Mild cognitive impairment and dementia in neuro-degenerative disorders

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KEEP MEMORY ALIVE
Supporting the Mission of Cleveland Clinic Lou Ruvo Center for Brain Health
ALZHEIMER'S | HUNTINGTON'S | PARKINSON'S
MULTIPLE SYSTEM ATROPHY | MULTIPLE SCLEROSIS

NEVADA ADRC

Incidence of Common Neurological Diseases

Disease	Incidence (per 100,000)	New Cases (per year)
Dementia	268	670,000
Alzheimer's disease	188	470,000
Stroke	200	500,000
Seizures	50	124,000
Parkinson's disease	16	40,000
Primary neoplasm	15	37,500
Amyotrophic lateral sclerosis	6	15,000
Primary brain tumor	6	15,000
Multiple sclerosis	2	5,000
Gullain Barre'	1	2,500
Huntington's disease	0.3	750

Timely Diagnosis of AD Is an Unmet Need

- Diagnosis is delayed by an average of 2-3 years after symptom onset[1,2]
- 25% of patients clinically diagnosed with probable AD during their lifetime did not have AD pathology at autopsy[3,4]
- 50% of patients with any form of dementia are not formally diagnosed[5]

AD=Alzheimer's Disease

[1]Balasa M et al; Neurological Tissue Bank/University of Barcelona/Hospital Clínic NTB/UB/HC Collaborative Group. *Neurology*. 2011;76(20):1720-1725. [2]Boise L et al. *Am J Alzheimers Dis Other Dem*. 1999;14(1): 20-26. [3]Beach TG et al. *J Neuropathol Exp Neurol*. 2012;71(4):266-273. [4]Sabbagh MN et al. *J Alzheimers Dis*. 2017;56(2):441-446. [5]Boustani M et al; U.S. Preventive Services Task Force. *Ann Intern Med*. 2003;138(11):927-937.

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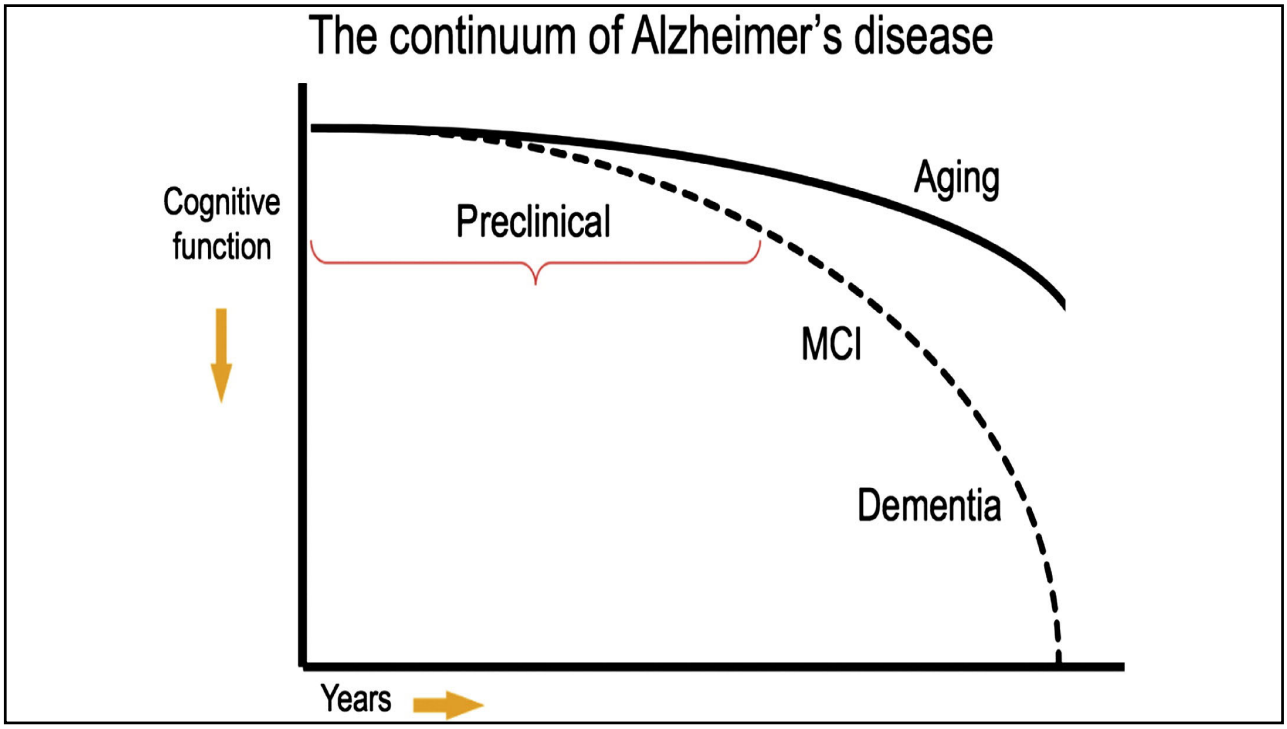


Concept #1

- Subjective memory complaint is no longer considered the “worried well”
- The ICD10 code is R41.3
- A self report of a memory complaint should not be dismissed or downplayed but should be evaluated

Subjective memory complaint has predictive value

- A Brazilian study examined 248 subjects. They were asked whether they had memory complaints and underwent a cognitive impairment screening.
- A total of 147 patients presented with subjective memory complaints, and 43 were further classified as demented or "cognitively impaired not demented". Subjective memory complaints presented a sensitivity of 100% and a negative predictive value of 100%. This suggests that subjective memory complaints are an indicator for cognitive impairment screening.

Subjective memory complaints in the elderly: a sign of cognitive impairment? Jacinto AF, Brucki SM, Porto CS, Arruda Martins Md, Nitrini R, - Clinics (Sao Paulo) - March 1, 2014; 69 (3); 194-7

SMC is predictive of progression and pathology

- SMC is associated with increased risk of progression
- SMC is associated with higher amyloid burden on PET
- ApoE4 carrier status influences the effect of SMC on burden and progression
- SMC associated with neuropathology of AD

Concept # Mild Cognitive Impairment could be the prodrome of AD Dementia

- Cognitive
  - Mild Cognitive Impairment MCI (memory)
    - 10% - 15% conversion to AD per year
    - 50% Conversion after 5 yrs >90% conversion by 10 years
  - Criteria
    - Memory difficulties corroborated by informant that interfere with adaptive functioning
    - Selective deficit as measured by neuropsychological tests; other functions normal or near normal
    - Intact IADLs
    - Not demented

Petersen 98 Neurology; Fisk 03 Neurology, Morris 01, Neurology

Diagnostic Criteria of MCI

Clinical and cognitive criteria

- Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (historical or observed evidence of decline)
- Objective evidence of impairment in one or more cognitive domains, typically including memory (formal or bedside testing)
- Preservation of independence in functional abilities
- Not demented

Examine etiology of MCI consistent with AD pathophysiology

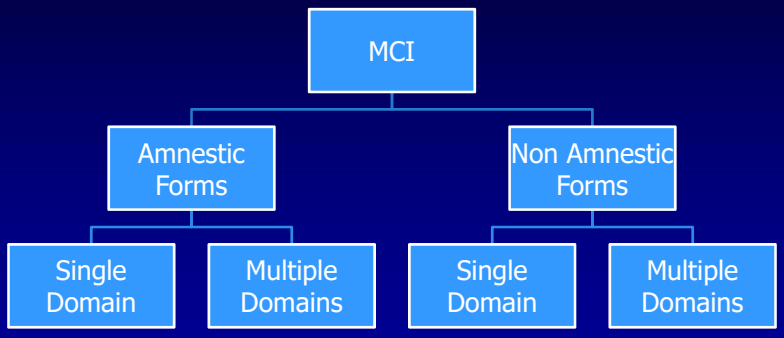
- Rule out vascular, traumatic, medical causes of cognitive decline
- Provide evidence of longitudinal decline in cognition
- Report history consistent with AD genetic factors

Albert et al, Alzheimer's and Dementia 2011

Clinical Criteria for MCI of AD Type

- Subjective memory complaint reported by subject or informant
- Global cognition intact (MMSE >25)
- Memory impairment confirmed objectively
- ADL impairment is insufficient for diagnosis of dementia; IADL may be effected (GDS = 3 or CDR = 0.5)
- No medical / other etiology for memory deficit.

MCI: Definitions and Categories



Albert 2011, Alzforum.org

Diagnosis of MCI

- Not established by consensus criteria
- Clinically apply Petersen criteria 2004 recast by Albert 2011
- Neuropsychological assessment
- Apo E genotyping
- Screening eval (imaging, standard labs) low yield

Prediction of Conversion from MCI to AD

- **MCI conversions to AD can be predicted by**
  - **Worse memory scores (<<1.5 SD below age and education adjusted norms)**
  - **Smaller hippocampi on NeuroQuant (5th percentile or below)**
  - **Low CSF Aβ and high tau (ADNI reports that 33/37 subject converting to AD within one year had the CSF profile)**
- **ApoE4 positivity**
- **PIB uptake**

Follow-Up of PIB-Positive ADNI MCI's N = 65, 12 mo. follow-up

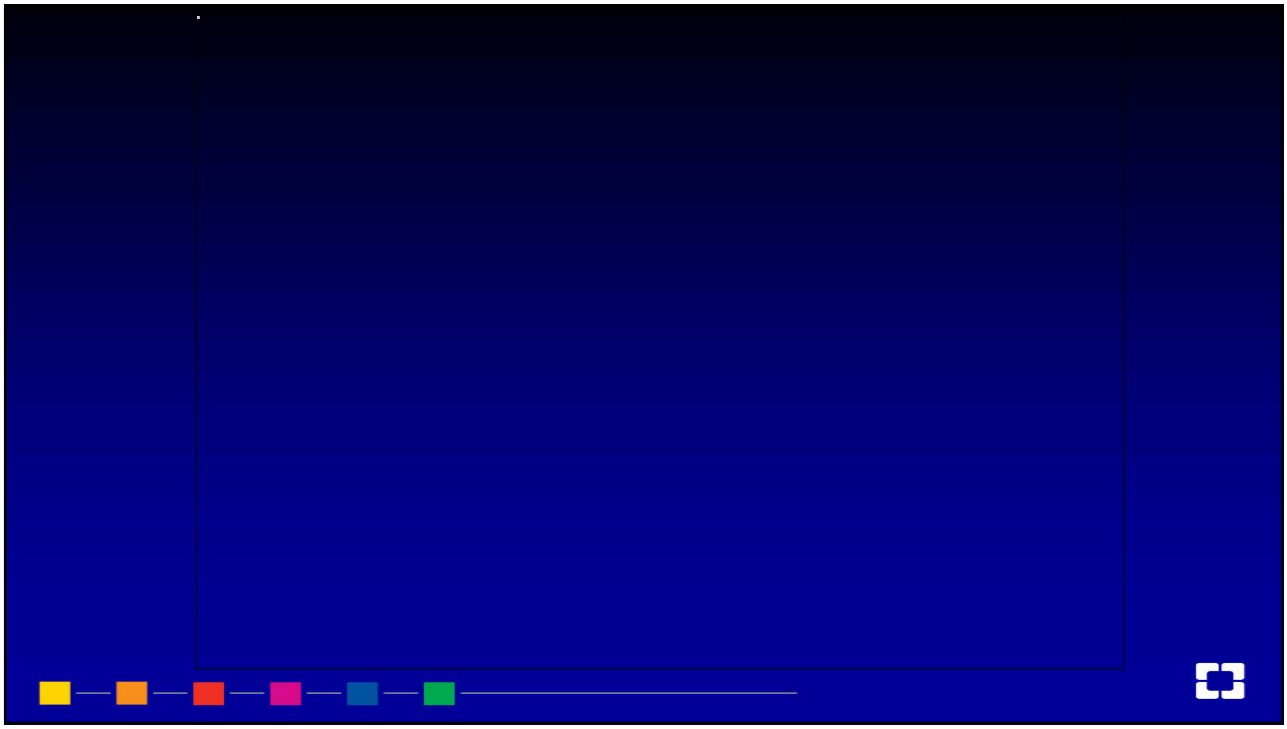
- PiB(+)= 47
- Converters to AD=14

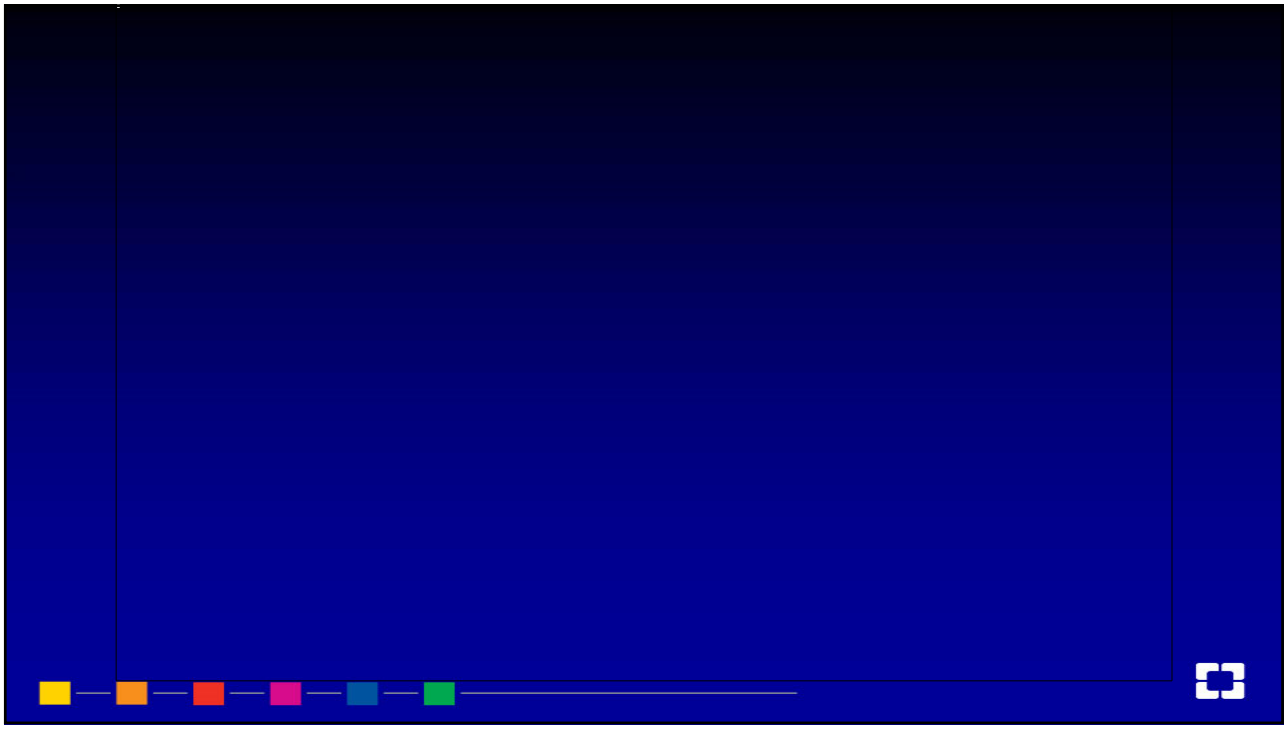
- PiB(-)=18
- Converters to AD=3

PiB-Positivity in Predicting Clinical Conversion in MCI

- Melbourne Cohort N=28, 21 mo. follow-up
- PiB(-)=13
  - Converters to AD=1
- PiB(+)=15
  - Converters to AD=12

- Pittsburgh Cohort N=23, 24 mo. follow-up
- PiB(-)=10
  - Converters to AD =0
- PiB(+)=13
  - Converters to AD =5





Diagnostic Criteria of Dementia

A. Dementia
- Interferes with ability to function at work or at usual activities
- A decline from a previous level of functioning
- Not delirium or psychiatric disorder
- Diagnosed by history, examination
- Involves at least 2 cognitive domains:
  - Memory
  - Reasoning and judgment
  - Visuospatial
  - Language
  - Personality, behavior, comportment

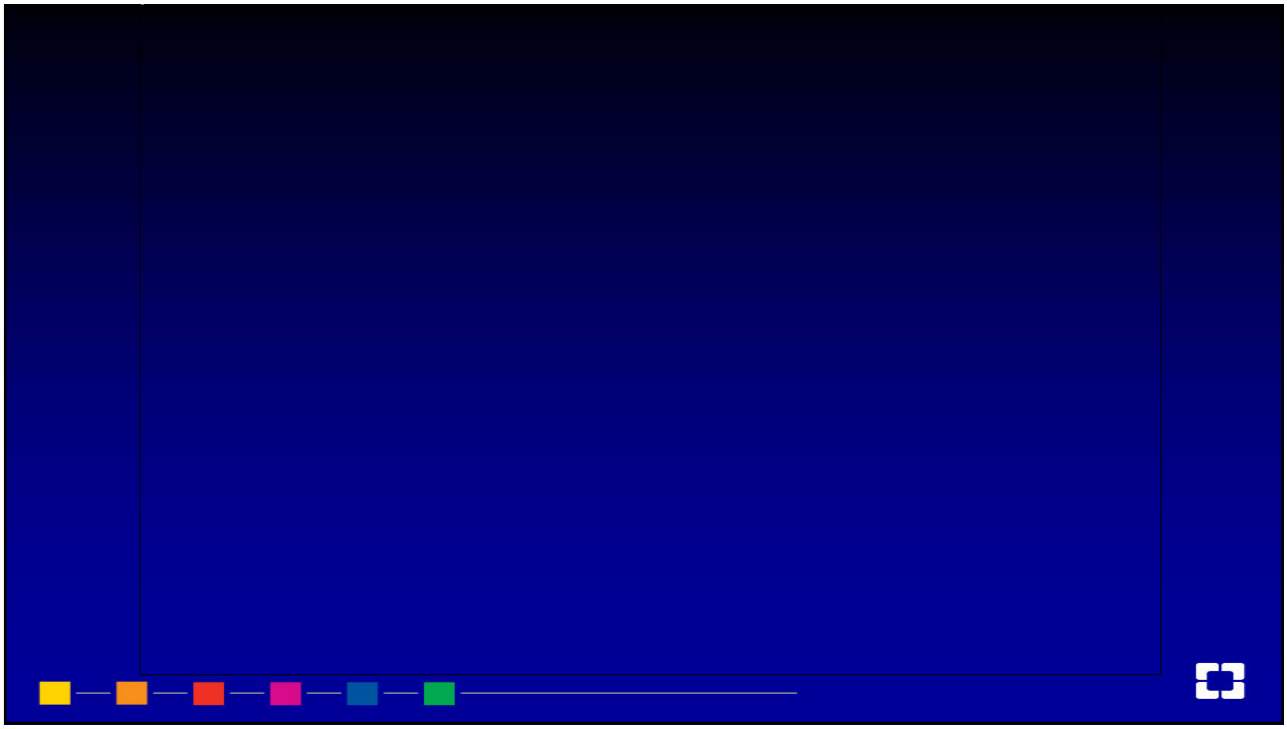
McKhann et al, Alzheimer's and Dementia 2011

Diagnostic Criteria of AD

A. Probable AD [based on clinical criteria]
- Dementia
- Insidious onset
- Worsening of cognition over time
- Amnestic vs. non-amnestic presentation
- Not due to another dementia diagnosis

B. Probable AD with evidence of AD pathophysiology
- Ab (CSF or amyloid PET)
- Neuronal injury (CSF tau, FDG-PET, structural MRI)

McKhann et al, Alzheimer's and Dementia 2011



Concept # 3 ATN Criteria will reframe our approach clinically

A/T/N score	NIA-AA classification
A-/T-/N-	Dementia, unlikely due to AD
A+/T-/N-	Intermediate likelihood; probable AD dementia based on clinical criteria
A+/T+/N-	High likelihood; probable AD dementia; based on clinical criteria
A+/T-/N+	High likelihood; probable AD dementia; based on clinical criteria
A+/T+/N+	High likelihood AD pathophysiology
A-/T+/N-	Probable AD dementia; based on clinical criteria
A-/T-/N+	Intermediate likelihood; probable AD dementia based on clinical criteria
A-/T+/N+	Intermediate likelihood; probable AD dementia based on clinical criteria

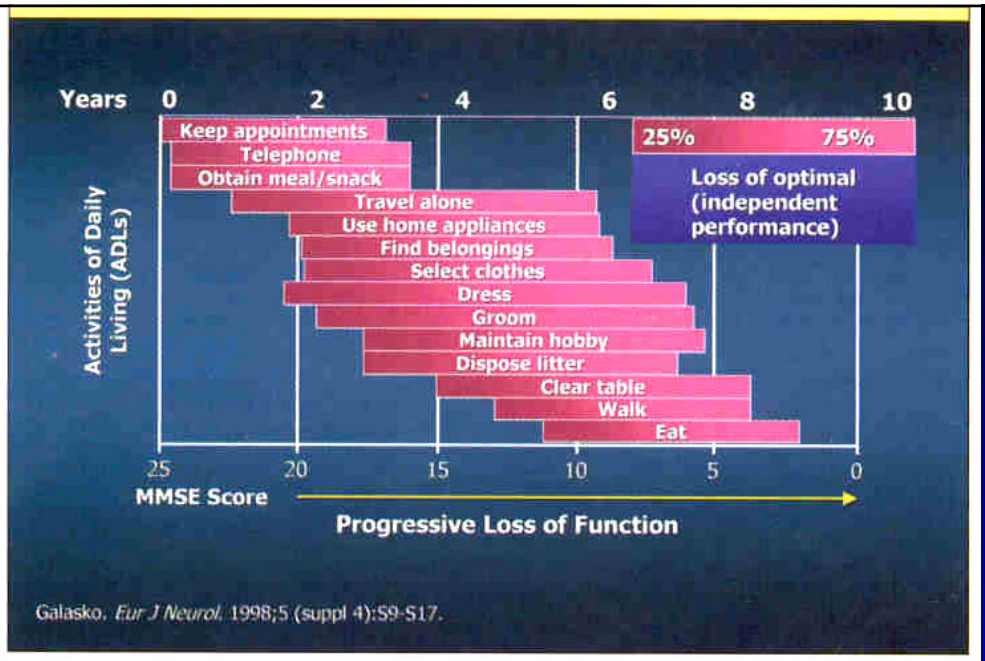


Figure 6 Loss of activities of daily living (ADLs) correlated with MMSE scores.

Concept # 4 The Differential Diagnosis of Dementia is broad

- Alzheimer's Disease (AD)
- Dementia with Lewy Bodies (DLB)
- AD & Vascular Dementia (mixed)
- Vascular Dementia
- Frontotemporal Dementia (FTD)
- Parkinson's Disease
- Huntington's Disease
- Other Degenerative Diseases (PSP, OPCA, ALS with dementia)
- Dementias Secondary to Alcohol
- Depression/Pseudodementia
- Normal Pressure Hydrocephalus (NPH)
- Structural Lesions
- Metabolic Disorders (Hypothyroidism)
- Infections (e.g. neurosyphillis, AIDS, CJD)
- Drug Intoxication

Dementia with Lewy Bodies

- **Parkinsonism coexisting with cognitive decline**
- **Visual hallucinations**
- **Clinical fluctuations**
- **Neuroleptic sensitivity**
- **Newest criteria: REM behavioral disturbance**
- **Cognitive pattern may be subcortical or mixed cortical/subcortical with prominent visuospatial abnormalities**
- **Prone to other neuropsychiatric features**
- **May possibly progress faster**
- **Pathologically characterized by worse cholinergic loss, fewer plaques and tangles, neocortical Lewy bodies, lower Braak stages.**
- **Treatment could include cholinesterase inhibitors and L-dopa**

Vascular Dementia

- May start abruptly immediately after a cerebrovascular accident
- Multi-focal distribution of cognitive decline
- Focal neurologic exam
- Gait disturbance, incontinence, and fluctuating changes are common (aka Binswanger's [290.12]
- Vascular changes on imaging obligatory
- NINDS-AIREN criteria applicable
- Most vascular dementia mixed with AD
- Hachinski Score ≥ 7
- Treatment involves management of stroke risk factors and ChEIs

Frontotemporal Dementias

- Also known as Pick's disease
- Now many linked to Chromosome 17 ("the tau-opathies")
- Usually earlier age of onset compared to AD (average 40-65 years old)
- Early prominent language changes including anomia, aphasia, echolalia, and perseverative speech
- Social skills lost early
- Inappropriate behavior and judgment, disinhibition, and lack of insight
- Personality changes and withdrawal prominent

Progressive Aphasias

- Early prominent language changes including anomia, aphasia, echolalia, and perseverative speech
- Three subtypes now recognized (logopenic progressive aphasia-frontal variant, semantic dementia, progressive non fluent aphasia
- Progressive non fluent aphasia
  - Involves effortful speech with agrammatism and frequent apraxia of speech
  - Post-hoc comparisons with HC showed bilateral GM atrophy in the caudate, putamen and thalamus, in bvFTD; a left-confined GM reduction in the amygdala in SD; and bilateral GM atrophy in the caudate and thalamus, and left-sided GM reduction in the putamen and amygdala in PNFA. Left insula and adjacent inferior frontal gyrus
  - Pathologically associated with CBD or FTLD pathology with tau inclusions or PSP
- Semantic dementia
  - Characterized by loss of word and object meaning and understanding
  - Abnormalities in the left rostral temporal lobes
  - Ubiquitin positive TDP proteinopathy pathology have both been associated with it
- Logopenic Progressive Aphasia
  - speech rate was slow, with long word-finding pauses.
  - Grammar and articulation were preserved, although phonological paraphasias could be present. Moderate anomia
  - Repetition and comprehension were impaired for sentences but preserved for single words, and naming was moderately affected.
  - Atrophy or decreased blood flow was consistently found in the posterior portion of the left superior and middle and posterior temporal gyri and inferior parietal lobule.
  - Recent studies suggest that Alzheimer disease may be the most common pathology underlying the LPA clinical syndrome.

Degenerative Dementias

- AD
- DLB
- FTD
- Mixed Dementias
- Prion Diseases
- Parkinson's Disease
- Huntington's Disease
- Progressive Supranuclear Palsy
- Guamanian ALS-PD-AD

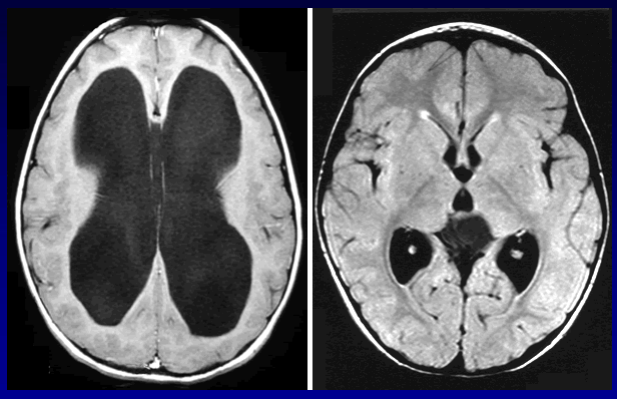
Dementias Possibly Amenable to Treatment

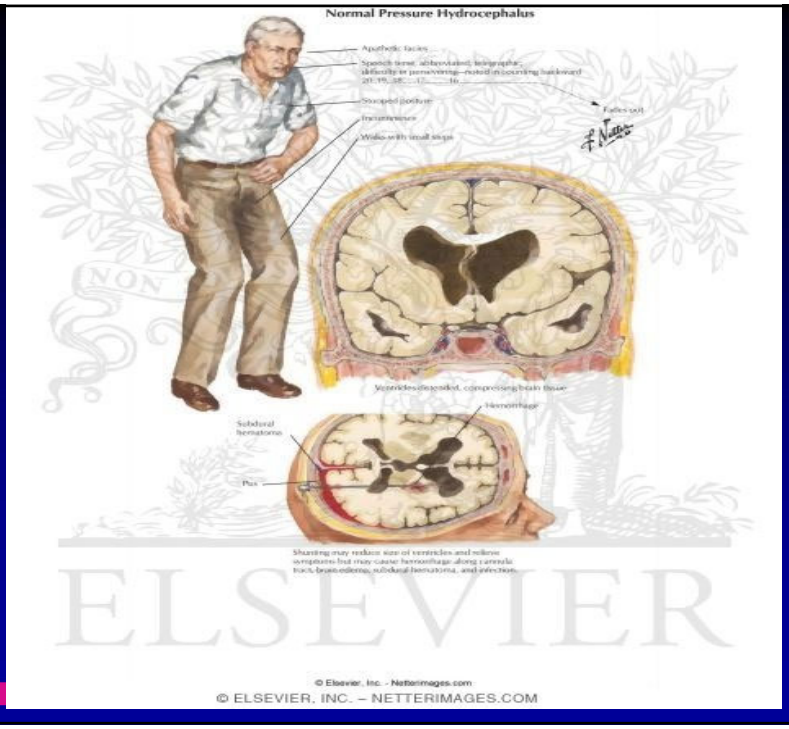
- Hypothyroidism
- Neurosyphillis/ Infectious Etiologies
- Normal Pressure Hydrocephalus
- Vascular Dementia
- Vitamin B12 Deficiency
- Structural Lesions
- Metabolic Disorders
- Drug Intoxication
- Depression/Pseudodementia
- Wilson's Disease
- Alcohol Related Dementias

Dementias Associated with Other Neurological Signs and Symptoms

- AIDS (neuropathy, myopathy)
- Normal Pressure Hydrocephalus (gait disturbance, incontinence)
- Tumors/Mass Lesions (stroke-like symptoms that are subacute and evolving)
- Subdural Hematoma (stroke-like symptoms that are acute or subacute and evolving)

Normal Pressure Hydrocephalus




Normal Pressure Hydrocephalus
Apathetic facies
Stooped posture
Incontinence
Wide-with small steps
Ventricles dilated, compressing brain tissue
Hemorrhage
Subdural hematoma
Pus
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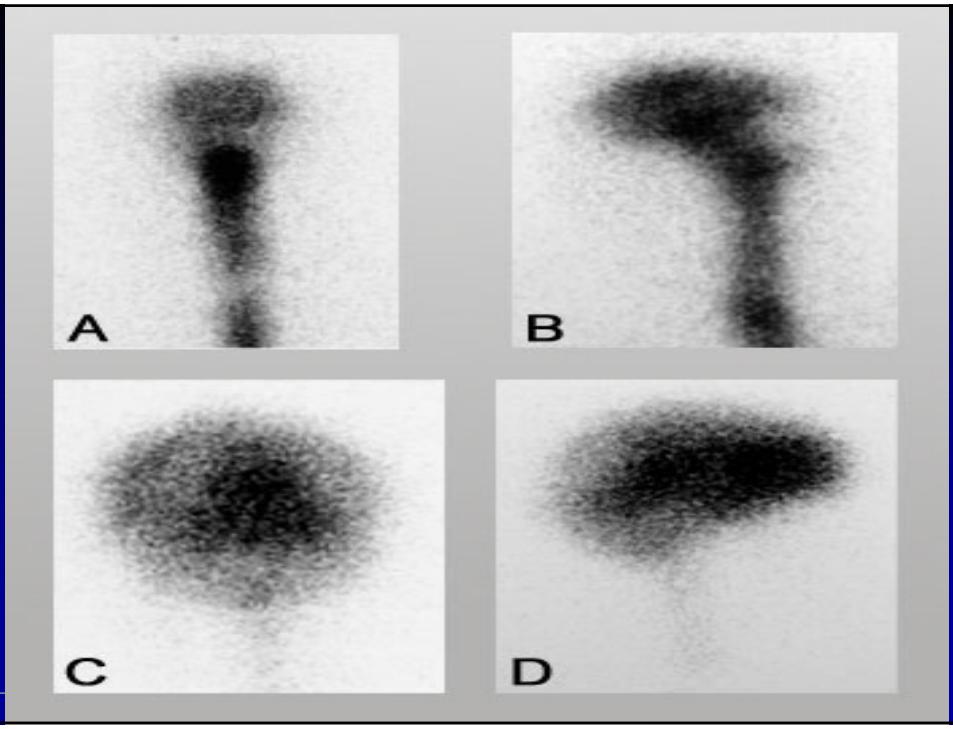
A
B
C
D

Dementias Associated with Other Neurological Signs and Symptoms

- Huntington's Disease (chorea, depression, psychosis, parkinsonism)
- Creutzfeldt Jakob Disease (myoclonus, rapid dementia, EEG changes)
- Parkinson's Disease (rigidity, bradykinesia, gait disturbance, tremor)
- B12 Deficiency (Often associated with subacute combined degeneration: proprioceptive loss, parethesias, hyper-reflexia)

The Current Approach for Evaluation of Patients With Dementia

Routine

- History
- Mental Status Exam
- Neurological Exam
- Chemistry Panel
- Complete Blood Count
- Vitamin B12 level
- Thyroid function studies
- CT/MRI

Optional

- Syphilis serology
- Sedimentation Rate
- Chest X-Ray
- Electrocardiogram
- Urinalysis
- Drug Levels
- HIV testing
- Lyme Serology
- EEG
- PET/SPECT
- ApoE genotyping
- CSF (Aβ42/tau or 14-3-3 for CJD)

Initial consultation: $350
Screening labs: $200
CT/MRI: $1500 to $2000

CT/MRI=computerized tomography/magnetic resonance imaging; CJD=Creutzfeldt-Jakob disease; EEG=electroencephalogram; SPECT=single, photon emission computed tomography.

Farlow MR. Neurologic conditions in the elderly; Alzheimer's disease. In: Nair AK, Sabbagh MH,eds. *Geriatric Neurology*. Hoboken, NJ: Wiley-Blackwell; 2014:9.2.

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Concept # 5: The Clinical Diagnosis of AD is not accurate

- Of 57 individuals clinically diagnosed with AD:
  - 23% (n=13) had no (n=7) or sparse (n=6) Aβ plaques at autopsy
  - Neuropathologically, 12 were diagnosed with a dementia disease other than AD, most frequently caused by aggregation of tau
- **Thus, diagnostic accuracy is 77% for a clinical diagnosis of AD, even among the experts**
- Florbetaben PET was consistent with histopathology in all 12 patients for whom cSUVRs were available

Sabbagh MN et al. *J Alzheimers Dis*. 2017;56(2):441-446.

cSUVRs=composite standardized uptake value ratios

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Concept # 6 AD Biomarkers Are Available, But Not Routinely Used in Clinical Practice in the US

Biomarkers of Aβ amyloid deposition

- Low CSF Aβ42
- PET amyloid imaging

Biomarkers of neuronal injury

- High CSF tau/phosphorylated tau
- Hippocampal volume or medial temporal atrophy
- Rate of brain atrophy
- FDG-PET imaging
- SPECT perfusion imaging
- Less well-validated: fMRI activation studies, resting BOLD functional connectivity, MRI perfusion, MRI spectroscopy, diffusion tensor imaging, voxel-based and multivariate measures

Associated biochemical change

- Inflammatory biomarkers (cytokines)
- Oxidative stress (isoprostanes)
- Other markers of synaptic damage and neurodegeneration

BOLD=blood oxygen level-dependent; FDG=fluorodeoxyglucose; fMRI=functional magnetic resonance imaging.

Albert MS et al. *Alzheimers Dement*. 2011;7(3):270-279.

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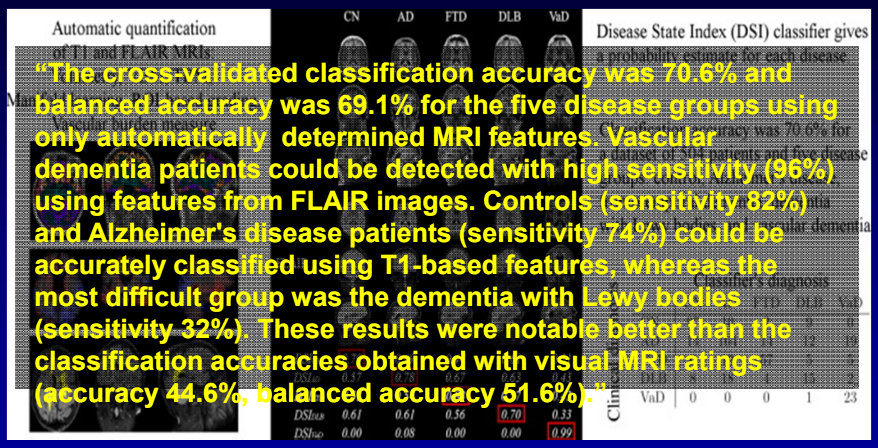
Differential Diagnosis of Neurodegenerative Diseases Using Structural MRI Data

Abstract

Different neurodegenerative diseases can cause memory disorders and other cognitive impairments. The early detection and the stratification of patients according to the underlying disease are essential for an efficient approach to this healthcare challenge. This emphasizes the importance of differential diagnostics. Most studies compare patients and controls, or Alzheimer's disease with one other type of dementia. Such a bilateral comparison does not resemble clinical practice, where a clinician is faced with a number of different possible types of dementia. Here we studied which features in structural magnetic resonance imaging (MRI) scans could best distinguish four types of dementia, Alzheimer's disease, frontotemporal dementia, vascular dementia, and dementia with Lewy bodies, and control subjects. We extracted an extensive set of features quantifying volumetric and morphometric characteristics from T1 images, and vascular characteristics from FLAIR images. Classification was performed using a multi-class classifier based on Disease State Index methodology. The classifier provided continuous probability indices for each disease to support clinical decision making. A dataset of 504 individuals was used for evaluation. Different quantification methods provided complementary information, and consequently, the best results were obtained by utilizing several quantification methods. The results prove that automatic quantification methods and computerized decision support methods are feasible for clinical practice and provide comprehensive information that may help clinicians in the diagnosis making.



"The cross-validated classification accuracy was 70.6% and balanced accuracy was 69.1% for the five disease groups using only automatically determined MRI features. Vascular dementia patients could be detected with high sensitivity (96%) using features from FLAIR images. Controls (sensitivity 82%) and Alzheimer's disease patients (sensitivity 74%) could be accurately classified using T1-based features, whereas the most difficult group was the dementia with Lewy bodies (sensitivity 32%). These results were notable better than the classification accuracies obtained with visual MRI ratings (accuracy 44.6%, balanced accuracy 51.6%)."

Koikkalainen J et al. *Neuroimage Clin*. 2016;11:435-449.

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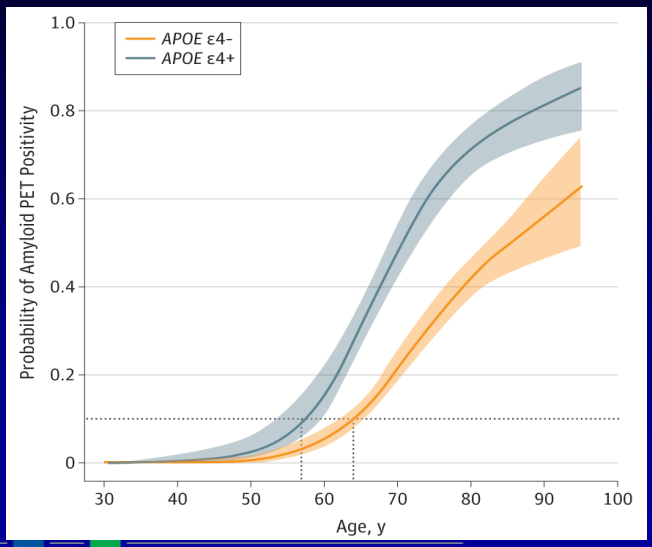
Age and ApoE Genotype Influence Amyloid PET Positivity



Jack CR Jr et al. *JAMA Neurol*. 2015;72(5):511-519.

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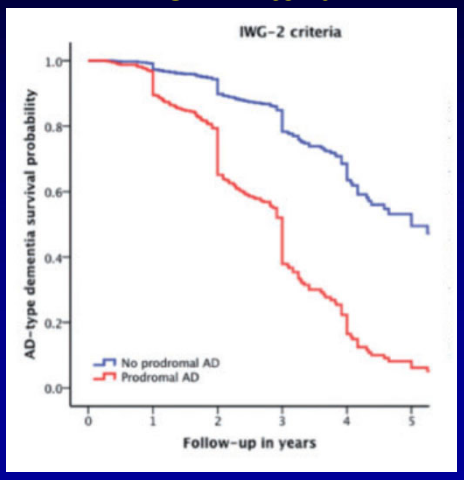
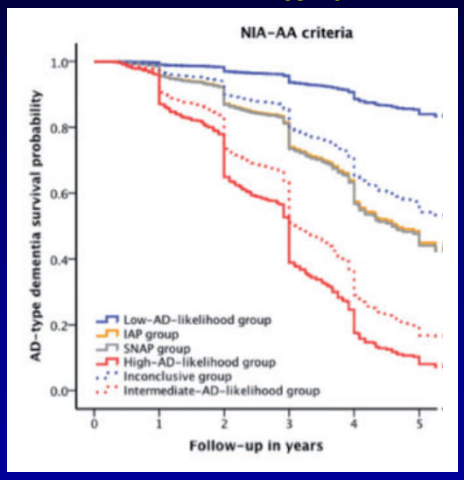
AD Survival Probability by Criteria

IWG-2 Criteria



NIA-AA Criteria



IAP=isolated amyloid pathology; SNAP=suspected non-Alzheimer pathophysiology.

Vos SJ et al. *Brain*. 2015;138(Pt 5):1327-1338.

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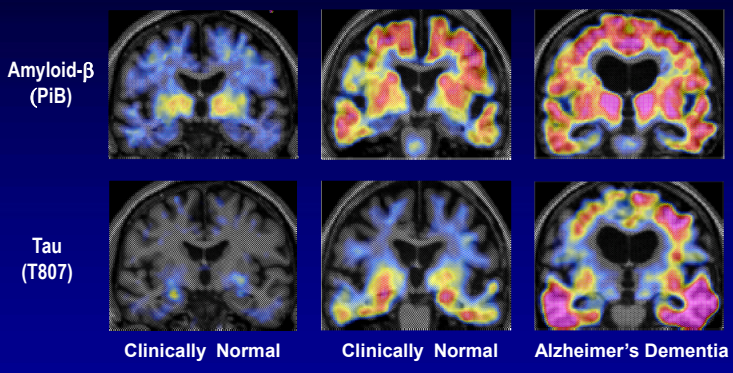
PET Amyloid and Tau Imaging highly sensitive in detecting target pathology but are expensive

Amyloid PET:

- The negative predictive value is very high. A negative scan excludes AD
- A positive PET can occur in NC subjects
- It is not considered diagnostic, only an adjunct
- It is very expensive and has very limited coverage worldwide

Tau PET:

- Likely correlates better with clinical progression than amyloid PET, but the clinical utility has yet to be determined



NC=Normal Control; PiB=Pittsburgh Compound B

Sperling R et al. *Neuron*. 2014;84(3):608-622.

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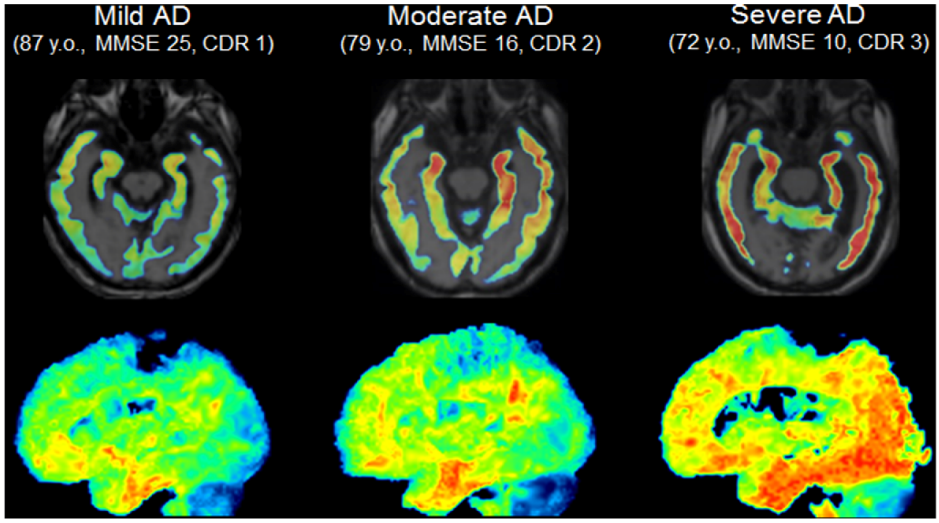
Tau imaging and Braak Staging



[18F]THK-5117 PET images in mild, moderate and severe AD shows additional [18F]THK-5117 retention in association areas

IT'S TIME TO CONSIDER RESTRUCTURING THE DIAGNOSTIC APPROACH FROM A DIAGNOSIS OF EXCLUSION TO… A DIAGNOSIS OF INCLUSION

The imprimatur would be to increase specificity and sensitivity without a commensurate increase in cost

Why do we need biomarkers for Alzheimer's Disease?

- Clinical criteria for AD have poor diagnostic accuracy (70%-80% sensitivity and specificity)
- Except for plaques and tangles, late onset AD cases pathology:
  - 65% TDP-43 pathology
  - 29% Microscopic infarcts
  - 32% Arteriolosclerosis
  - 25% Lewy bodies
  - 11% Hippocampal sclerosis

Biomarkers are needed for:

• Diagnostics	• Select true AD cases for inclusion in clinical trials • Make a correct diagnosis for initiation of treatment
• Clinical research	• Study disease pathogenesis directly in patients to understand the temporal evolution and contribution to symptoms of the different pathologies
• High variability in clinical rating scores in the clinical stages of disease – difficult to identify clinical benefit • Minimal change in the preclinical stage – very long trials needed	
• Theragnostics	• Identify downstream effects on neurodegeneration by anti-Aβ (and tau) drugs

AD=Alzheimer's disease; TDP-43=transactive response DNA-binding protein 43.

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FLUID BIOMARKERS FOR AD: CSF

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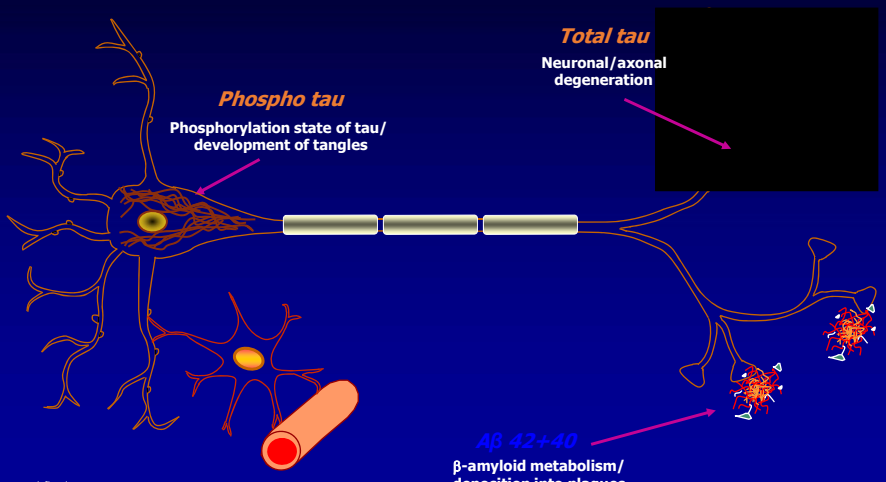
The Core CSF biomarkers for Alzheimer's disease



CSF=cerebrospinal fluid.

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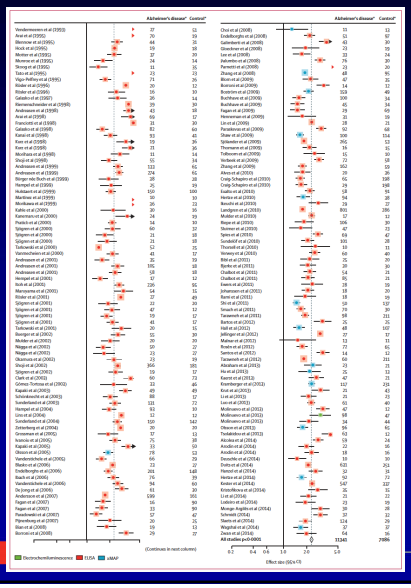
Core AD CSF biomarkers: highly clinically validated



Articles

CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis

Bob Olsson, Ronald Lautner, Ulf Andreasson, Annika Öhrfelt, Erik Portelius, Maria Bjerke, Mikko Hölttä, Christoffer Rosén, Caroline Olsson, Gabrielle Strobel, Elizabeth Wu, Kelly Dakin, Max Petzold, Kaj Blennow, Henrik Zetterberg

ALZFORUM NETWORKING FOR A CURE

Version 2.0
2017 April 26

CSF T-tau
- 188 studies
- 20.600 AD patients and controls
- Effect size 2.48

CSF P-tau
- 116 studies
- 14.300 AD patients and controls
- Effect size 1.88

CSF Aβ42
- 168 studies
- 19.600 AD patients and controls
- Effect size 0.56

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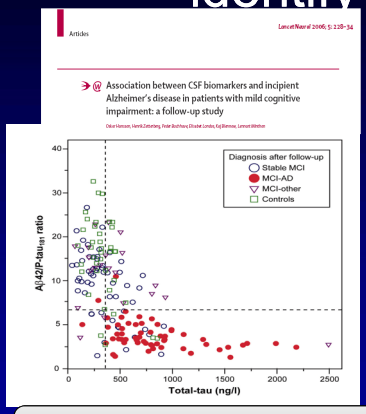
Core AD CSF biomarkers: performance to identify prodromal AD



Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study

Cerebrospinal Fluid Biomarker Signature in Alzheimer's Disease Neuroimaging Initiative Subjects

ORIGINAL CONTRIBUTION

JAMA, July 22/29, 2009—Vol 302, No. 4

CSF Biomarkers and Incipient Alzheimer Disease in Patients With Mild Cognitive Impairment

MCI=mild cognitive impairment.

Sensitivity for MCI-AD 95%
Specificity for stable MCI and MCI-other 87 %

Large multicenter studies confirm high predicitve value of the AD core biomarker profile for prodromal AD

➔ The core AD CSF biomarkers show high diagnostic performance also in the MCI stage

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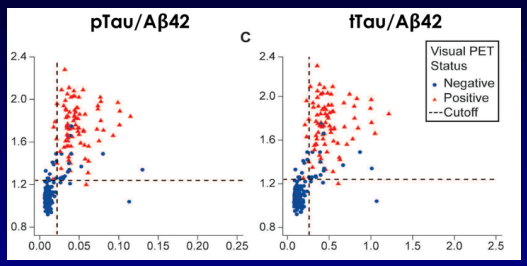
Core AD CSF biomarkers: Performance compared with amyloid PET

ELSEVIER

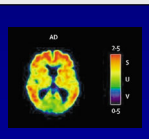
Alzheimer's & Dementia

Featured Article

CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts



Study design:
Elecsys assays for Aβ1-42, tTau and Ptau
BioFINDER (n=277) and ADNI (n=646)



Concordance with visual amyloid PET:	**CSF pTau/Aβ42**	**OPA = 89.9% - 90.3%**
	CSF tTau/Aβ42	**OPA = 89.2% - 89.9%**
	Inter-rater PET agreement	**OPA = 90%**
	Visual vs SUVR PET agreement	**OPA = 90-91%**

➔ CSF pTau/Aβ42 and tTau/Aβ42 show very high concordance with amyloid PET

ADNI=Alzheimer's Disease Neuroimaging Initiative; BioFINDER=Biomarkers For Identifying Neurodegenerative Disorders Early and Reliably; OPA=overall percent agreement; PET=positron emission tomography; SUVR=standardized uptake value ratio.

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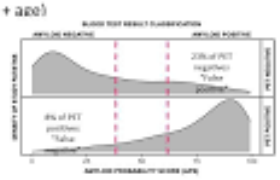
A blood test now has CLIA certification

C2N Diagnostics

The first blood test for detection of amyloidosis in individuals with cognitive impairment is now available for clinical use

- PrecivityAD test from C2N Diagnostics (IPMS plasma Aβ42/Aβ40 + *APOE* genotype + age)

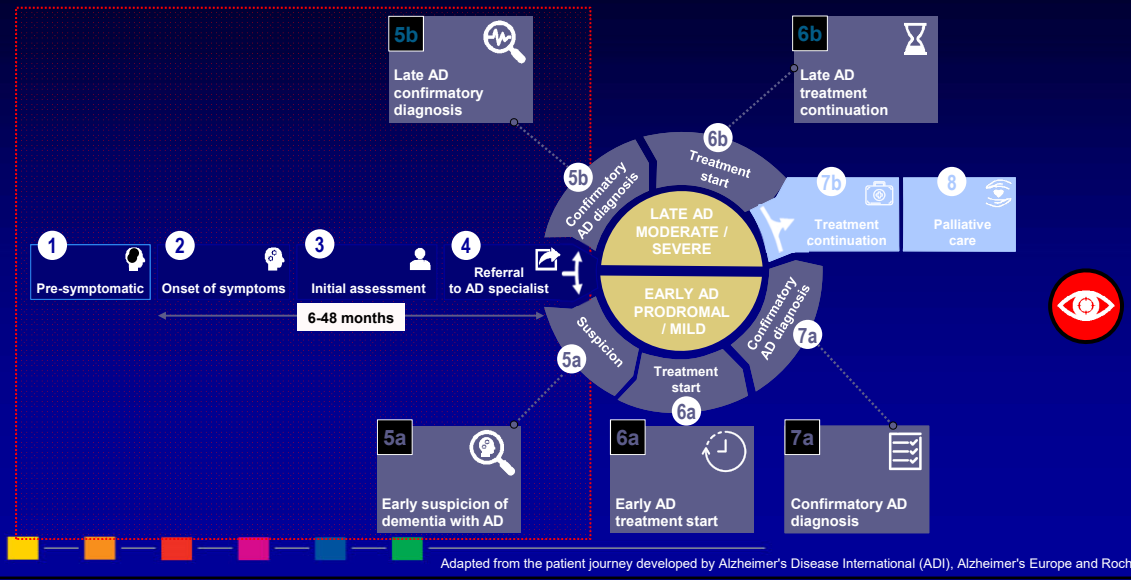


PrecivityAD™

https://precivityad.com

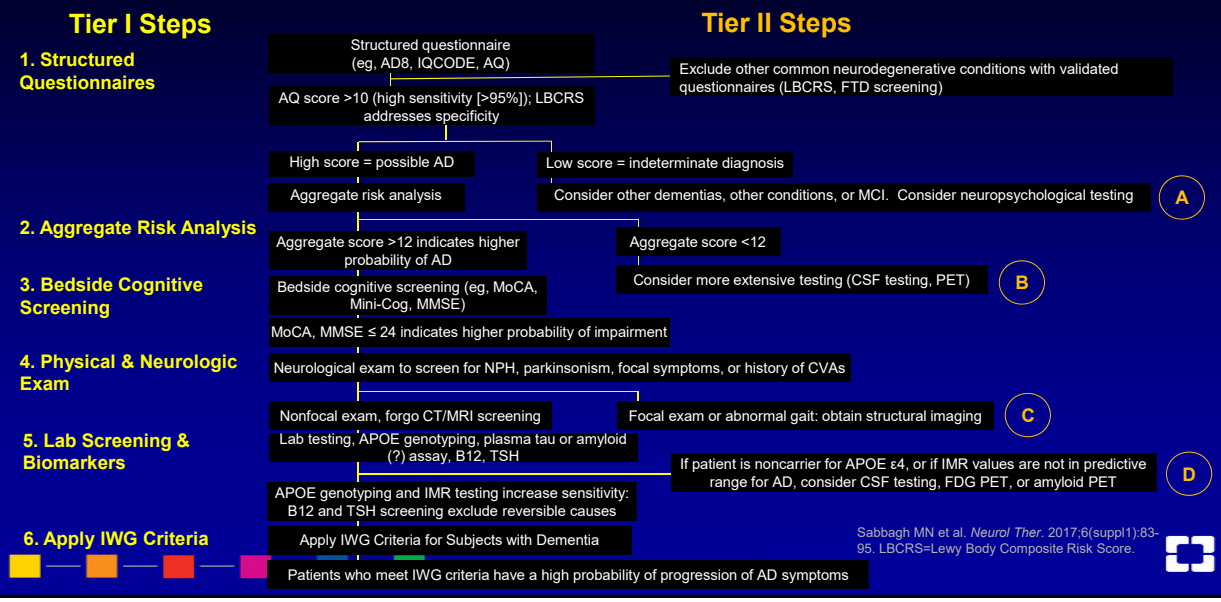
- More AD blood tests will likely follow soon (e.g. pTau181, pTau217, NfL)

Patient journey



Adapted from the patient journey developed by Alzheimer's Disease International (ADI), Alzheimer's Europe and Roche [Oct 2019]

New Conceptual Framework for Assessment of Dementia Due to AD



Sabbagh MN et al. *Neurol Ther*. 2017;6(suppl1):83-95. LBCRS=Lewy Body Composite Risk Score.

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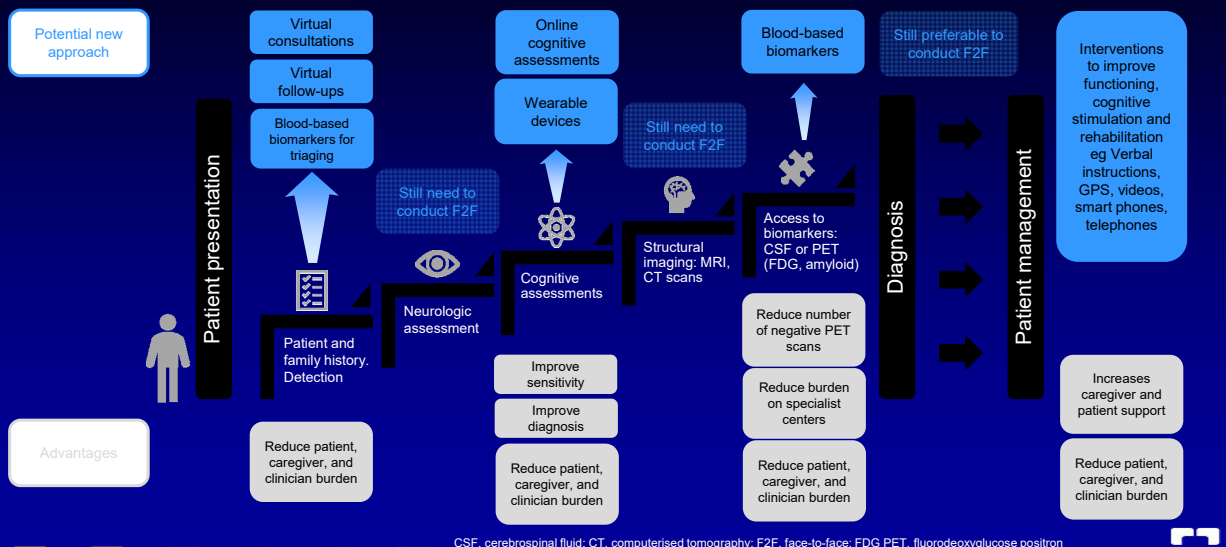
Evolving the patient journey post Covid-19



CSF, cerebrospinal fluid; CT, computerised tomography; F2F, face-to-face; FDG PET, fluorodeoxyglucose positron ~~emission tomography; MRI, magnetic resonance imaging;~~ PET, positron emission tomography

Constanzo MC, et al. Int J Geriat Psych 2020;35:12–28

Conclusions

- The identification of MCI can be made with more confidence
- The prediction of conversion from MCI to AD can be made with greater accuracy
- AD is no longer a diagnosis of exclusion
- Technology is becoming available that greatly improves the diagnostic accuracy of AD