Updates in Dementia Diagnosis

DATE: APRIL 19, 2024 PRESENTED BY: ANDREW NATONSON, MD/MS

Disclosures

- Dr. Natonson has no financial disclosures related to this talk

Outline

- Discuss growing importance of recognizing and diagnosing cognitive disorders in a timely manner
- Review recent updates in biomarkers for dementia and how these tests can impact diagnosis and treatment

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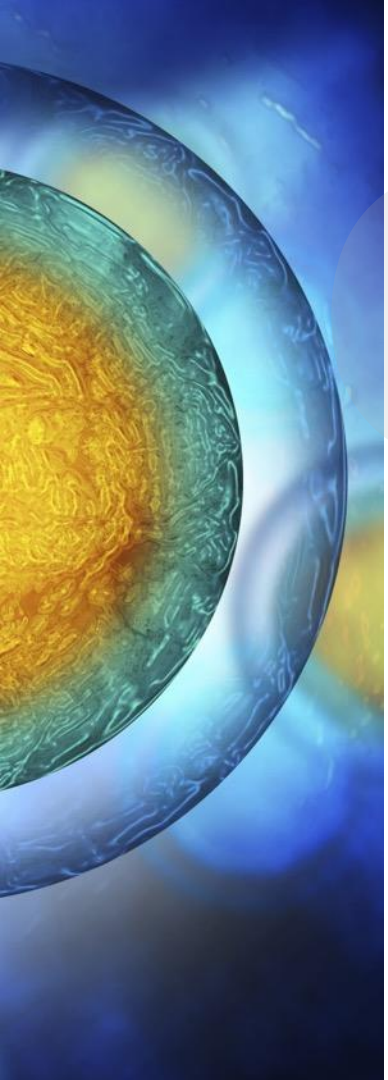
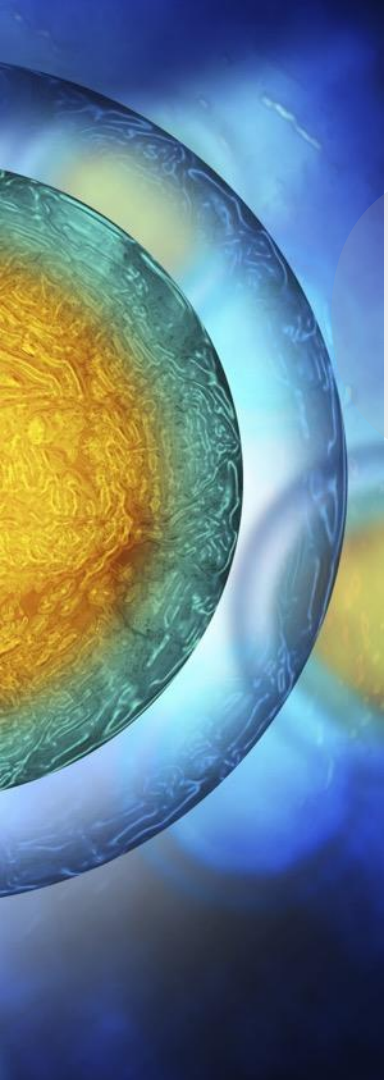
What is dementia?



Definition of Dementia, aka Major Neurocognitive Disorder

- A decline in one or more cognitive domains: memory, language, executive function, attention, perceptual-motor, social cognition

- Must represent an *objective* decline from previous level of function **AND** be severe enough to interfere with daily function and independence

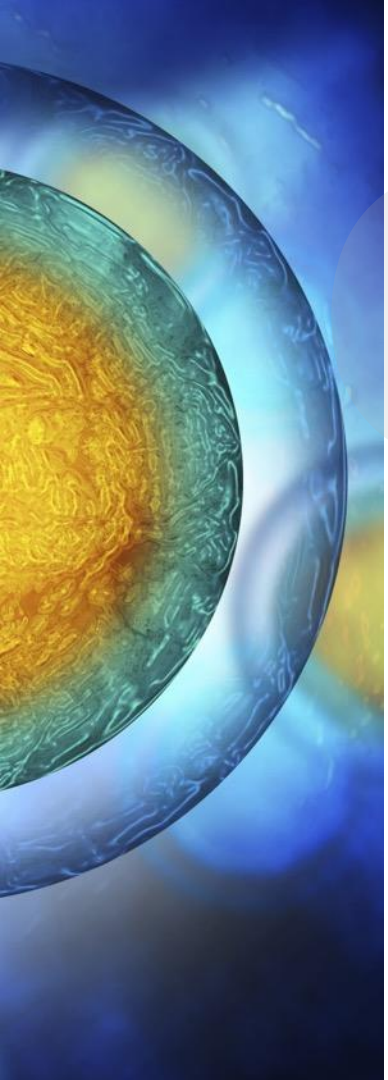


Definition of MCI, aka Minor Neurocognitive Disorder

- A decline in one or more cognitive domains: memory, language, executive function, attention, perceptual-motor, social cognition

- Must represent an *objective* decline from previous level of function **~~AND be severe enough to interfere with daily function and independence~~**, **BUT** not impact daily function or independence

- MCI increases risk of developing dementia in the future



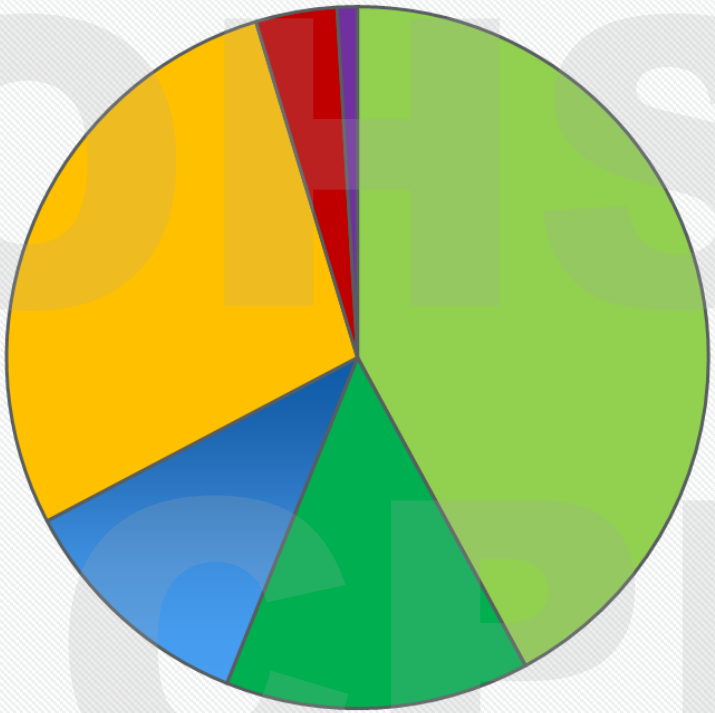
“Reversible” causes of dementia

- Delirium
  - infection
  - metabolic
  - drugs

- Metabolic:
  - hypothyroidism
  - B12 deficiency
  - vitamin D deficiency?
- Structural
  - subdural hematoma
  - frontal lobe meningioma
  - normal pressure hydrocephalus

- Depression

Dementia Variants

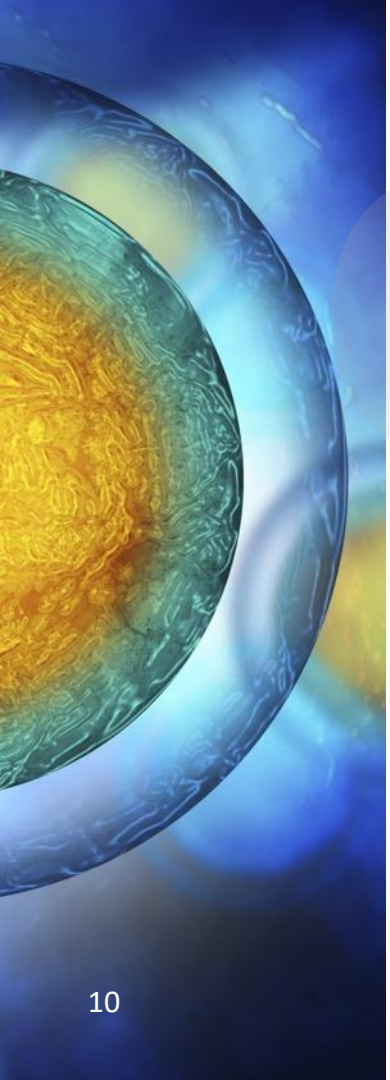


- Alzheimer's Dementia (40-50%)
- Vascular Dementia (10-20%)
- Dementia with Lewy Bodies (8-15%)
- Mixed Dementia (30%, overlaps VaD & AD)
- Parkinson's Disease Dementia (4%)
- Frontotemporal Dementias (<1%)

Dementia Treatments: mildly effective for all variants (-FTD)

- Cholinesterase Inhibitors
  - Donepezil
  - Galantamine
  - Rivastigmine
- Memantine

NONE of these agents are beneficial for MCI
None of these agents are disease specific



2023-24:
The dementia revolution begins…

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

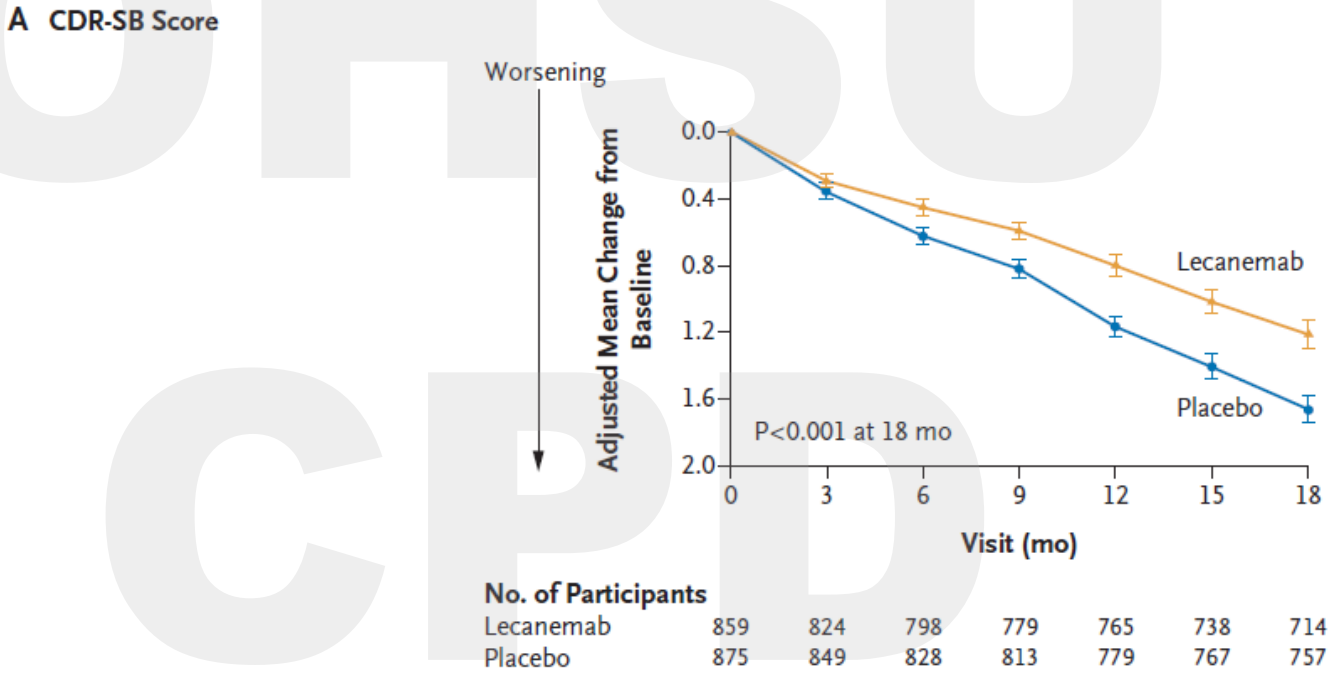
JAMA | Original Investigation

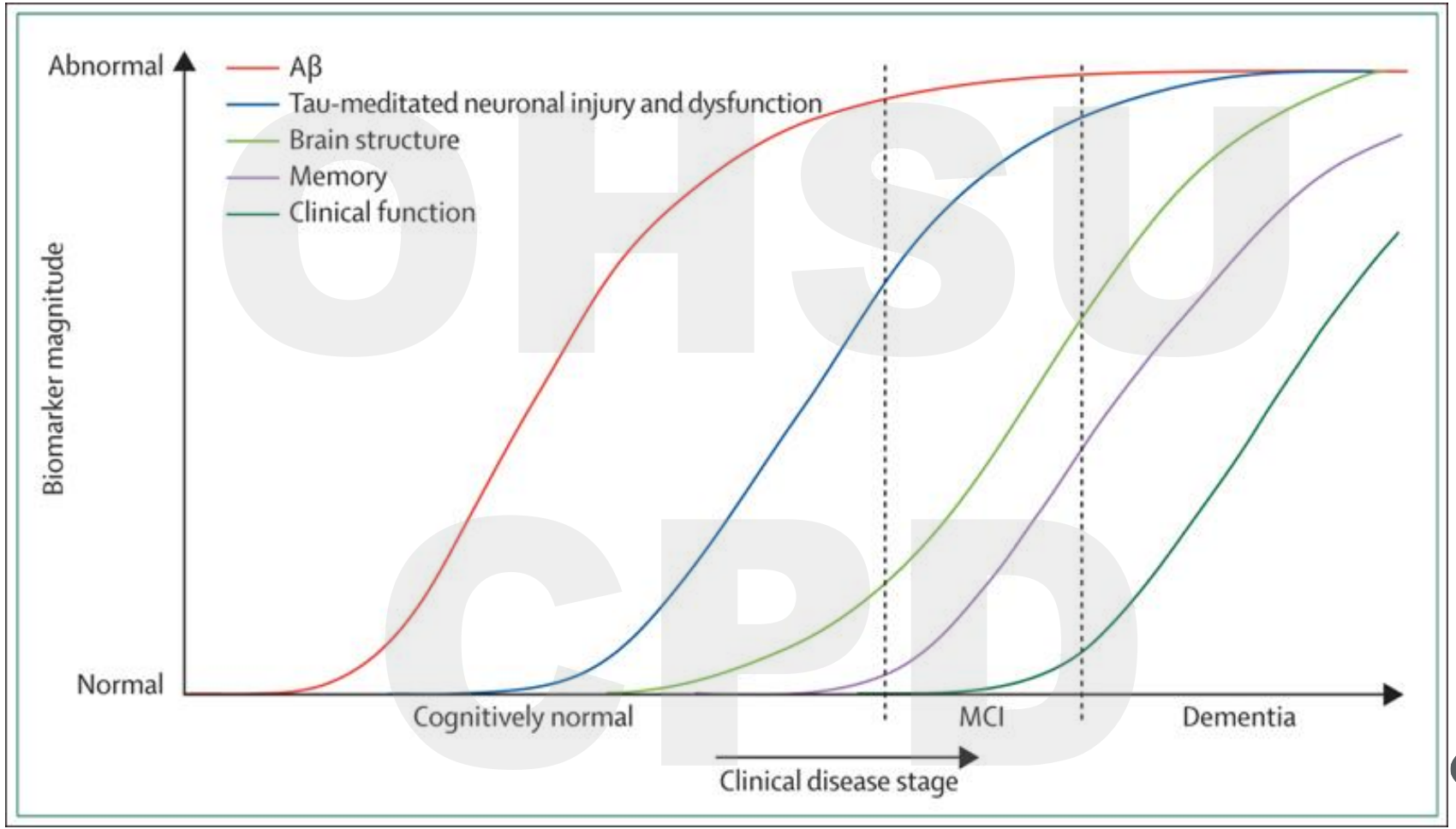
Donanemab in Early Symptomatic Alzheimer Disease
The TRAILBLAZER-ALZ 2 Randomized Clinical Trial

John R. Sims, MD; Jennifer A. Zimmer, MD; Cynthia D. Evans, PhD; Ming Lu, MD, MS, MPH; Paul Ardayfio, PhD; JonDavid Sparks, PhD; Alette M. Wessels, PhD; Sergey Shcherbinin, PhD; Hong Wang, PhD; Emel Serap Monkul Nery, MD; Emily C. Collins, PhD; Paul Solomon, PhD; Stephen Salloway, MD; Liana G. Apostolova, MD; Oskar Hansson, MD, PhD; Craig Ritchie, MD, PhD; Dawn A. Brooks, PhD; Mark Mintun, MD; Daniel M. Skovronsky, MD, PhD; for the TRAILBLAZER-ALZ 2 Investigators

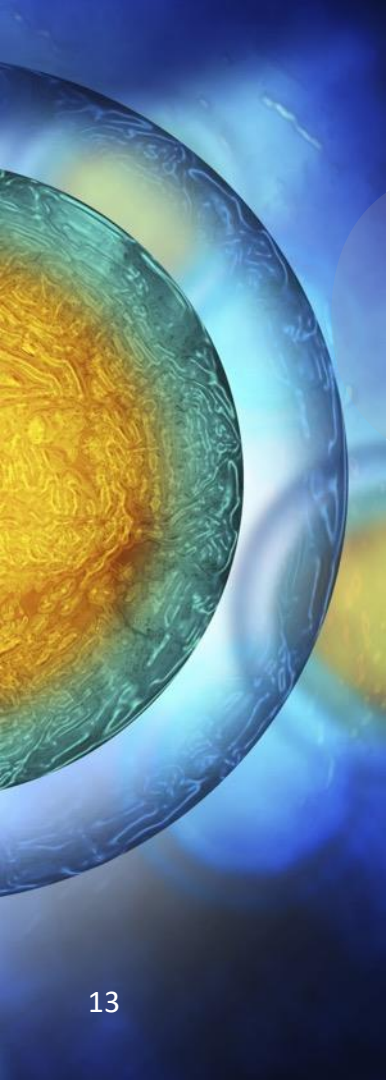
Lecanemab Phase 3 Results

- Change in CDR-SB of 0.45 at 18 months





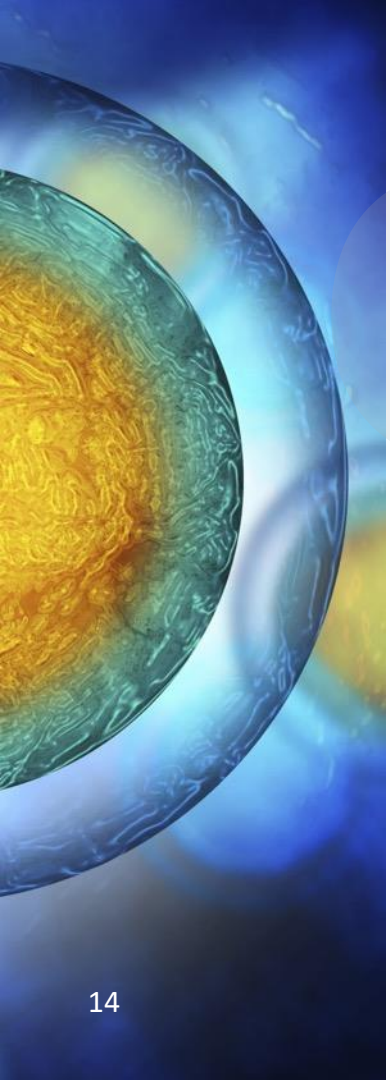
Jack, C.R., et al Lancet Neurol 2013



New Alzheimer's Framework

- **AT(N)**, ranges preclinical to dementia
- Amyloid verified by: amyloid PET +, low CSF $A\beta_{42}$
- Tau: high CSF p- tau, tau PET +
- Neurodegeneration: Structural MRI, FDG-PET, CSF total tau

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	



Diagnostics – PET

Benefits

- Non-invasive
- Increases diagnostic accuracy
- Amyloid PET can qualify for antiamyloid therapy if positive

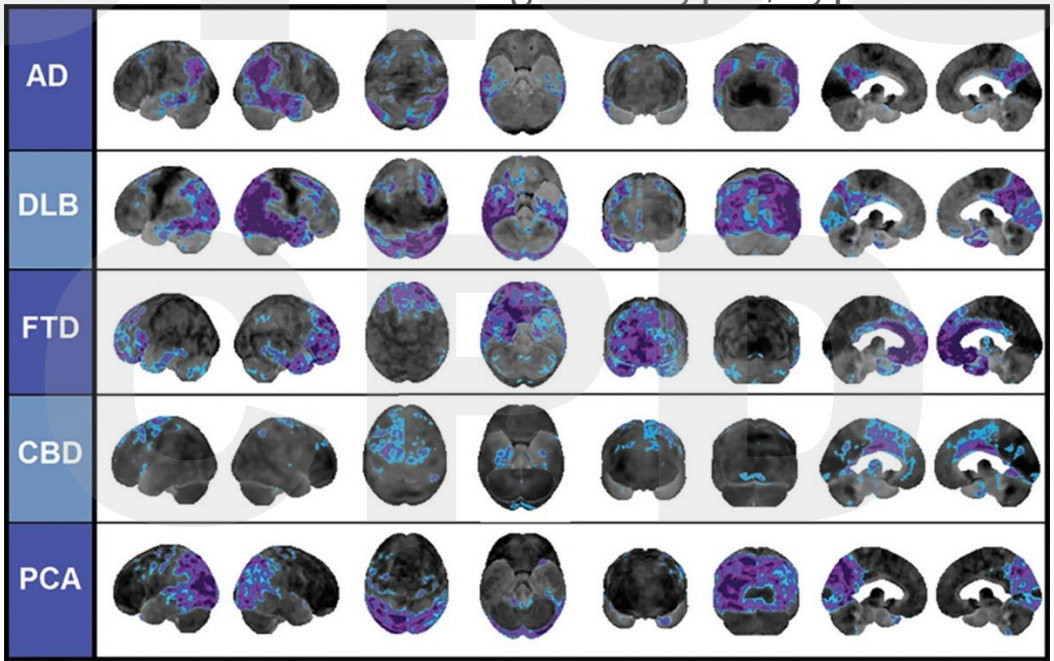
Challenges

- Cost
- Tracer availability
- Radiation if CT

Diagnostics – FDG-PET

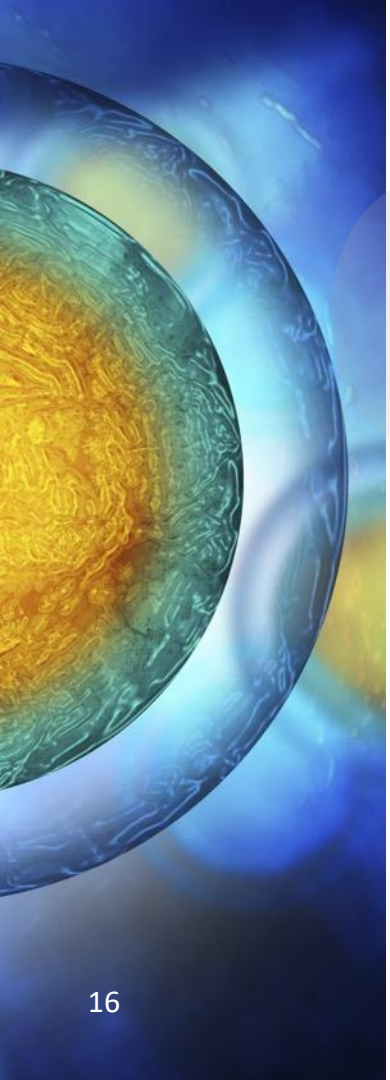
Indicates neuronal dysfunction – not specific pathology

- Measures uptake of a labeled glucose derivative
- Patterns of regional hyper/hypo metabolism



- Can be non-spec

Continuum 2022

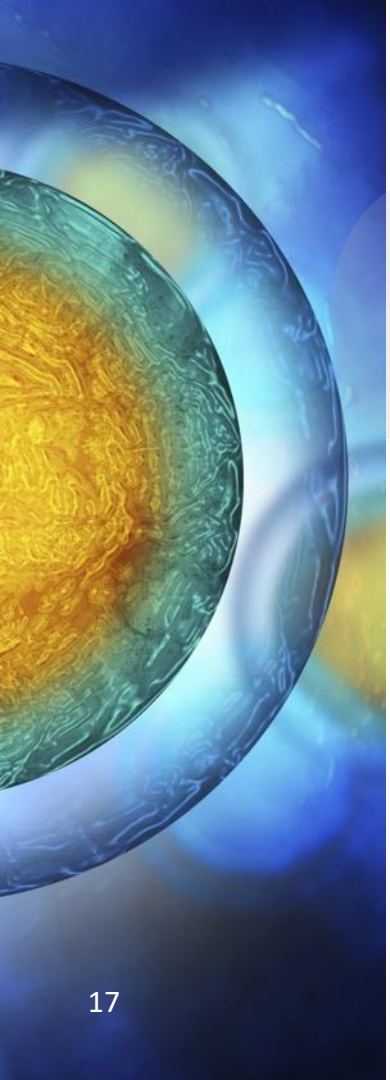


Amyloid PET

- Several tracers available on market
  - Utilizes a radiotracer which binds to aggregated amyloid
  - Compared to autopsy data:
    - sens 96% (91-98%)
    - spec 100% (89-100%)

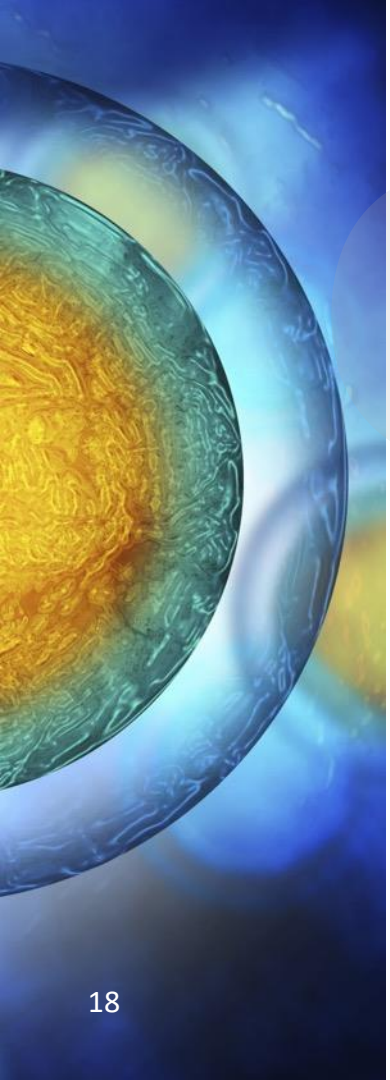
Clark, CM., et al. Lancet Neurol 2012.

  - Gives no information about tau status
  - Correlates with risk of MCI-> dementia
  - Hard to interpret meaning in Cog Normal pts -? Preclinical AD
  - Does not correlate with disease severity
  - Also binds to other disease with amyloid (CAA) & DLB



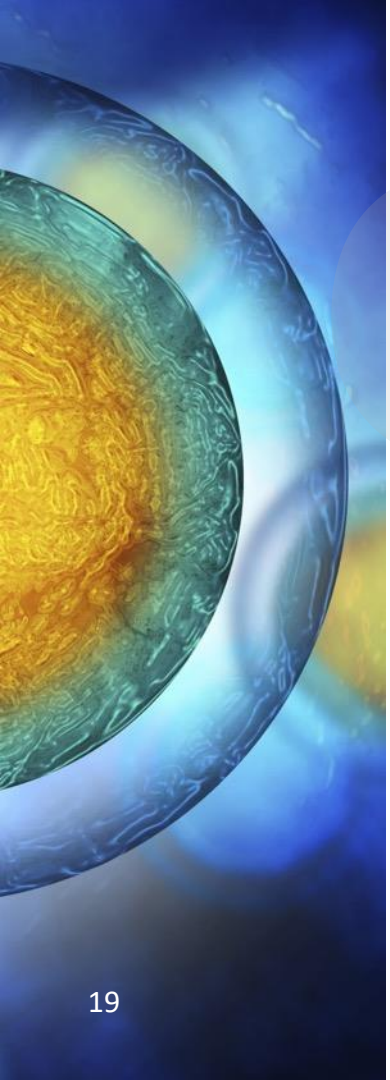
Amyloid PET – non-demented

- Prevalence of amyloid PET positivity in cognitively unimpaired older adults increases linearly with age ~20% age 70, 30% age 80, 40% age 90
- As a group, older patients with positive amyloid scans are higher risk of MCI, but not an individual basis
- A negative amyloid PET is very predictive of NOT having AD, the PPV of amyloid PET decreases with advancing age



Amyloid PET – Availability

- Recently made available at OHSU via orders in EPIC
- Medicare has stated they will cover test, copay may be 20% (of between 3-6k)
- Qualifies patients for anti-amyloid therapy if positive and documented cognitive impairment
- Available as both PET/CT amyloid brain and PET/MRI amyloid brain orders
  - PET/MRI is better choice if they do not have a recent MRI, as can get both same time



Tau PET

- Tau PET (multiple compounds available)
  - ADNI data shows highest correlation to onset of memory loss
  - Strongest predictor of cognitive decline compared to other markers

Bucci, M., et al. Molecular Psychiatry 2021
Ossenkoppele, R., et al. EMBO Mol Med 2021

  - Not as useful for preclinical stages
  - Can be elevated in non-AD dementia syndromes
  - **Research tool only for now**

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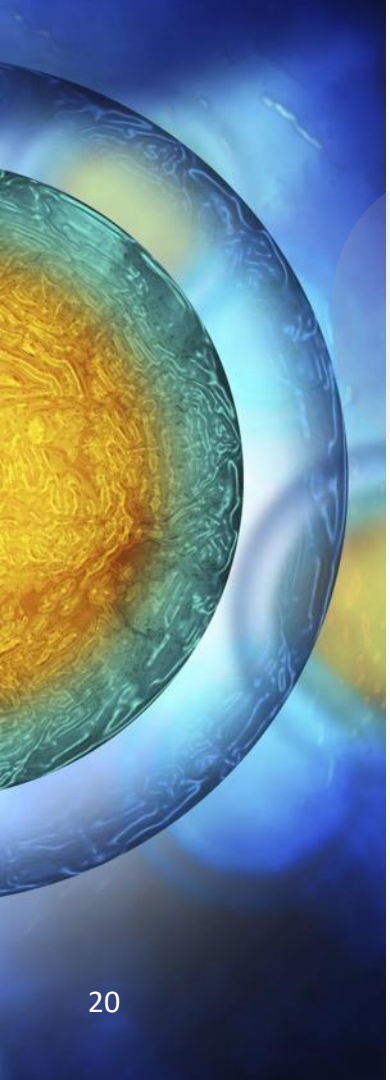


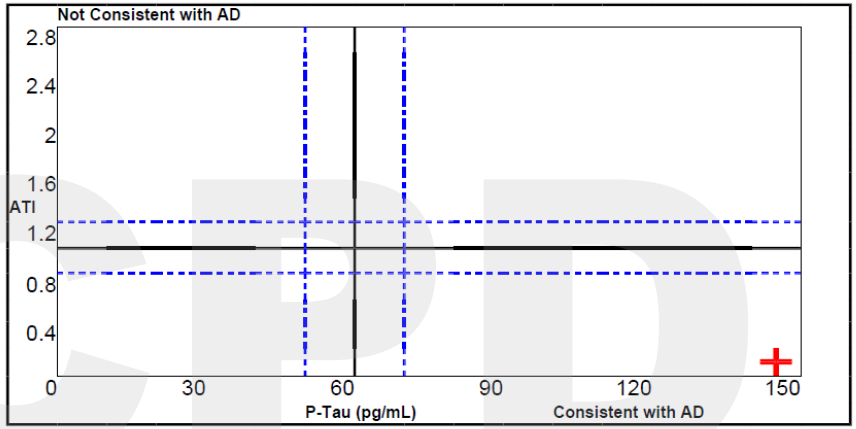
Diagnostics – AD CSF

- CSF has been studied in dementia clinics for >20 years
- Commercial kits (ADMark) use ELISA Aβ42/40, total tau, and p-tau181, with low Aβ42/40 and high tau levels being consistent with AD pathological changes;
  - confirmed with multiple studies and meta-analysis
- Levels stay fairly constant throughout dementia stages, does not correlate with stage.
- In MCI patients, CSF had sens/spec of 85-90%
- MCI patients with + CSF results have more neuropsychiatric symptoms than MCI - patients

Krell-Roesch, et al. Alz & Dementia 2022

CSF analysis - ADMark

INTERPRETIVE RESULTS TABLE			
Interpretation	**Test**	**Technical Result**	**Reference Range (if applicable)**
Alzheimer Disease	A-beta 42	**170.7 pg/mL**	Not consistent with AD: P-Tau <54 pg/mL and ATI >1.2, Borderline: P-Tau 54-68 pg/mL and/or ATI 0.8-1.2, AD: P-Tau >68 pg/mL and ATI <0.8
	T-Tau	**1135.15 pg/mL**	
	P-Tau	**198.5 pg/mL**	
	ATI	**0.11**	



Comments: This analysis detected levels of CSF A-beta 42 peptide (A-beta 42) and total tau (T-tau) proteins, reflected in a reduced A-beta 42 to T-tau Index (ATI). The level of phospho-tau (P-tau) was also elevated. These results are consistent with a diagnosis of Alzheimer's disease (AD).

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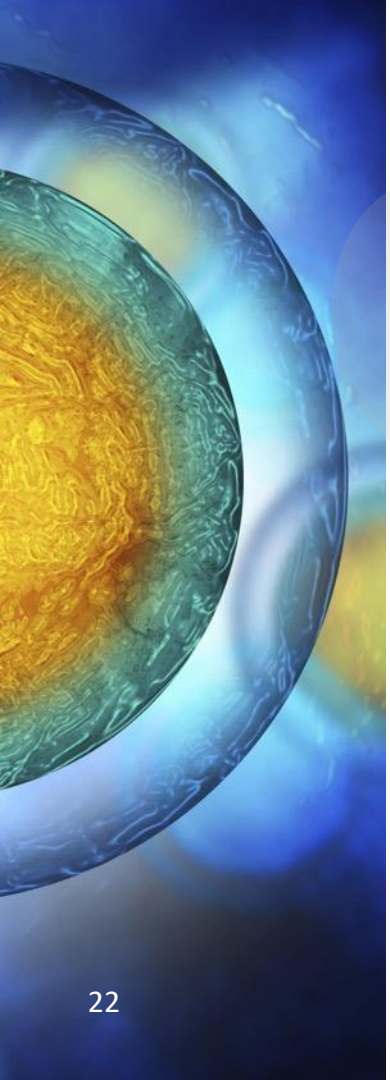

CSF analysis - ADMark

- Advantages:
  - Readily available, can order LP under xray guidance, order ADMark future collect, radiology collect. Results in approx. 2 wks.
  - Usually easy to interpret result
  - Usually covered by insurance for MCI or dementia work up
  - Qualifies for anti-amyloid therapy consideration if documented cognitive impairment
- Disadvantages:
  - Invasive procedure
  - Small risk of complication (10% risk post LP headache)

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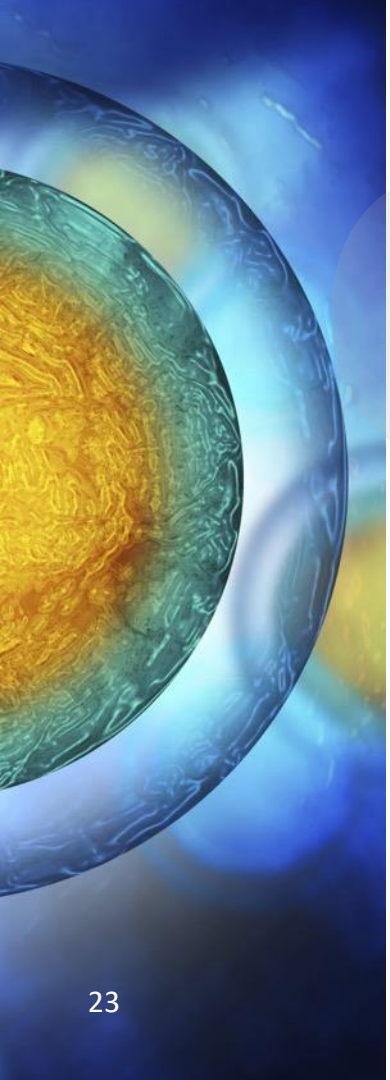

CSF analysis – Others

- Neurofilament Light Chain
  - Marker of neuronal degeneration
  - Non specific, can help delineate psych vs neuro
- Neurogranin
  - Protein secreted by neuronal cells, esp hippo & amygdala
  - Recent studies show increased levels in patients with AD and MCI compared to healthy elderly controls
- TREM2
  - Marker of microglial activation/neuroinflammation
  - Elevated in early stages of AD, but also several FTDs and PD

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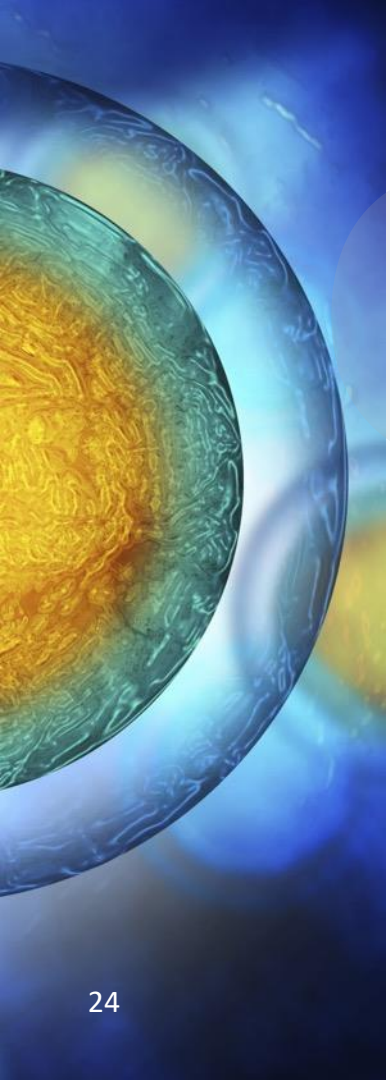

Diagnostics – AD Serum

- Aβ42/Aβ40
  - Initial studies did not reveal differences using ELISA
- Palmquvist, et al using automated immunoassays demonstrated AUC of 0.8, increased to 0.85 if APOE status added, no significant improvement with addition of tau (JAMA Neurol 2019)

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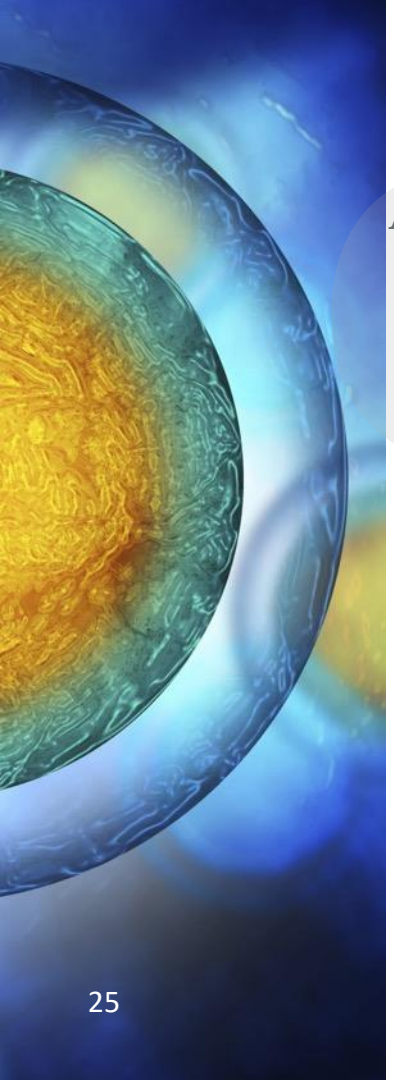

Diagnostics – AD Genetics

APOE screen

- Lab Other (code 2013341)
- Useful for amyloid therapy risk stratification
- E2 = protective for AD
- E3 = wildtype
- E4 = risk for AD, risk increases with 2 copies

E4/E4 minimal benefit, high risk with amyloid therapy

E2 carries increased risk of CAA/hemorrhage

Autosomal Dominant Panel

- Invitae (?availability)
- APP, PS1, PS2 genes
- Typically very young, <50
- No utility for amyloid therapy

Qualify for DIAN studies

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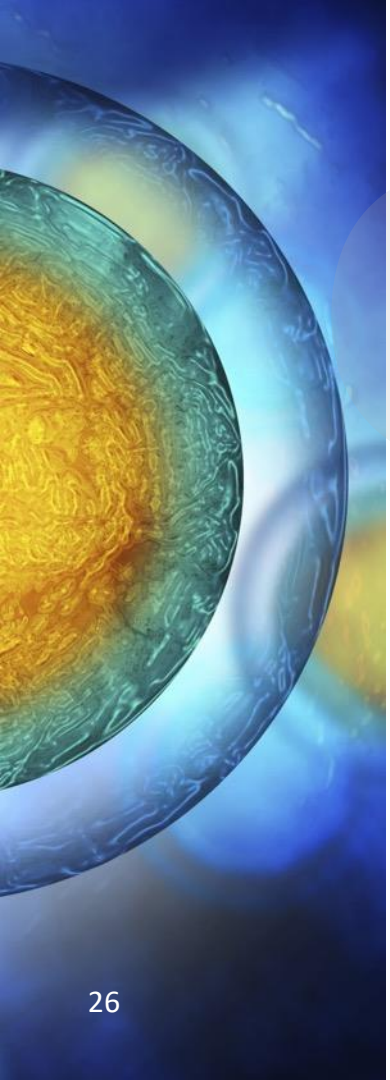

Diagnostics – AD Serum

- Aβ42/Aβ40 +/-ApoE genetic screen 158 cog norm adults, using liquid chromatography
  - High correlation with amyloid PET status (AUC 0.88) & CSF p-tau (AUC 0.85).
  - APOE4 status increased correlation (AUC 0.94)
  - Pts with neg amyloid PET and '+' serum test had 15x increased risk of progression to positive PET compared to Pts with '–' serum test

Schindler, S.E., et al. Neurology 2019.

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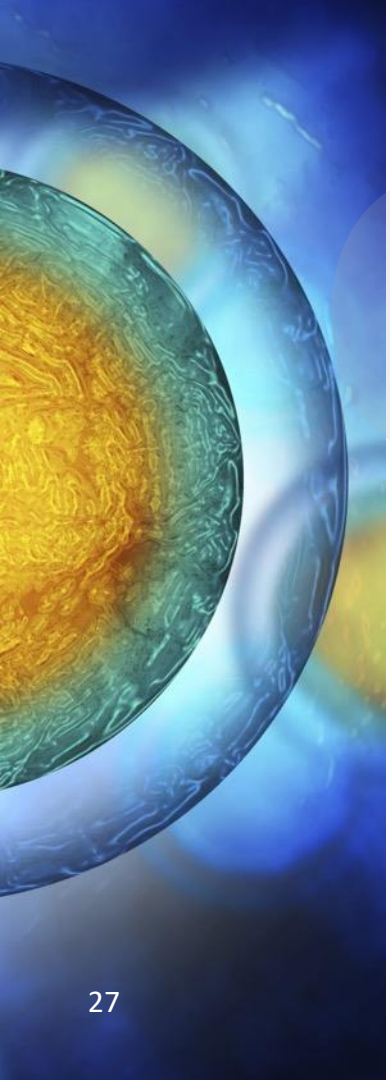
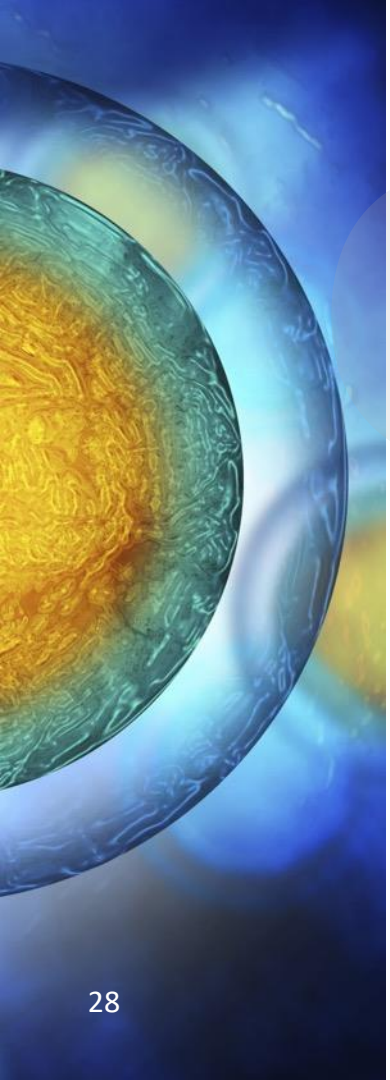


Diagnostics – Commercial Kits

- NONE qualify for anti-amyloid therapies currently, not usually covered by insurance. Could use as screen, neg rule out…
- Quest AD-Detect – FDA Approved May 2022
  - Uses Liquid Chromatography/Mass Spectroscopy
  - Measures AB42/40 ratio
  - Gives tiered risk of having AD, with lower ratio having higher risk, AUC compared to PET 0.862
- PrecivityAD 1/2 – CLIA approved November 2020
  - Developed at UW, had highest accuracy of any blood assay in head to head of 8 assays vs PET status
  - Uses immunoprecipitation/MassSpec
  - PrecivityAD1 measured AB42/40 and APOE AUC 0.86
  - PrecivityAD2 adds p-tau217 AUC 0.94



Diagnostics –AD Serum- Future

- p-tau181 – 172 normal, 57 MCI, 40 AD patients
  - Compared to amyloidPET + (AUC 0.803)

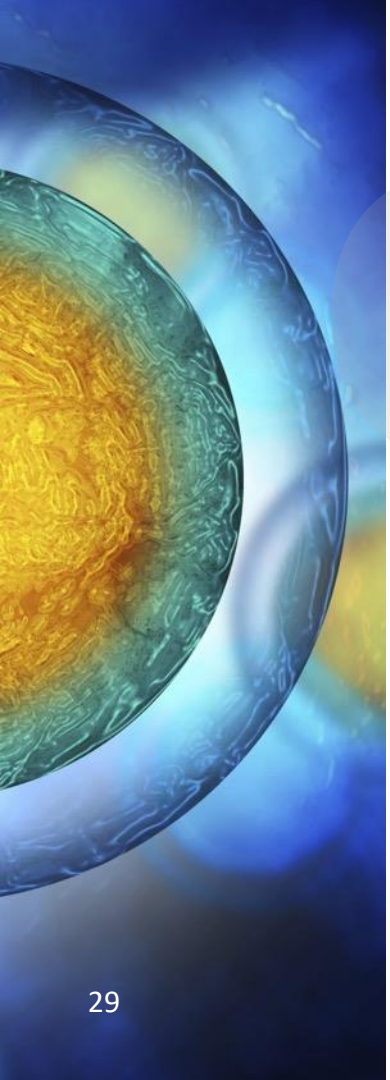
Mielke, M.M., et al. Alz & Dem 2018.

- p-tau217 – studied among combined cohorts 1400 pts
  - Correlated with neuropathology confirmed AD (AUC 0.89) and better than p-tau181 (AUC 0.72)
  - Discriminated against other neurodegenerative disease (AUC 0.95), comparable to CSF markers/tauPET

Palmqvist, S., et al. JAMA 2020.

  - Studied in 3 longitudinal cohorts, more accurate than all other biomarkers studies in predicting amyloid PET + in all 3 other than CSF, which was equal. 786 pts total.

JAMA Neurol. doi:10.1001/jamaneurol.2023.5319



Diagnostics –AD Serum- Future is now…

- p-tau181 – 172 normal, 57 MCI, 40 AD patients
  - Compared to amyloidPET + (AUC 0.803)

- p-tau217 – studied among combined cohorts 1400 pts
  - FDA granted breakthrough device designation to Quanterix 3/14/2024!

- Keep a look out, this is being looked at for future clinical studies and will likely start replacing CSF/PET clinically

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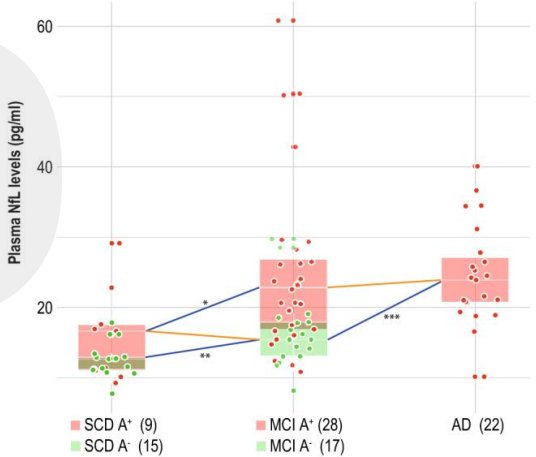
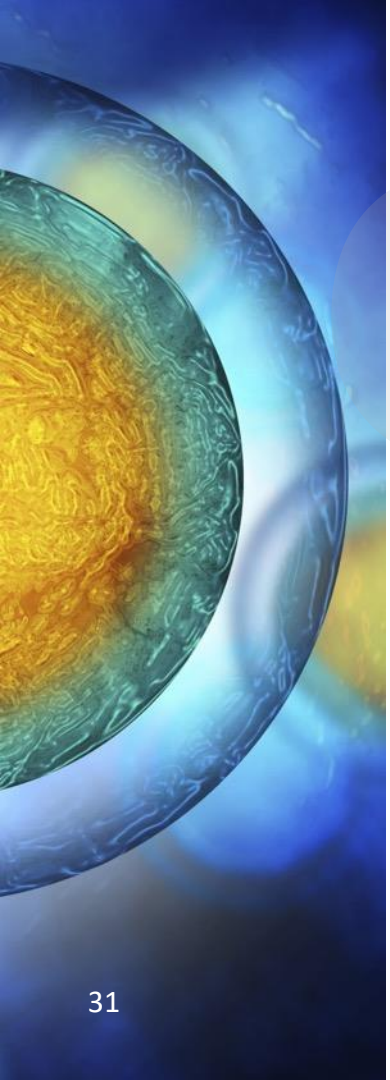
Diagnostics – Other Serum

- Neurofilament light chain (Nfl) – available lab other
  - Can help discriminate between true neuronal degeneration and non-degenerative disorders
  - Elevated in MCI/Dementia due to AD, as well as in FTD, DLB, and VascD
  - Levels appear to correlate with disease progression



FTD: van der Ende, E.L., et al. Lancet Neuro 2019
AD: Giacomucci, G., et al. J Neurol. 2022



Lewy Body Dementias (DLB & PDD)

- LBD is umbrella term for both Dementia with Lewy Bodies, and Parkinson's related Disease Dementia
- Second most common form of dementia in elderly patients
- Pathology is due to misfolded alphasynuclein, detectable at preclinical stages
- Typically see co-pathology with Alzheimer's disease, unclear how significant this is.
- As there are still no DMTs, there is less utility in the following tests

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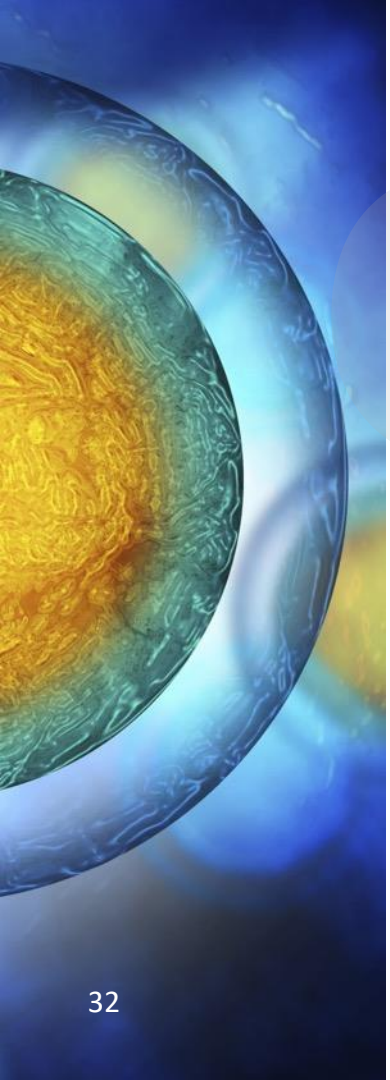

Dementia with Lewy Bodies

- Updated diagnostic criteria 2017 now with 4 Cores: visual hallucinations, fluctuations, parkinsonism, RBD*
- Probable = 2 or more cores, or 1 core plus indicative biomarker
- Possible = 1 or more cores
- RBD is seen in up to 76% of all LBD cases
- >90% of RBD positive patients develop a degenerative disorder over 20 years, usually related to alphasynuclein disease

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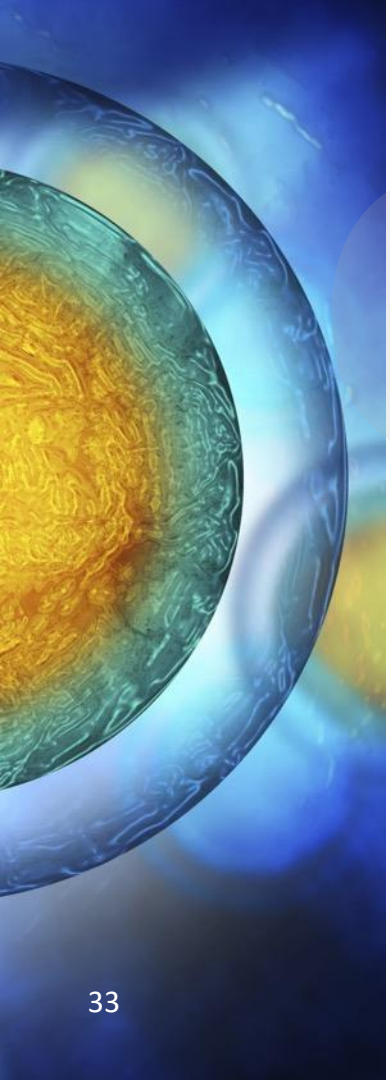


Diagnostics - DLB

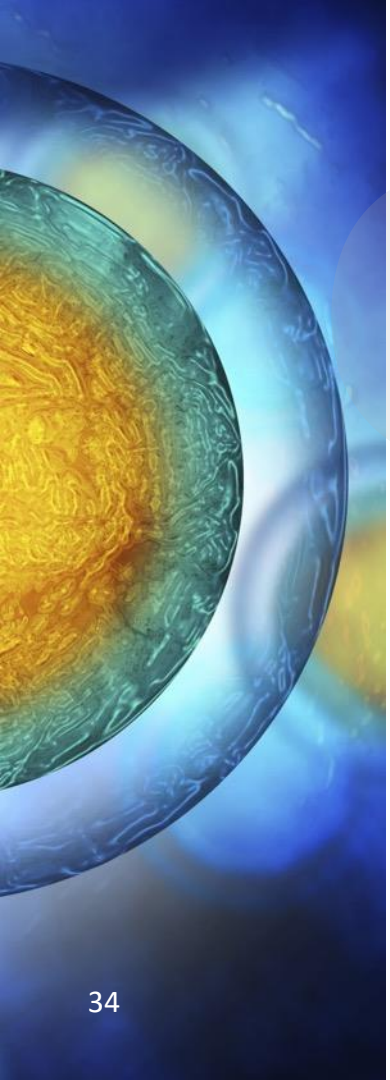
- Indicative biomarkers (improve diagnostic accuracy)
  - DaT scan – abnormal PD, DLB, MSA, PSP, CBD
  - Polysomnography confirming atonia during REM
  - Cardiac MIBG scan correlates with dysautonomia
- Experimental biomarkers (available, difficult to order)
  - Skin biopsy RT-QuIC (89% sens, 96% spec, LBD vs healthy controls),

Mammana, A., et al. Movement disorders 2021

  - skin taken from C spine more sensitive than from thigh

Rossi, M., et al. Neurology 2021

  - CSF RT-QuIC (95% sens, 97% spec MCI-LB vs healthy)



Diagnostics - FTDs

- Medicare will pay for FDG-PET brain if query FTD after cognitive testing and MRI brain do not reveal a cause
  - See hypometabolism in frontal/temporal lobes, often anterior cingulate
- Serum Neurofilament light chain (lab other)
  - Will be negative in the absence of neuronal dysfunction, suggests primary psychiatric etiology
- Rule out other disorder with amyloid test?

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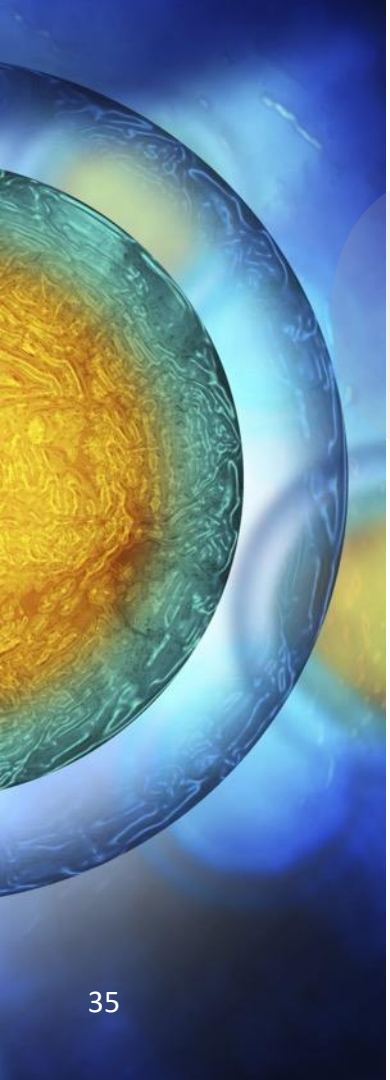

Summary

- With new disease modifying therapies available for Alzheimer's, there is a growing need to identify and confirm disease status earlier in the course of the disease

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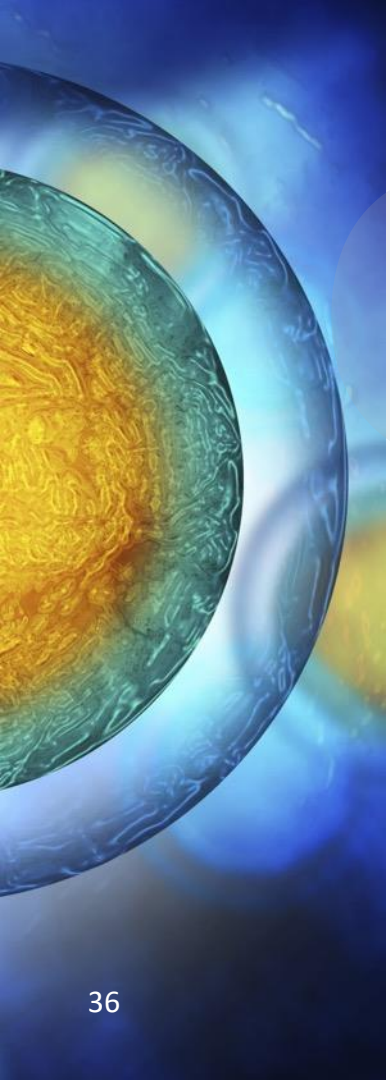

Summary

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- Currently available CSF and Amyloid PET scans are the only tests considered sufficient for these new therapies

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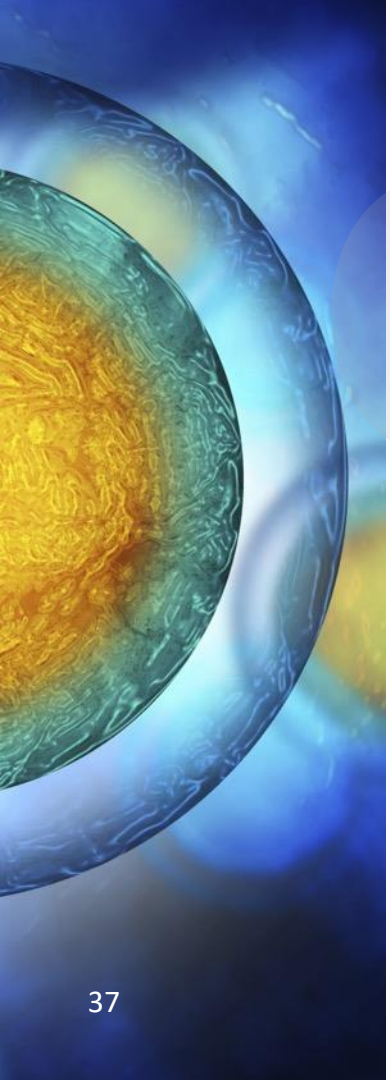

Summary

- With new disease modifying therapies available for Alzheimer's, there is a growing need to identify and confirm disease status earlier in the course of the disease
- Currently available CSF and Amyloid PET scans are the only tests considered sufficient for these new therapies
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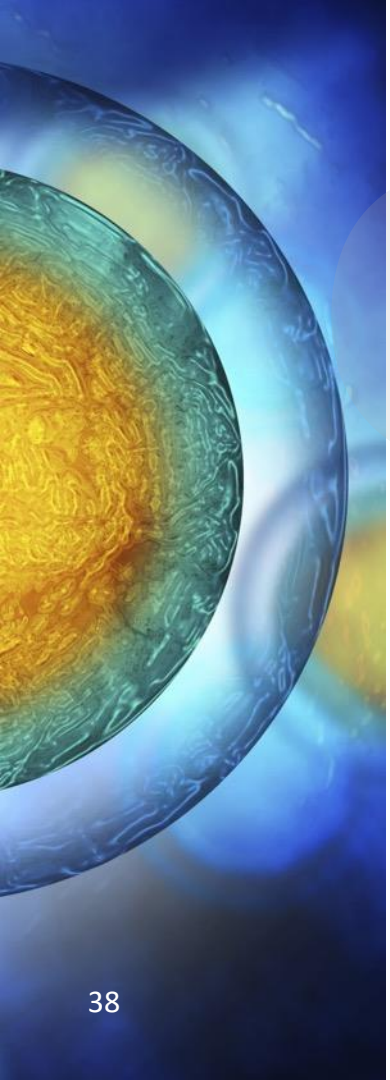
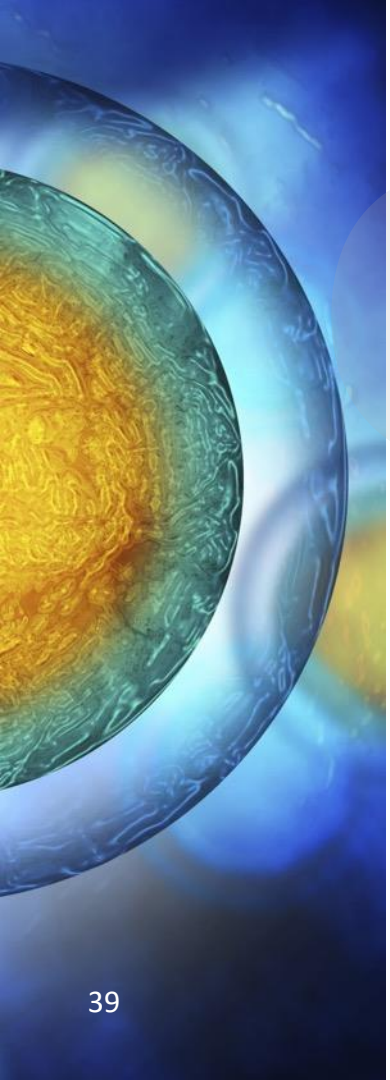


Summary

- With new disease modifying therapies available for Alzheimer's, there is a growing need to identify and confirm disease status earlier in the course of the disease
- Currently available CSF and Amyloid PET scans are the only tests considered sufficient for these new therapies
- New blood tests for Alzheimer's are very sensitive and specific, unclear if or when they may replace CSF/PET, but are coming to a clinic near you
- Other dementia syndromes are still without DMTs, but diagnostics are improving, and clinical trials are progressing



Future

- Refer patients to ADResearch@ohsu.edu if interested in clinical trials

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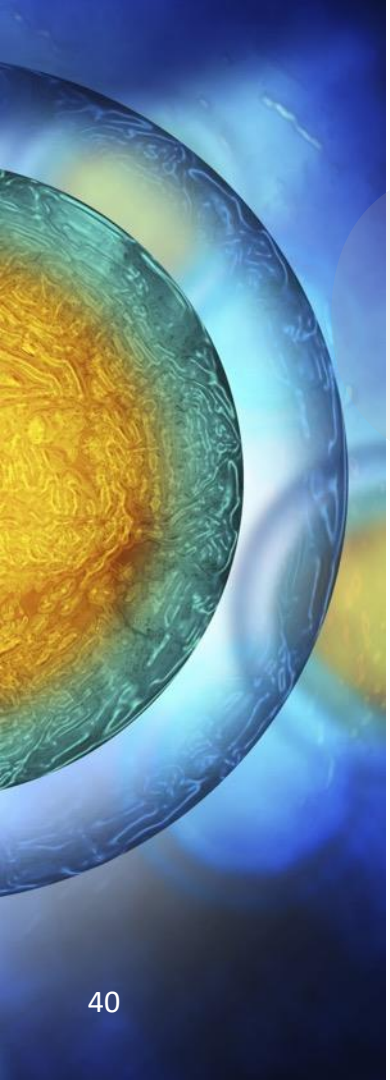

Questions?

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Thank You