

**BRAIN IMAGING, BLOOD AND
CEREBROSPINAL FLUID
BIOMARKERS FOR
DIAGNOSIS OF ALZHEIMER'S
DISEASE**

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TOPICS REQUESTED

- Current use of imaging/biomarkers in diagnosis
- Current use of imaging/biomarkers in research
- Distinguish FDA approved/non-approved diagnostic tests
- What should be considered as definitive for Social Security's purposes??????

GENERAL USE OF TECHNOLOGY FOR DIAGNOSIS

- A century ago, all medical diagnosis was based on self-report/physical exam
- Widespread use of technology for diagnosis, early detection, risk assessment
 - Blood tests, imaging, EKG,etc
- Most diagnosis of neurological/psychiatric disorders based on self report/physical examination
 - Imaging/biomarkers have limited but growing use

CURRENT DIAGNOSIS OF ALZHEIMER'S DISEASE

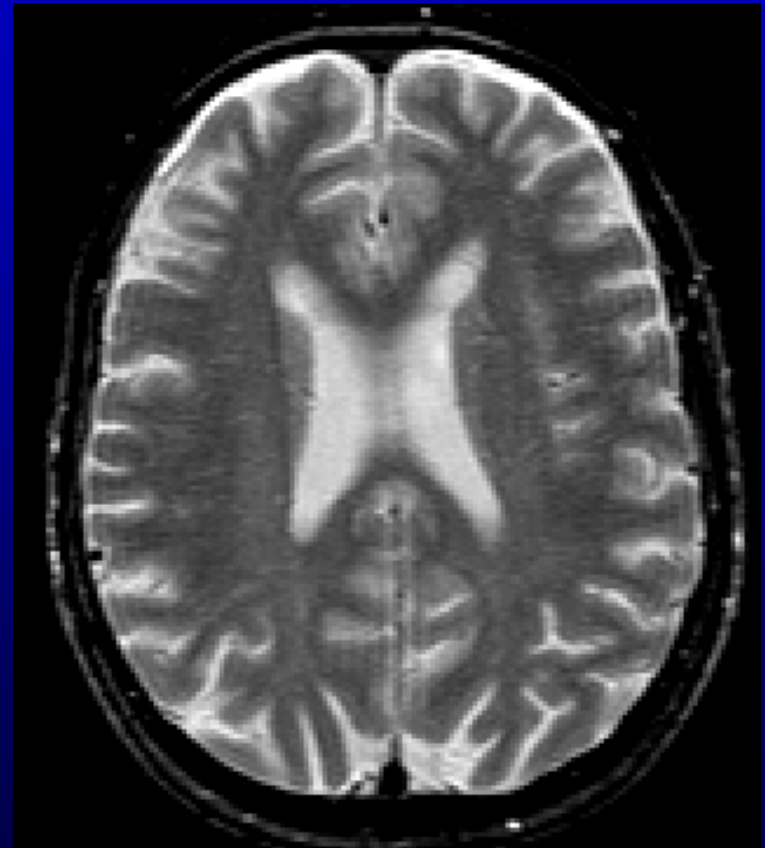
- Clinical diagnosis
- Requires presence of dementia
- Growing recognition that AD pathology exists for many years prior to dementia
 - Asymptomatic phase
 - Mild symptoms, mild cognitive impairments
 - Dementia

IMAGING FOR DIAGNOSIS OF ALZHEIMER'S DISEASE

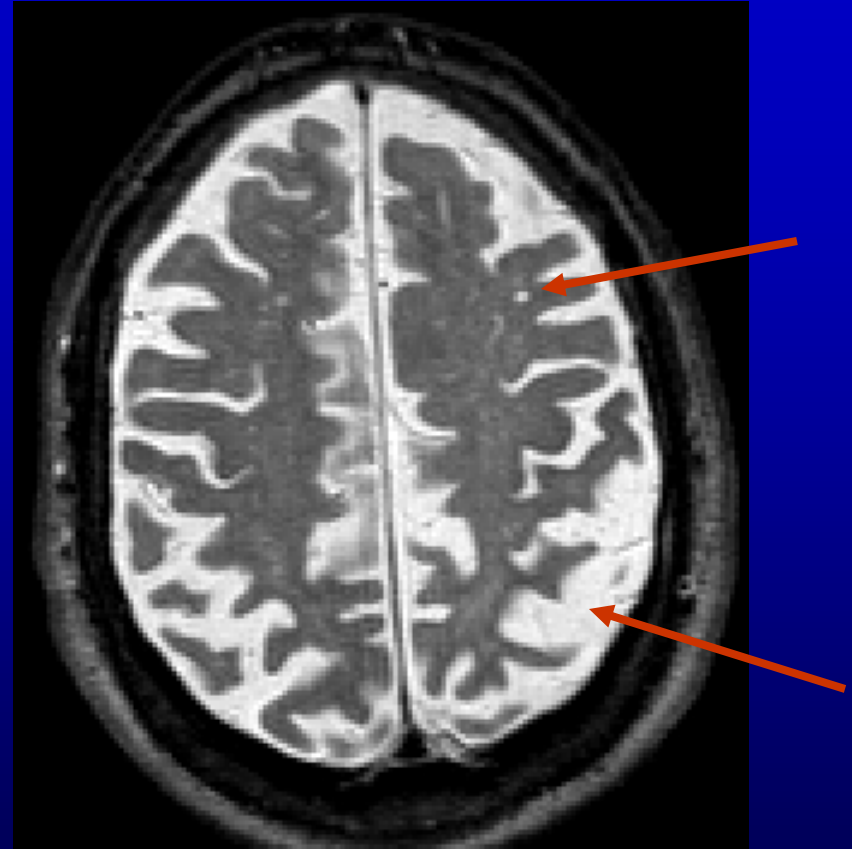
- Uses:
 - Diagnosis
 - Prediction of future decline/dementia (Research!)
 - early detection
 - Risk assessment
 - Clinical trials
- Imaging Modalities
 - Computerized tomography
 - MRI: many types of MRI scans
 - PET: FDG, amyloid scans

STRUCTURAL MRI

Normal Elderly Brain (FDA approved)



Alzheimer's Atrophy

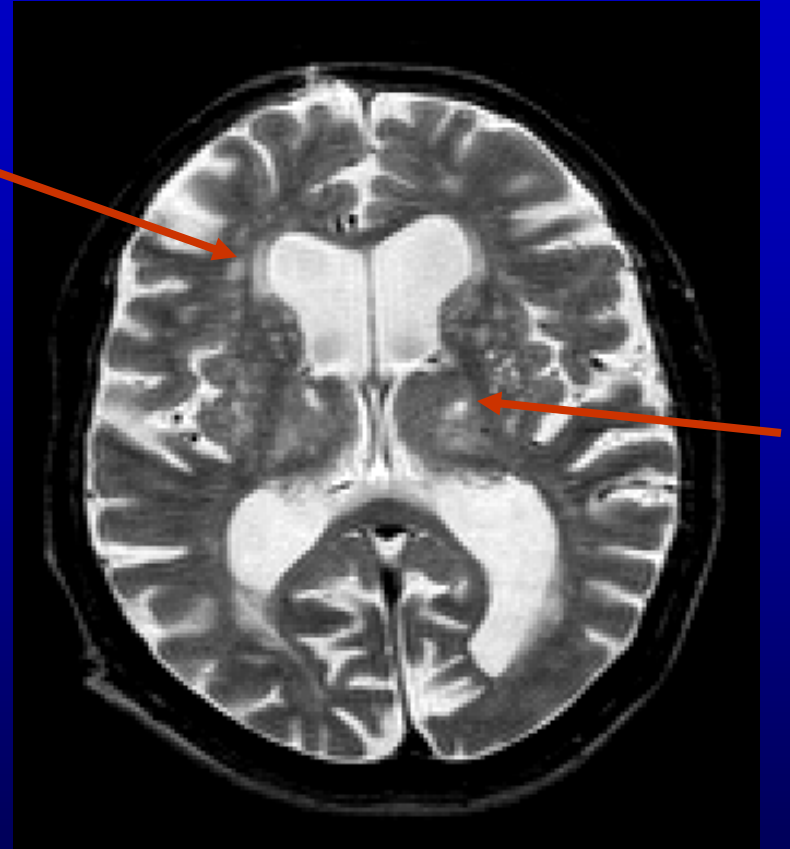
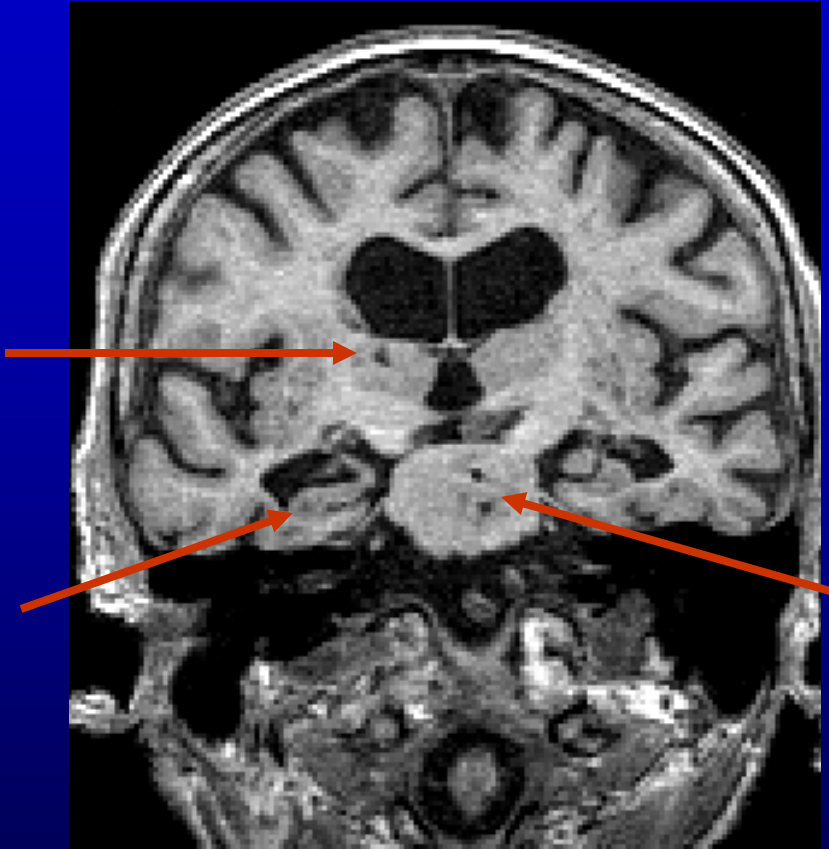


Age: 62

Sex: Male

Dx: AD Probable

Alzheimer's Atrophy

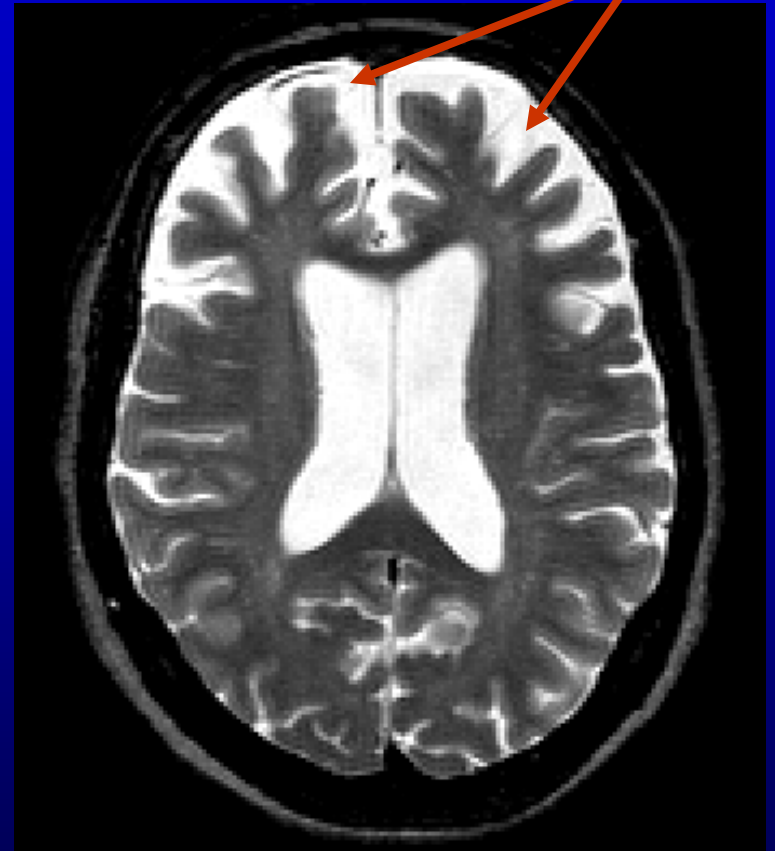


Age: 87

Sex: Female

Dx: AD Probable

Frontal-Temporal Dementia (FTD)

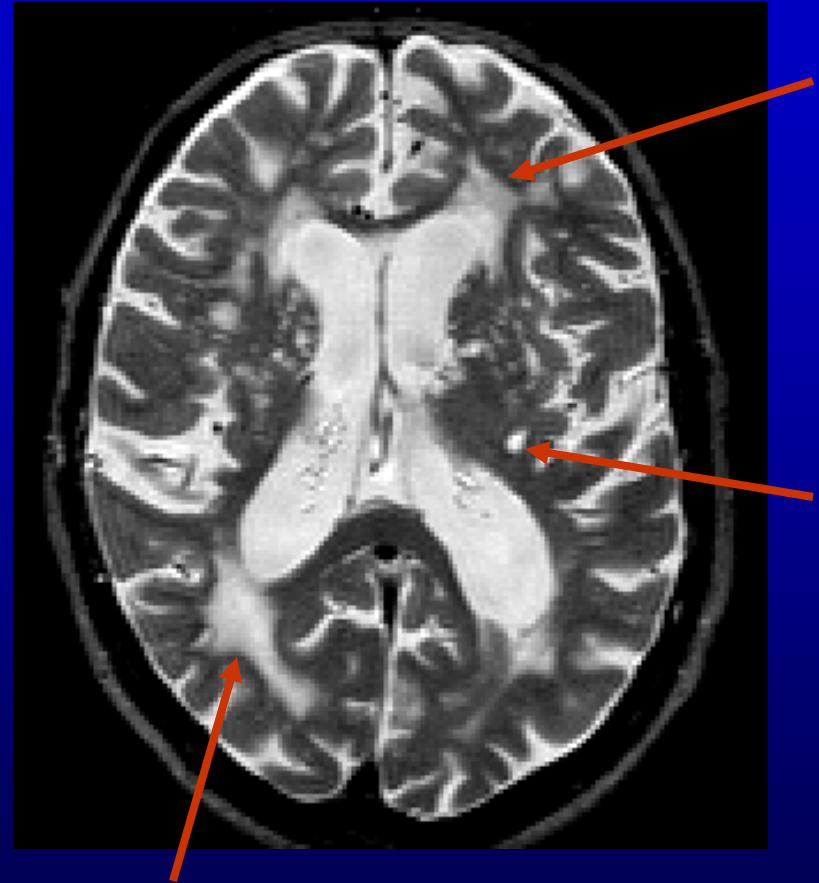
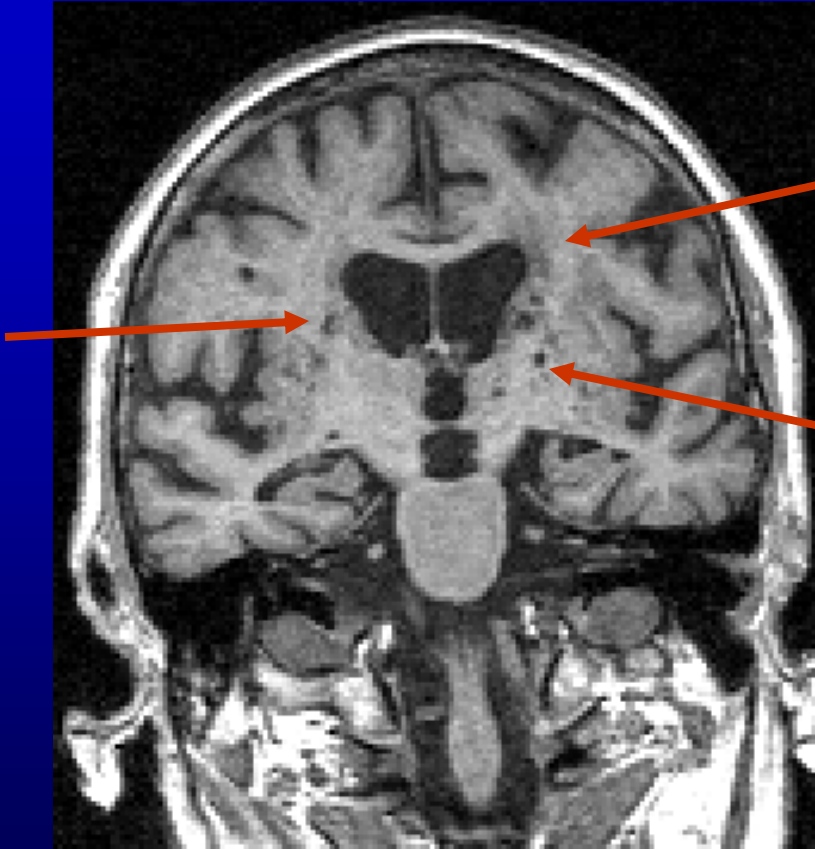


Age: 52

Sex: Female

Dx: FTD

WMSH With Lacunes



Age: 80

Sex: Male

Dx: IVD

USE OF MRI

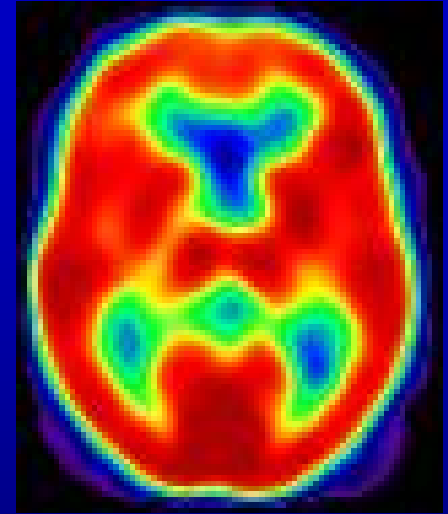
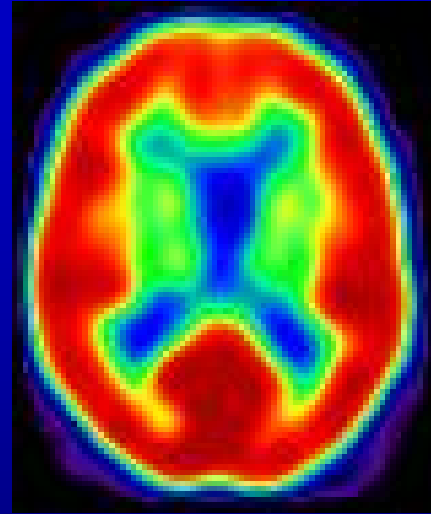
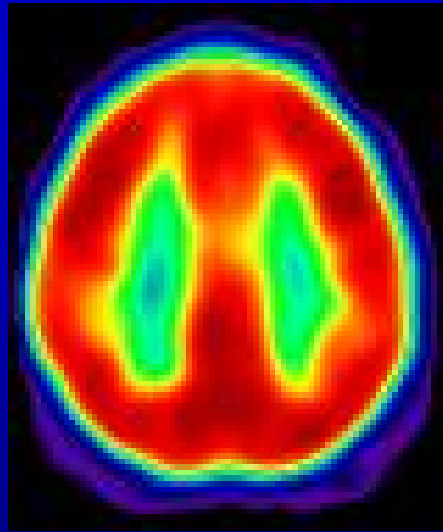
- Rules out other causes
 - Tumors, bleeding, multiple sclerosis etc
 - Suggests other causes of dementia
 - Frontotemporal dementia
- Provides confirmatory evidence
 - Atrophy of brain esp hippocampus: not diagnostic
- Many research uses
 - Emphasis on predicting future decline
 - Identifying AD pathology

POSITRON EMISSION TOMOGRAPHY (PET)

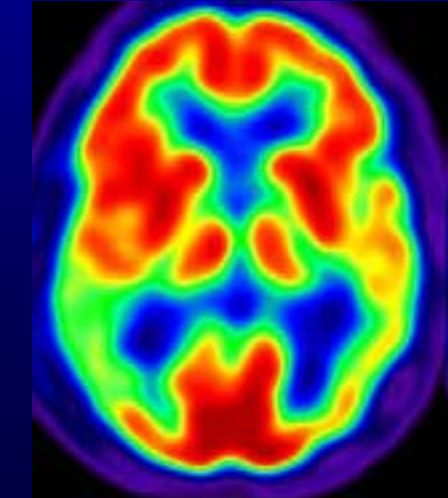
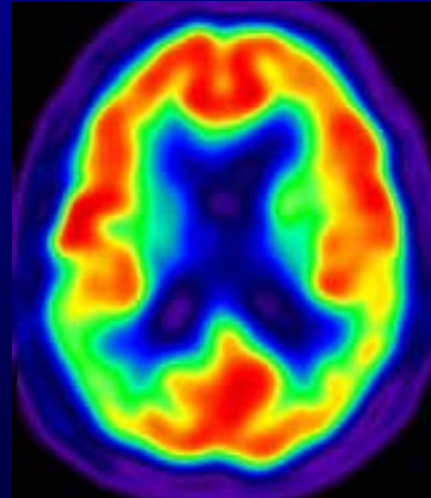
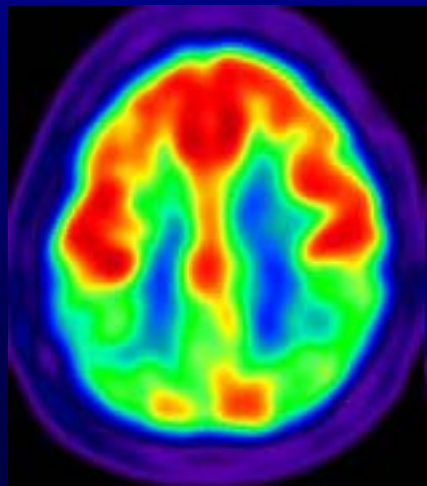
- Fluro Deoxyglucose PET: FDA approved
 - Widely used for cancer staging
 - Approved by CMS for ‘differentiating AD from FTD (long story)
 - Some evidence of widespread abuse/misuse
 - Not approved for Dx of AD
- FDG PET does help “rule in” AD
- Many research uses

Normal Aging vs. Alzheimer's Disease Positron Emission Tomography (PET)

Normal



AD

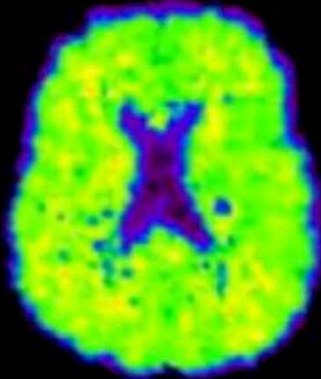


AMYLOID PET

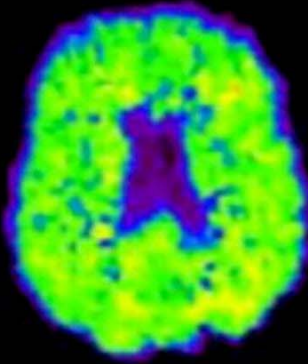
- A technique to detect presence of amyloid plaques in the brain
 - Amyloid plaques = AD pathology (?)
- Carbon 11 Pittsburgh compound B
- Four commercially produced F18 amyloid agents: GE, Bayer, AstraZeneca, AVID
 - In phase 3
- Likely to be approved ‘to detect amyloid’
 - Diagnostic claims uncertain

PIB in Controls, MCI, AD

**Control
Subject**

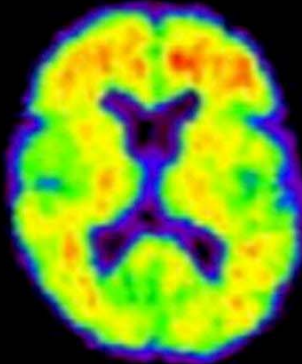


MCI-1

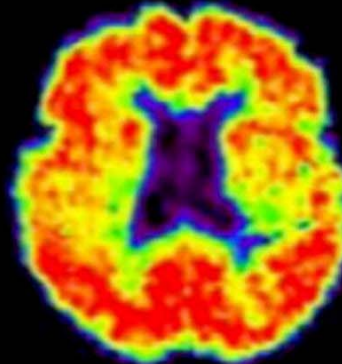


MCI Patients

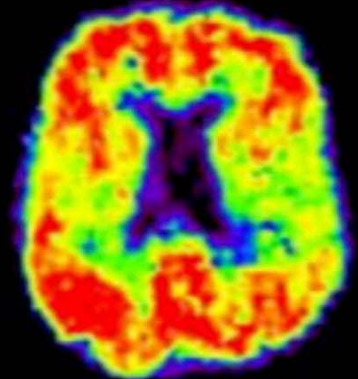
MCI-2



MCI-3



**AD
Patient**



University of Pittsburgh
PET Amyloid Imaging Group

Min

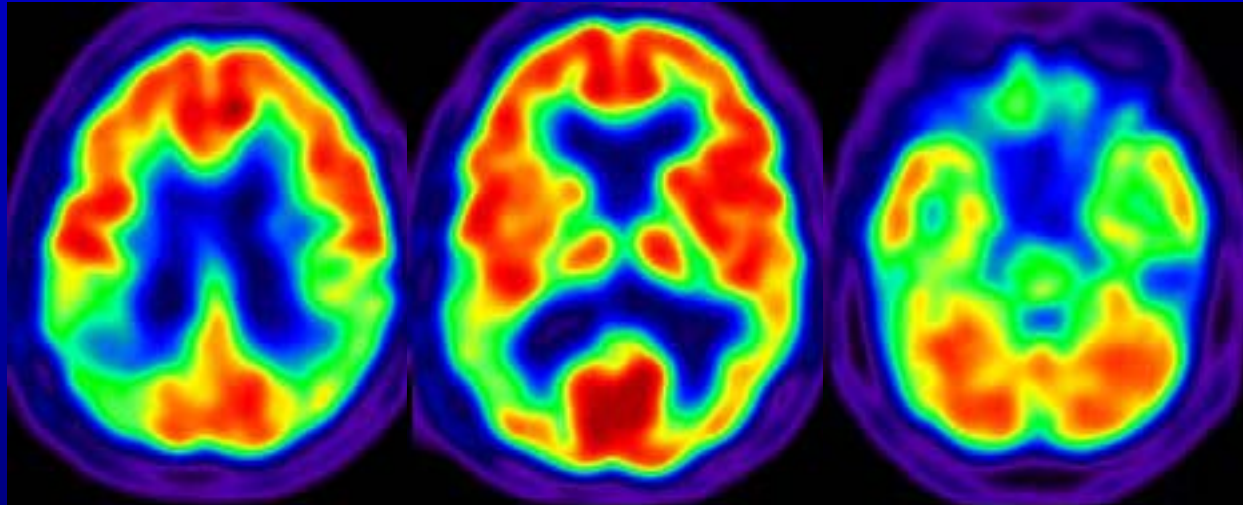


Max

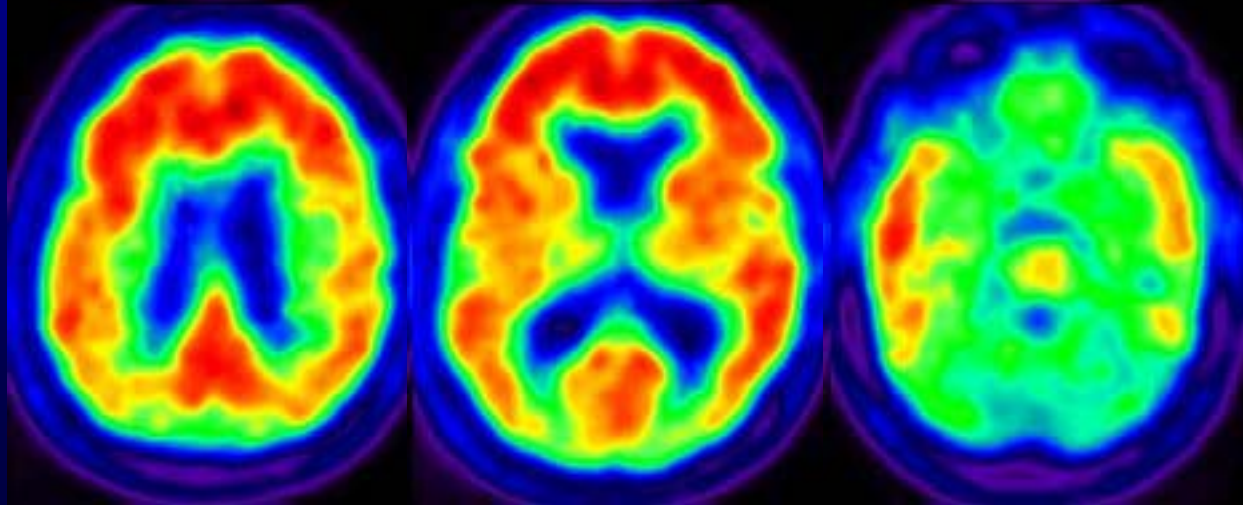
[¹¹C]PIB

PIB Imaging: Alzheimer's Disease

FDG



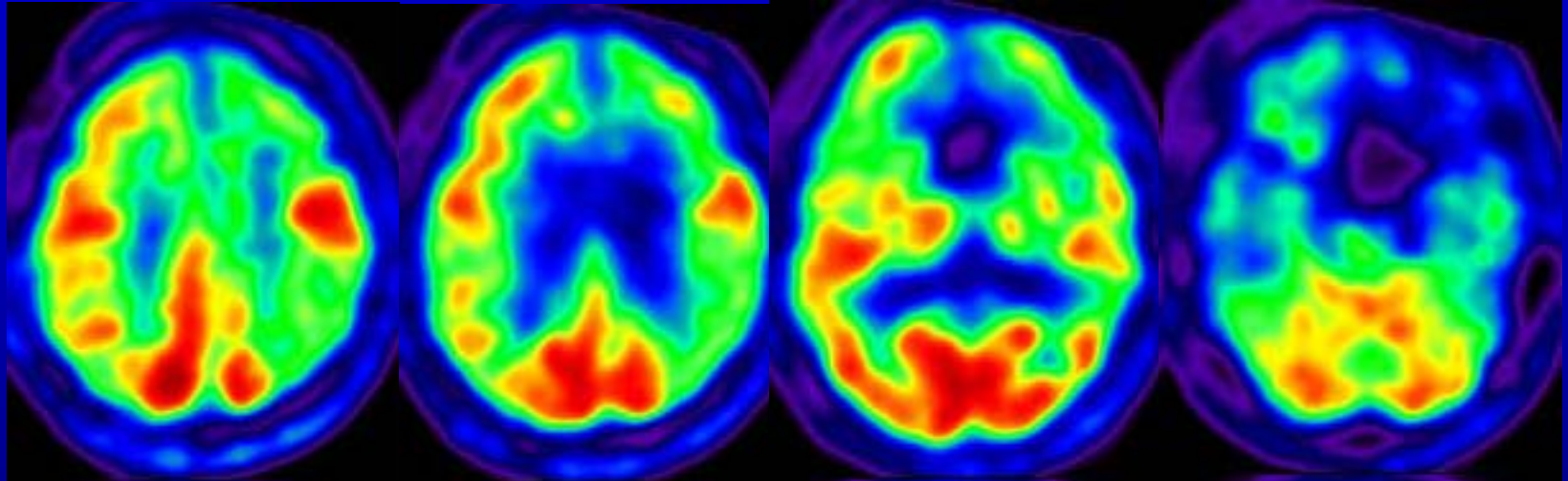
PIB



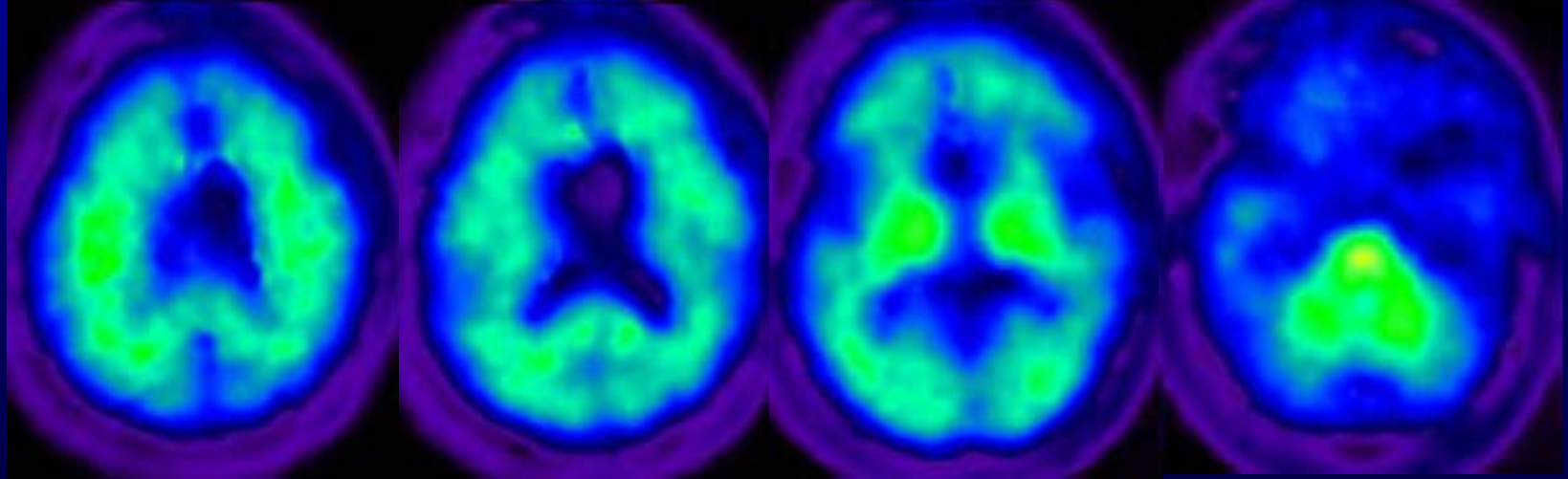
FDA AND PIB PET

Frontotemporal Dementia

FDG



PIB



WHAT IS ROLE OF AMYLOID PET FOR DIAGNOSIS ETC?

- Currently undetermined
- Could be used to “rule out” AD pathology
- Could be used for early detection of AD pathology
 - A risk factor for cognitive decline/dementia
 - PIB+ seems to predict future decline/dementia
- Lots of research to do: will take years

BLOOD AND CSF BIOMARKERS

- Abeta amyloid (various species)
 - Measurement in CSF
 - Seems to have some diagnostic use
 - Use by some in clinical practice: not widespread
 - Measurement in blood: research value only
- Tau: a measure of neurodegeneration CSF
 - May have clinical value: lots of research
- Other proteins: Blood and CSF
- RNA expression: Blood

BIOMARKERS

John Trojanowski, Les Shaw, U Penn.

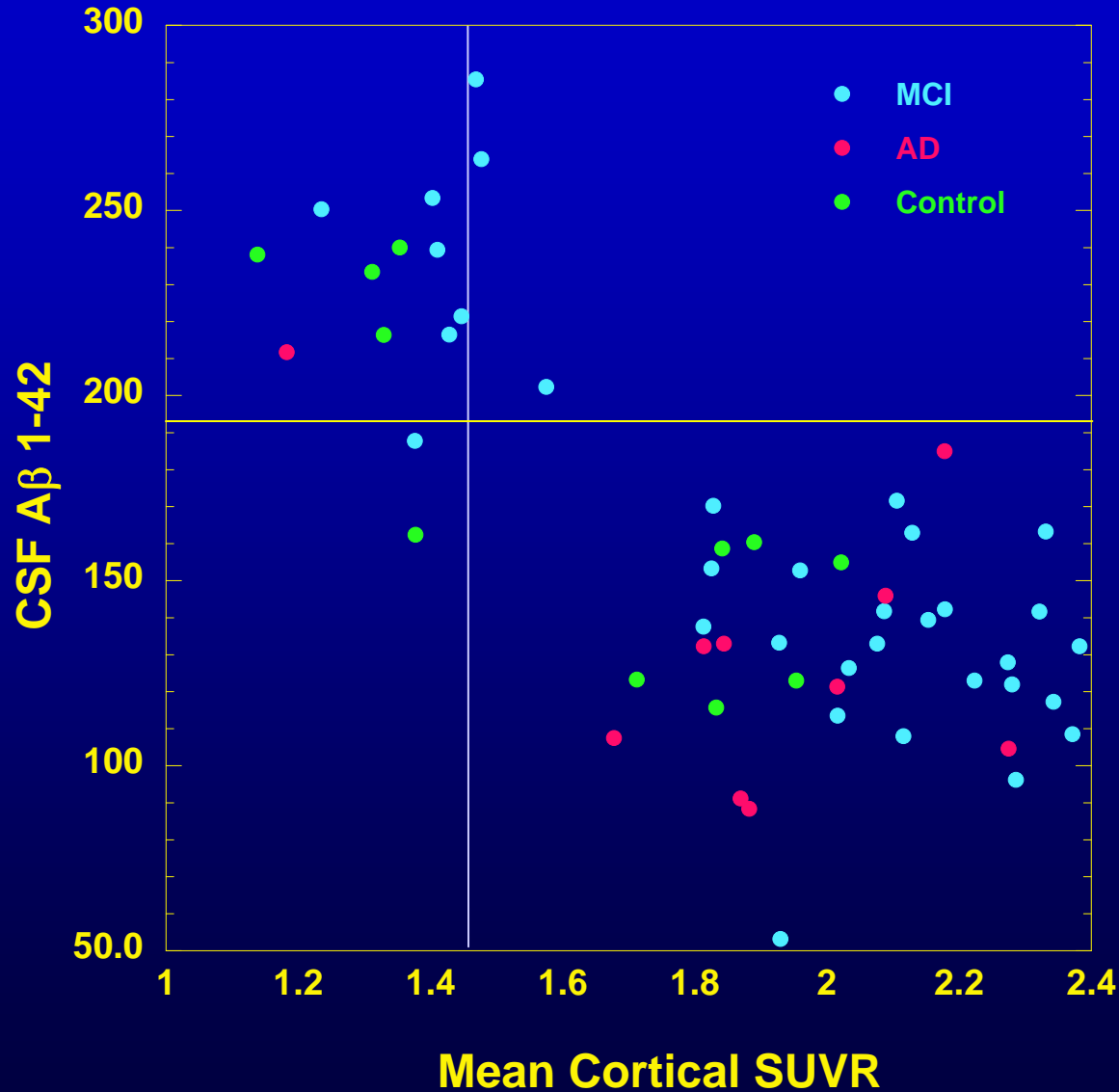
AD (n=102)	Tau	A β_{1-42}	P-Tau _{181P}	Tau/A β_{1-42}	P-Tau _{181P} /A β_{1-42}
Mean \pm SD	122 \pm 58	143 \pm 41	42 \pm 20	0.9 \pm 0.5	0.3 \pm 0.2
MCI (n=200)					
Mean \pm SD	103 \pm 61	164 \pm 55	35 \pm 18	0.8 \pm 0.6	0.3 \pm 0.2
NC (n=114)					
Mean \pm SD	70 \pm 30	206 \pm 55	25 \pm 15	0.4 \pm 0.3	0.1 \pm 0.1

p<0.0001, for each of the 5 biomarker tests for AD vs NC and for MCI vs NC.

For AD vs MCI: p<0.005, Tau; p<0.01, A β_{1-42} ; p<0.01, P-Tau_{181P}; p<0.0005, Tau/A β_{1-42} ; p<0.005, P-Tau_{181P}/A β_{1-42} . Mann-Whitney test

PIB vs CSF Biomarkers: $A\beta$

Total N = 55 (11 Control, 34 MCI, 10 AD)



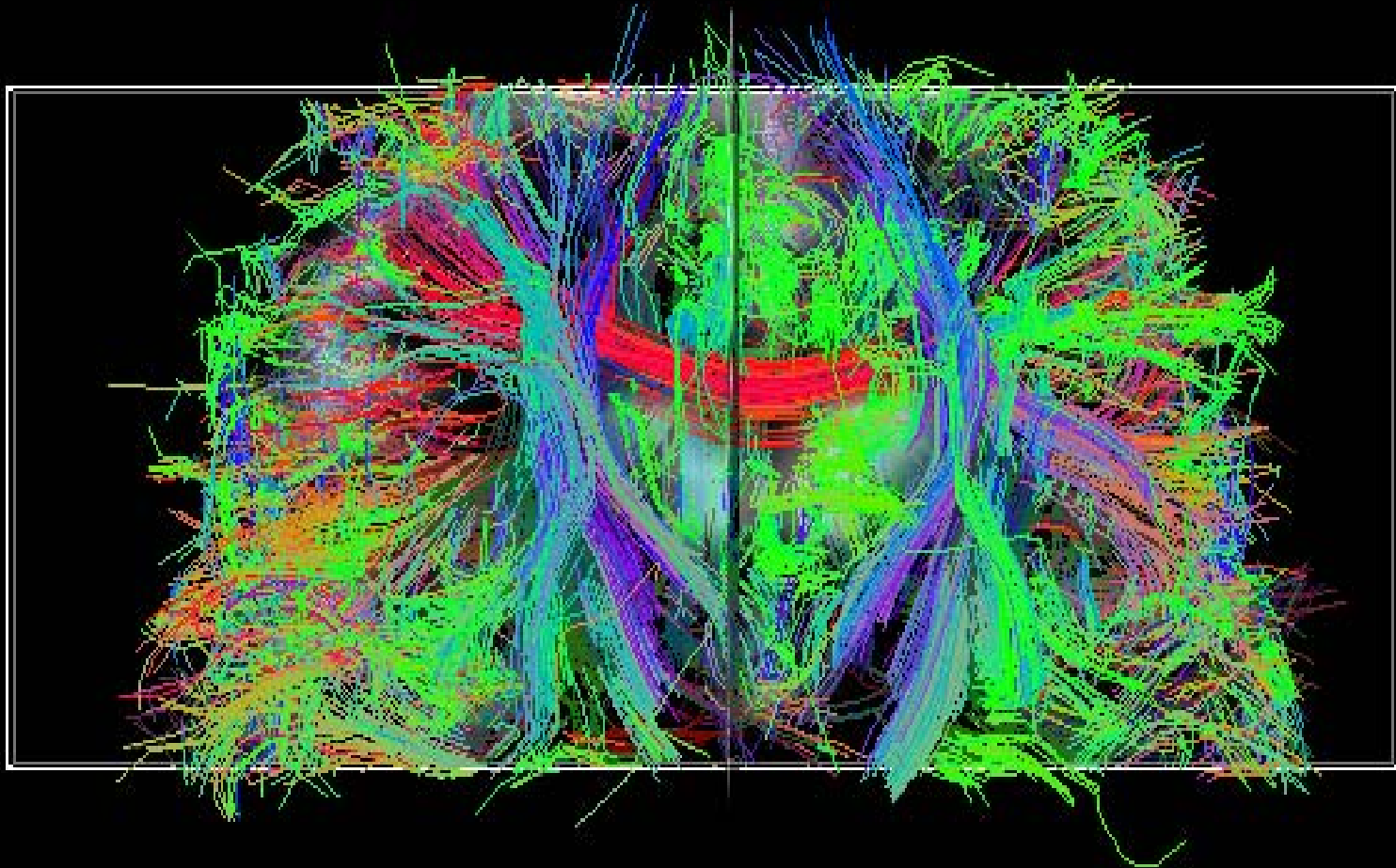
AMYLOID IMAGING VS CSF ANALYSIS

- Thus far CSF analysis (\$300) seems to provide similar predictive information to amyloid imaging (\$>3000)
- But there is resistance to lumbar puncture
- More research needed
- Public acceptance of LPs would be helpful

USING IMAGING/CSF BIOMARKERS TO DETECT AD IN HEALTHY NORMALS

- Early data suggests that a substantial minority of healthy normal
 - + amyloid imaging
 - Low CSF amyloid
- These subjects *may* be at increased risk for cognitive decline and dementia
- Much important research to do
- Technologies will improve

DIFFUSION SPECTRUM IMAGING MEASURES BRAIN CONNECTIVITY



SUMMARY

- **Currently MRI is approved**
 - To rule out other causes of dementia
 - Also provide evidence in favor of Dx
- **FDG PET approved AD/FTD**
 - Also provides evidence in favor of Dx
- **CSF analysis is used by some**
 - For diagnosis risk assessment
- **F 18 amyloid imaging has promise**
 - Advantage over CSF?
- **Much research to be done**



WW-ADNI

J-ADNI

Planned n=600
4.7M USD / year

EU-ADNI

AddNeuroMed n=700
Pilot E-ADNI n=59
~8.6M Euro

A-ADNI

N=1111; 286 MRI
2.5M USD

NA-ADNI

Planned n=800
~60M USD

COSTS TO SOCIAL SECURITY

- Dementia already costs US economy over \$120 billion/yr
- AD research is underfunded compared to heart disease (NHBL) and cancer (NCI)
- How could SS/CMS funds be used to support dementia prevention research?
- It would be useful to estimate the savings to SSN/CMS by treatment/prevention of AD