Identify prospectively individuals that would benefit from therapy prior to irreversible cognitive decline

Nuclear Toolbox for Dementia Imaging

Brain Perfusion

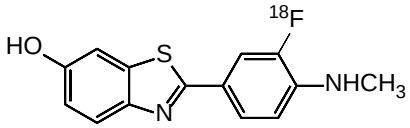


ECD

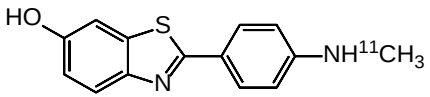


HMPAO

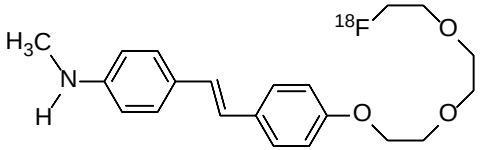
Beta-amyloid



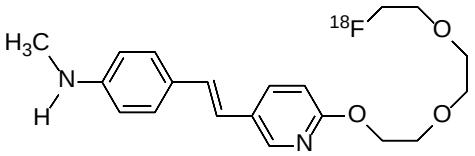
Flutemetamol



PiB

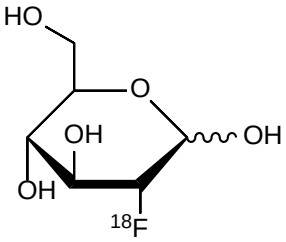


Florbetaben



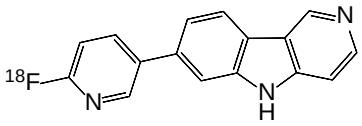
Florbetapir

Glucose Metabolism

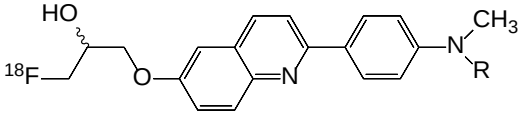


FDG

Tau

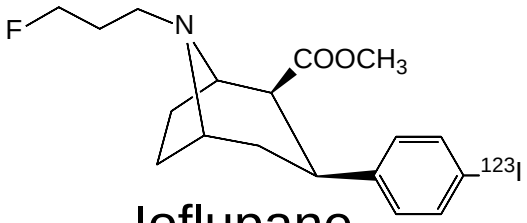


T807

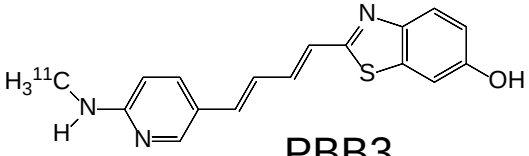


THK-5105 (R=CH_3) and 5117 (R=H)

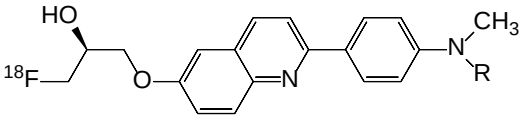
Dopamine transporters



Ioflupane

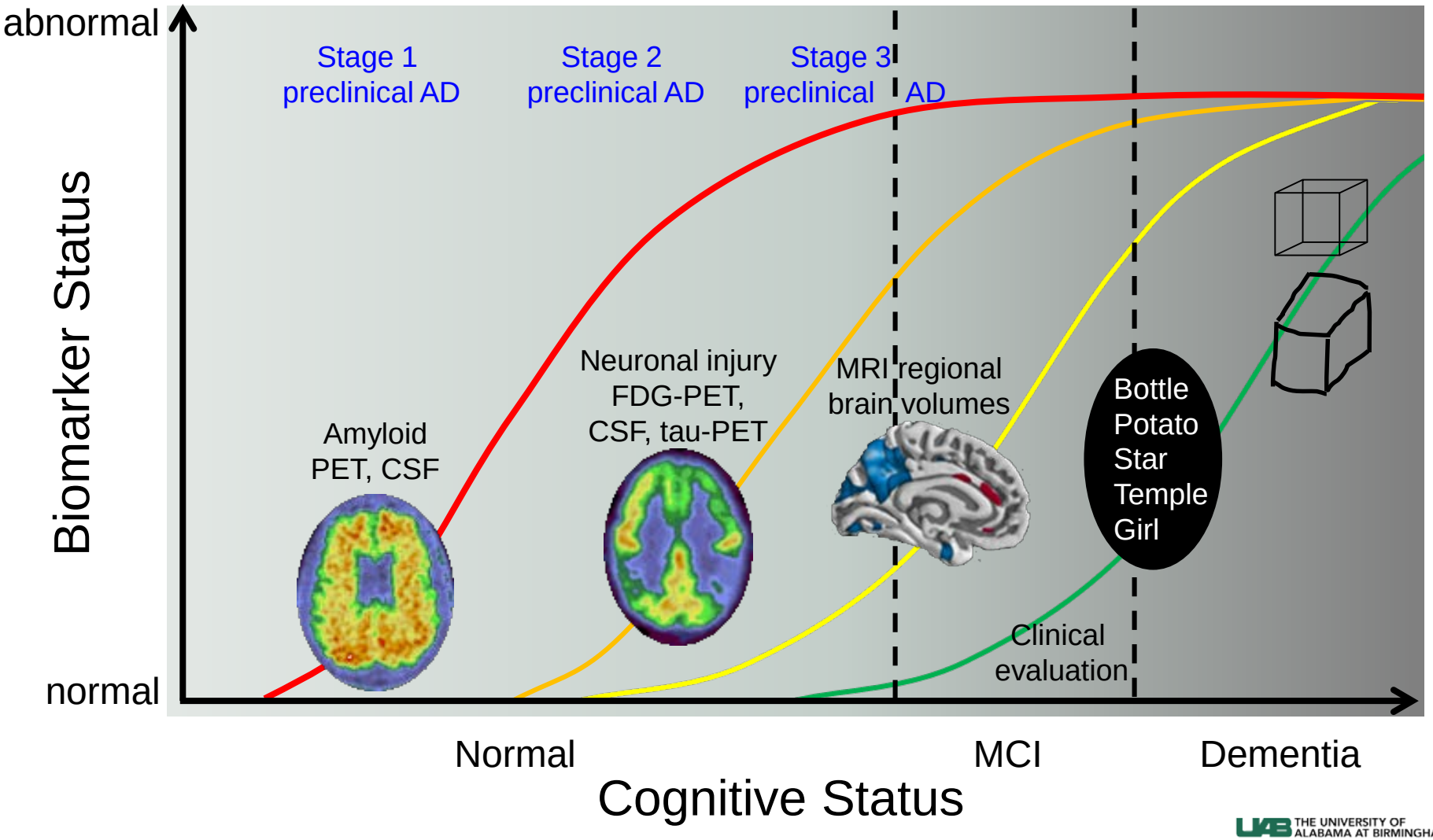


PBB3



THK-5351

Time course of biomarkers in Alzheimer's Disease



Adapted from Alzheimer's Disease Neuroimaging Initiative (ADNI) http://adni.loni.ucla.edu/about/biomarkers/brain MR/.

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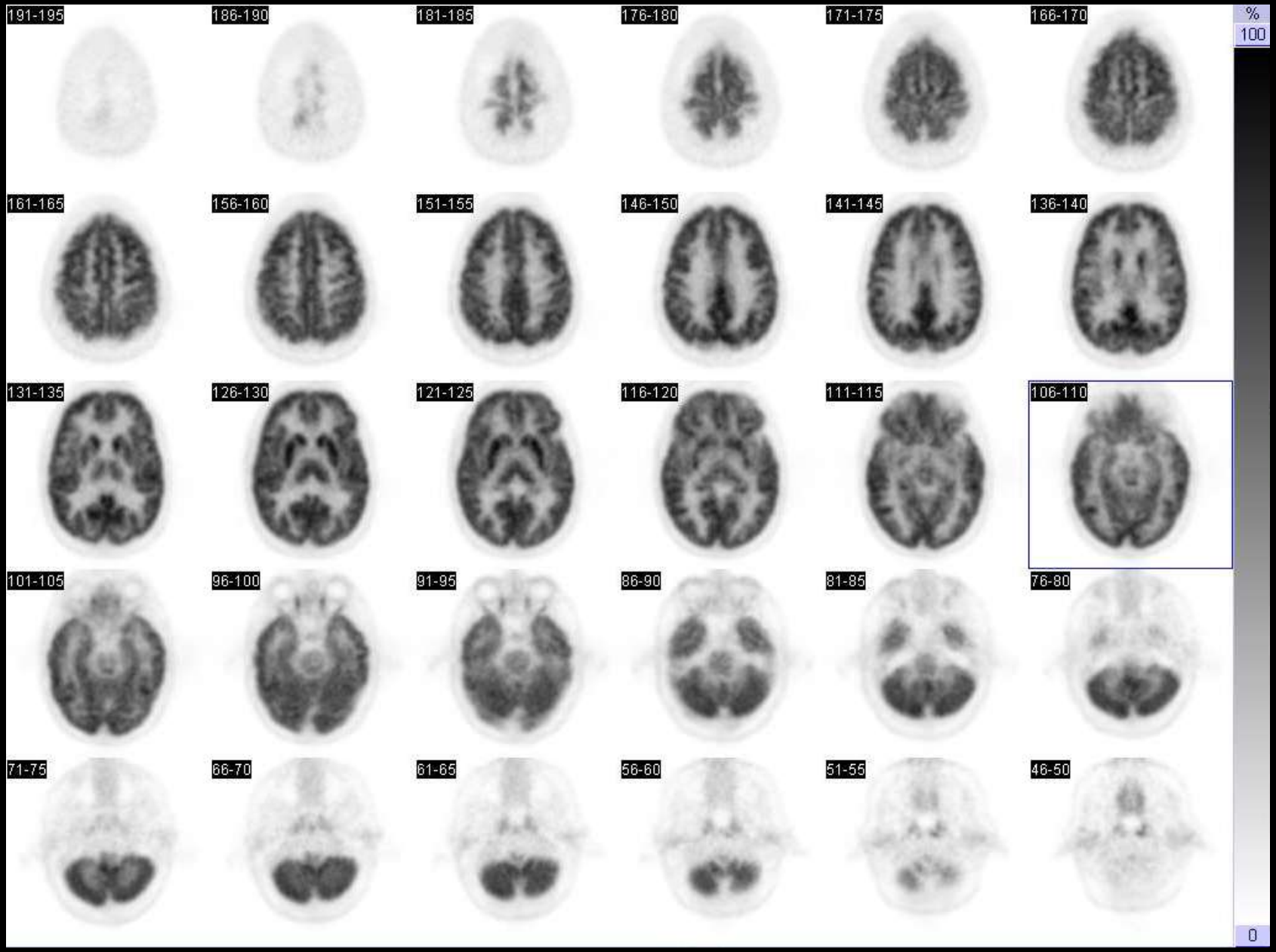
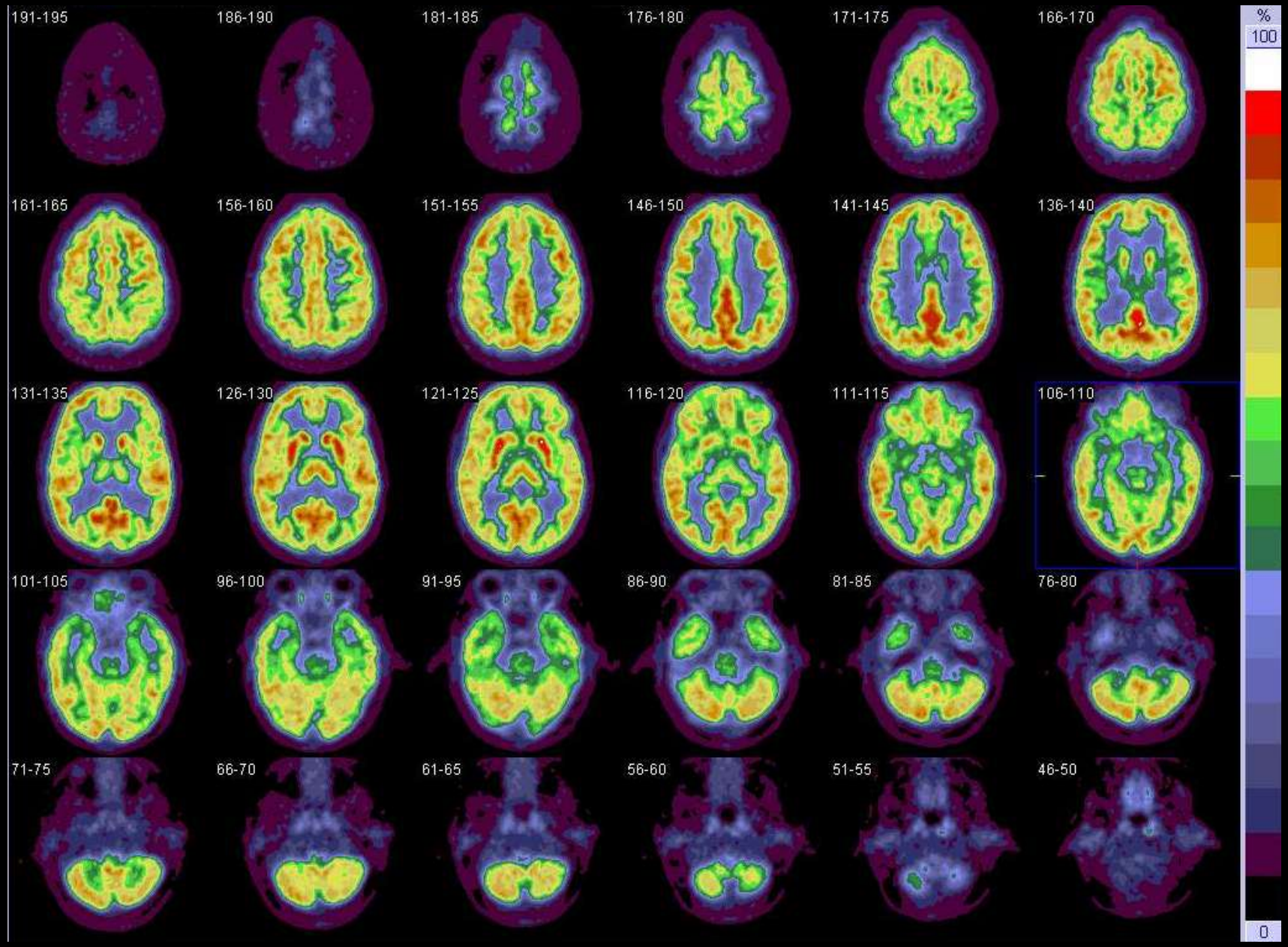
FDG for neuroimaging

- 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) is a glucose analogue that is widely used clinically
- Cellular uptake and retention of FDG is a marker of glycolysis
- The brain uses glucose as its primary source of energy and has high physiologic levels of FDG uptake
  - FDG uptake is a marker of synaptic activity and neuronal density
- For clinical neuroimaging, FDG is used primarily for dementia, neuro-oncology, and epilepsy



Normal brain [^{18}F]FDG-PET



Normal brain [^{18}F]FDG-PET

FDG-PET for dementia

- Changes in FDG uptake in the brain can be altered by many physiologic and pathologic factors
  - clinical context is critical
  - correlative structural imaging may be useful

- Decreases in FDG uptake in dementia occur due to loss of synaptic activity and neuronal loss
  - FDG is a marker of neuronal injury and dysfunction

- Pattern of FDG uptake provides specificity of diagnosis

[^{18}F]FDG-PET for Alzheimer's disease

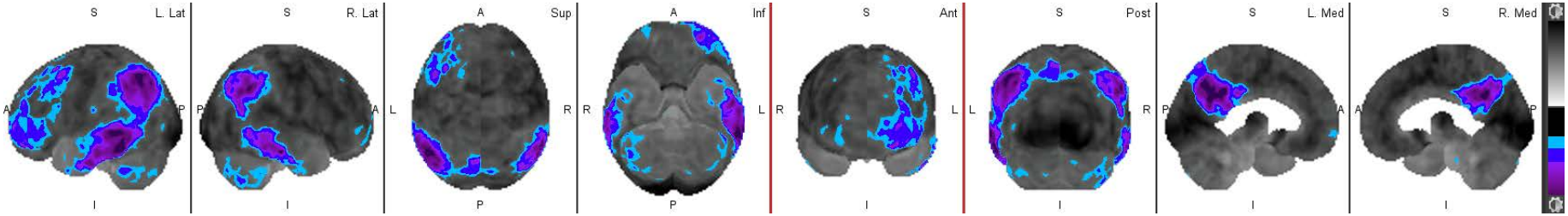
- Sensitivity for detection of AD is about 90% with specificity of 71-73% based on autopsy data
  - lower specificity is due to overlap with other dementias
  - for AD versus FTD, the specificity is higher (~85-95%)

- Typical uses of [^{18}F]FDG-PET in dementia
  - distinguish AD from FTD
  - evaluate early-onset (ages 45-64) or atypical dementia

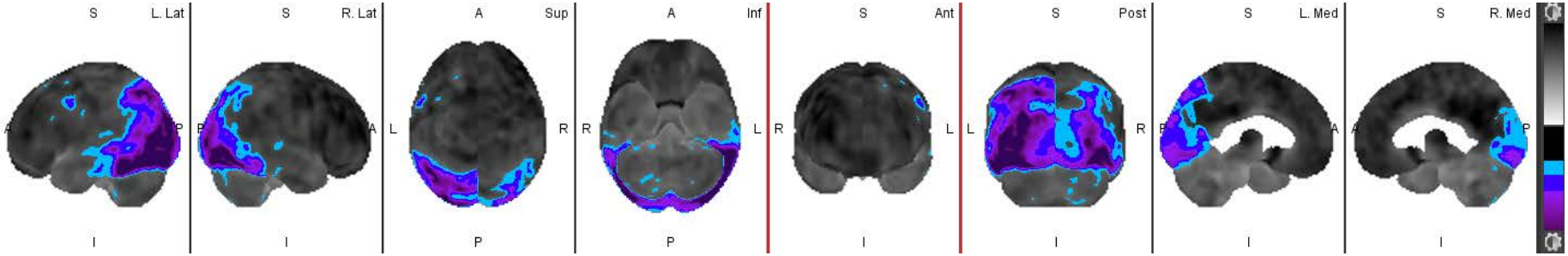
Mosconi, L, 2005. Brain glucose metabolism in the early and specific diagnosis of Alzheimer's disease. FDG-PET studies in MCI and AD. Eur J Nucl Med Mol Imaging, 32: 486-510.
Foster, NL, et al., 2007. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. Brain, 130: 2616-35.
Jagust, W, et al., 2007. What does fluorodeoxyglucose PET imaging add to a clinical diagnosis of dementia? Neurology, 69: 871-7.

Typical patterns of FDG hypometabolism in AD, DLB, and FTD

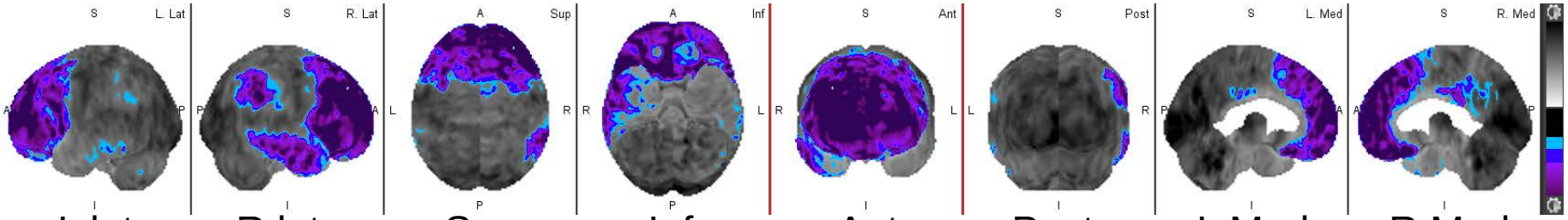
AD pattern: posterior parietotemporal



DLB pattern: AD pattern plus occipital



FTD pattern: anterior frontal and/or temporal



L lat R lat Sup Inf Ant Post L Med R Med

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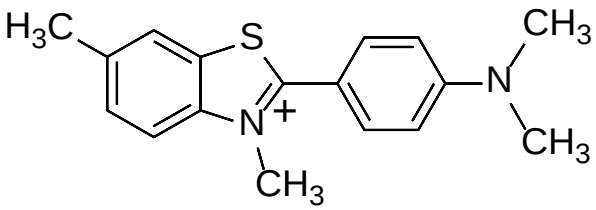
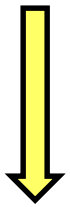
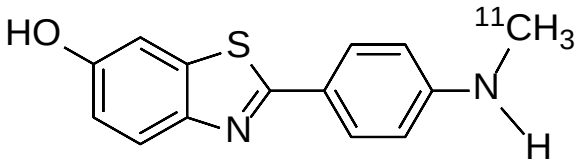
Amyloid plaque imaging agents: Pittsburgh Compound B (PiB)

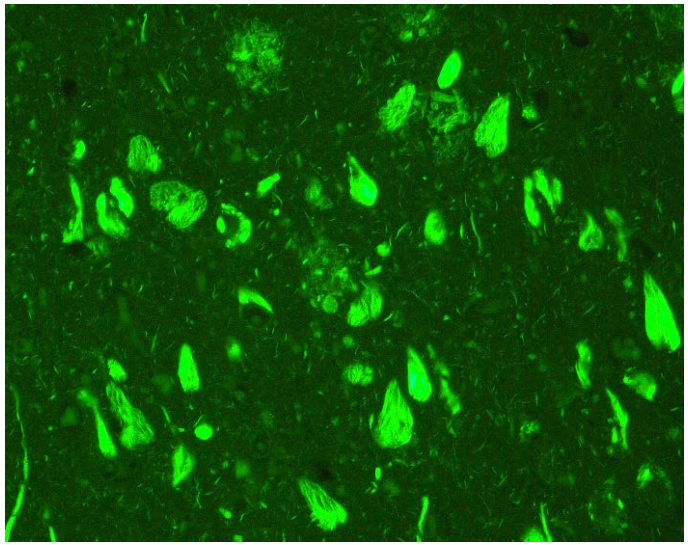


Thioflavin T





[^{11}C]PiB



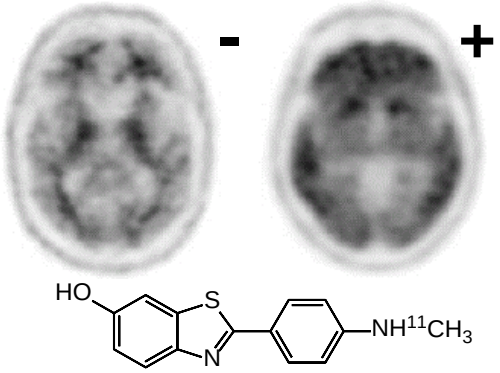
Thioflavin S staining of amyloid plaques and neurofibrillary tangles in a patient with AD

[^{11}C]PiB has been used extensively in research studies for amyloid plaque imaging

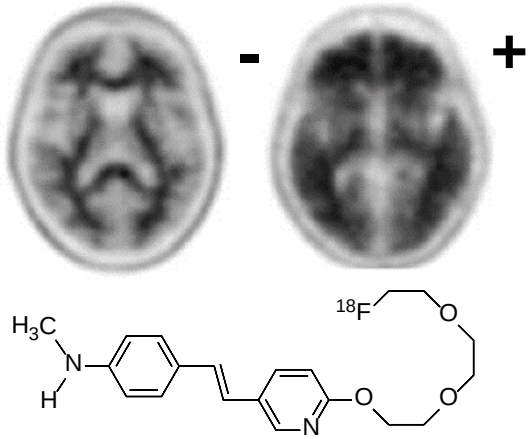
Image Courtesy of Dr. Nigel Cairns and the ADRC Neuropathology Core at Washington University in St. Louis

PET tracers for amyloid plaque imaging

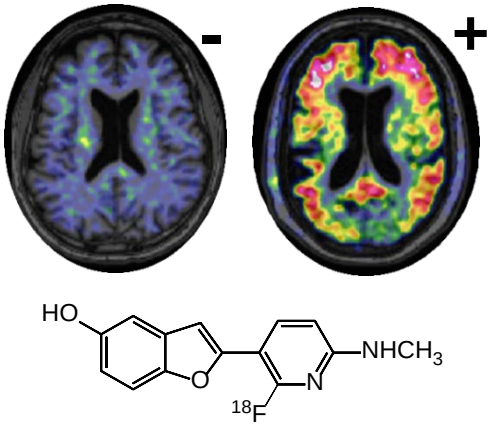
[^{11}C]PiB



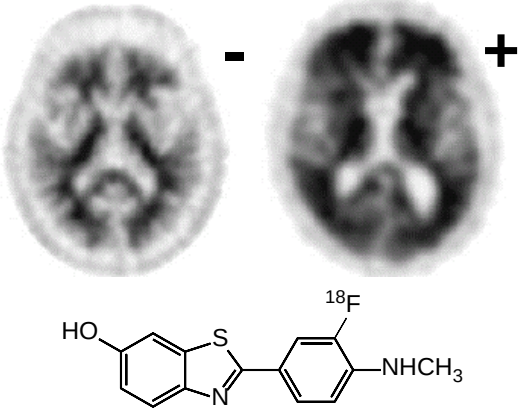
[^{18}F]florbetapir (Ely Lilly/Avid)



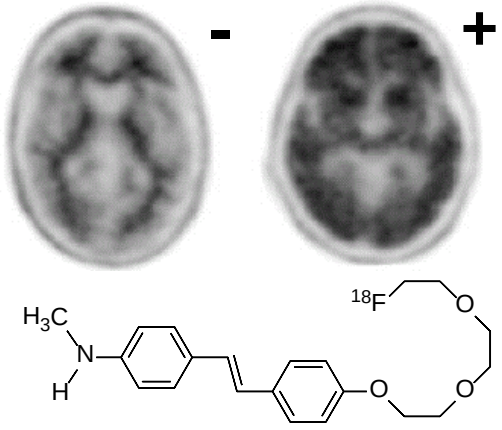
[^{18}F]AZD4694 (Navidea, formerly Astra-Zeneca)



[^{18}F]flutemetamol (GE)



[^{18}F]florbetaben (Piramal, formerly Bayer-Schering)



Rowe CC et al., 2011. Brain amyloid imaging, J Nucl Med. 52:1733-40.

Cselenyi Z et al., 2012. Clinical validation of ^{18}F-AZD4694, an amyloid-beta-specific PET radioligand, J Nucl Med. 53:415-24.

Diagnostic performance of ^{18}F-labeled amyloid PET tracers in clinical trials

Tracer	Sensitivity (%)	Specificity (%)
Florbetaben	**98** (96-98)	**80** (77-83)
Florbetapir	**92** (69-95)	**95** (90-100)
Flutemetamol	**88** (81-93)	**88** (44-92)

Sensitivity and specificity shown as median from multiple readers in bold and range of readers in parentheses.
Data from interpretations after in-person training.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202008s000lbl.pdf (florbetapir)
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203137s000lbl.pdf (flutemetamol)
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204677s000lbl.pdf (florbetaben)

Implications of amyloid-PET results

- Amyloid-PET serves as a biomarker for pathological amyloid deposition

- Amyloid pathology is thought to precede clinical findings of dementia by 10-25 years
  - AD pathophysiology ≠ AD dementia

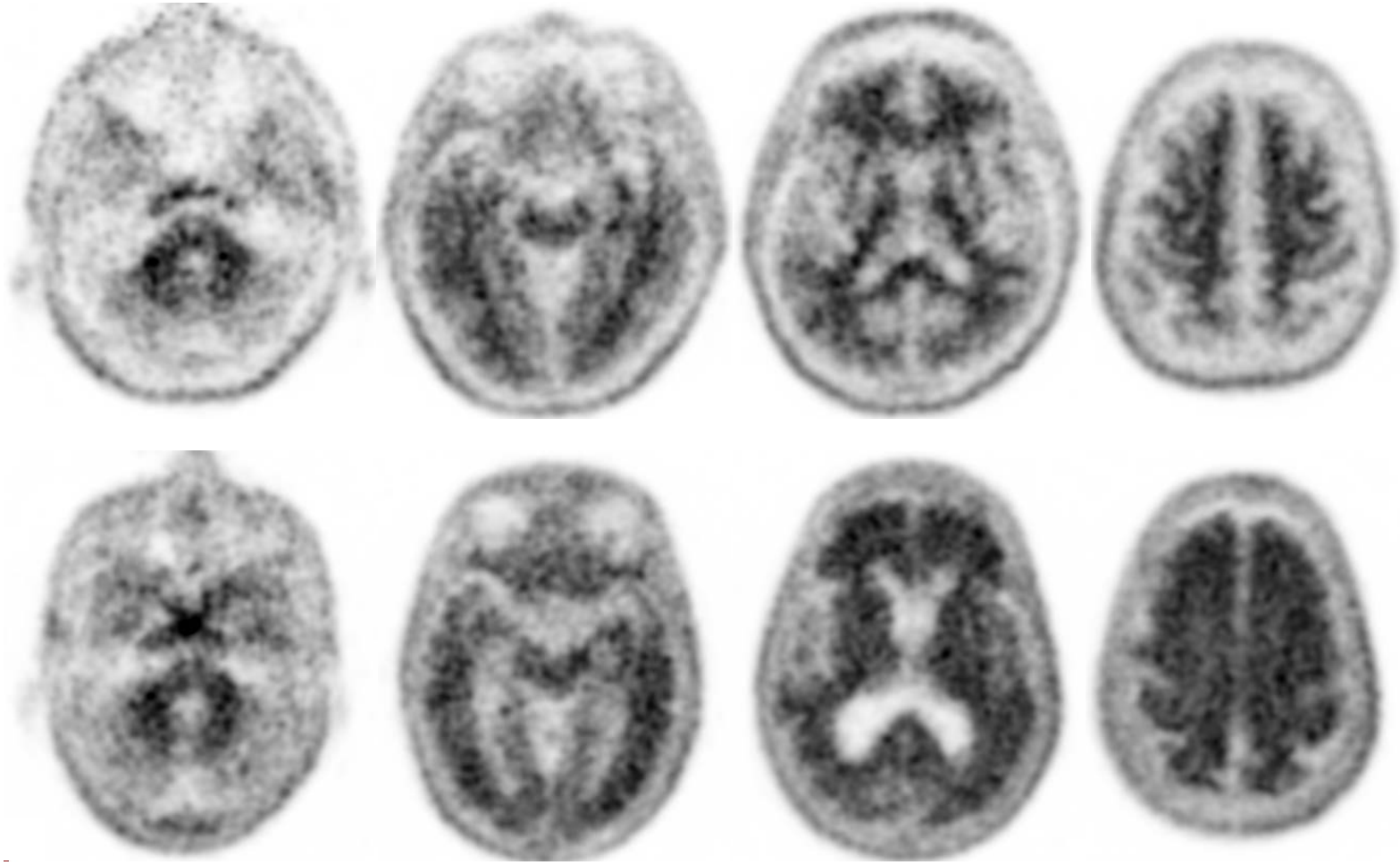
- A negative amyloid-PET scan makes Alzheimer's disease unlikely as the cause of a patient's cognitive impairment

- A positive amyloid PET does not establish the diagnosis of AD or other neurological disorders

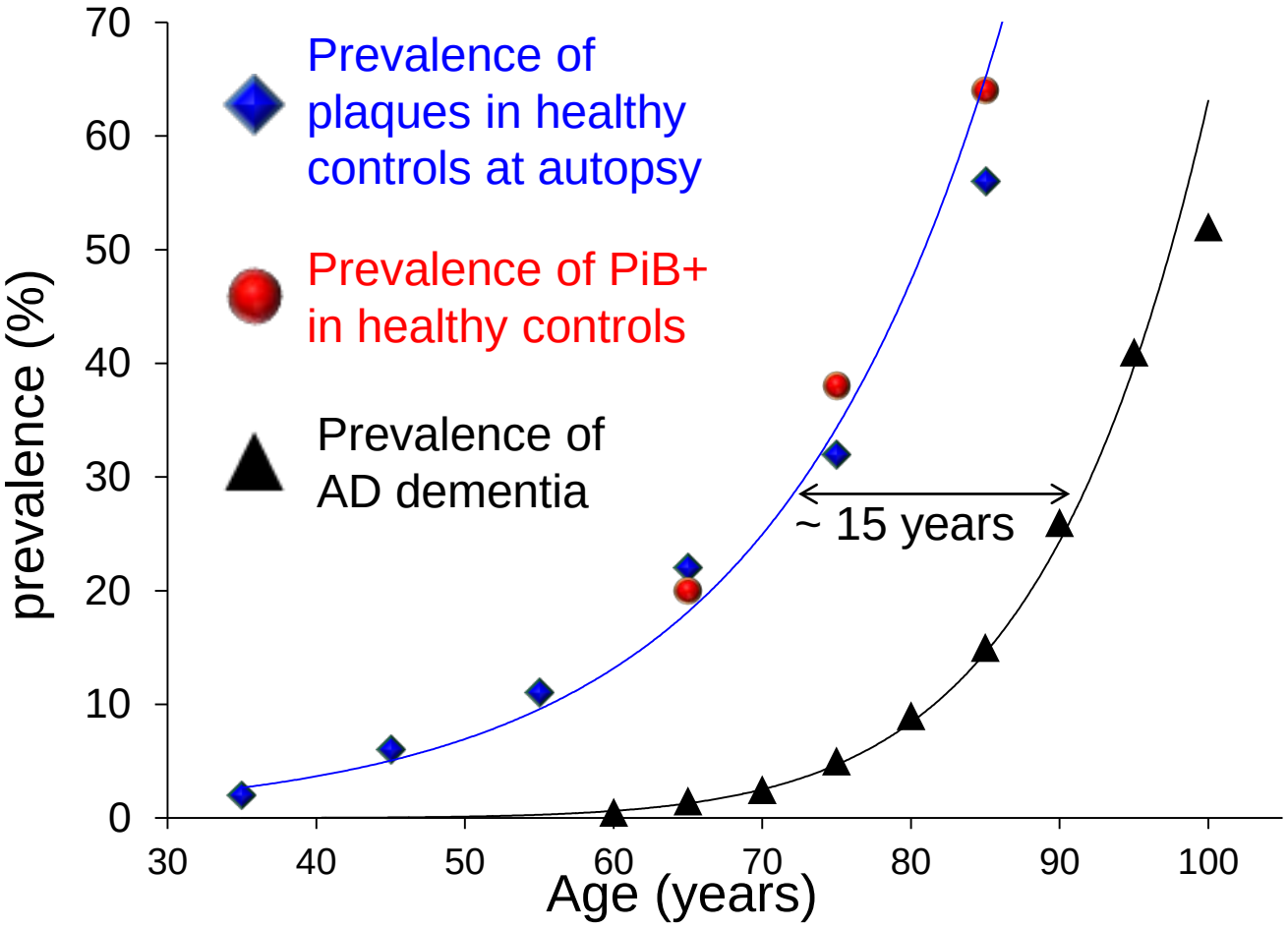
Comparison of negative (top) and positive (bottom) amyloid-PET scans

Negative

Positive



β-amyloid plaque deposition precedes AD dementia



Adapted from Rowe CC et al., 2010. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging, Neurobiol Aging. 31:1275-83.

Davies L et al., 1988. A4 amyloid protein deposition and the diagnosis of Alzheimer's disease: prevalence in aged brains determined by immunocytochemistry compared with conventional neuropathologic techniques, Neurology. 38:1688-93.

Braak H et al., 1996. Age, neurofibrillary changes, A beta-amyloid and the onset of Alzheimer's disease, Neurosci Lett. 210:87-90.

Sugihara S et al., 1995. Cerebral beta amyloid deposition in patients with malignant neoplasms: its prevalence with aging and effects of radiation therapy on vascular amyloid, Acta Neuropathol. 90:135-41.

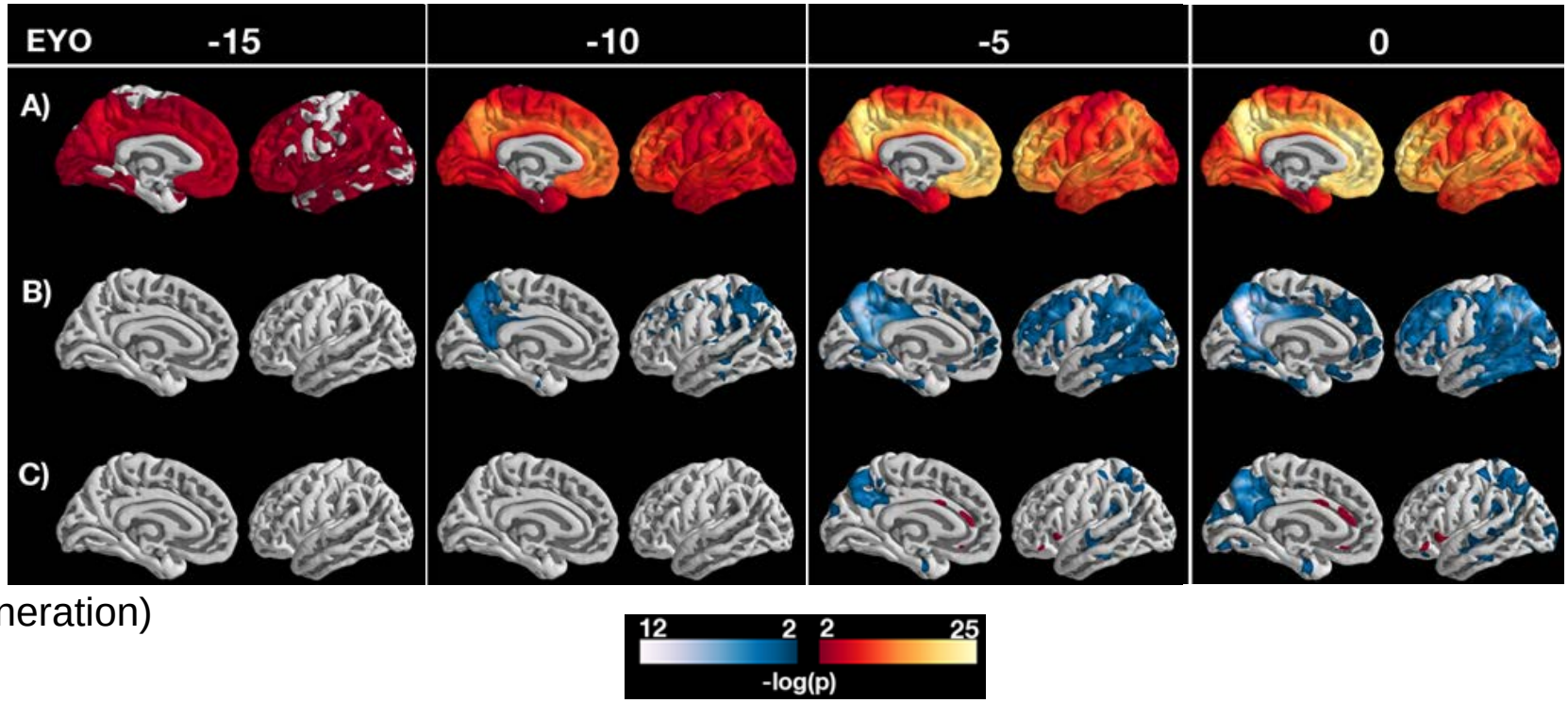
Tobias M et al., 2008. Burden of Alzheimer's disease: population-based estimates and projections for New Zealand, 2006-2031, Aust N Z J Psychiatry. 42:828-36.

Imaging of disease time course in autosomal dominant AD

PIB (amyloid)

FDG (metabolism)

Thickness (neurodegeneration)



EYO Estimated years to onset of symptoms

EYO = parents age of onset – current participant age

Bateman RJ et al., 2012. Clinical and biomarker changes in dominantly inherited Alzheimer's disease, N Engl J Med. 367:795-804.

Appropriate use criteria (AUC) for amyloid-PET

- Patients considered for amyloid PET should have the following characteristics:
  - Cognitive complaint with objectively confirmed impairment
  - AD as a possible diagnosis with uncertainty remaining after comprehensive evaluation by a dementia expert
  - Knowledge of amyloid status will increase diagnostic certainty and alter management

Johnson, K. A. et al., 2013. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association, Alzheimer's & Dementia : the Journal of the Alzheimer's Association. 9: e-1-16; Journal of Nuclear Medicine 54: 476-490.

Coverage with Evidence Development (CED)

- Amyloid Imaging Coverage with Evidence Development workgroup submitted a protocol to CMS for PET amyloid imaging in patients satisfying the AUC

- "IDEAS" Study: Imaging Dementia - Evidence for Amyloid Scanning

  - Began enrolling in February 2016
  - makes amyloid-PET reimbursable clinically when performed as part of CED
  - http://www.ideas-study.org/

IDEAS Study

- Open-label, longitudinal cohort study to assess the impact of amyloid PET on patient outcomes in patients meeting AUC

- The primary hypothesis is that, in diagnostically uncertain cases, knowledge of amyloid status as determined by amyloid PET will change patient management and improve medical outcomes

- Patients will be recruited into one of two sub-cohorts:
  - Progressive, unexplained mild cognitive impairment (MCI)
  - Dementia of uncertain etiology

IDEAS Aim 1

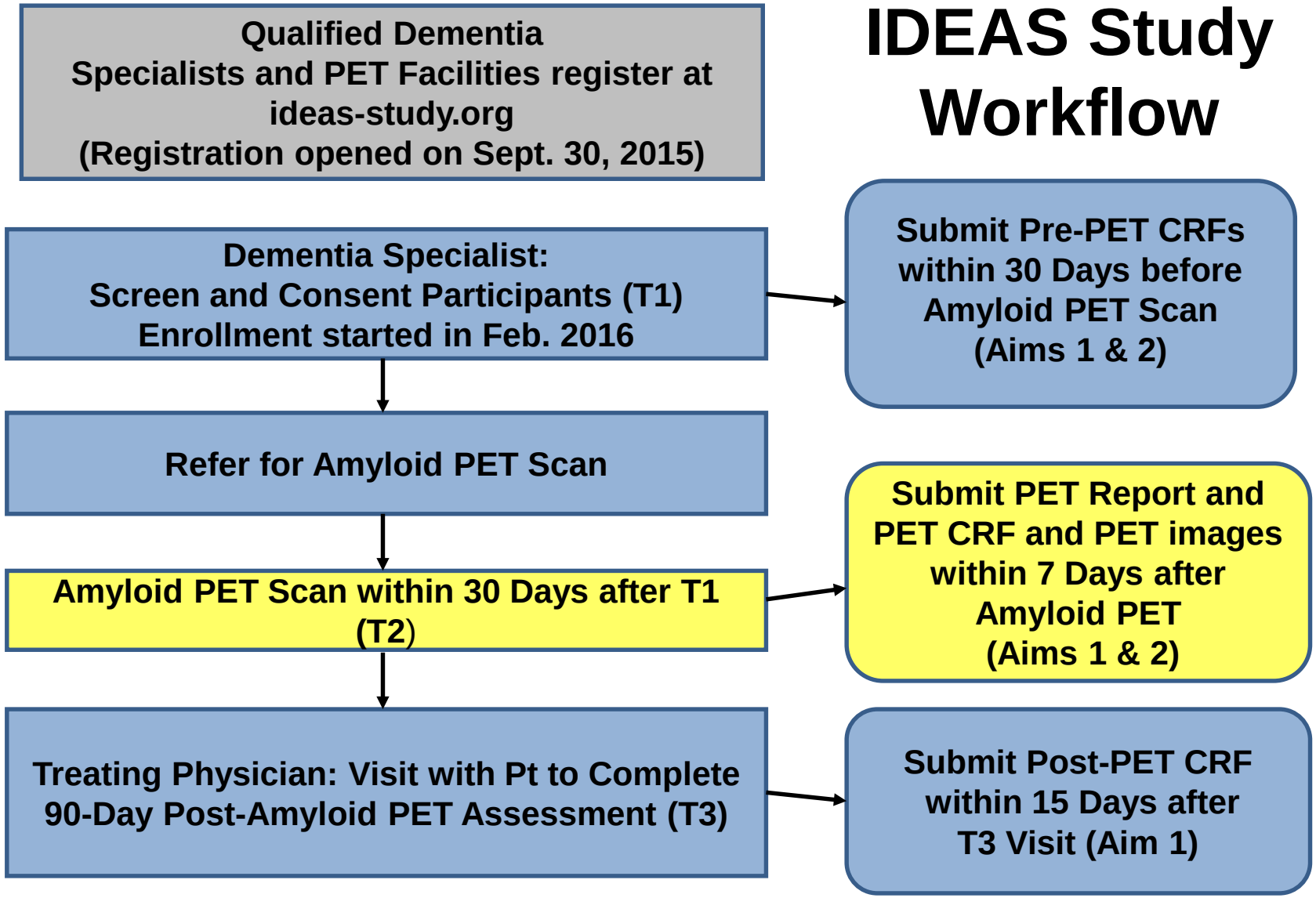
- Test whether amyloid PET imaging will lead to a ≥ 30% change between intended and actual patient management within ~90 days in a composite measure of at least one of the following:
  - AD drug therapy
  - Other drug therapy
  - Counseling about safety and future planning
- The hypothesis will be tested separately for MCI and dementia

IDEAS Aim 2

- To assess the impact of brain amyloid PET on hospital admissions and emergency room visits in study patients (*amyloid PET-known*) compared to matched patients not in the study (*amyloid PET-naïve*) over a 12 month interval

  - CMS Claims Data to address Aim 2 will be collected for all study participants and from concurrent controls matched according to a validated algorithm

IDEAS Study Workflow



Outline of presentation

- Overview
- FDG-PET
- Amyloid-PET
- Future directions
- Cases

Emerging tracers for neuroimaging in patients with cognitive impairment

- **Ioflupane** for dopaminergic imaging
  - relevant to dementia with Lewy bodies (DLB) and certain other less common neurodegenerative diseases

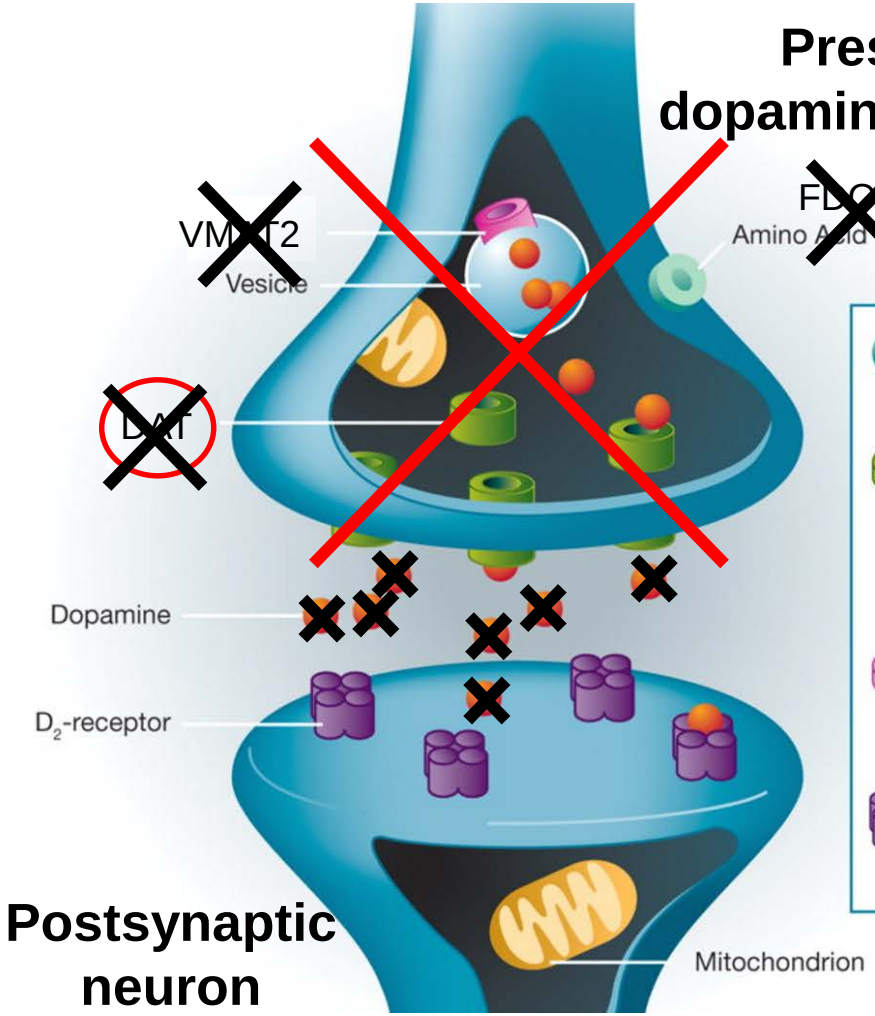
- **Tau imaging** with novel PET tracers
  - relevant to Alzheimer's disease, certain forms of FTD and other neurodegenerative diseases with tauopathies

[^{123}I]Ioflupane for dopamine transporter (DAT) imaging

- FDA approval is for distinguishing Parkinsonian syndromes (PS) from essential tremor
  - striatal DAT is lost in Parkinson's disease and PS but not essential tremor and drug induced parkinsonianism
  - high positive and negative agreement (>90%) with clinical diagnosis in patients with and without Parkinsonian syndromes

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/022454s000ltr.pdf (ioflupane)

Loss of dopaminergic neurons is a hallmark of Parkinson's disease and syndromes

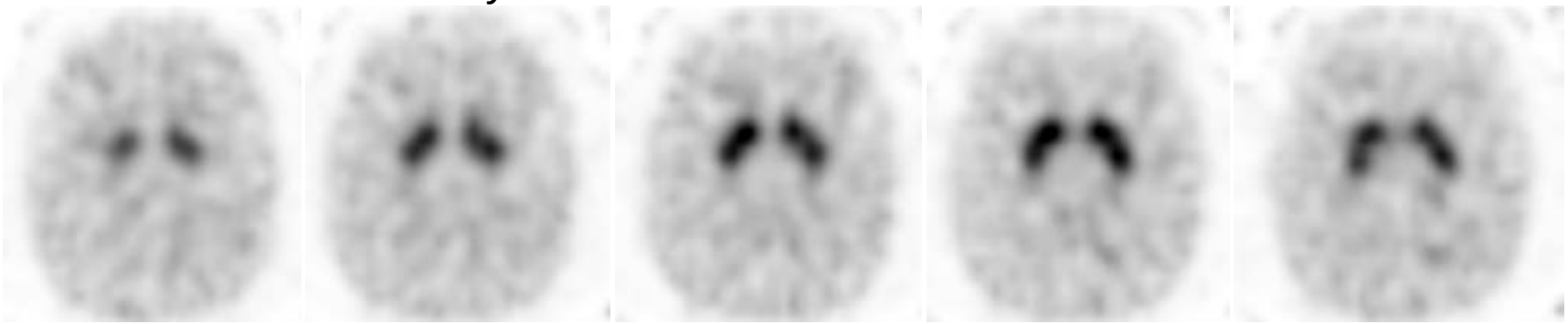


		SPECT	PET
	Presynaptic radioligands DOPA decarboxylase (Measures dopamine synthesis)		[^{18}F]dopa [^{11}C]dopa
	DAT (Provides measure of functioning dopaminergic terminals)	[^{123}I]FP-CIT [^{123}I]β-CIT [^{99m}Tc]TRODAT-1 [^{123}I]PE2I [^{123}I]-altropane	[^{11}C]cocaine [^{3}H]WIN [^{11}C]altropane [^{11}C]/[^{18}F]β-CFT [^{11}C]FE-CIT [^{11}C]dMP
	VMAT-2 (Marker for dopaminergic terminals)		[^{11}C]DTBZ
	Postsynaptic radioligands D_2 receptor	**SPECT** [^{123}I]IBZM	**PET** [^{11}C]raclopride [^{18}F]DMFP [^{11}C]NMSP

Haas et al, 2012. Premotor biomarkers for Parkinson's disease - a promising direction of research. Translational Neurodegeneration, 1: 1-11.

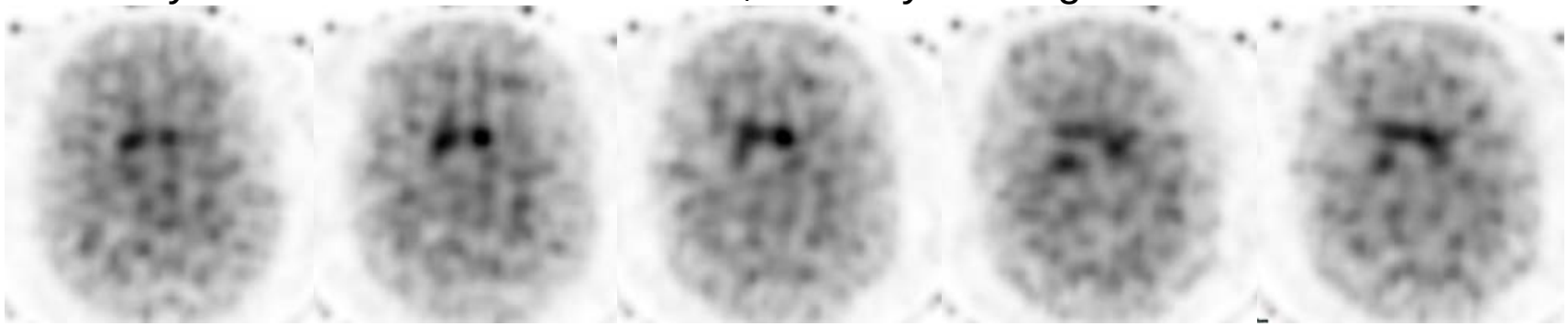
Brain Ioflupane-SPECT

55 year old woman with hand tremor



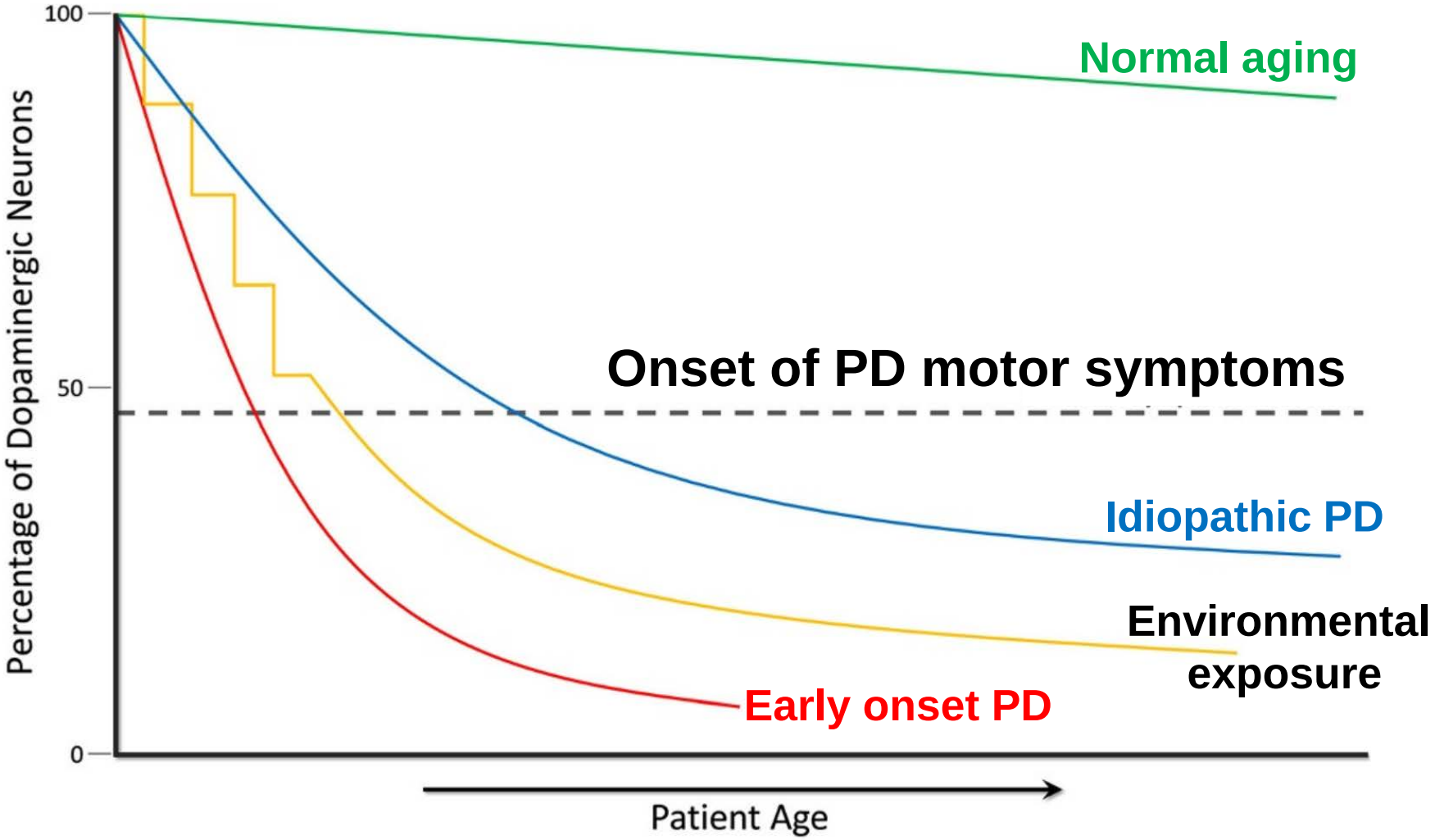
Normal Ioflupane study

62 year old woman with stiffness, difficulty walking and hallucinations



Abnormal Ioflupane study

Loss of dopaminergic neurons precedes symptomatic Parkinson's disease



Haas et al, 2012. Premotor biomarkers for Parkinson's disease - a promising direction of research. Translational Neurodegeneration, 1: 1-11.

Parkinsonian syndromes associated with DAT loss

- Parkinson's disease (PD)
- Dementia with Lewy bodies (DLB)
- Corticobasal degeneration (CBD)
- Multiple system atrophy (MSA)
- Progressive supranuclear palsy (PSP)

- Ioflupane-SPECT can distinguish DLB from AD and FTD but it not part of the FDA-approved use of ioflupane

  mean sensitivity for probable DLB = 78%
  mean specificity for probable DLB = 90%

  - clinical diagnosis used as reference standard

McKeith, I. et al., 2007. Sensitivity and specificity of dopamine transporter imaging with ^{123}I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study, Lancet Neurol. 6: 305-313.

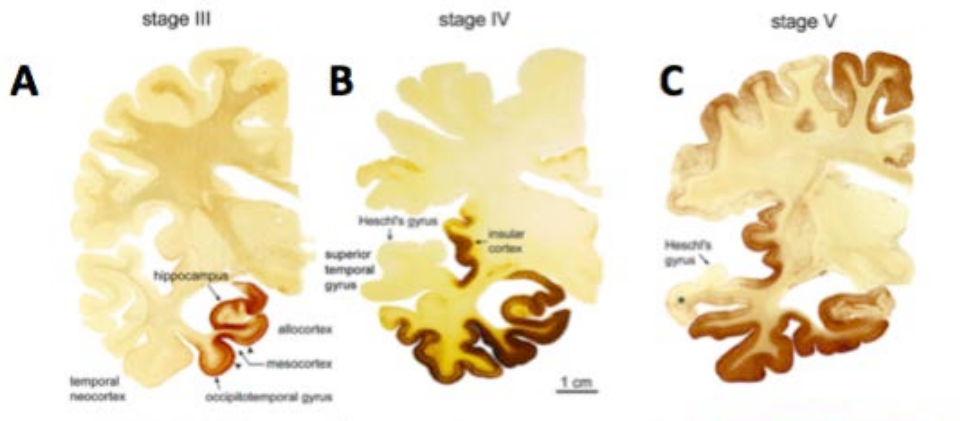
Tau imaging

- Several PET tracers are being used in human studies to measure brain tau
  - currently only used on a research basis

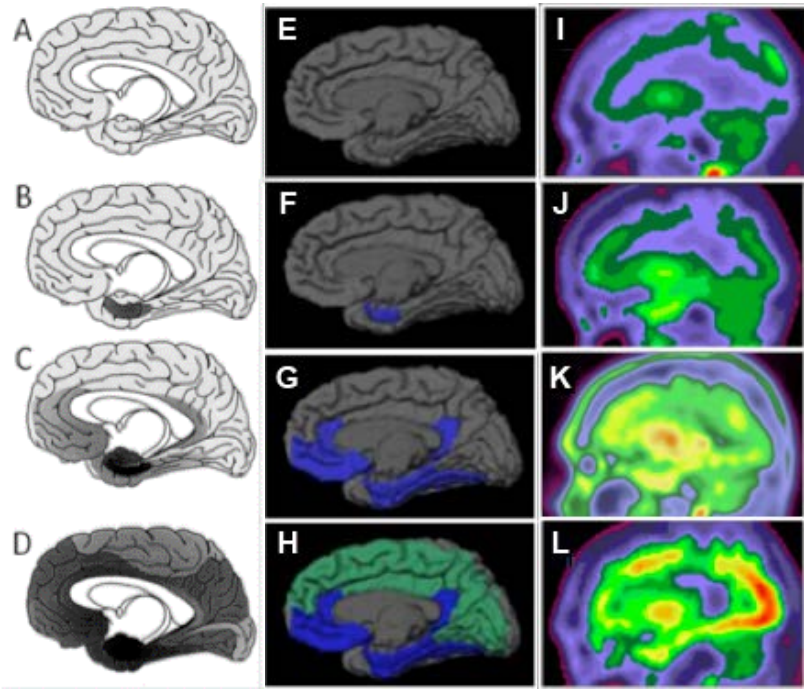
- Pathological tau deposition appears to occur in temporal association with cognitive impairment and neurodegeneration

- Tau is not specific to a particular neurodegenerative disease

Spread of tau pathology in AD



Stage 1-2: Transentorhinal
Stage 3-4: Limbic
Stage 5-6: Isocortical

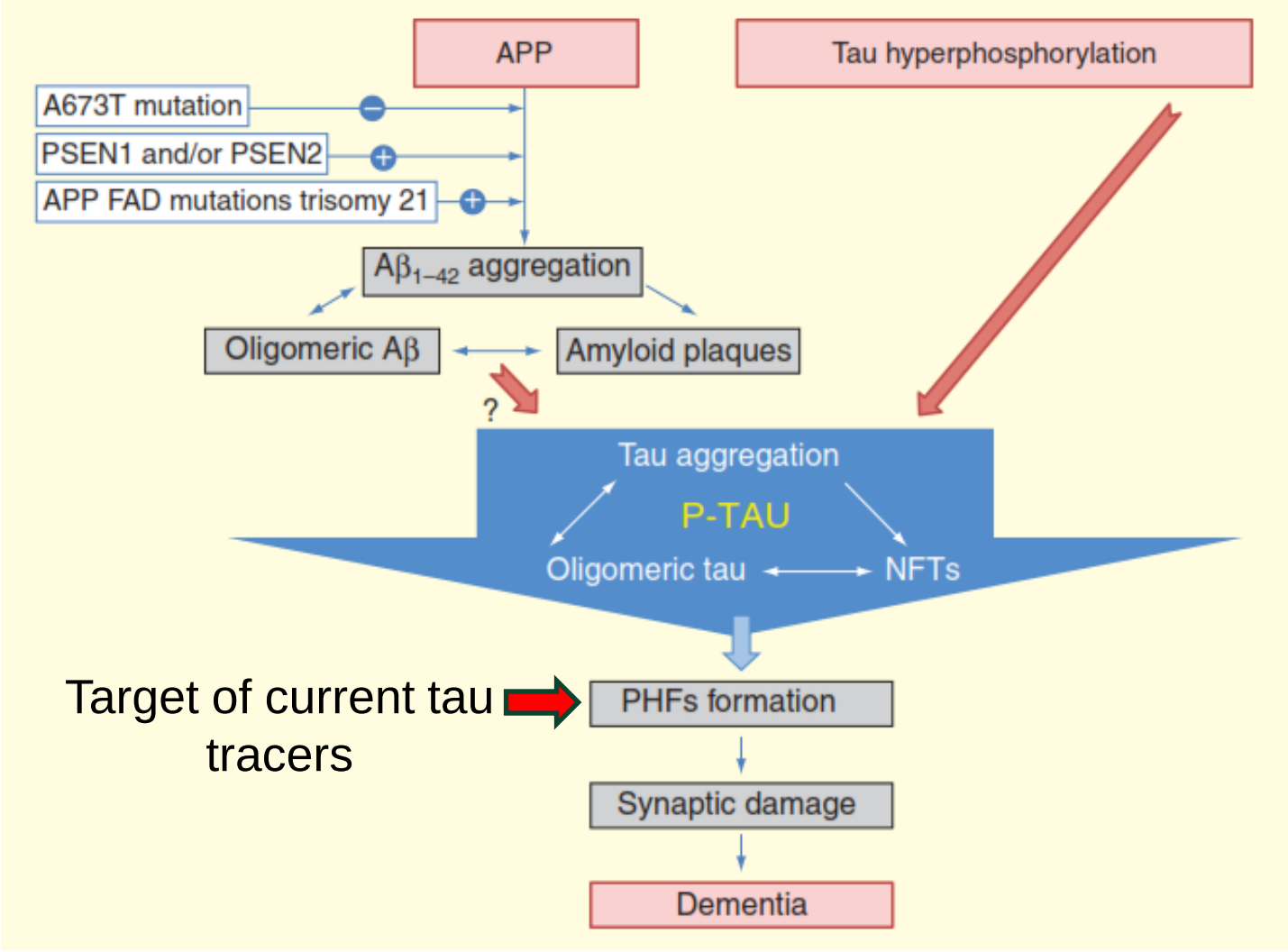


A-C adapted from Baak H, Del Tredici K. The Pattern of Lesions During the Transition to the Symptomatic Phase and in Fully Developed Alzheimer's Disease. Neuroanatomy and Pathology of Sporadic Alzheimer's Disease: Springer; 2015. p. 95-130.

A-D adapted from Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging. 1997;18(4):351-7. Epub 1997/07/01. PubMed PMID: 9330961.

Slide courtesy of Tammie Benzinger M.D., Ph.D.

Putative role of tau in the pathophysiology of AD



Hampel, H. et al., 2015. Advances in the therapy of Alzheimer's disease: targeting amyloid beta and tau and perspectives for the future, Expert Rev Neurother. 15: 83-105.

Therapeutics targeting tau in development

Tau aggregation and deposition

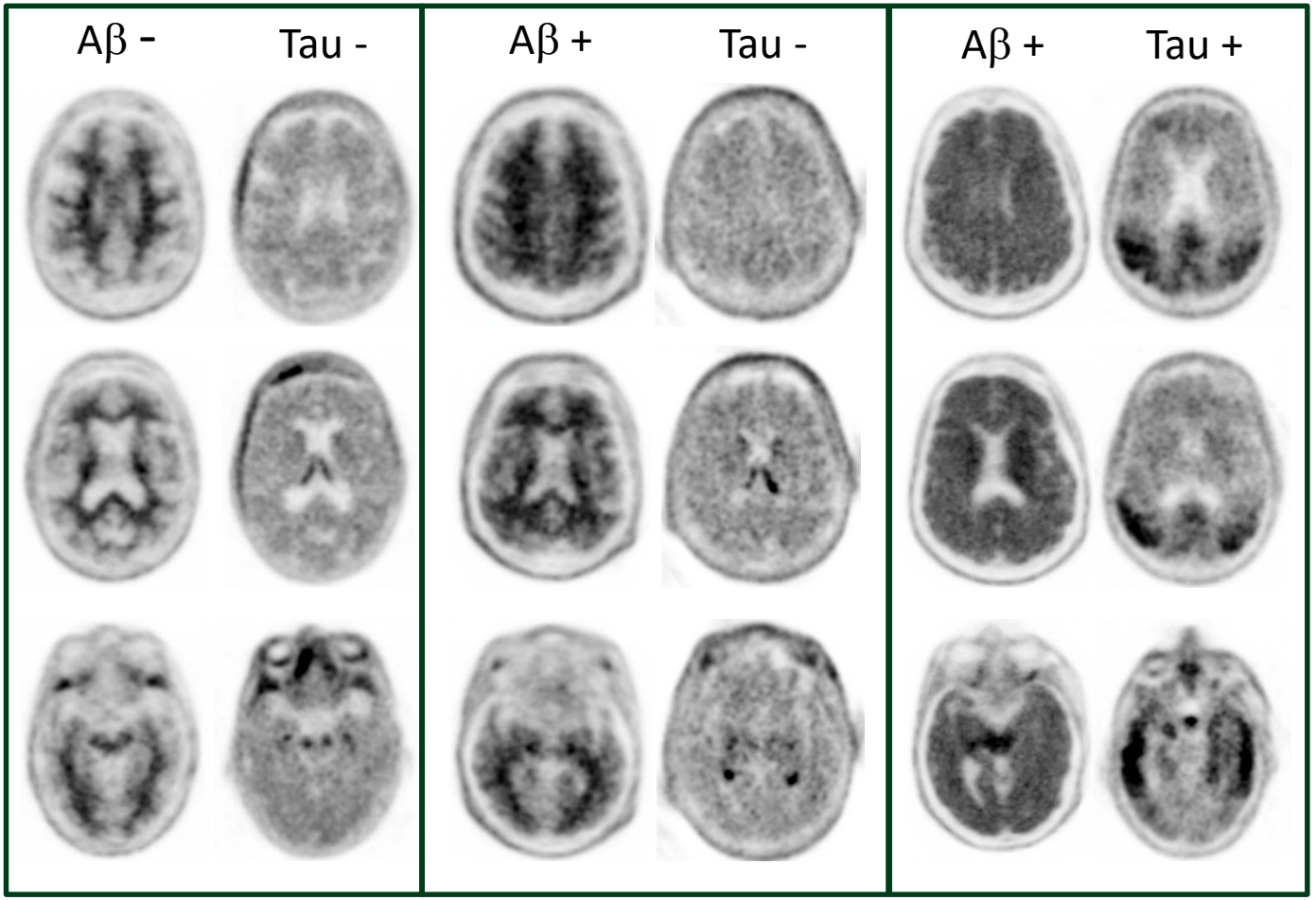
Kinase inhibitors

Immunotherapeutics

Drug name, category and clinical trials	Mechanism of action	Company
Tau aggregation or deposition inhibitors		
Paclitaxel	Tau deposition and aggregation inhibitor; microtubule stabilizing agent	Generic
Davunetide, AL-108, NAP Phase II clinical trial in aMCI patients: negative	Tau deposition and aggregation inhibitor; microtubule stabilizing agent	Allon Therapeutics–Biogen Idec
BMS-241027	Tau deposition and aggregation inhibitor; microtubule stabilizing agent	Bristol-Myers Squibb
TRx0237, (methylthioninium chloride, methylene blue) LMTX: two Phase III clinical trials	Inhibitor of tau protein aggregation	University of Aberdeen, UK, and TauRx Therapeutics
Pyridazines	Tau aggregation inhibitors	University of Pennsylvania
BLV-0703	Tau aggregation inhibitor	Bioalvo
ReMIND NV	Tau deposition inhibitor	Roche
Nicotinamide Phase II clinical trial	Inhibitor of microtubule polymerization	Generic
Kinase inhibitors		
GSK-3 inhibitors (various)	Kinase inhibition (GSK-3)	AstraZeneka, Takeda, CrystalGenomics
Valproate, divalproex sodium Phase III clinical trial: negative and worsening	Inhibitor of the kinase GSK-3	Generic
Tideglusib, NPO3112, NP-12 Two Phase II clinical trials	Inhibitor of the kinase GSK-3	Noscira
SAN-161	Inhibitor of the kinase GSK-3	Sanoimmune
Lithium chloride: two negative and one positive Phase II clinical trials. Not being developed.	Kinase inhibitor	Generic
Tau protein modulators	Enzyme modulator	Biogen Idec
Immunotherapies		
Monoclonal antibodies	Passive tau immunization	AC Immune, Prothena Elan, Neotope Biosciences
Supra-antigen vaccines	Active tau immunization	AC Immune
AADvac-1 clinical Phase I/II	Vaccine : synthetic peptide targeting pathological tau protein	Axon Neuroscience

GSK-3: Glycogen synthase kinase-3.

Hampel, H. et al., 2015. Advances in the therapy of Alzheimer's disease: targeting amyloid beta and tau and perspectives for the future, Expert Rev Neurother. 15: 83-105.



Progression from normal to asymptomatic to symptomatic AD

Outline of presentation

- Overview
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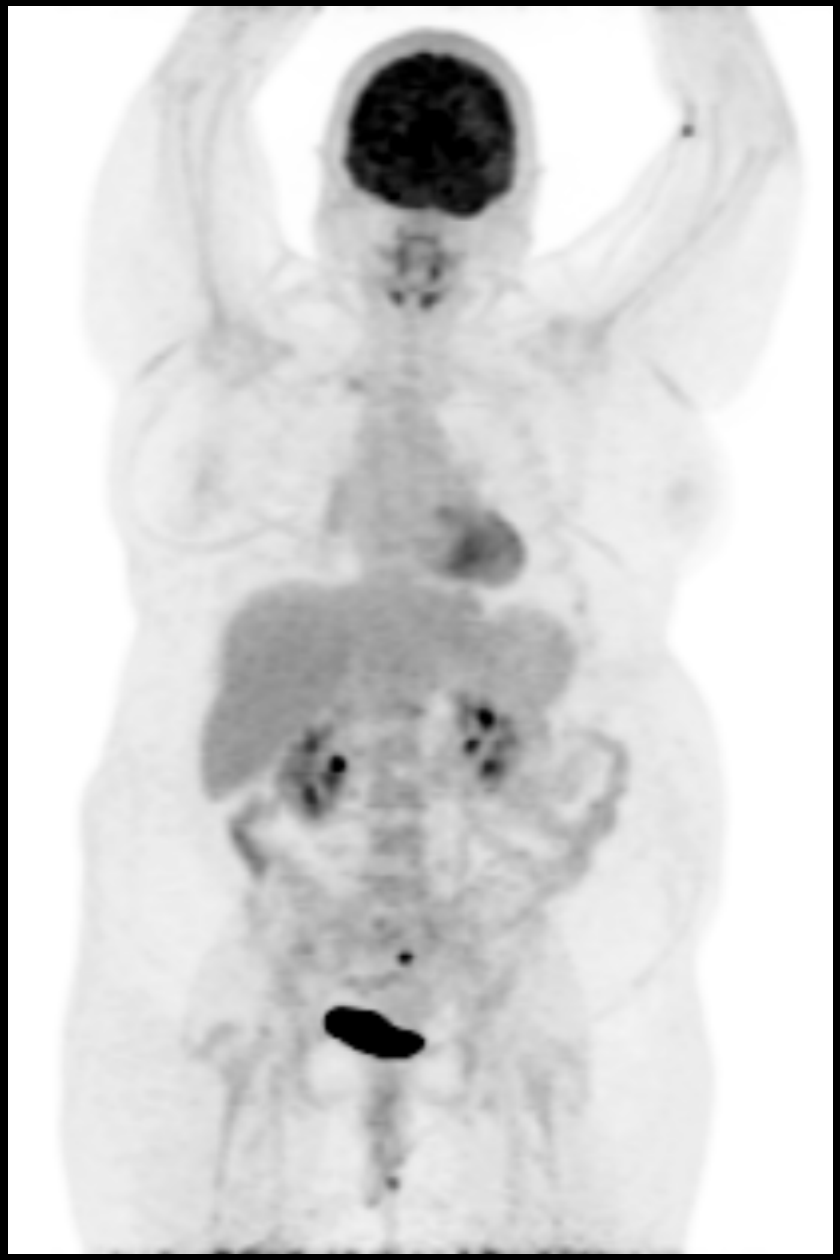
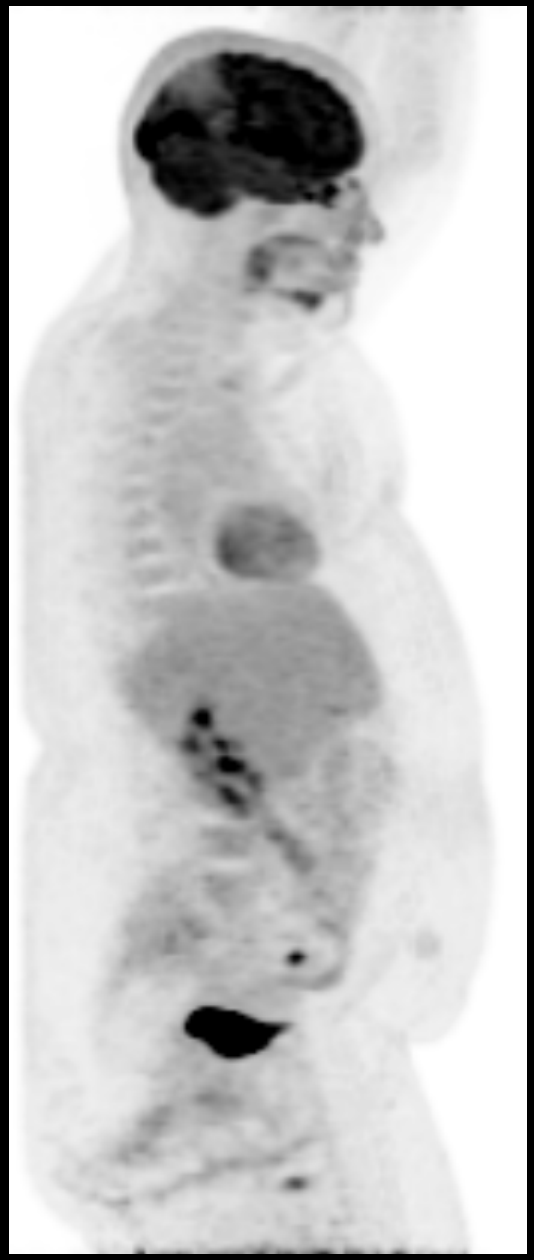
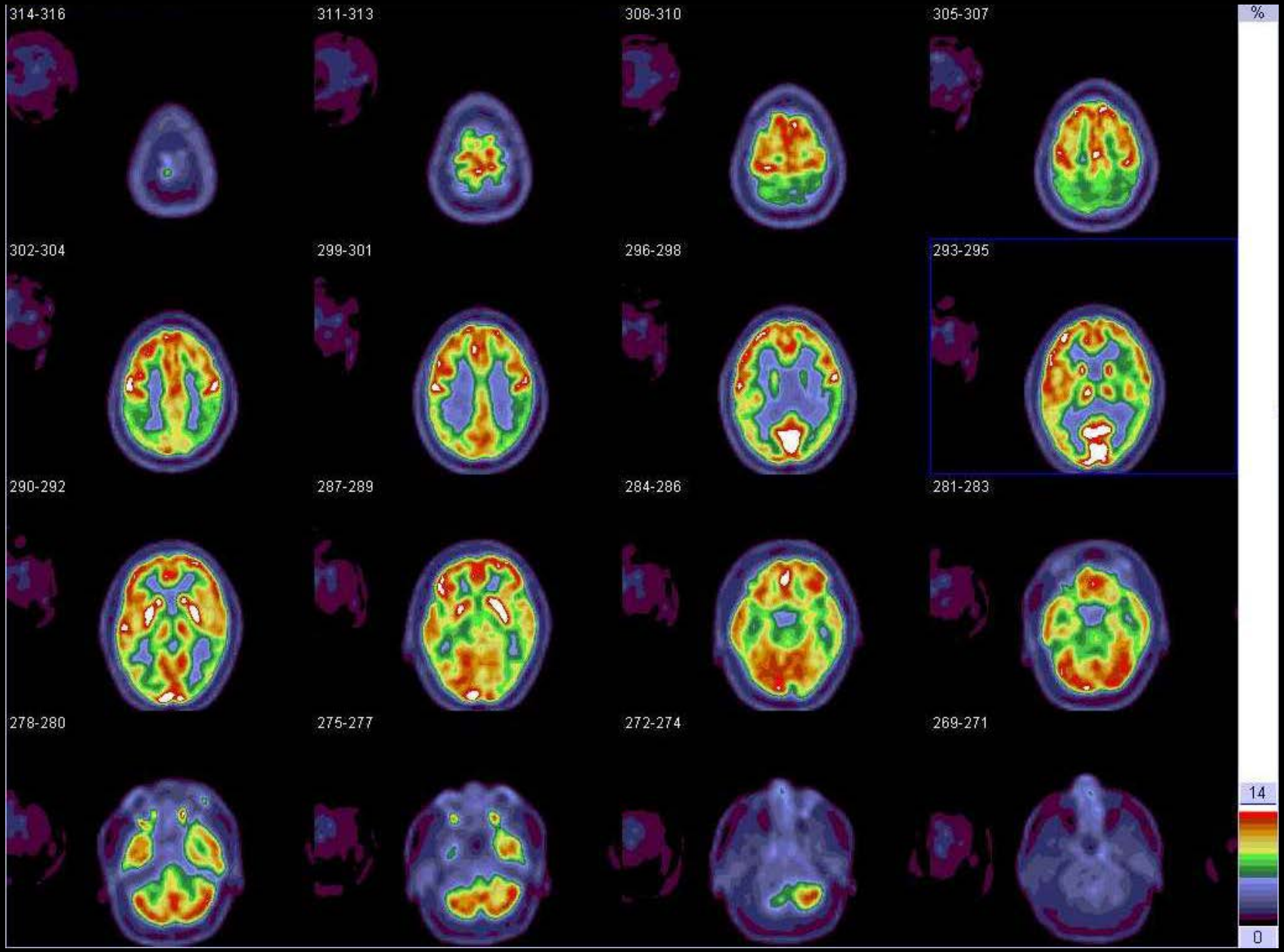
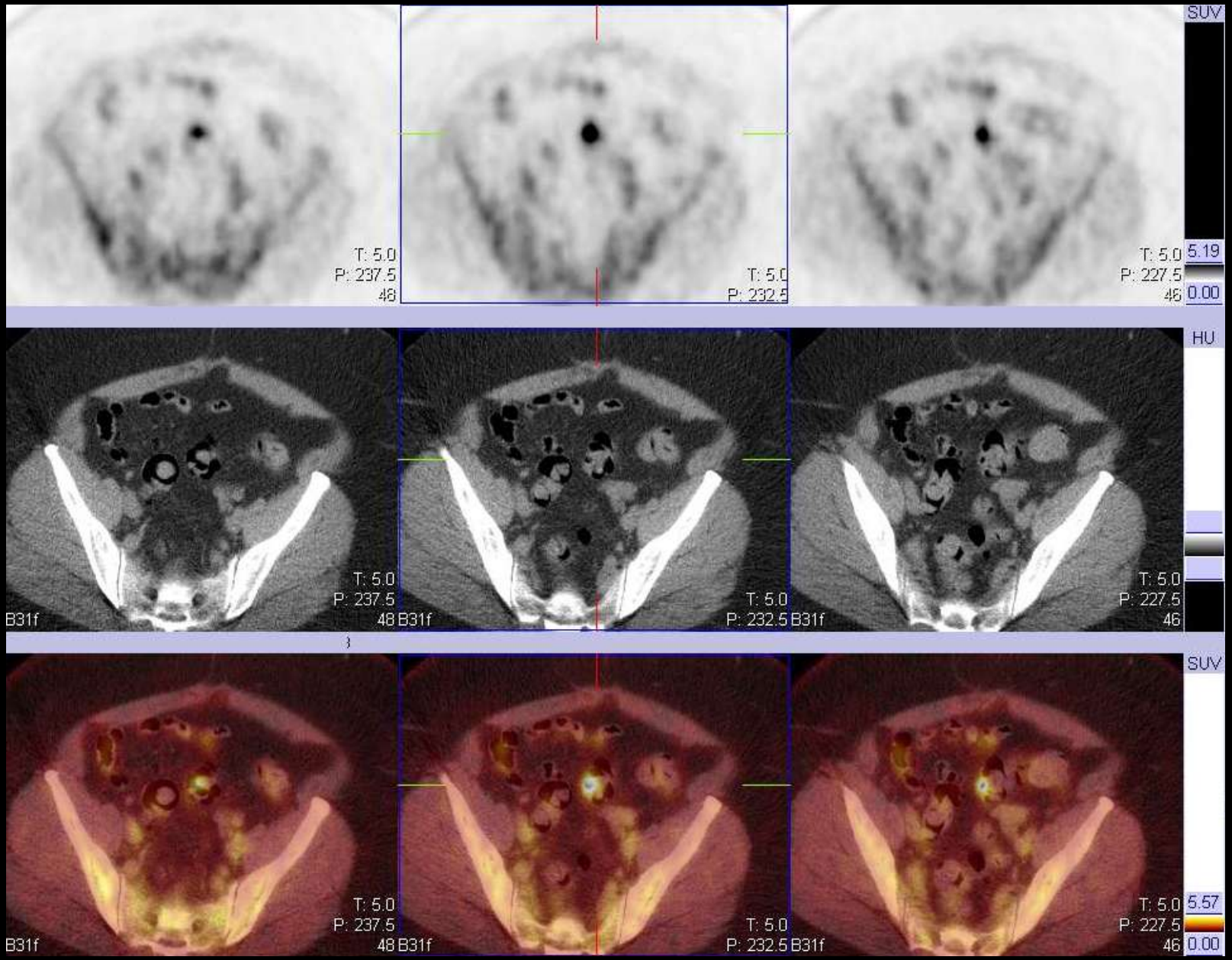
Case

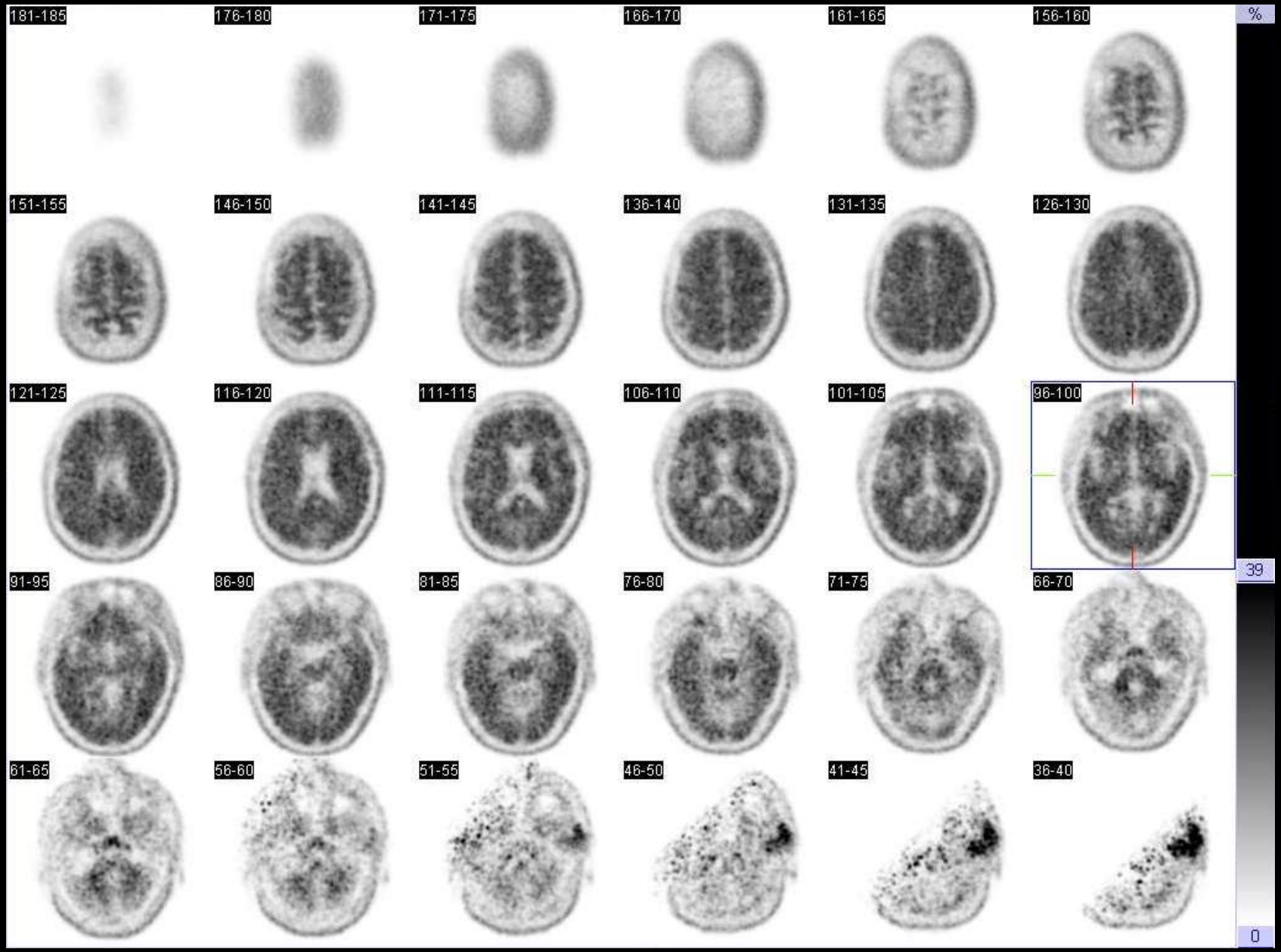
- HISTORY: 47-year-old woman with rapidly progressive dementia and positive paraneoplastic panel (anti-ganglionic acetylcholine receptor). The study is requested for diagnosis of unknown primary malignancy as an etiology of a paraneoplastic syndrome.









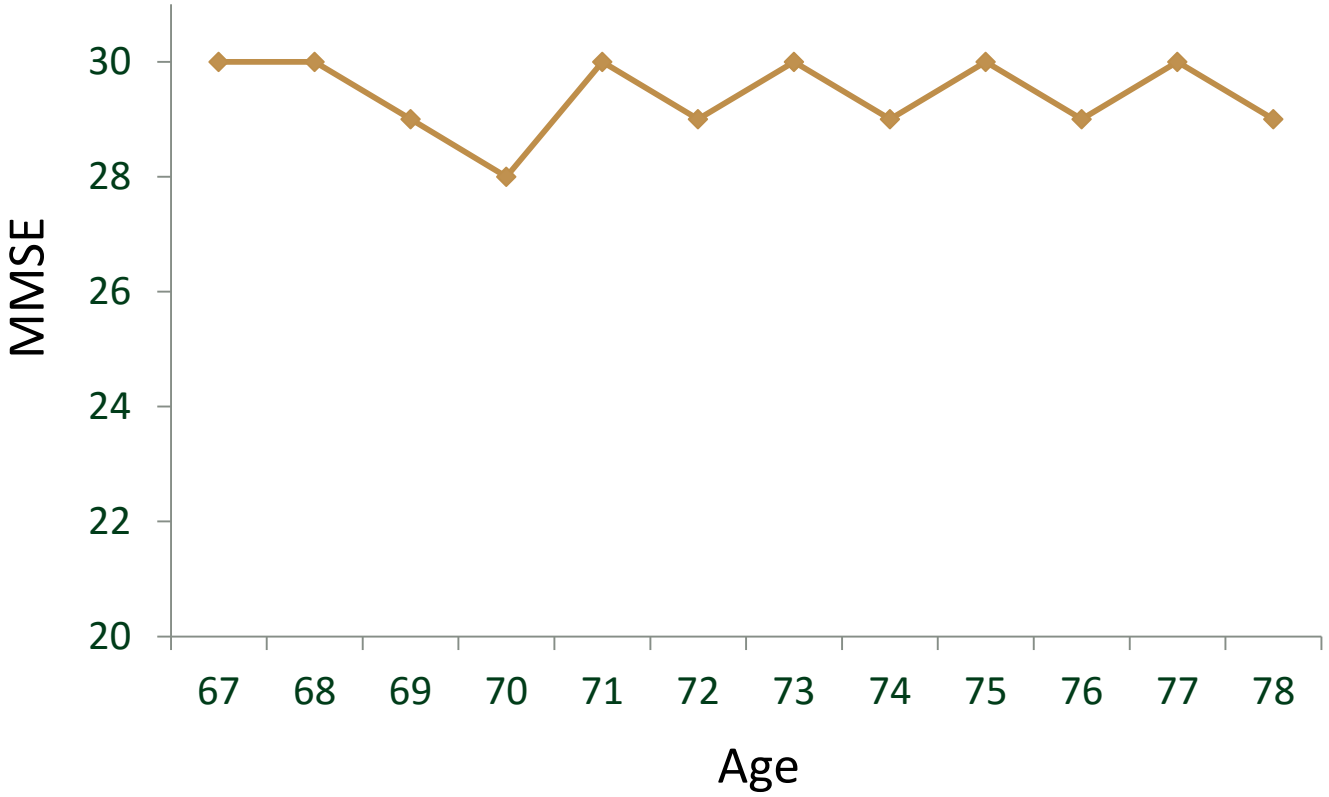


Final Diagnosis

- Early onset Alzheimer's disease
  - clinical course consistent with diagnosis

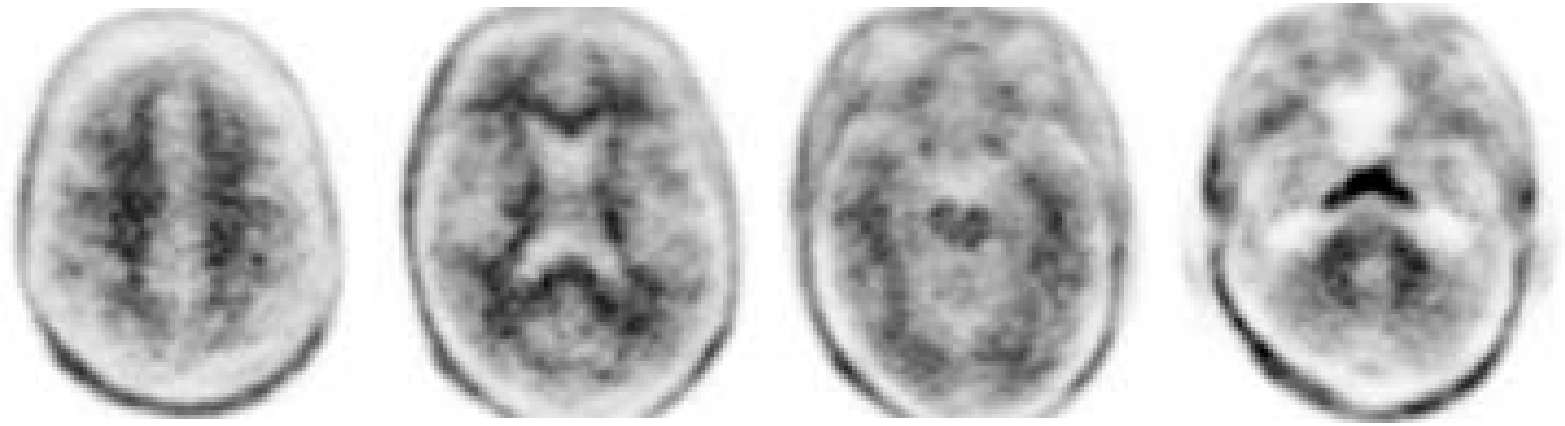
Case 2

- 78 year old man with memory and thinking problems reported by wife since age 57

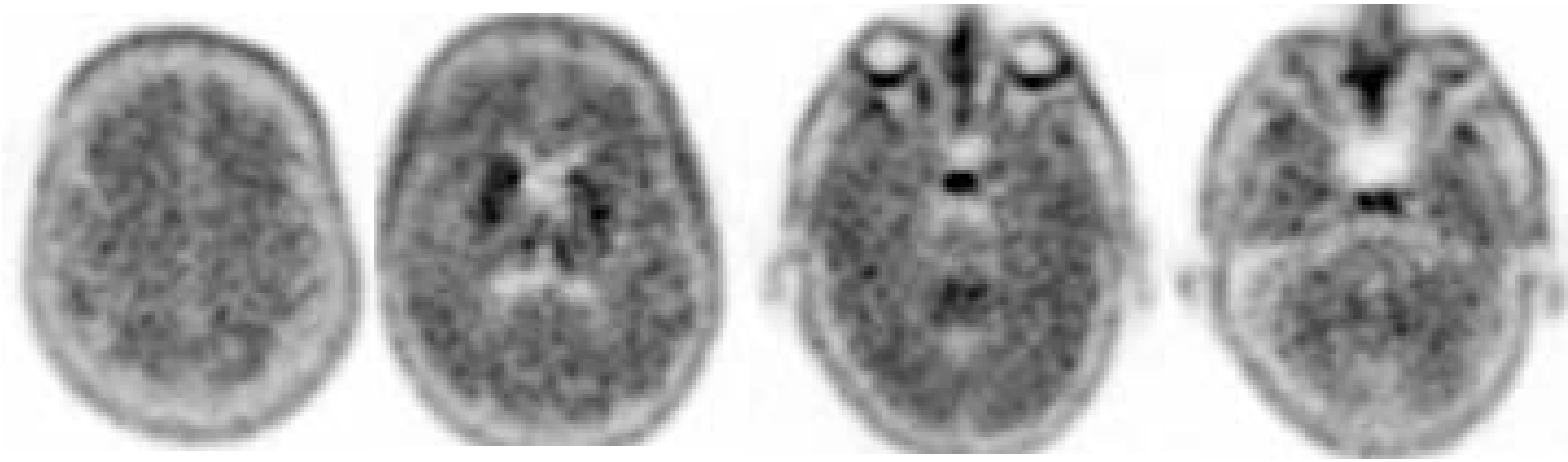


Case 2

Amyloid PET



Tau PET

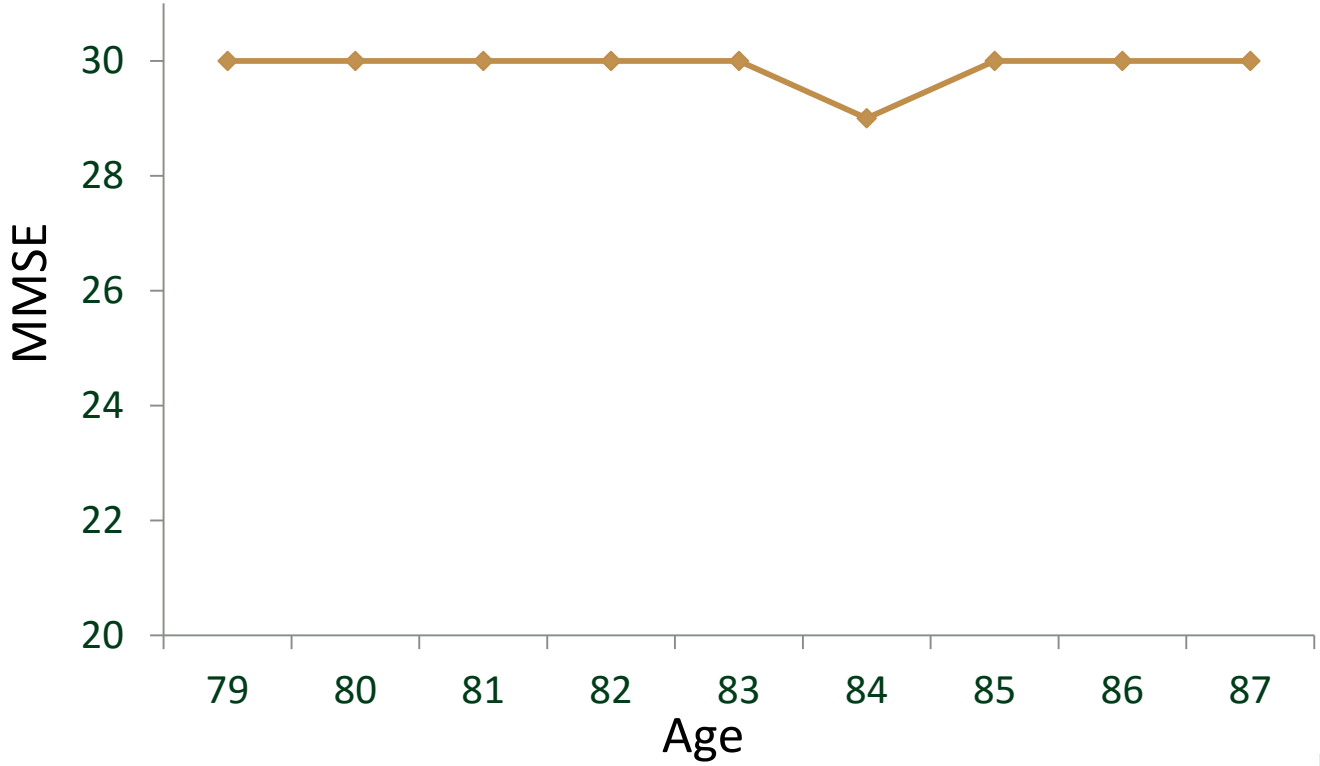


Case 2 summary

- Amyloid and tau PET negative
- MR volumes normal
- Cognitively intact
- Normal studies, stage 0

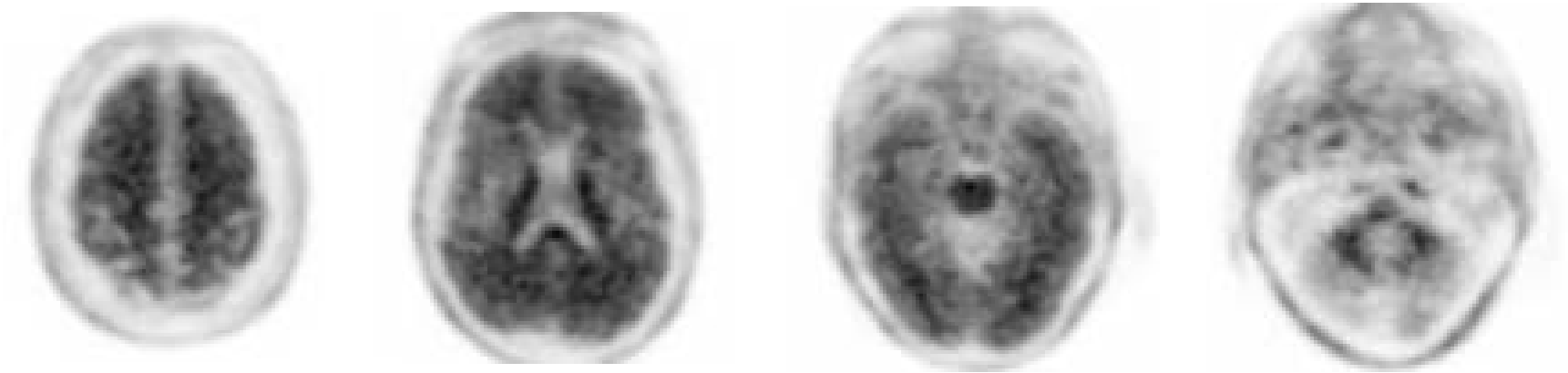
Case 3

- 87 year old man with subtle memory changes beginning at 77
  - MMSE = 30, on donepezil

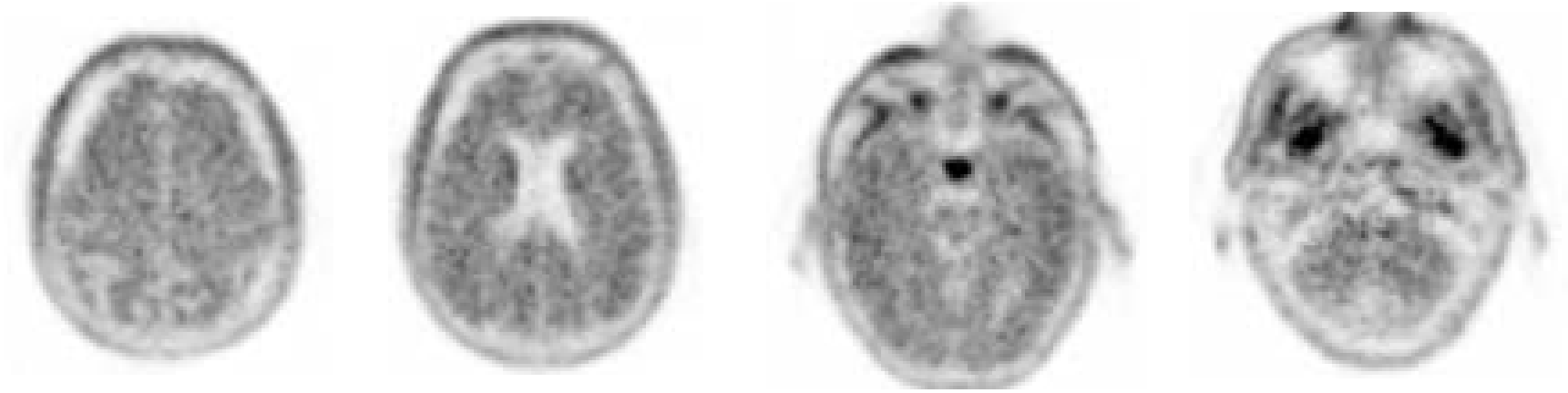


Case 3

Amyloid PET



Tau PET



Case 3 summary

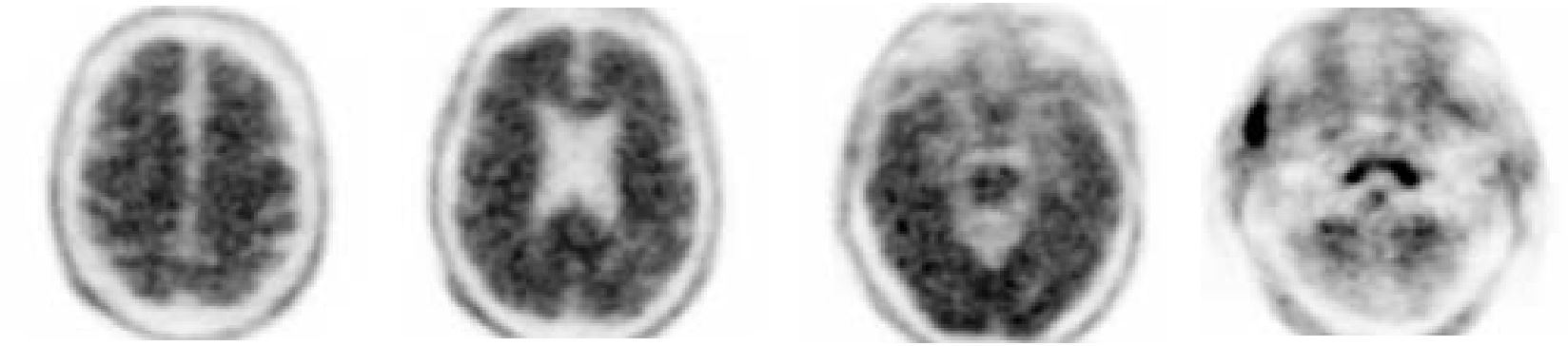
- Amyloid positive, tau negative PET studies
- Stable subtle cognitive impairment
- Stage 1 preclinical AD

Case 4

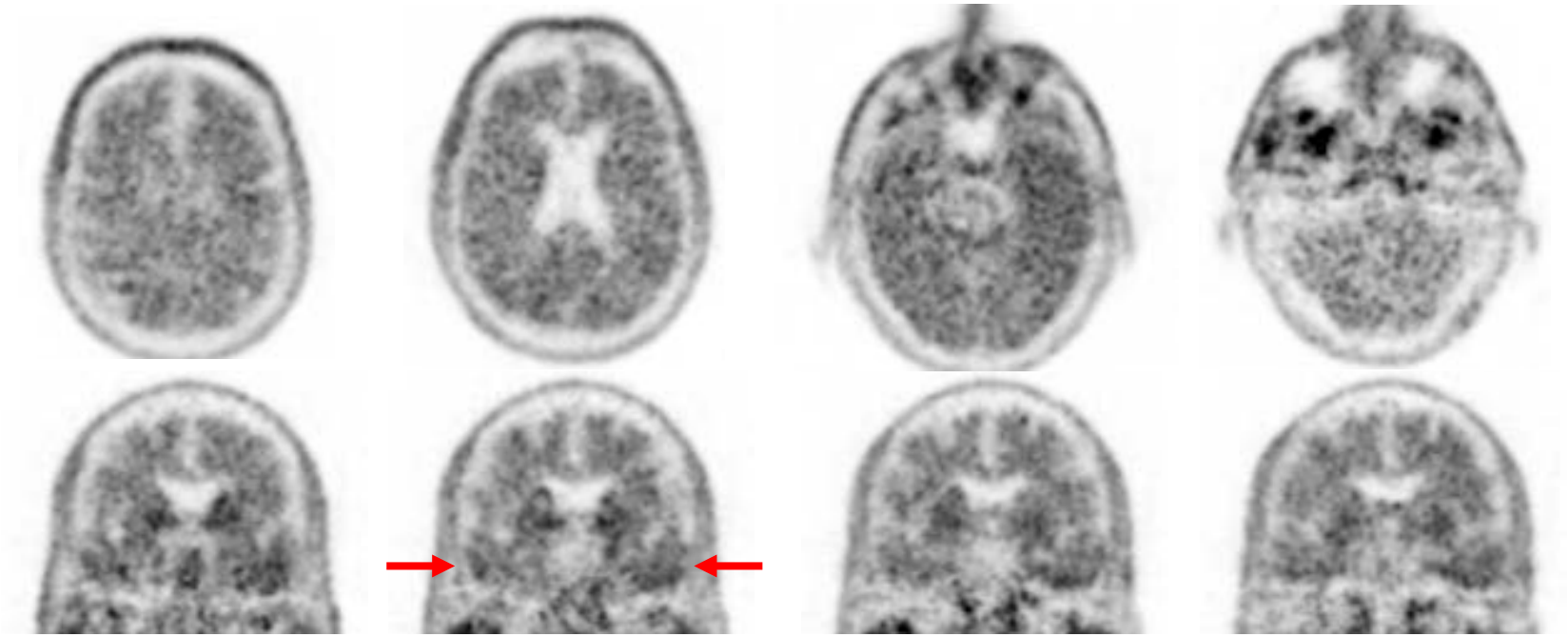
- 73 year old man with no cognitive complaints, MMSE 30

Case 4

Amyloid PET



Tau PET

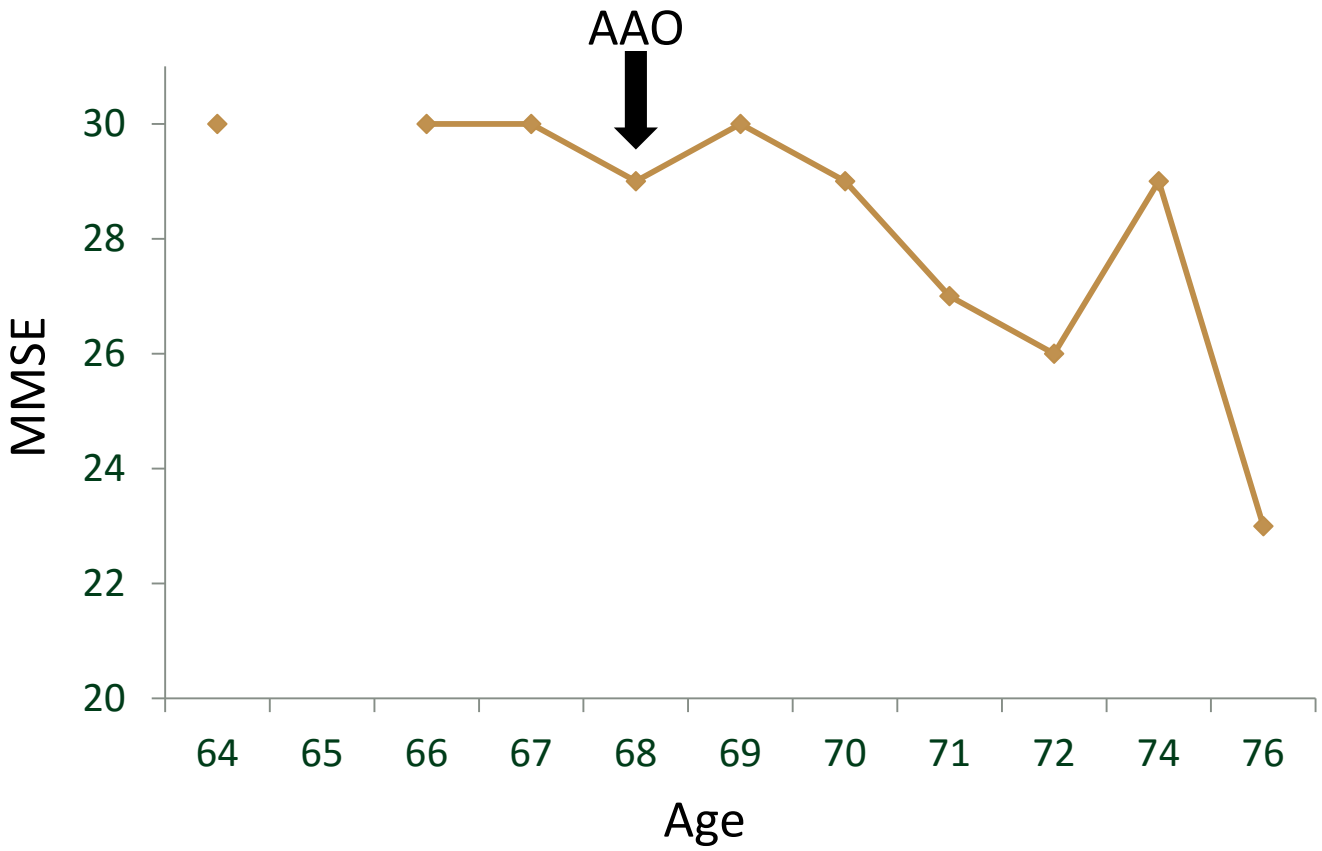


Case 4 summary

- Amyloid positive and subtle tau positive PET
- Cognitively intact
- Suspect stage 2 presymptomatic AD

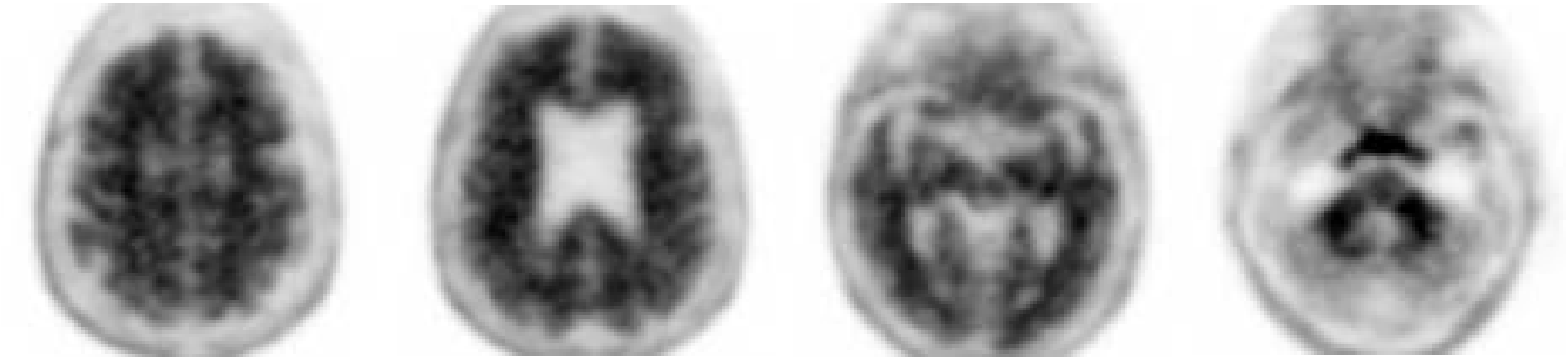
Case 5

- 76 year old woman with gradual onset of cognitive impairment, now moderate in severity

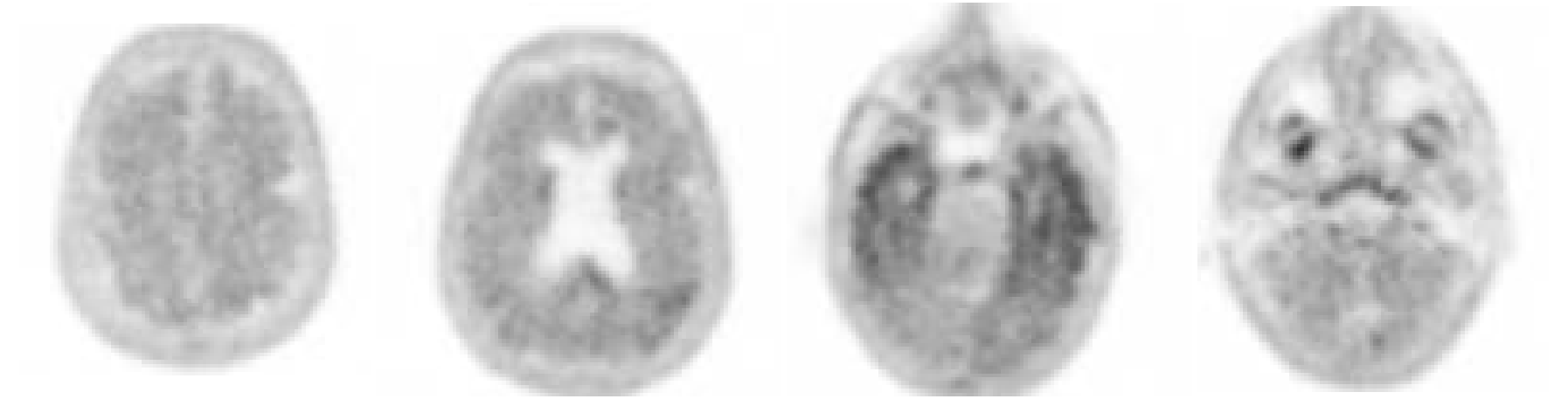


Case 5

Amyloid PET



Tau PET

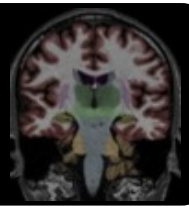


Case 5 summary

- Amyloid and tau PET positive
- Hippocampal atrophy on MRI
- Clinical evaluation shows progressive cognitive impairment
- Symptomatic AD with concordant imaging biomarkers

Potential neuroimaging algorithm for dementia for AD, DLB, and FTD

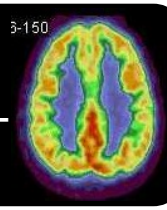
MRI for structure, volume, functional imaging



dementia remains in the DDx

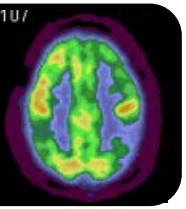
FDG-PET for glucose metabolism

normal FDG-PET



no dementia

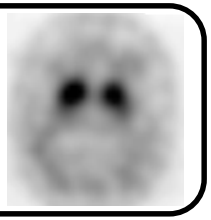
FDG-PET: AD or DLB pattern



normal ioflupane

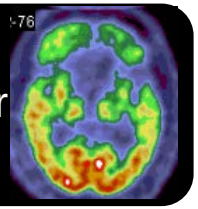
AD

abnormal ioflupane

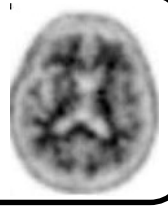


DLB

FDG-PET: FTD or other pattern

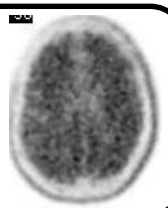


negative amyloid



FTD

positive amyloid



AD

Adapted from Kirk Frey, U Michigan

Summary

- A range of molecular imaging agents are clinically available including FDG, amyloid tracers, and ioflupane
- Coverage with evidence development will likely increase the clinical use of molecular neuroimaging
- Tau-PET represent a new class of investigational tracers for Alzheimer's disease and some other neurodegenerative diseases
- If disease-modifying therapies become available, the volume of molecular neuroimaging will likely increase dramatically

Research support

- The Charles F. and Joanne Knight Alzheimer's Research Initiative
- Support from Fred Simmons and Olga Mohan
- NIH/NIA P01AG026276, P01AG003991, P50AG05681, 2UL1TR000448
- Avid Radiophamaceuticals (a wholly owned subsidiary of Eli Lilly)

- Special acknowledgements to Tammie Benzinger, M.D., Ph.D. and the ADRC at Washington University

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End

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Knowledge that will change your world