Pascoal Lab

Can we diagnose Alzheimer's disease with a blood test? The current and future role of biomarkers in the diagnosis of Alzheimer's disease.

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Disclosures

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Learning Objective

Describe the biomarker diagnostic tests that can be used at UPMC to confirm the diagnosis of Alzheimer's disease.

EARLY NOTION OF DEMENTIA

- Late nineteenth, early twentieth century.

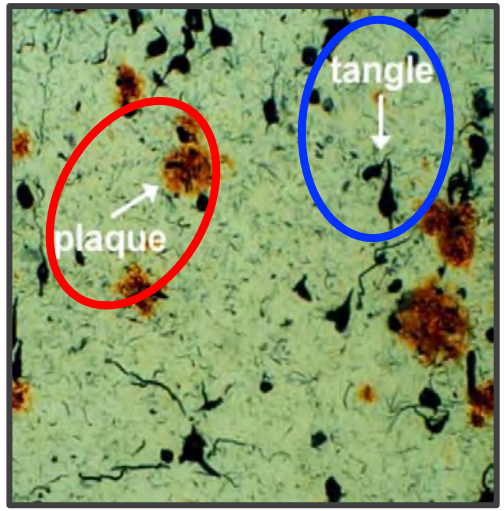
(1857 lithograph by Armand Gautier) showing personifications of dementia, megalomania, acute mania, melancholia, idiocy, hallucination, erotomania and paralysis in the gardens of the Hospice de la Salpêtrière.

DISCOVERY OF ALZHEIMER'S DISEASE

Dr. Alois Alzheimer

Clinico - pathophysiological

Auguste D, June 18, 1902 at asylum for the insane and epileptics in Frankfurt on Main (Maurer et al, 2006)



Silver stain, Real amyloid beta plaques and tau protein tangles. Source: Dr. Dale Bredesen website.

ALZHEIMER'S DISEASE (AD)

- **Clinico-pathophysiological** entity responsible for most cases (60-70%) of dementia (>30 million people) (Prince at al, 2014).

Clinico

- NINCDS-ADRDA criteria 1984
- DSM 2000
- NIA-AA criteria 2011
- IWG 2007 / 2014

Pathophysiological

- **Histopathological studies**
- **In vivo biomarkers (Amyloid-β and tau)**

Dementia symptoms + Pathology associated with symptoms (Aβ,tau)

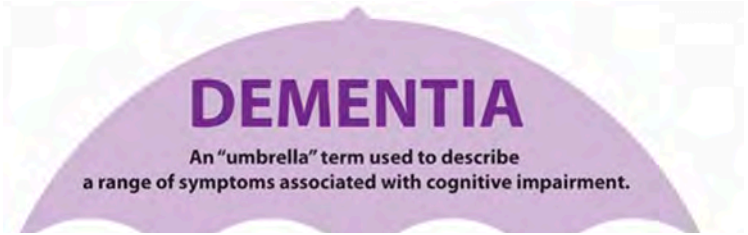
Problem with the purely clinical diagnosis of AD

- Post-mortem studies show that ~30% of patients diagnosed with AD by dementia specialists did not have significant underlying Aβ and tau pathologies in the autopsies (Beach *et al.*, 2012).

Dementia versus Alzheimer's disease

- **What is dementia ?**

  A clinical syndrome characterized by a progressive cognitive decline that leads to an impairment of the activities of daily living.



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Pathophysiological

- **Histopathological studies**
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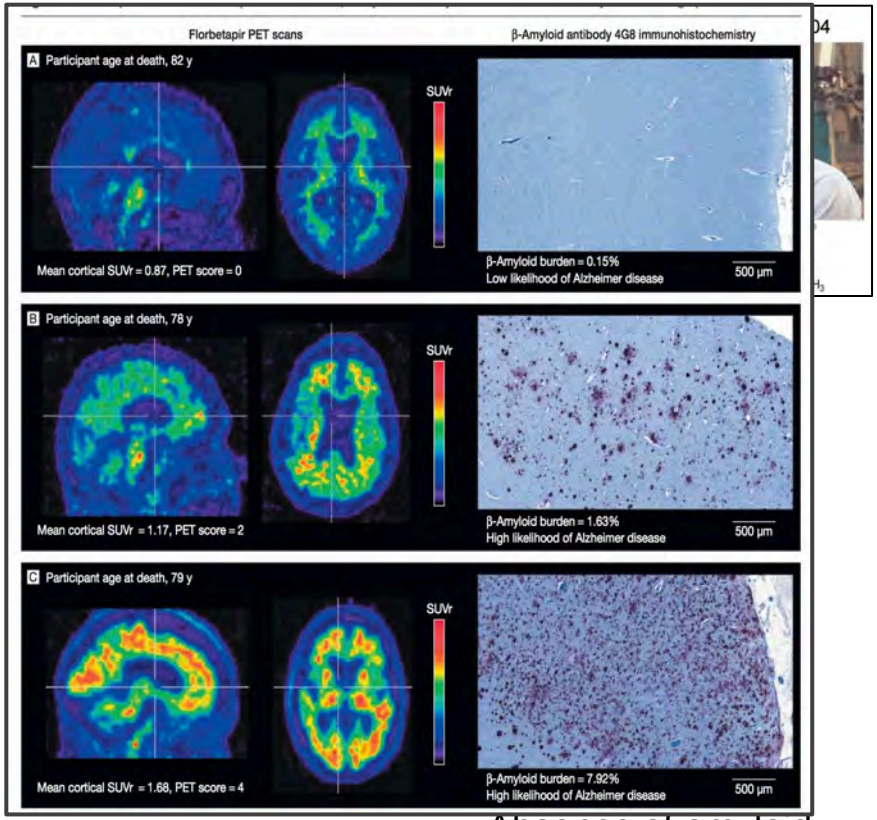
Dementia symptoms + Pathology (Aβ,tau)

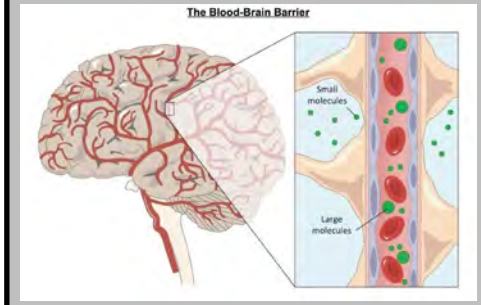
Biomarkers of AD pathology available in clinical practice



presence amyloid

Absence of amyloid

FLUID BIOMARKERS OF AD



Cerebrospinal fluid

Blood

Can we diagnose Alzheimer’s disease with a blood test?

Answer: No

Alzheimer's disease biomarker -aid diagnosis

STEP 1 OBJECVITIVE COGNITIVE IMPAIRMENT ?

↓ YES

STEP 2 ALZHEIMER'S DISEASE IN THE DIFFERENTIAL ?

- Ekplecn"ej ctcevgtkuvke"*ej cpi g."hkuv"u{o rvqo u+
- Ncd"vguvkpi "vq"kf gpvkh{"vtgcvcdng"ecwugu
- Dtckp"EV1O TK

↓ YES

STEP 3 ALZHEIMER'S DISEASE PATHOPHYSIOLOGY ?

- Alzheimer's disease pathology biomarkers

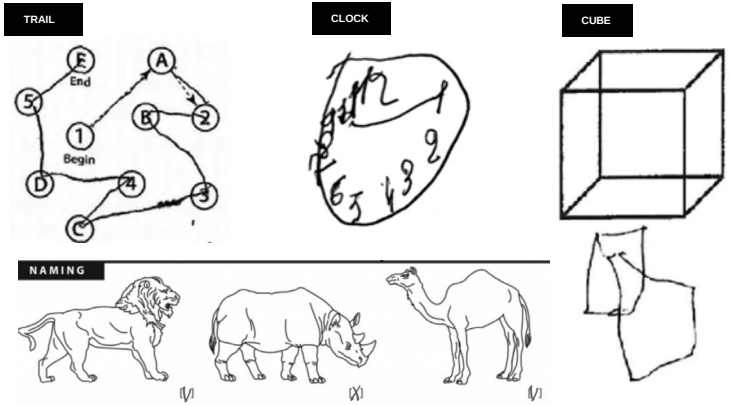
STEP 4 DKQO CTMGT/CKF"FKCI P QUKU"QH"CN\ J GKO GT□U"FKUGCUG

Objective cognitive impairment ?

Main Cognitive Domains
Memory
Executive
Language
Attention
Visuo-spatial

- Clinical Assessment
- Cognitive Testing

Brief bedside testing
Neuropsychological evaluation



Objective cognitive impairment ?

No → Cognitively Normal → Subjective impairment

Yes → Mild Cognitive Impairment → Dementia

Objective cognitive impairment ?

Objective cognitive impairment ?

Yes

Mild Cognitive Impairment

Dementia

Alzheimer's disease biomarker -aid diagnosis

STEP 1 OBJECVITIVE COGNITIVE IMPAIRMENT ?

↓ YES

STEP 2 ALZHEIMER'S DISEASE IN THE DIFFERENTIAL ?

- Clinical characteristic (change, beginning of symptoms)
- Lab testing to identify treatable causes RPR, HIV, TSH, B12
- Brain CT/MRI

Case – The importance of blood lab testing

ML, female, 66, memory decline over the past 2 years, worsening in the past 6 months. She reported 2 falls in the past month and in the exam presented some unsteadily walk (neuropathy).
MOCA score: 24/30, 2/5 delayed recall
Did not want perform neuropsyc
MRI: no cerebrovascular disease, atrophy compatible with the age
B12: 126 pg/ml (Reference 200-400)
Plan: B12 replacement and reevaluation / MOCA score: 27/30, 4/5 delayed recall

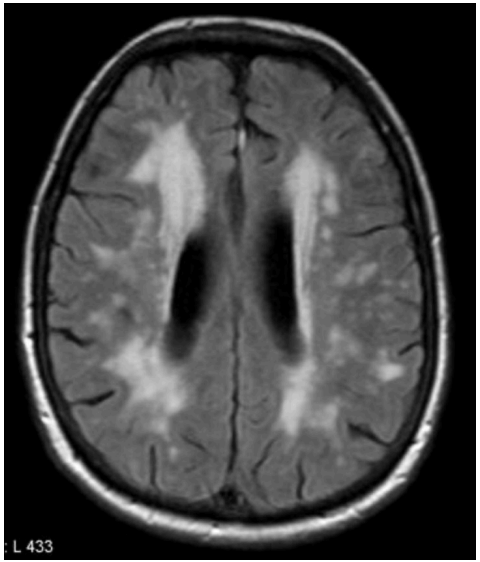
Case – Brain MRI to assess cerebrovascular disease

S. is a 78-year-old man who smokes for 30 years, overweight, has a resistant hypertension. Mild global disfunction that appeared suddenly 3 years (MOCA = 24/30) ago when had a diagnosis of MCI and remains stable (based on testing done by PCP). No problem to perform ADLs

MOCA = 24

B12 and TSH- No particularities

MCI due to cerebrovascular disease



Alzheimer’s disease biomarker -aid diagnosis

STEP 1 OBJECVITIVE COGNITIVE IMPAIRMENT ?

↓ YES

STEP 2 ALZHEIMER’S DISEASE IN THE DIFFERENTIAL ?

- Clinical characteristic
- Lab testing to identify treatable causes
- Brain CT/MRI

↓ NO

STEP 3 ALZHEIMER’S DISEASE PATHOPHYSIOLOGY ?

- Alzheimer's disease pathology biomarkers

AD biomarkers available to order at UPMC with regulatory approval to be shared with patients and used in patient care

Who can order ? Any clinician providing dementia care

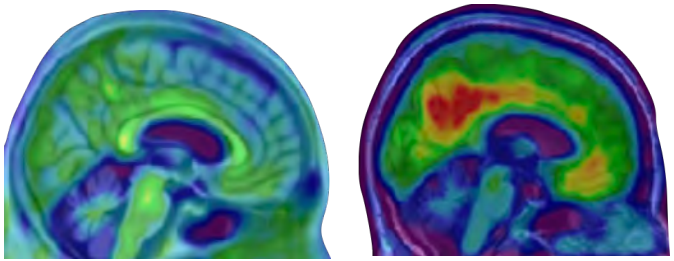
Precision

	Regulatory approval	Coverage
Aβ PET	FDA	No
CSF Aβ / p-tau	CLIA	Insurance
Blood p-tau	CLIA	Part of a study
Blood Aβ	CLIA	Out of pocket

Accessibility

Biomarkers of Aβ pathology

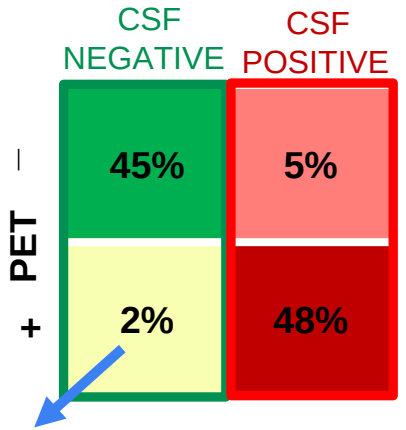
Aβ PET



NEGATIVE POSITIVE

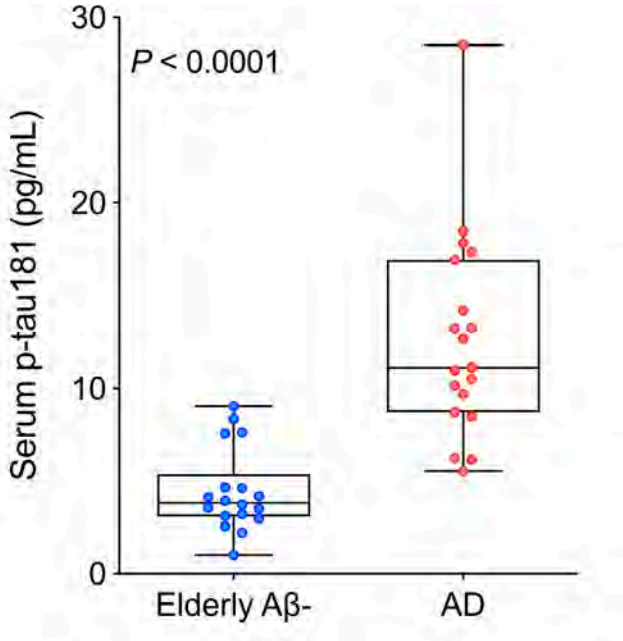
False N

CSF Aβ



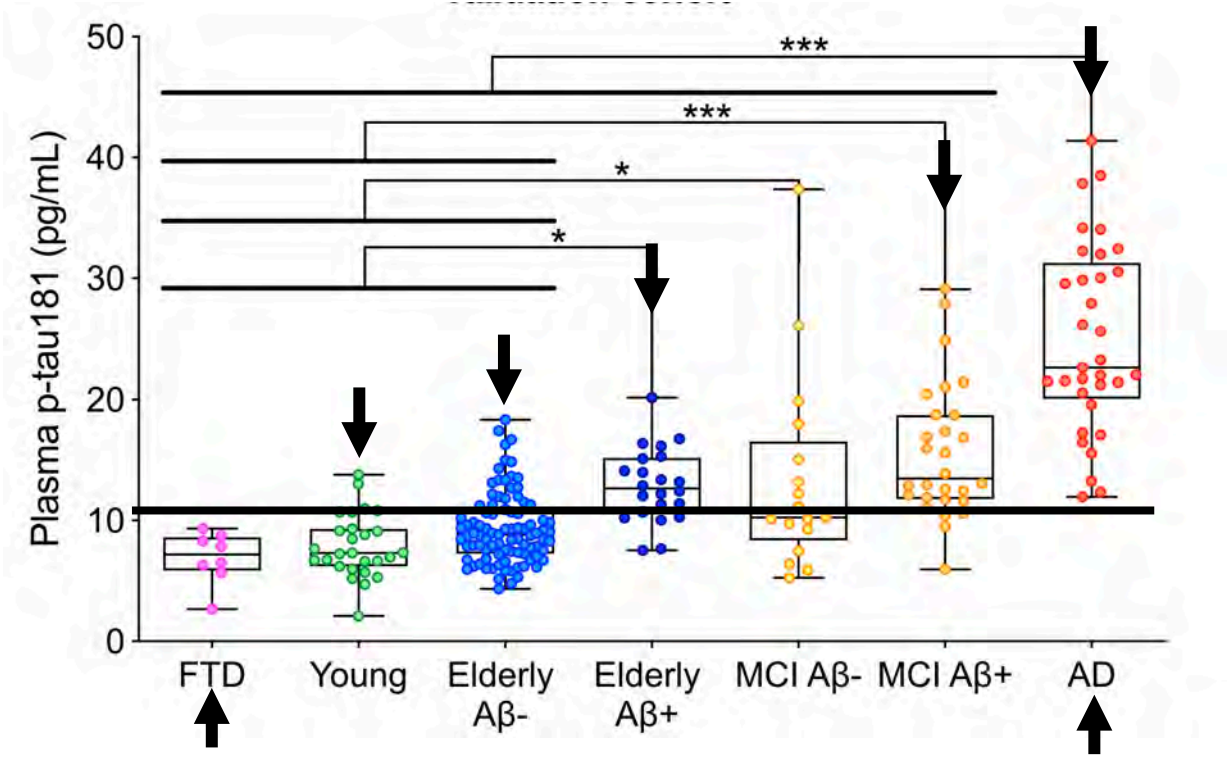
However, complex, invasive, expensive

SERUM AND PLASMA P-TAU181 DIFFERENTIATES ALZHEIMER'S DISEASE PATIENTS FROM AGE-MATCHED CONTROLS IN THE **DISCOVERY COHORT**



(Karikari & Pascoal *et al.,* Lancet Neurology 2020)

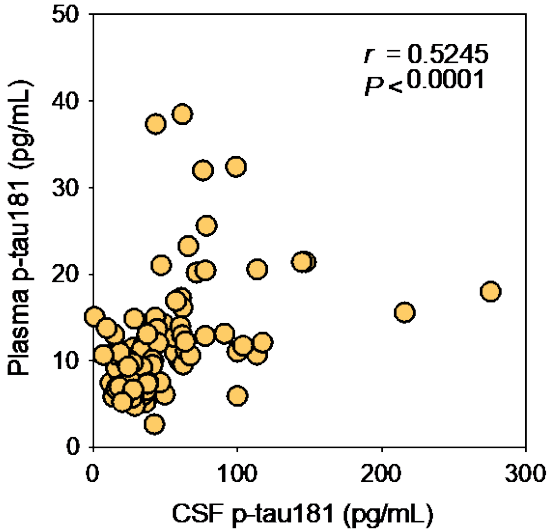
PLASMA P-TAU181 SHOWS A **GRADUAL INCREASE** ALONG THE ALZHEIMER'S DISEASE SPECTRUM IN THE **VALIDATION COHORT**



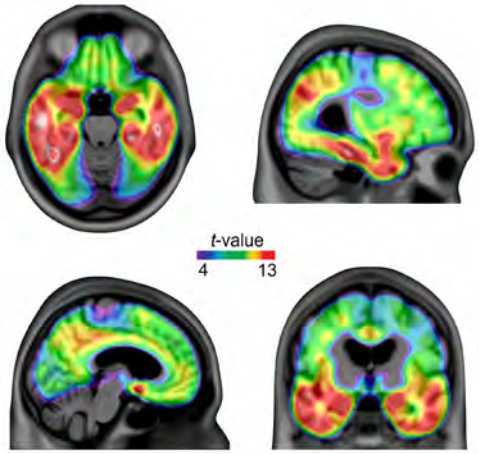
(Karikari & Pascoal *et al.,* Lancet Neurology 2020)

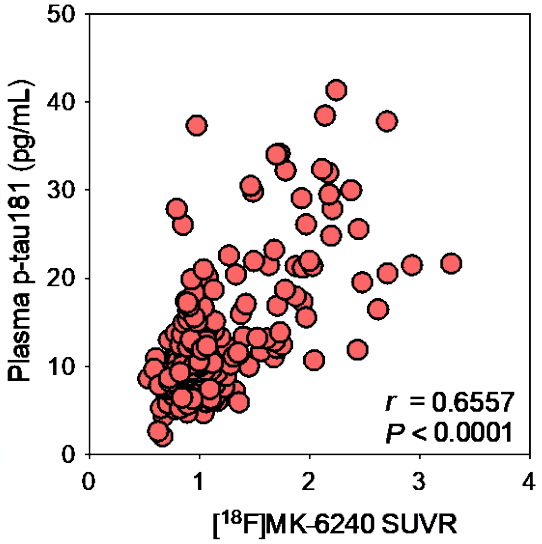
Plasma p-tau181 **correlates with BRAIN TAU PATHOLOGY**

CSF AD marker



PET AD marker

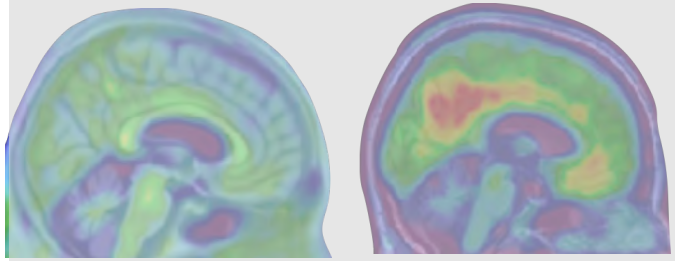




(Karikari & Pascoal *et al.,* Lancet Neurology 2020)

Biomarkers of Aβ pathology

Aβ PET



NEGATIVE POSITIVE

CSF Aβ

PET	CSF NEGATIVE	CSF POSITIVE
-	45%	5%
+	2%	48%

Blood p-tau181

PET	BLOOD NEGATIVE	BLOOD POSITIVE
-	30%	20%
+	3%	47%

However, complex, invasive, expensive

Alzheimer's disease biomarker -aid diagnosis

STEP 1 OBJECVITIVE COGNITIVE IMPAIRMENT ?

↓ YES

STEP 2 ALZHEIMER'S DISEASE IN THE DIFFERENTIAL ?

↓ YES ????

STEP 3 ALZHEIMER'S DISEASE PATHOPHYSIOLOGY ?

- Alzheimer's disease pathology biomarkers

JAMA Neurology | Original Investigation

Amyloid Positron Emission Tomography and Subsequent Health Care Use Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia

Gil D. Rabinovici, MD; Maria C. Carrillo, PhD; Charles Apgar, MBA; Ilana F. Gareen, PhD; Roee Gutman, PhD; Lucy Hanna, MS; Bruce E. Hillner, MD; Andrew March, MHA; Justin Romanoff, MA; Barry A. Siegel, MD; Karen Smith, BS; Yunjie Song, PhD; Christopher Weber, PhD; Rachel A. Whitmer, PhD; Constantine Gatsonis, PhD

Case – Biomarker for diagnostic closure

LN, 75yo, Male, visited a cognitive clinic due to progressive cognitive decline over
forgot his Social Security Number and had difficulty driving with an associate road

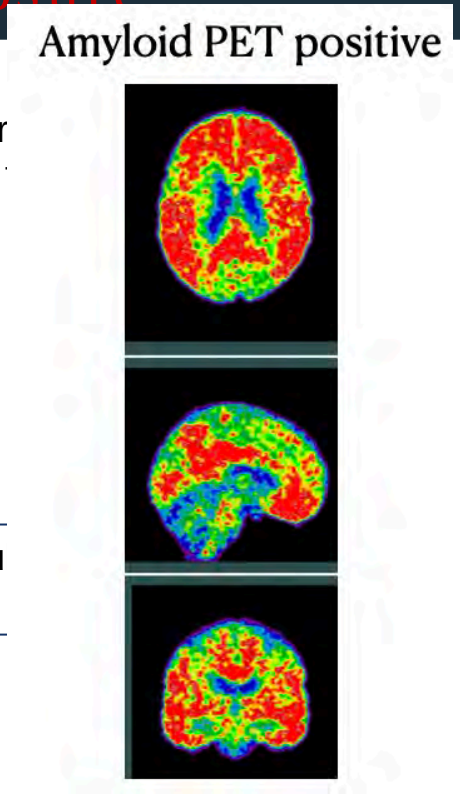
More recently, they report apraxia with difficulty buttoning his shirt.

The patient sleeps reasonably well.

Never took care of finances, but not driven anymore

NPS assessment: Major Neurocognitive Disorder/Dementia. The pattern of particu
executive function, and verbal memory compatible with AD

B12 and TSH- No particularities
MRI done outside , no major cerebrovascular disease



<u>The clinical and paraclinical data suggest mild dementia likely due to Alzheimer's disease</u>

Case– Biomarker for differential of other likely cause

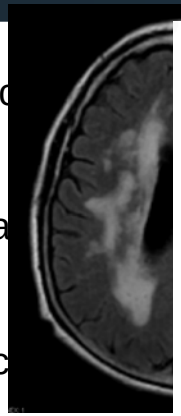
JD is a ~75-year-old male patient who presents to the cognitive clinic
problems.

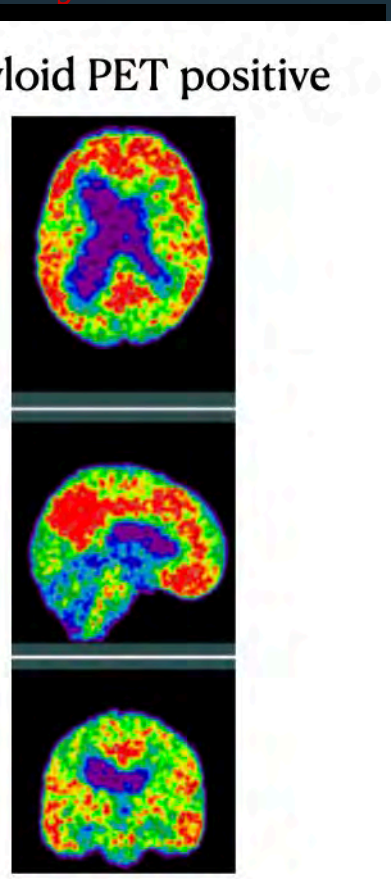
4 year before started with word substitution . Then, language issue a
that got progressively worse since then.

In the office, complaints of memory problems and word-finding diffic

MOCA=15. NPS assessment: The pattern of impaired language, executive func

The data suggest dementia with predominant decline in language and memory
in MRI suggests the possibility of vascular cognitive impairment. F
memory/language suggest the possibility of associated neurodegenerative dis





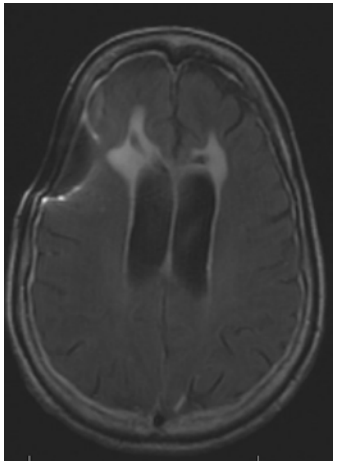
Mixed dementia vascular (MRI), AD (PET)

Case 1– Biomarker for prognosis

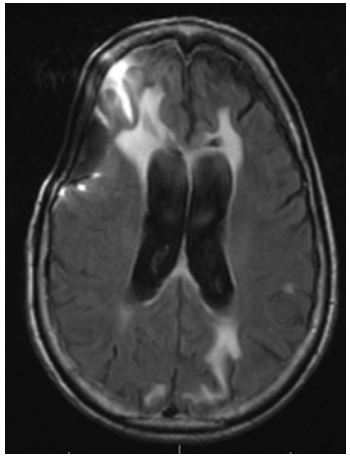
JM is a 65-year-old male who suffered from an aneurysmal rupture / subarachnoid hemorrhage in 8 years ago with residual cognitive impairment.

Approximately two years ago, patient's husband has reported a progressive decline, as well as severe apathy with the patient needing to be prompted to perform even the simplest tasks such as getting in and out of the shower. A recent MRI scan showed no new lesions.

2 years before



Consultation



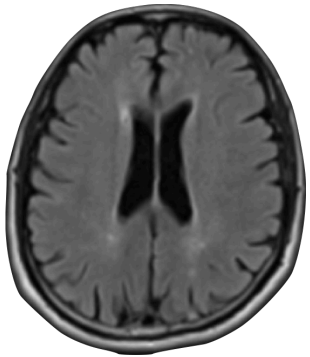
CSF amyloid- Positive

Mixed dementia
vascular (MRI), AD (CSF)

Case – Amyloid (+) is always AD?

F. is a 58 years old woman that hospitalized due to elaborated visual hallucinations (small animals in the room). The family reported that in a previous evaluation the PCP had mentioned that she had both AD and PD. During this hospitalization, the patient presented severe rigidity after the use of antipsychotics and CSF requested. Reported REM sleep disorder.

CSF amyloid - Positive



Brain MRI

Lewy body dementia

Case – Biomarker qualifying for treatment ?

JD is a ~65-year-old female patient who presents with isolate memory decline. Cannot take care of finances.

MOCA=20. NPS: impaired language, executive function, and verbal memory

CSF amyloid- Positive

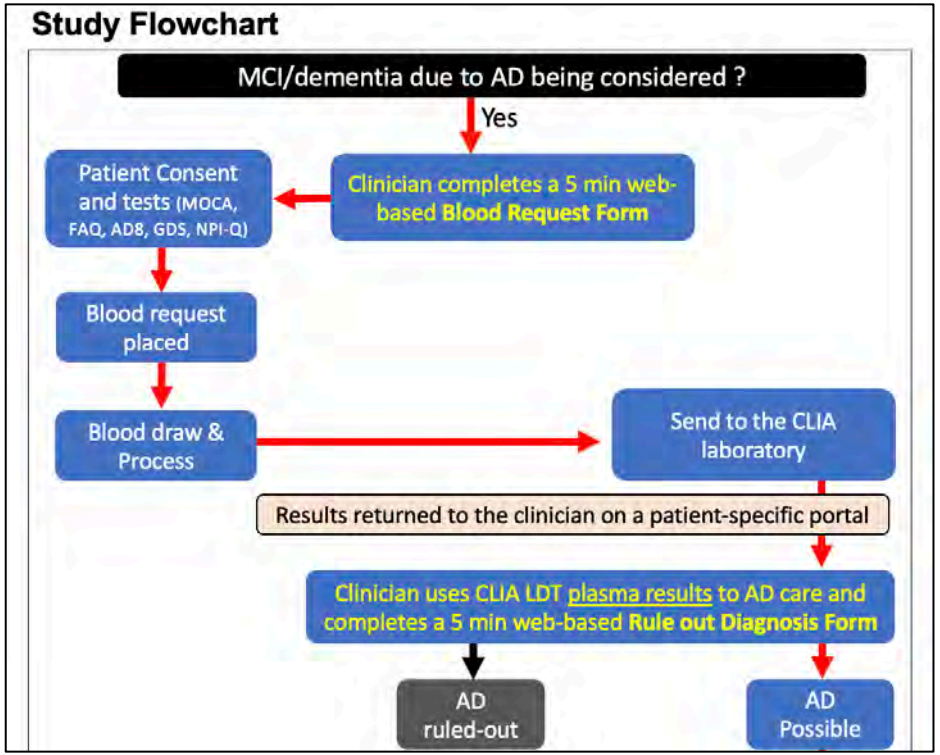
Mild dementia due to AD

CliPAD (Clinical utility of Plasma biomarkers of Alzheimer's Disease)

Pilot: 1,000
Start data: 01 Sept 2023

Link for UPMC clinicians to request blood tests for free

https:// research.wpic.upmc.edu/ clipad



University of Pittsburgh

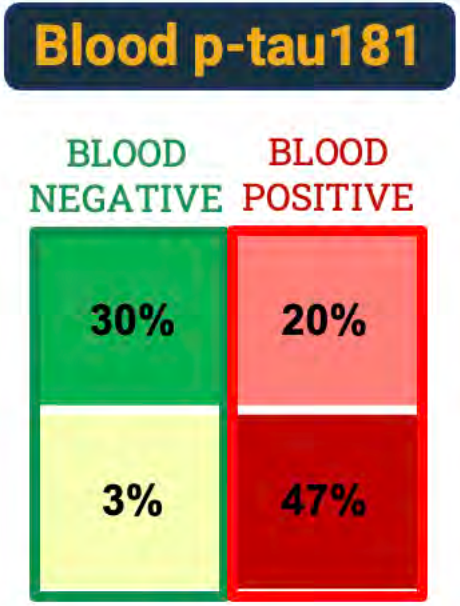
UPMC
University of Pittsburgh Medical Center

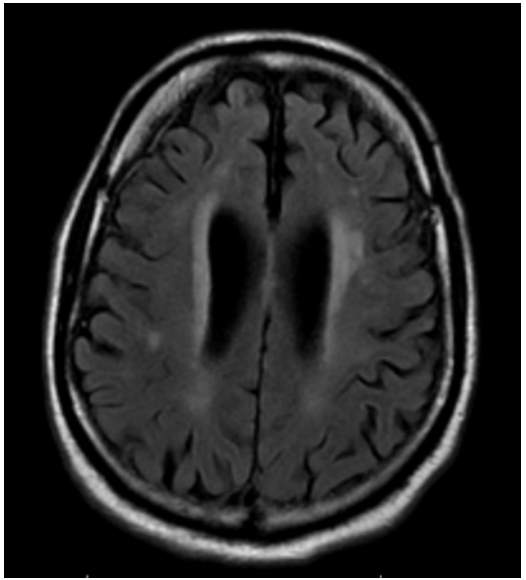
Case – Rule-out blood test

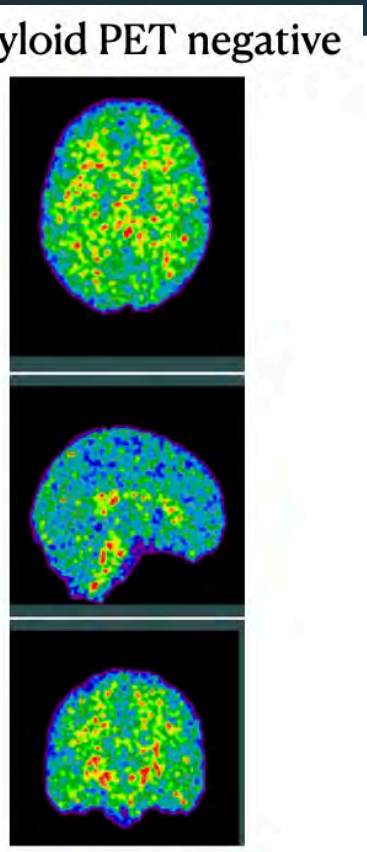
R is a 75-year-old male patient with memory decline over the past 3 years names of friends and doctors he know for many years . In addition, the pa impaired sense of direction and often forgets conversations with

recall

es







SUMARY/CONCLUSION

The use of in vivo biomarkers is crucial for an accurate diagnosis of the cause of dementia symptoms. Although an accurate diagnosis is important for families and patients in many cases, it does not necessarily alter the patient's prognosis without access to effective treatments.

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University of Pittsburgh

UPMC LIFE CHANGING MEDICINE

NIH National Institute on Aging

ALZHEIMER'S ASSOCIATION

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