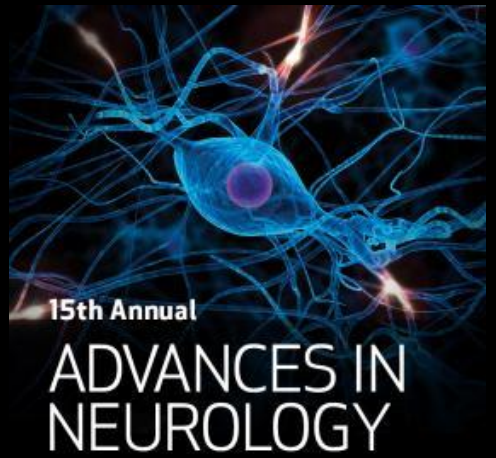
Biomarkers in Dementia and Other Neurodegenerative Disorders

Jon Toledo, md, phd

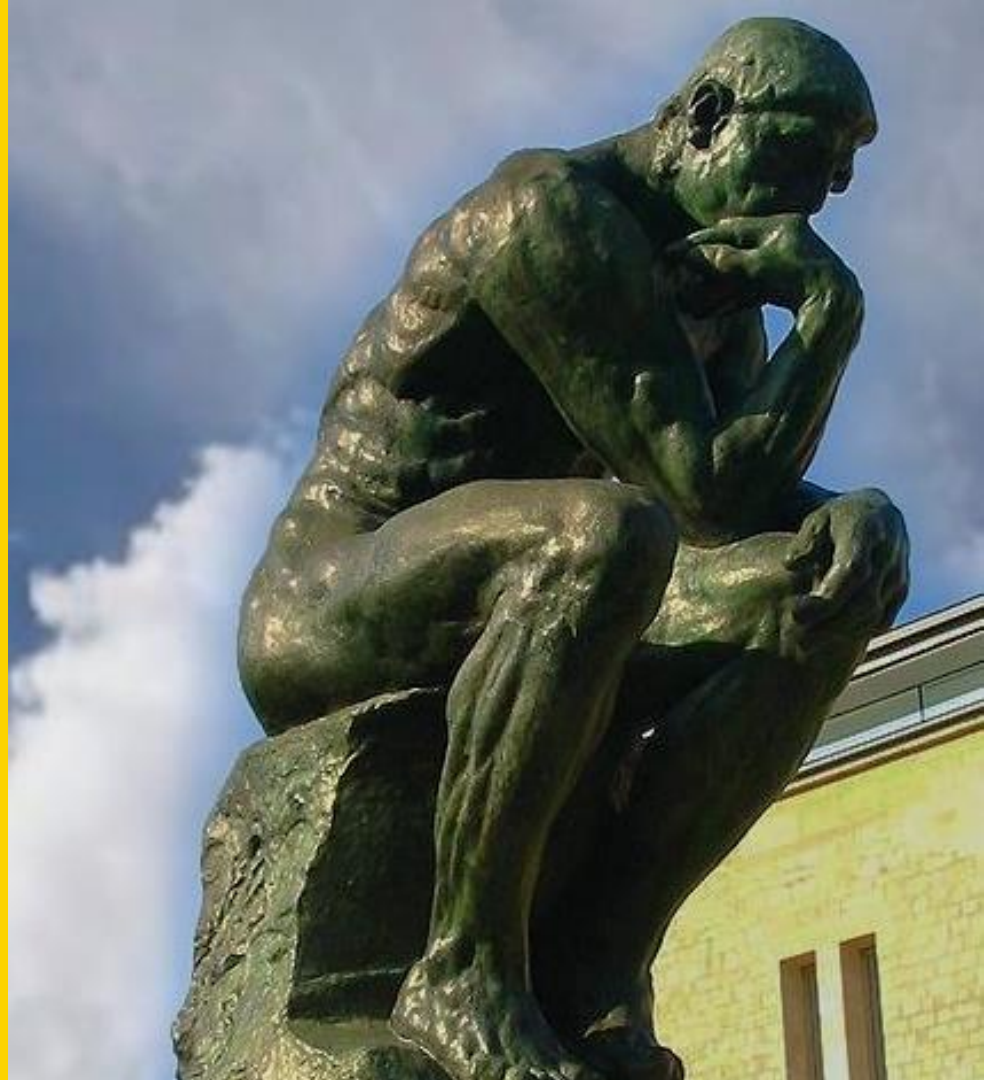


September 23rd
2022

https://learn.houstonmethodist.org/

"Nature did not deem it her business to make the discovery of her laws easy for us."

— A. Einstein



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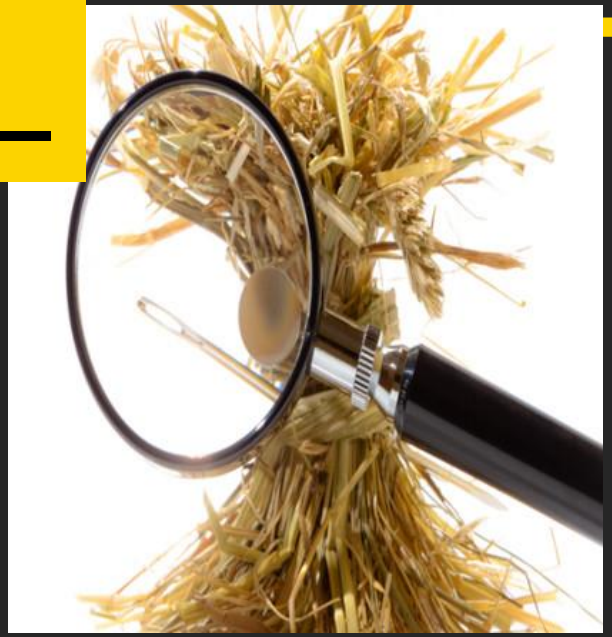


Section 1: BiomarkeR?

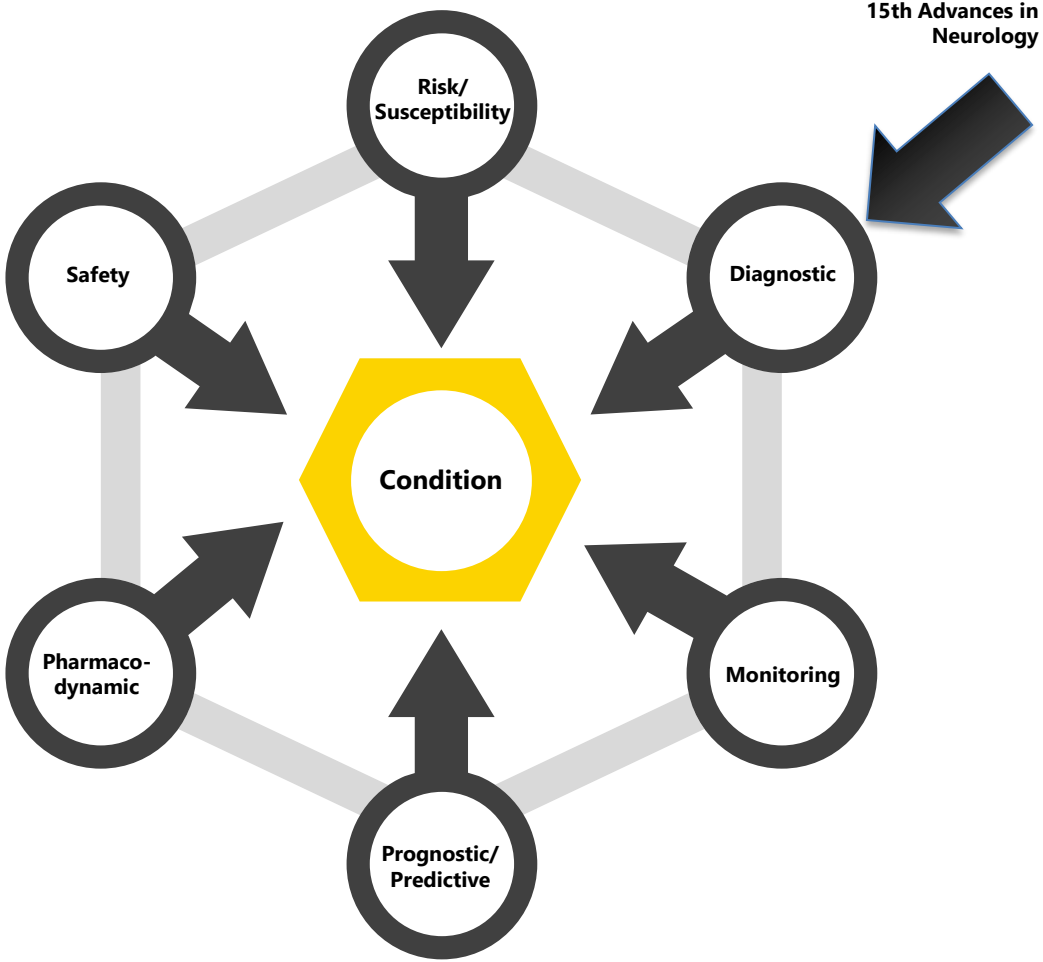
"Nothing in life is to be feared, it is only to be understood. Now is the time to understand more so that we may fear less."
-Marie Curie

toolkit.ncats.nih.gov/module/discovery/

What is a biomarker (BM)

"Biological markers (biomarkers) are characteristics that can be objectively measured and used as an indicator of normal biological processes, disease processes, or pharmacologic responses to a therapy."

Types of BM



Biomarkers have multiple purposes

Will not cover genetics

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Section 2: Why?

"Although this may seem a paradox, all exact science is dominated by the idea of approximation. When a man tells you that he knows the exact truth about anything, you are safe in inferring that he is an inexact man. Every careful measurement in science is always given with the probable error ..."

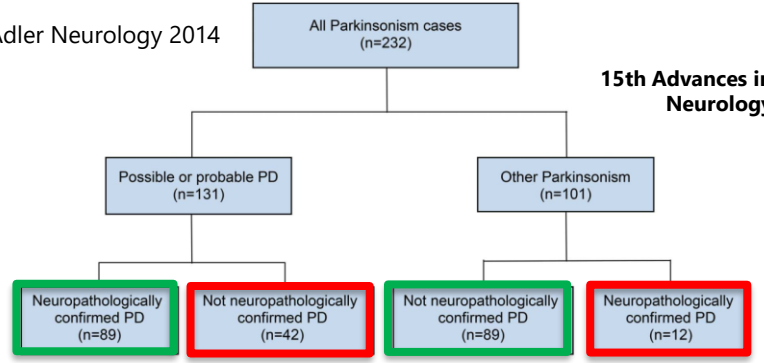
-Bertrand Russel

Recently, ~16% of participants in an anti-Aβ passive immunotherapy trial for mild-to-moderate Alzheimer disease (AD) had a negative baseline amyloid positron emission tomography (PET) scan. Whether they have AD or are AD clinical phenocopies remains unknown. We examined the 2005-2013 National Alzheimer's Coordinating Center autopsy database and found that ~14% of autopsied subjects clinically diagnosed with mild-to-moderate probable AD have no or sparse neuritic plaques, which would expectedly yield a negative amyloid PET scan. More than half of these "Aβ-negative" subjects have low neurofibrillary tangle Braak stages. These findings support the implementation of a positive amyloid biomarker as an inclusion criterion in future anti-Aβ drug trials.

Serrano-Pozo Ann Neurol 2014

Misdiagnosis in AD

Adler Neurology 2014



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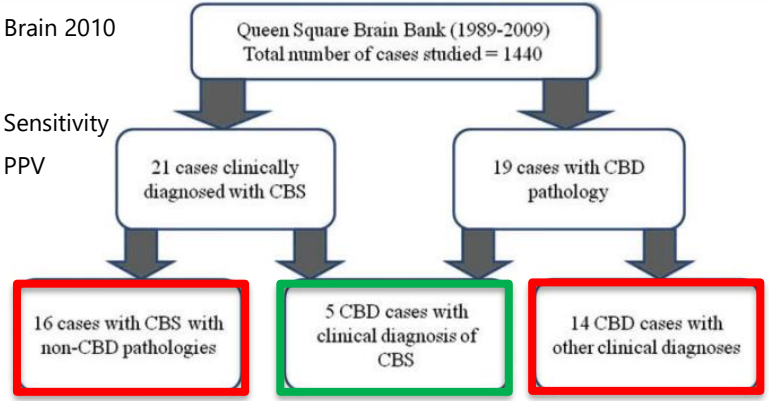
26% accuracy in untreated/not clearly responsive subjects, 53% accuracy in early responsive to medication (<5 y.' duration), and 85% accuracy of longer duration, medication-responsive

Misdiagnosis in PD

Ling Brain 2010

26.3% Sensitivity

23.8% PPV



Misdiagnosis in CBD

	Neuropath. AD vs. FTLD	Clinical AD vs. clinical FTLD
Selected biomarkers	P-Tau and $A\beta_{42}$	T-Tau and P-Tau
AUC	0.98	0.87
Sensitivity	100.0%	78.6%
Specificity	87.5%	77.8%

	Clinical AD	Clinical FTD
BM AD	48 AD (npath. Dx) (±)	12 AD (npath. Dx) (+) 1 FTLD (npath. Dx) (-)
BM non-AD	1AD (npath. Dx) (-) 3 FTLD (npath. Dx) (+)	10 FTLD (npath. Dx) (±)

Toledo Acta Neuropath 2012

Clinical Dx has 17% misclassification vs. 5.3% of the CSF

BM: We need adequate Gold STandard

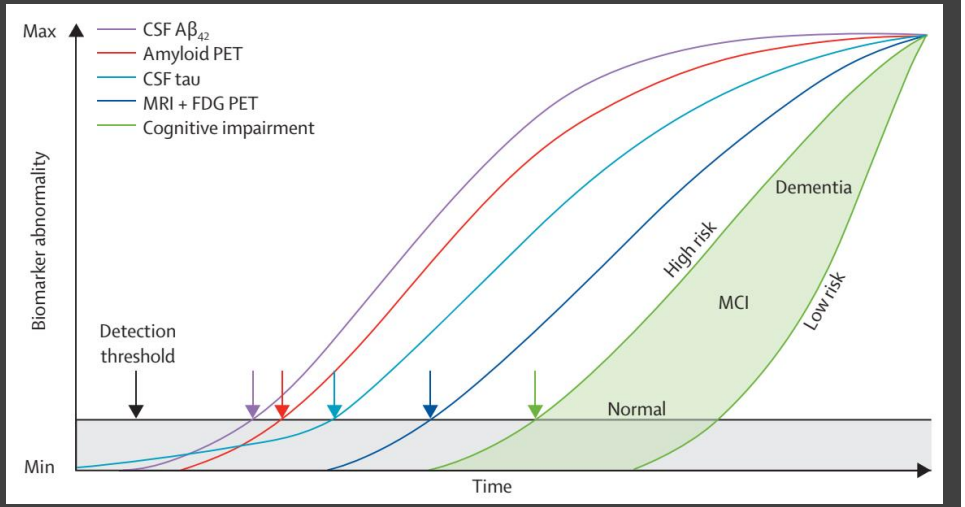
Conclusion:

Clinical diagnosis underestimates accuracy of biomarkers

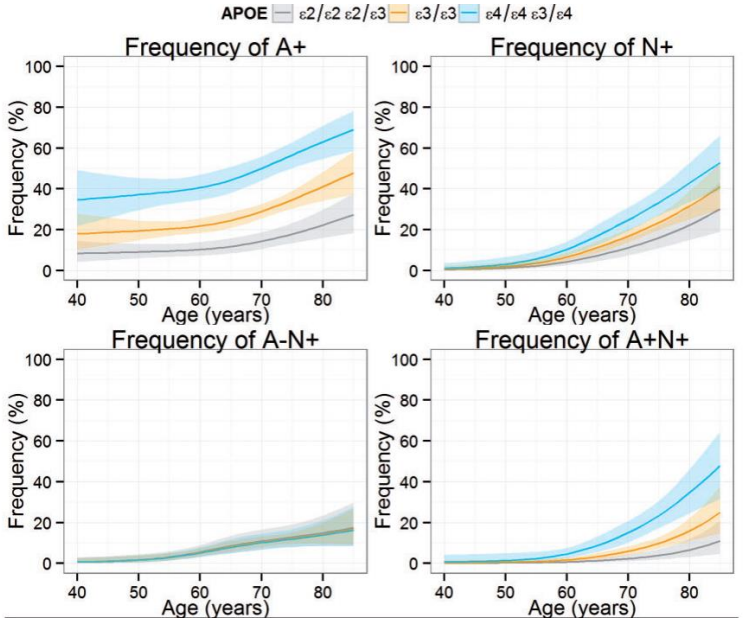
BM: Align with the clinical diagnosis?

Hypothesis:

Biomarkers align with the clinical presentation

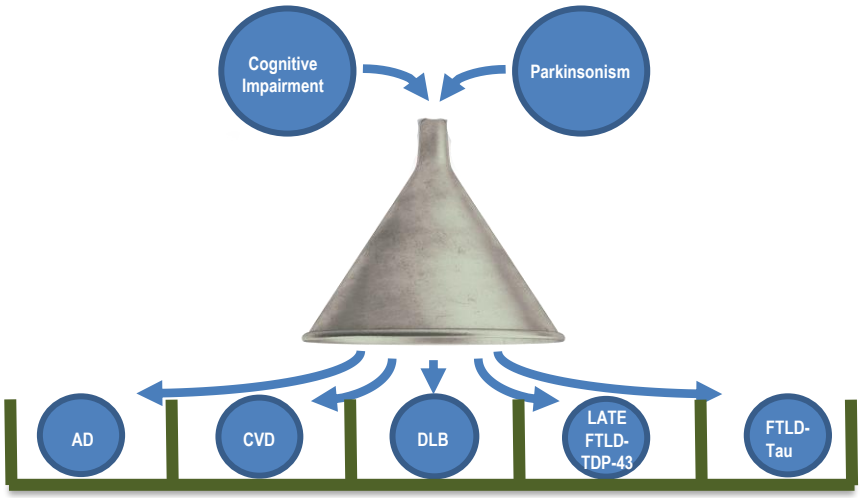


Jack Lan Neu 2013



Toledo Brain 2015

BM Already Change in Preclinical Stages

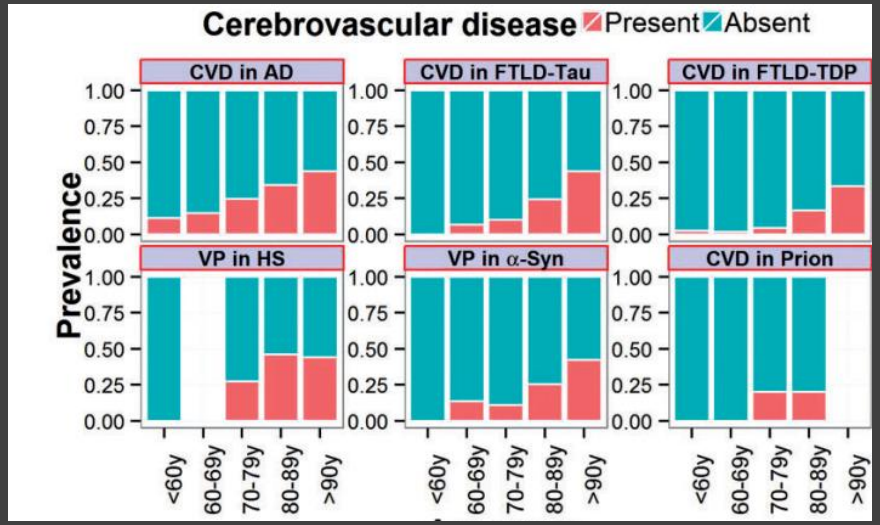


Toledo Alz & Dem (Accepted)

BM: Useful to differentiate/ separate?

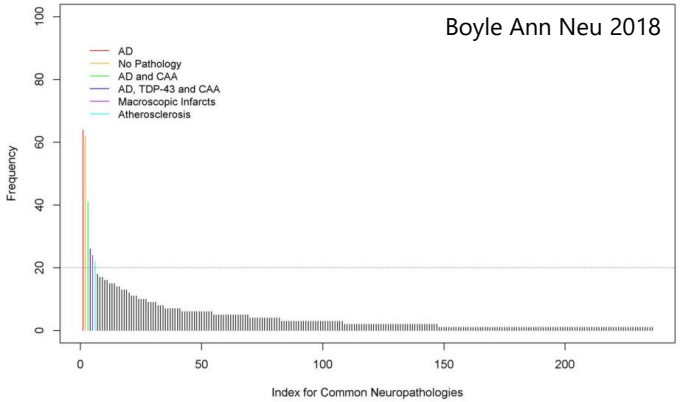
Hypothesis:

Useful diagnostic biomarkers could increase the diagnostic accuracy and certainty and differentiate between the different neurodegenerative diseases



Toledo Brain 2011

Increased Cerebrovascular Pathology w Aging

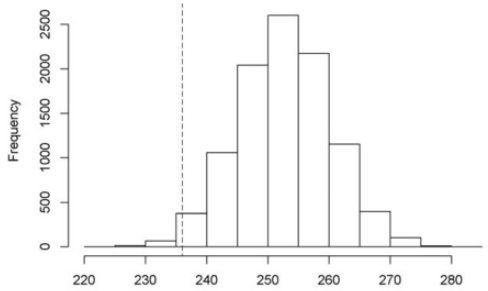


94% 1+

78% 2+

58% 3+

35% 4+

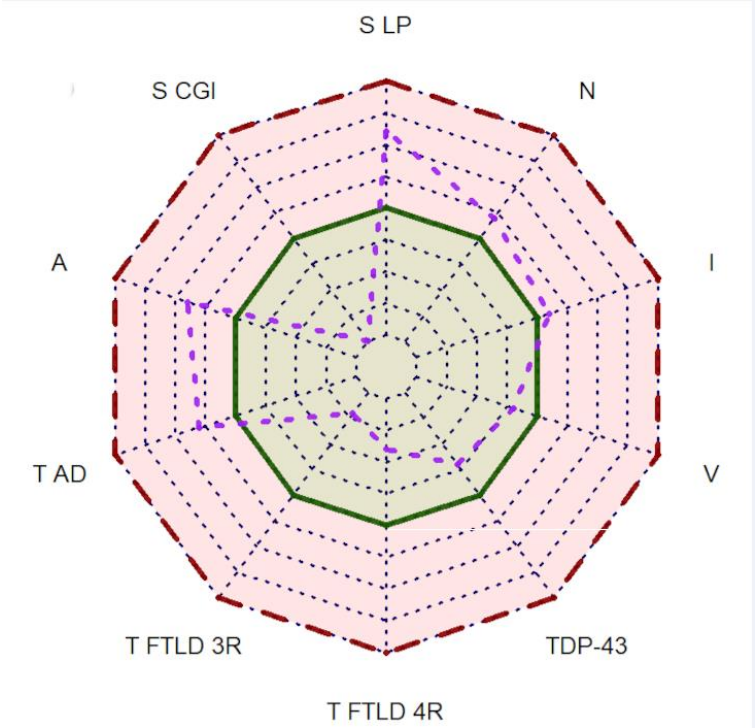


Presence of Multiple Co-Pathologies is the Norm

BM: Need to detect & quantify multiple pathologies

Conclusion:

Biomarkers should be able to detect multiple pathologies using a qualitative (normal/abnormal) and quantitative approach.



Toledo Alz & Dem (Accepted)

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Section 3: What & How

"Extraordinary claims require extraordinary evidence."

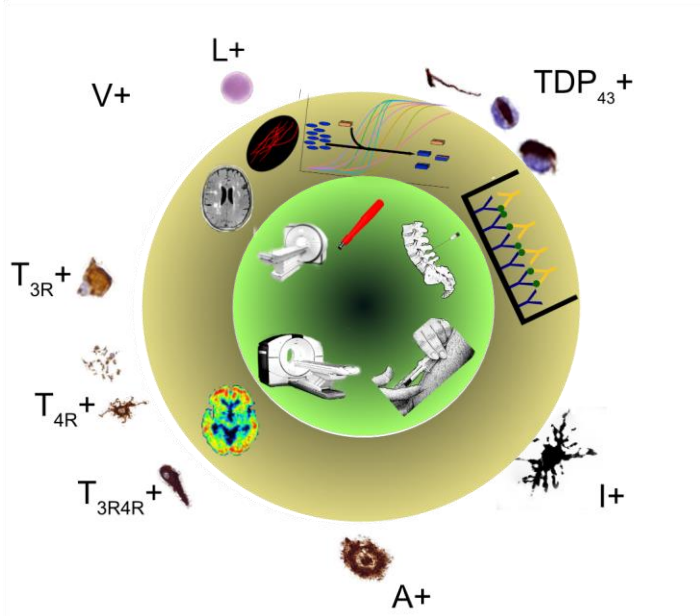
– Carl Sagan

What & How

Tool: MRI, PET, blood, cerebrospinal fluid, skin,…

Technique: MRI sequence, specific PET tracer, different types of immunoassays, protein misfolding cyclic amplification, real-time quaking-induced conversion, immunohistochemistrym,…

Pathology: Aβ, Lewy pathology, FTLD-TDP-43, FTLD tau 3R and 4R, AD Tau, inflammation, vascular, neurodegeneration



Toledo Alz & Dem (Accepted)

PET

Advantage

- ✓ Spatial Definition
- ✓ Clinical Correlation

Disadvantage

- ❖ Availability
- ❖ Cost
- ❖ Single tracer each time

CSF

Advantage

- ✓ Multiplexing/Multi-assay
- ✓ Cost

Disadvantage

- ❖ Invasive
- ❖ (Standardization)

Bloo d

Advantage

- ✓ Multiplexing/Multi-assay
- ✓ COST
- ✓ Non-invasive
- ✓ Availability

Disadvantage

- ❖ Equivalent?
- ❖ (Standardization)
- ❖ Clinical correlation

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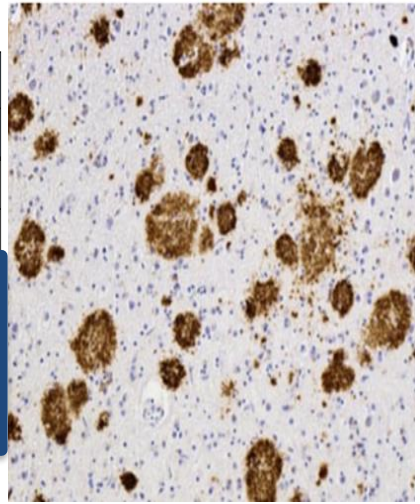
Section 4: Alzheimer’s Disease

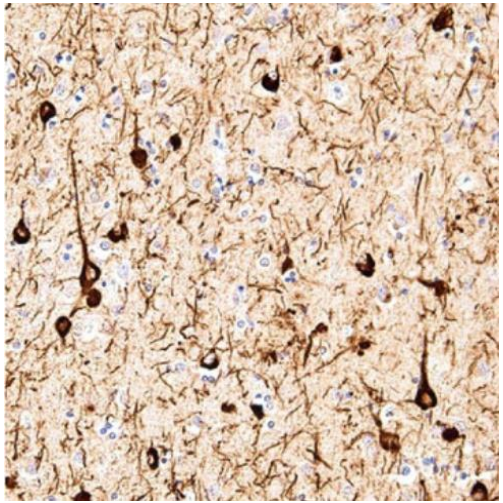
What defines AD?

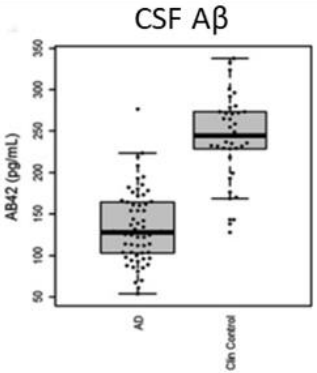
AD is neuropathologically defined by the presence of Aβ plaques and tau neurofibrillary tangles

AD neuropathologic change		B[a]		
A[b]	C[c]	0 or 1	2	3
0	0	Not[d]	Not[d]	Not[d]
1	0 or 1	Low	Low	Low[e]
	2 or 3[f]	Low	Intermediate	Intermediate[e]
2	Any C	Low[g]	Intermediate	Intermediate[e]
3	0 or 1	Low[g]	Intermediate	Intermediate[e]
	2 or 3	Low[g]	Intermediate	High

Montine Acta Neuropath 2012



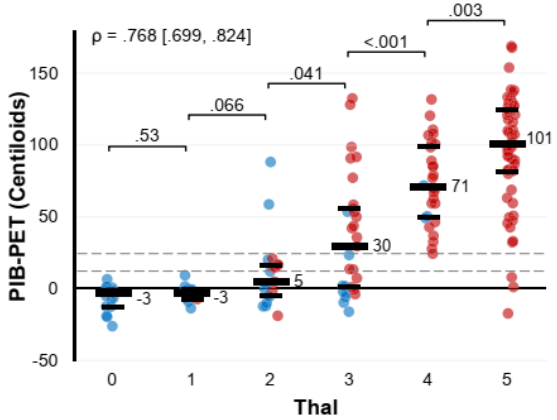




CSF Aβ

-Large group differences

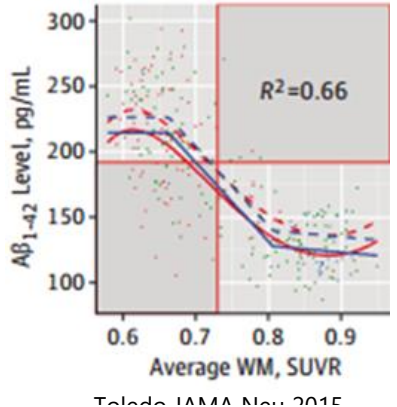
Toledo Acta Neuropath 2012



La Joie Alz & Dem 2019

PiB (Aβ) PET

-Correlation with Aβ distribution



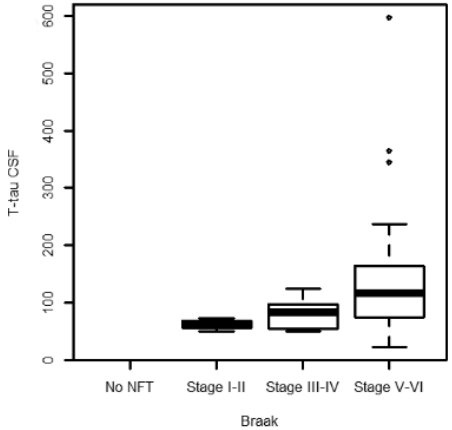
CSF & Aβ PET

-Not completely linear association

Toledo JAMA Neu 2015

CSF Tau

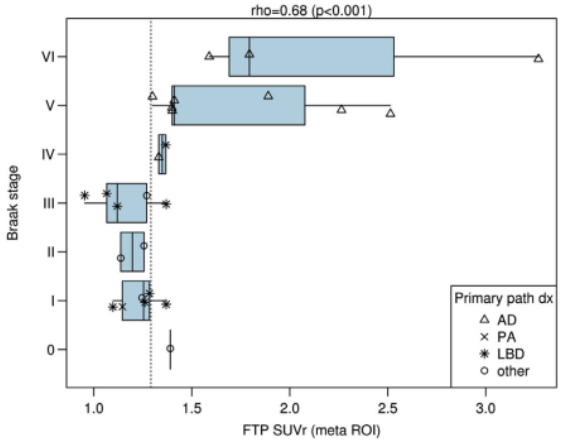
-Correlates with tau burden at autopsy



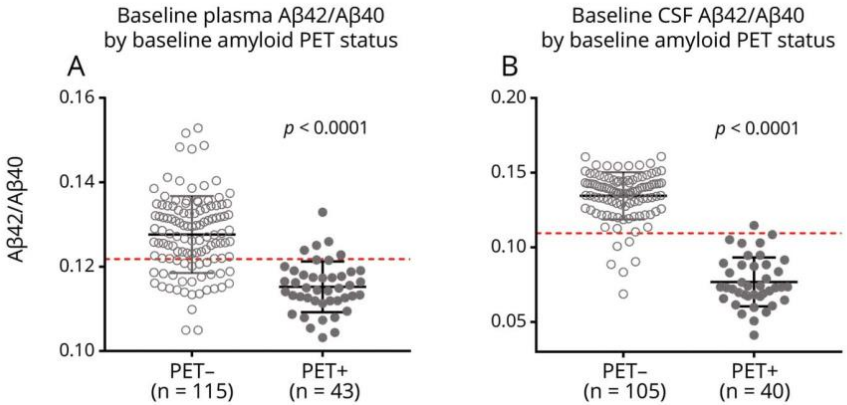
Toledo Acta Neuropath 2012

Tau PET

-Correlates with tau burden at autopsy

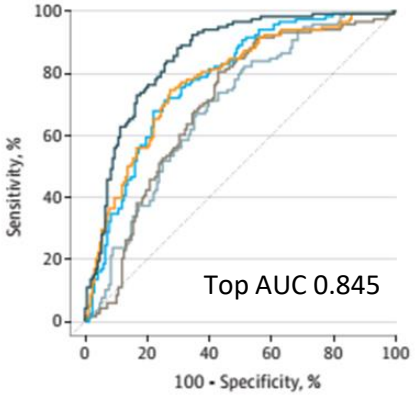


Lowe Alz & Dem 2019

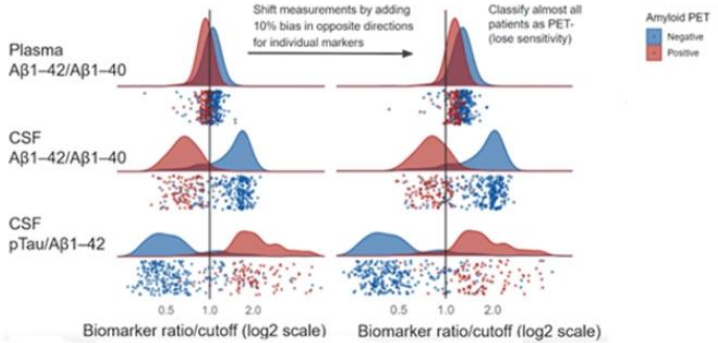


Schindler Neu 2019

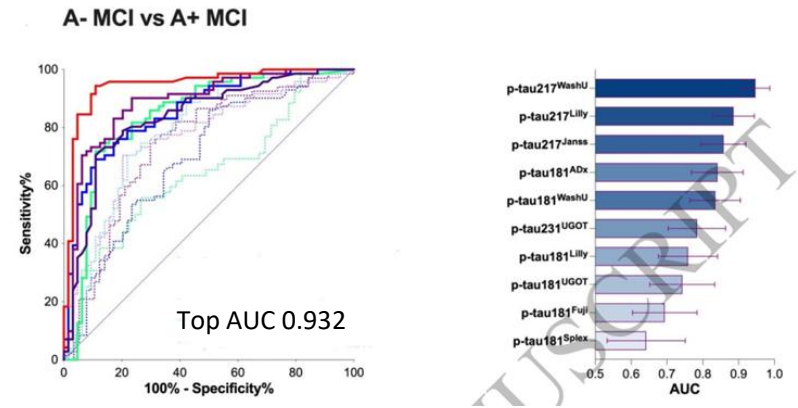
Blood would offer the ideal biomarker source



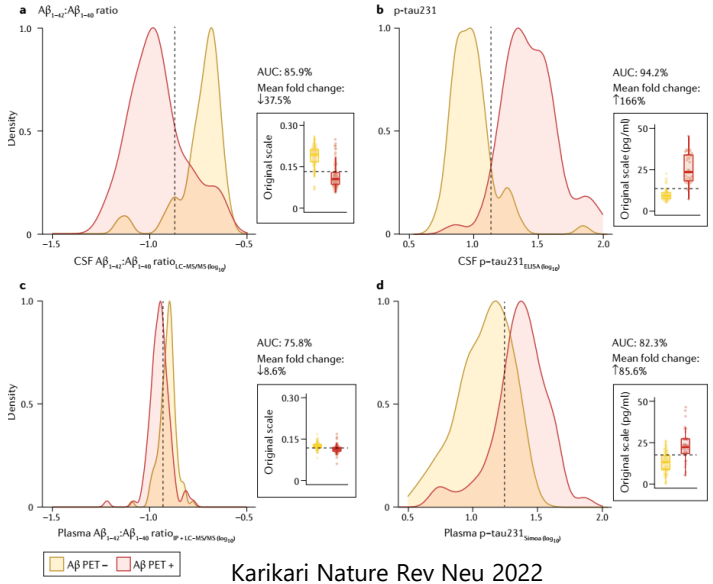
Janelidze Alz & Dem 2021



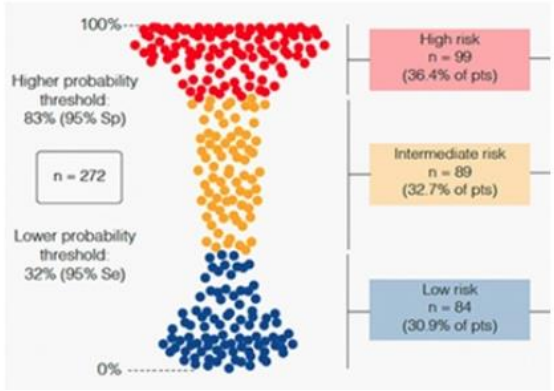
Christina Rabe Alzforum



Janelidze Brain 2022

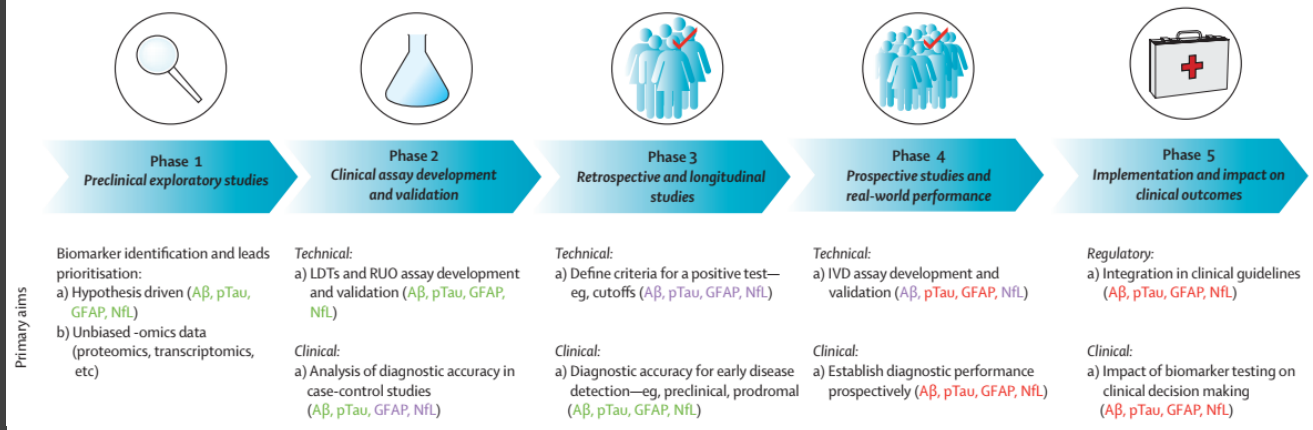


Karikari Nature Rev Neu 2022



Oscar Hansson Alzforum

Where are We now?



Teunissen Lan Neu 2022

Teunissen Lan Neu 2022

	Description	Expected timeframe
Memory clinic	Biomarkers are added to the repertoire of diagnostic tests in memory clinics. Performed in addition to medical and neurological examination, neuropsychological investigation, and imaging. In the future, might replace CSF or PET for Alzheimer's disease confirmation in some cases.	Short term (hopefully 3–5 years)
Primary care	Biomarkers to be used as a screening test, together with a brief cognitive test (eg, MMSE or MoCA). Results used to reassure patients or refer them for further testing to memory clinic. Confirmation of Alzheimer's disease pathology by CSF or PET in memory clinic.[52]	Intermediate term (hopefully 5–10 years)
Population screening	Three prerequisites for screening are: (1) near 100% accuracy of screening test; (2) low cost of screening test; and (3) availability of treatment. Even when accuracy is achieved, high costs and low availability mean that a population-wide screening programme for Alzheimer's disease is not yet on the horizon.	Long term (unlikely within the next 10 years)

Hansson Alz dem 2022

TABLE 2 Recommendations of the use of AD-associated BBMs in clinical trials and practice

Biomarkers as a first screening step in clinical trials:
(1) BBMs, especially plasma Aβ42/Aβ40 and p-tau assays with established thresholds, can already now be used as a first screening step in AD trials evaluating potential disease-modifying therapies, provided the AD status is confirmed with PET or CSF in the participants with abnormal BBM outcomes before final inclusion in the trials.
(2) In the future, it might be that only participants with uncertain BBM outcomes (e.g., biomarker results close to the cut-off for positivity) need to undergo PET and CSF to confirm a positive AD status, and that those with clearly abnormal BBMs can enter the trial without such evaluations (i.e., if longitudinal PET or CSF assessments are not used as outcome measures in the trial). However, additional data are needed to determine whether the BBMs have high enough positive predictive values to serve as stand-alone biomarkers for trial inclusion.
(3) In non-AD trials, BBMs (especially plasma Aβ42/Aβ40 and p-tau assays with established thresholds) can be used to exclude patients likely having AD co-pathology.
Surrogate biomarkers in clinical trials:
(4) BBMs can be used as exploratory outcomes in most clinical trials in AD and other neurodegenerative dementias. BBMs need further validation before they are used as primary endpoints in pivotal trials. BBMs could be used to inform decisions in clinical trials with adaptive design.
Use of BBMs in specialized memory clinic settings:
(5) BBMs (with established thresholds) should currently only be used in symptomatic patients at specialist clinics and the results should be confirmed whenever possible with CSF or PET. Additional data are needed before use of BBMs as stand-alone diagnostic markers.
Use of BBMs in primary care:
(6) Additional data are needed for use of BBMs in primary care.

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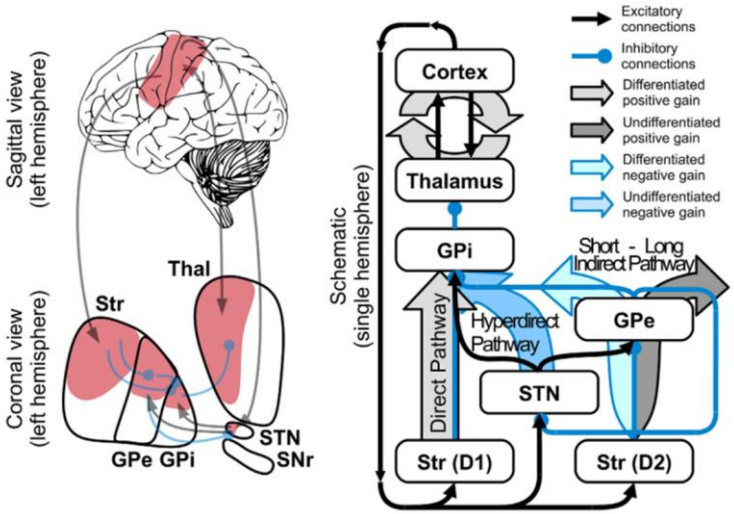
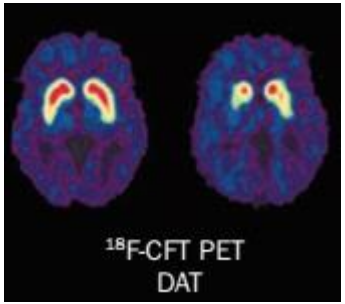
15th Advances in Neurology

Section 5: α-Synucleinopathies

Nigrostriatal Denervation



Fiore Sci Rep 2016

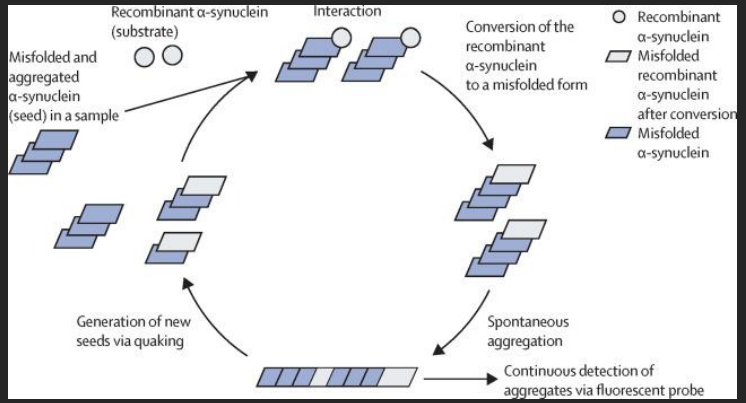


Politis Nat Rev Neu 2014

Abnormal in Parkinson's Disease

& Multiple System Atrophy

& Progressive Supranuclear Palsy



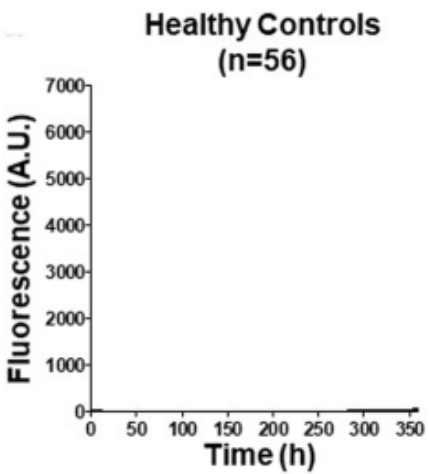
RT-QuIC

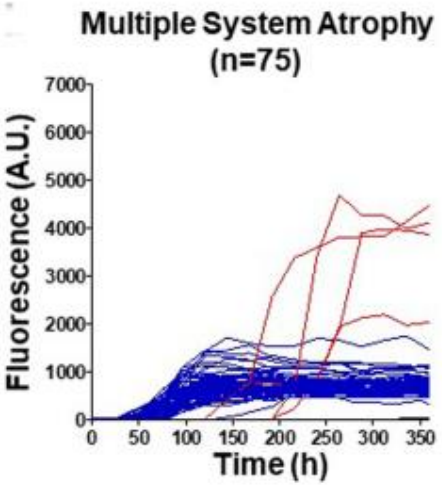
Real-Time Quaking-Induced Conversion

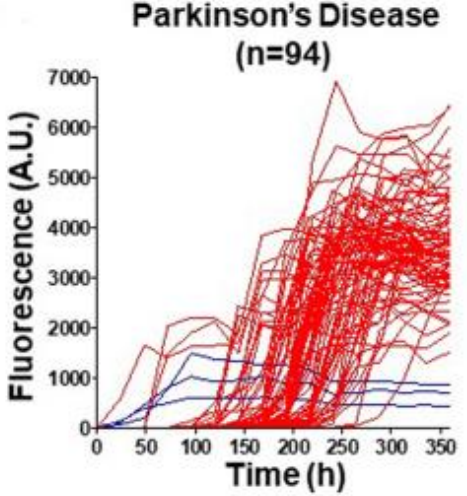
PMCA

Protein-Misfolding Cyclic Amplification

CSF Results



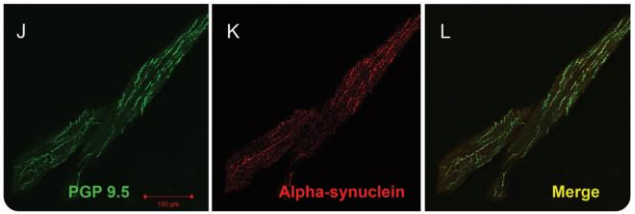




Shahnawaz Nature 2020

Skin

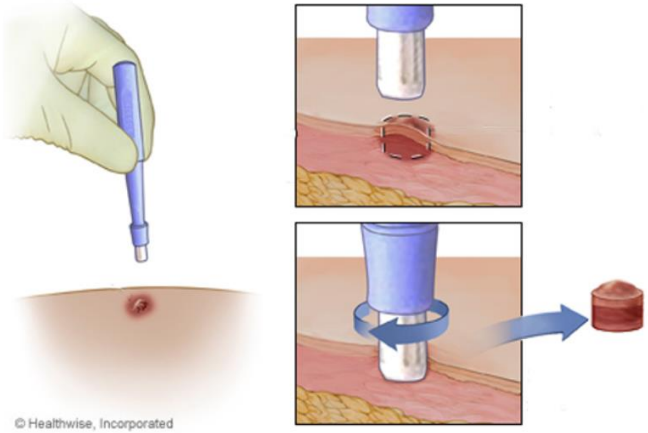
Parkinson's Disease



Gibbons Neu 2016 Se= 94.9%; Sp=91.1%

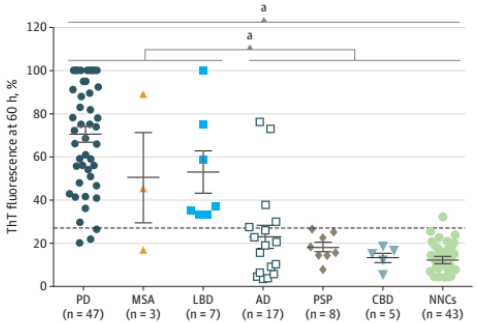
Isolated REM Behavior Sleep Disorder

Miglis 2021 Se= 64.0%

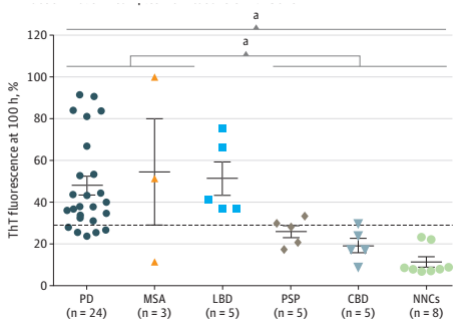


Lbda.org

RT-QuIC

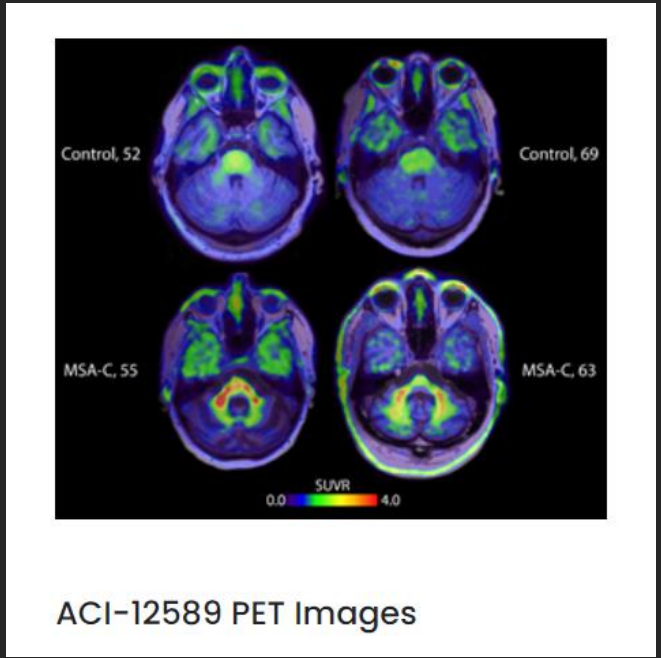


PMCA



Wang JAMA Neu 2021

α-Synuclein PET



https://ir.acimmune.com/

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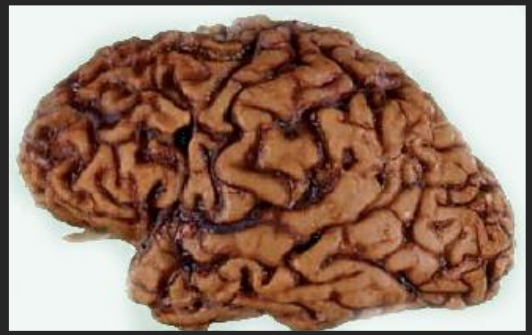
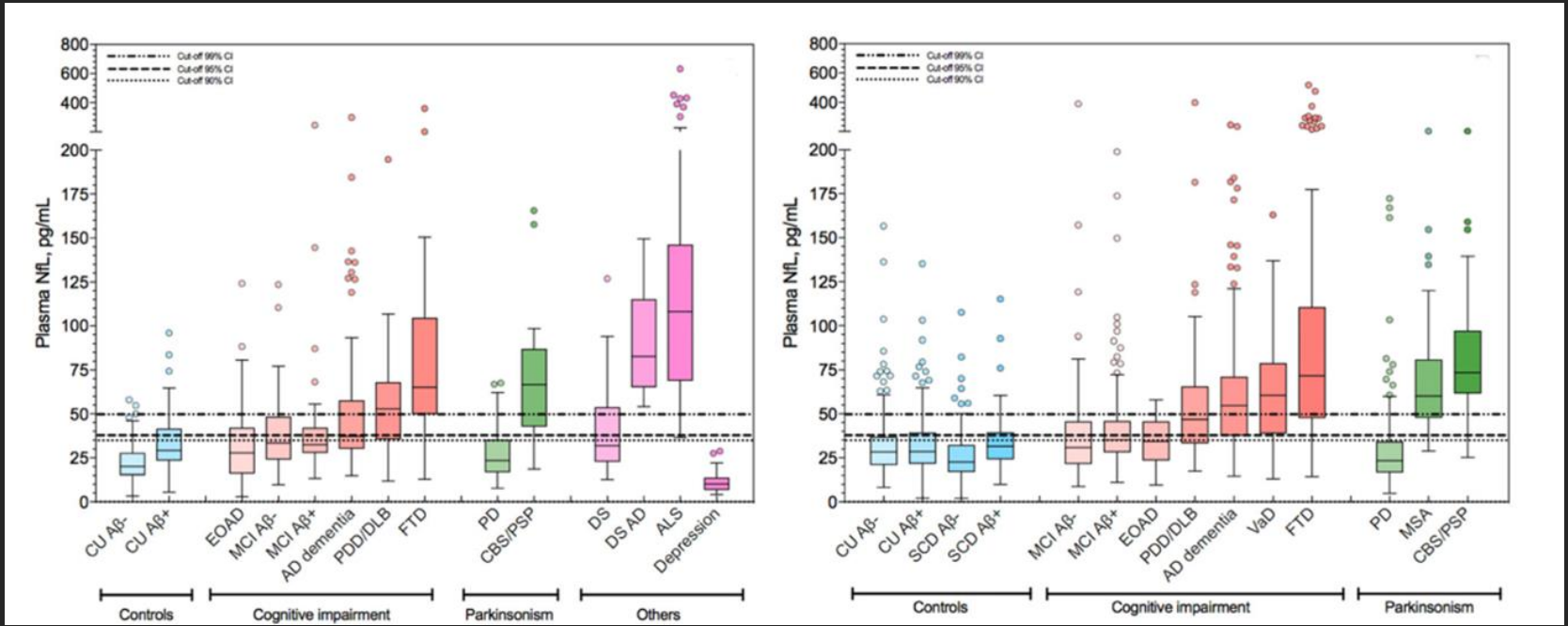


Neary Lan Neu 2005

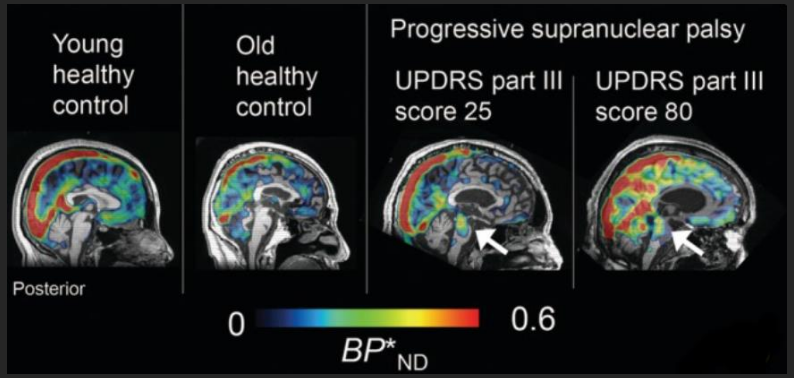
Section 6: Frontotemporal Lobar degeneration

Neurofilament Light Chain



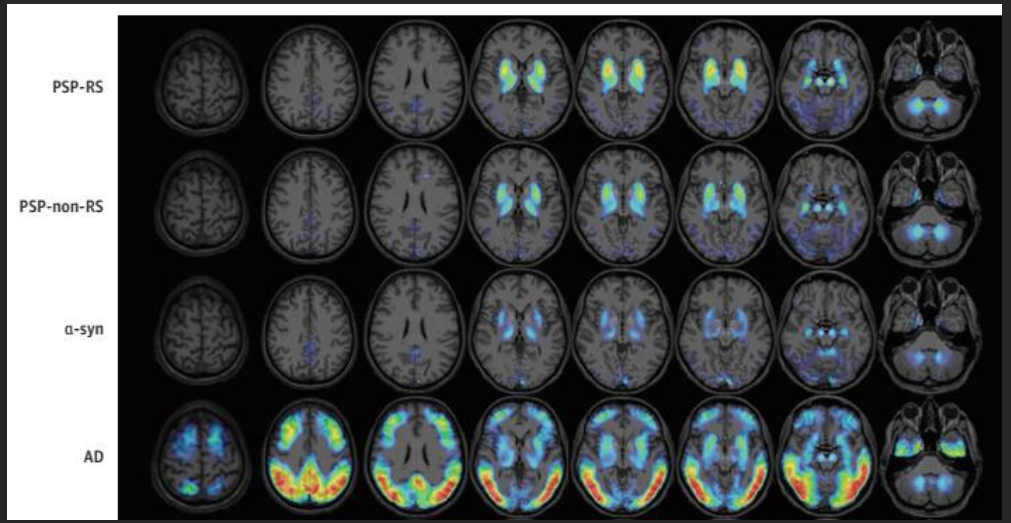
Ashton Nat Com 2021

Progressive Supranuclear Palsy



PPB3

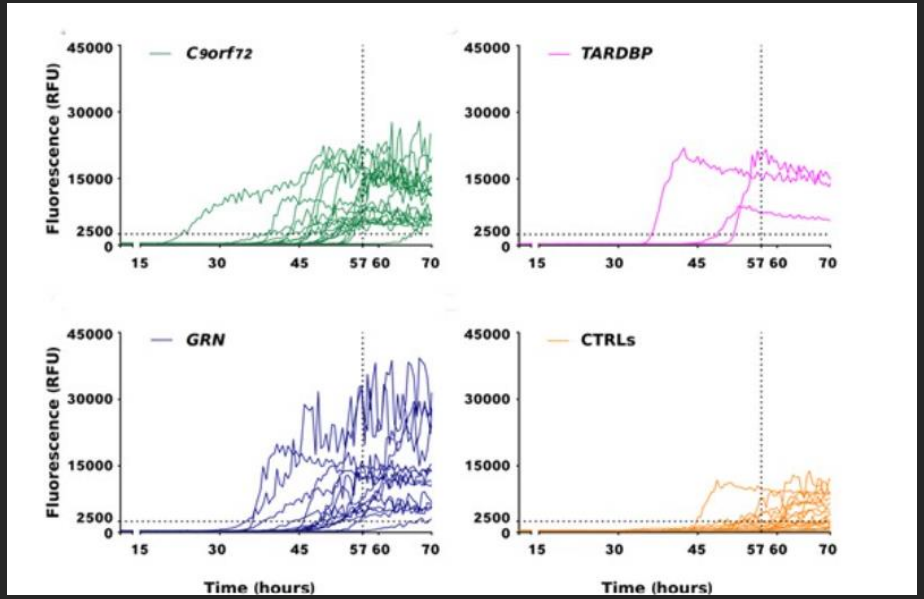
Endo Mov Dis 2019



18F-PI-2620

Brendel JAMA Neu 2020

TDP-43



Scialo Brain Com 2020

BOnus