Recent advances in neuroimaging technologies and future directions for early assessment and monitoring in Alzheimer's disease

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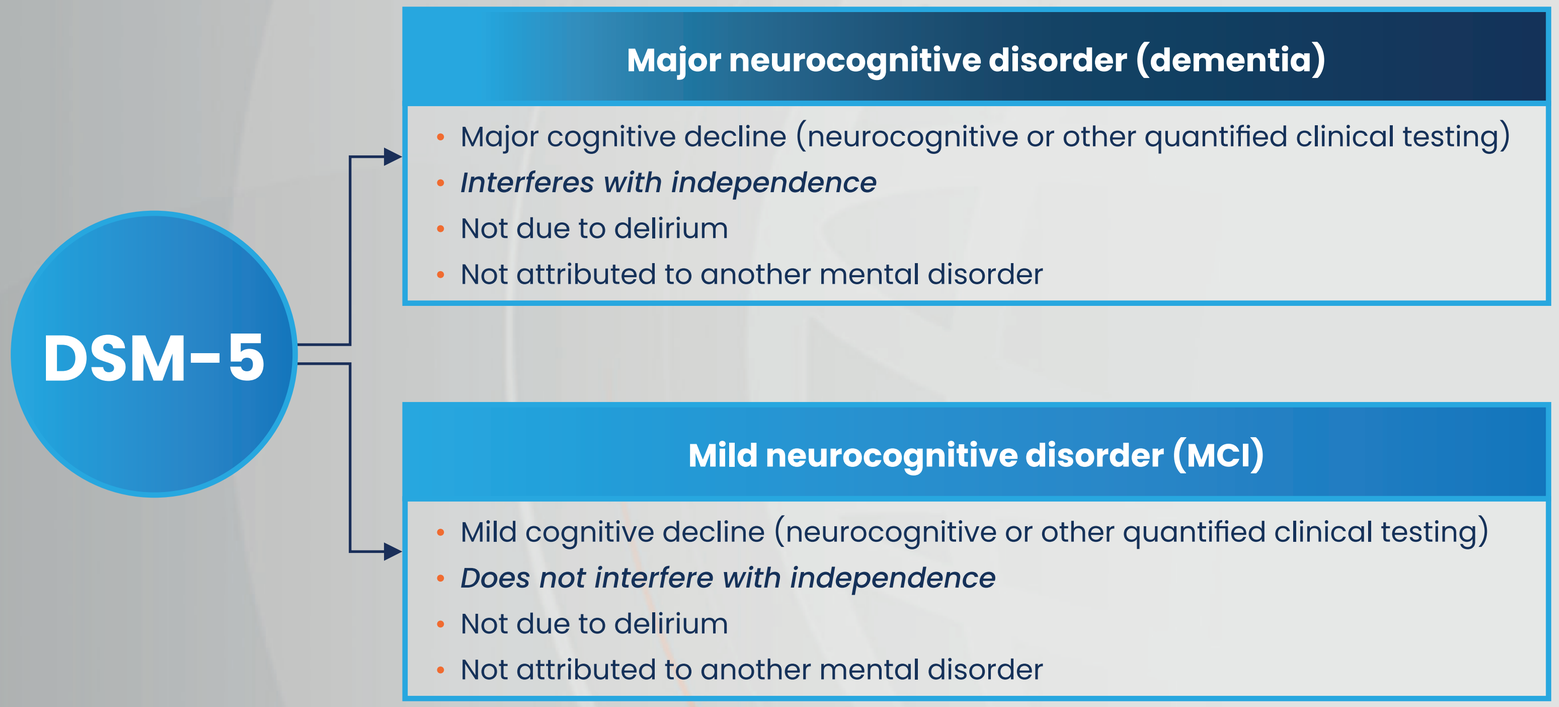
How can neuroimaging modalities help with early and accurate diagnosis of Alzheimer's disease?

Definition of neurocognitive disorders



DSM-5, Diagnostic and Statistical Manual of Mental disorders, 5th Edition; MCI, mild cognitive impairment.
Sachdev PS, et al. *Nature Rev Neurol.* 2014;10:634–42.

Diseases causing cognitive impairment and dementia

Alzheimer's disease

Vascular-ischaemic brain injury
- Cortical/subcortical

Lewy body disease

Frontotemporal lobar degeneration
- Tauopathies
- TDP-43 proteinopathies

Amyotrophic lateral sclerosis (Lou Gehrig's disease)

Hippocampal sclerosis; argyrophilic grain disease

Huntington's disease

Creutzfeldt–Jakob and rarer diseases

TDP-43, TAR DNA-binding protein 43.

Emmady PD, Tadi P. Dementia. [Updated 2021 Mar 11]. In: StatPearls [Internet]. Treasure Island (FL). Available at: www.ncbi.nlm.nih.gov/books/NBK557444/ (accessed 25 March 2021); Jicha GA, et al. *Continuum (Minneap Minn).* 2019;25:208–33; Sachdev PS, et al. *Nature Rev Neurol.* 2014;10:634–42; van Es MA, et al. *Lancet.* 2017;390:2084–98.

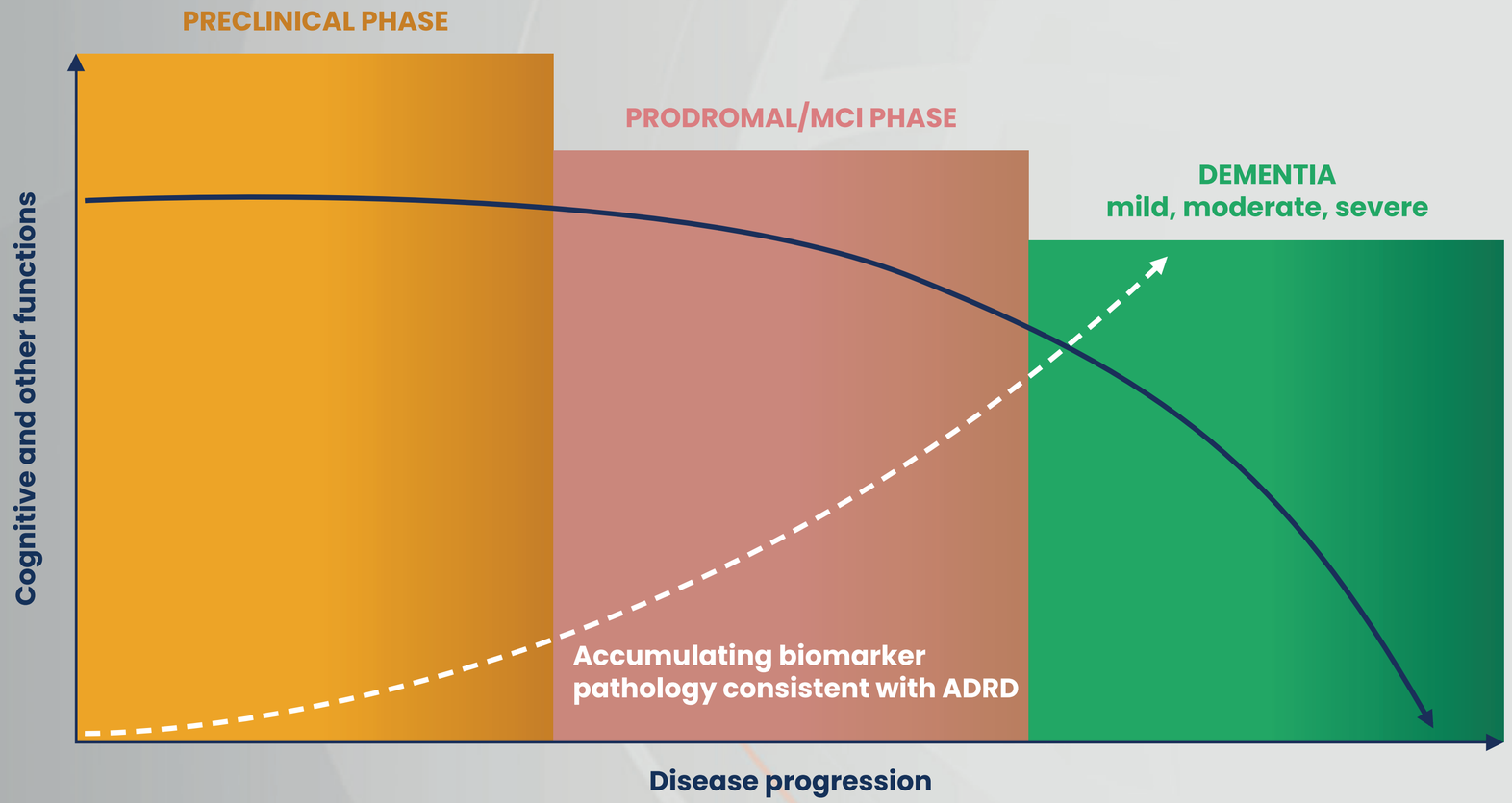
Diseases causing cognitive impairment and dementia

Other causes...

- Tumour
- Trauma
- Anoxia
- Sleep apnoea
- Toxins (medications)
- Hormonal/nutritional deficiencies (e.g. thyroid)
- Infections/inflammatory
- Other primary neurologic illness
- Organ failure

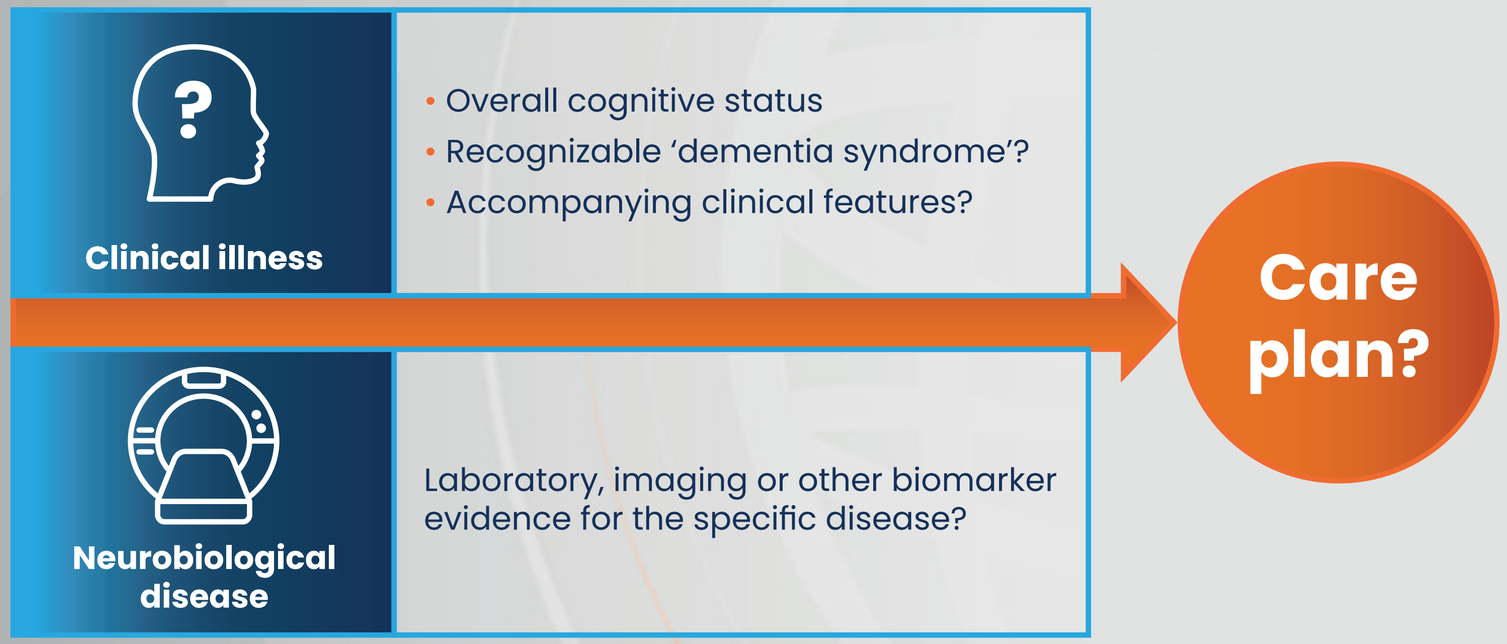
Emmady PD, Tadi P. Dementia. [Updated 2021 Mar 11]. In: StatPearls [Internet]. Treasure Island (FL). Available at: www.ncbi.nlm.nih.gov/books/NBK557444/ (accessed 25 March 2021); Kerner NA, Roose SP. *Am J Geriatr Psychiatry.* 2016;24:496–508; Langa KM and Levine DA. *JAMA.* 2014;312:2551–61; Sachdev PS, et al. *Nature Rev Neurol.* 2014;10:634–42.

Using biomarkers to separate the illness from the disease across the continuum of neurodegenerative dementias



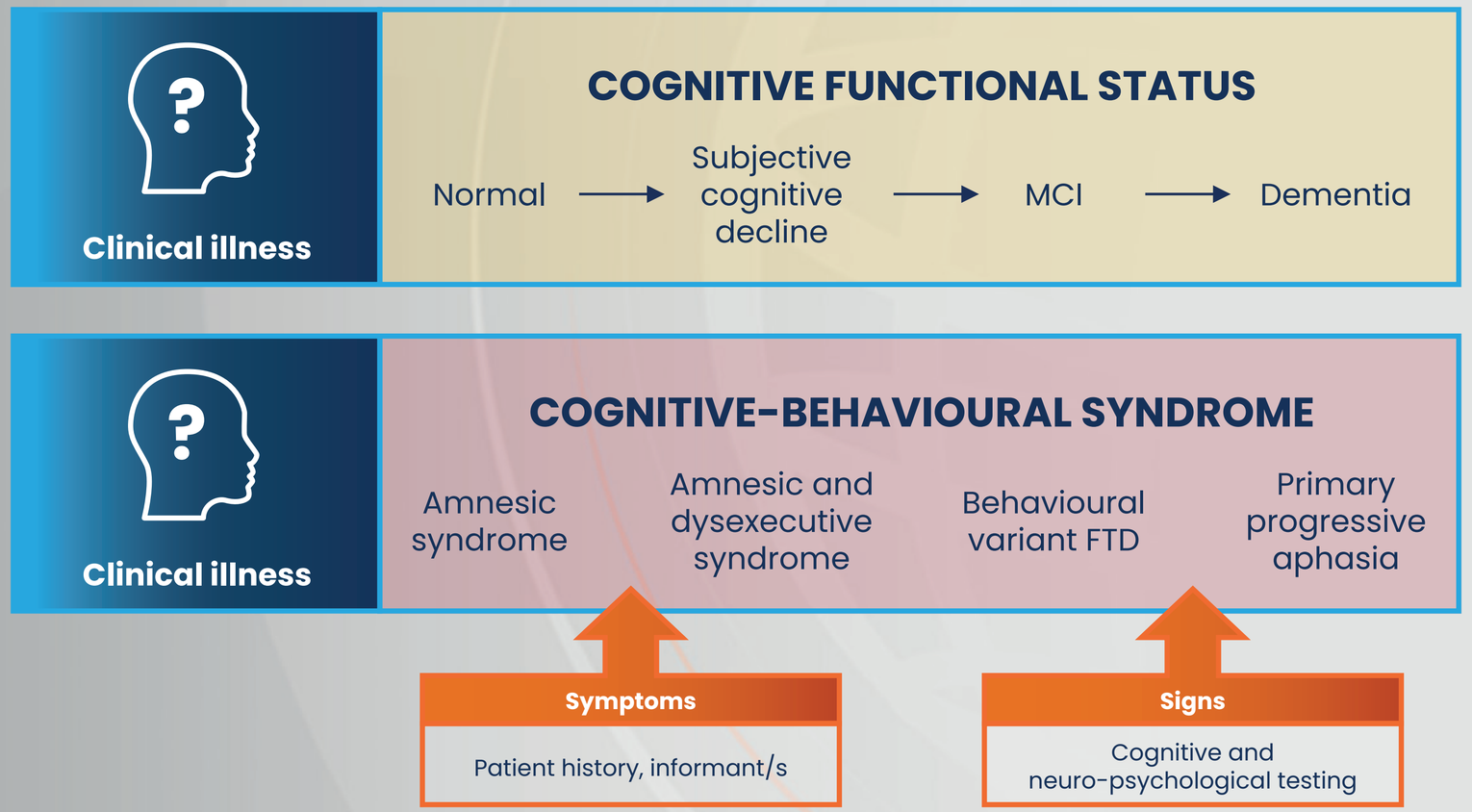
ADRD, Alzheimer's disease-related dementias.
Adapted from Wong B, et al. *Neurodegener Dis Manag.* 2019;9:217–39.

Evaluating patients with suspected neurodegenerative disease



Atri A. *Med Clin N Am.* 2019;103:263–93.

Evaluating neurodegenerative disease



FTD, frontotemporal dementia.

Wong B, et al. *Neurodegener Dis Manag.* 2019;9:217–39.

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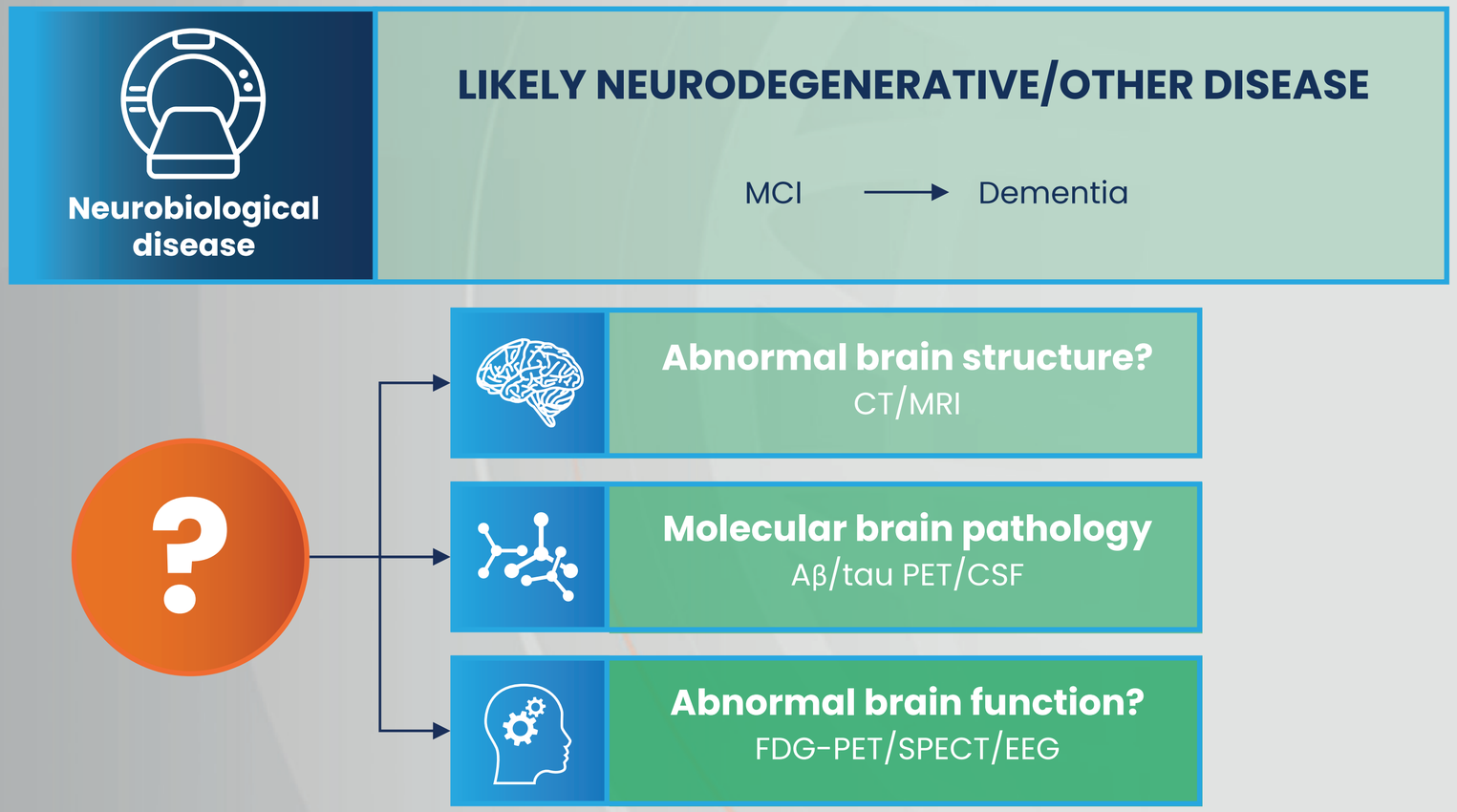
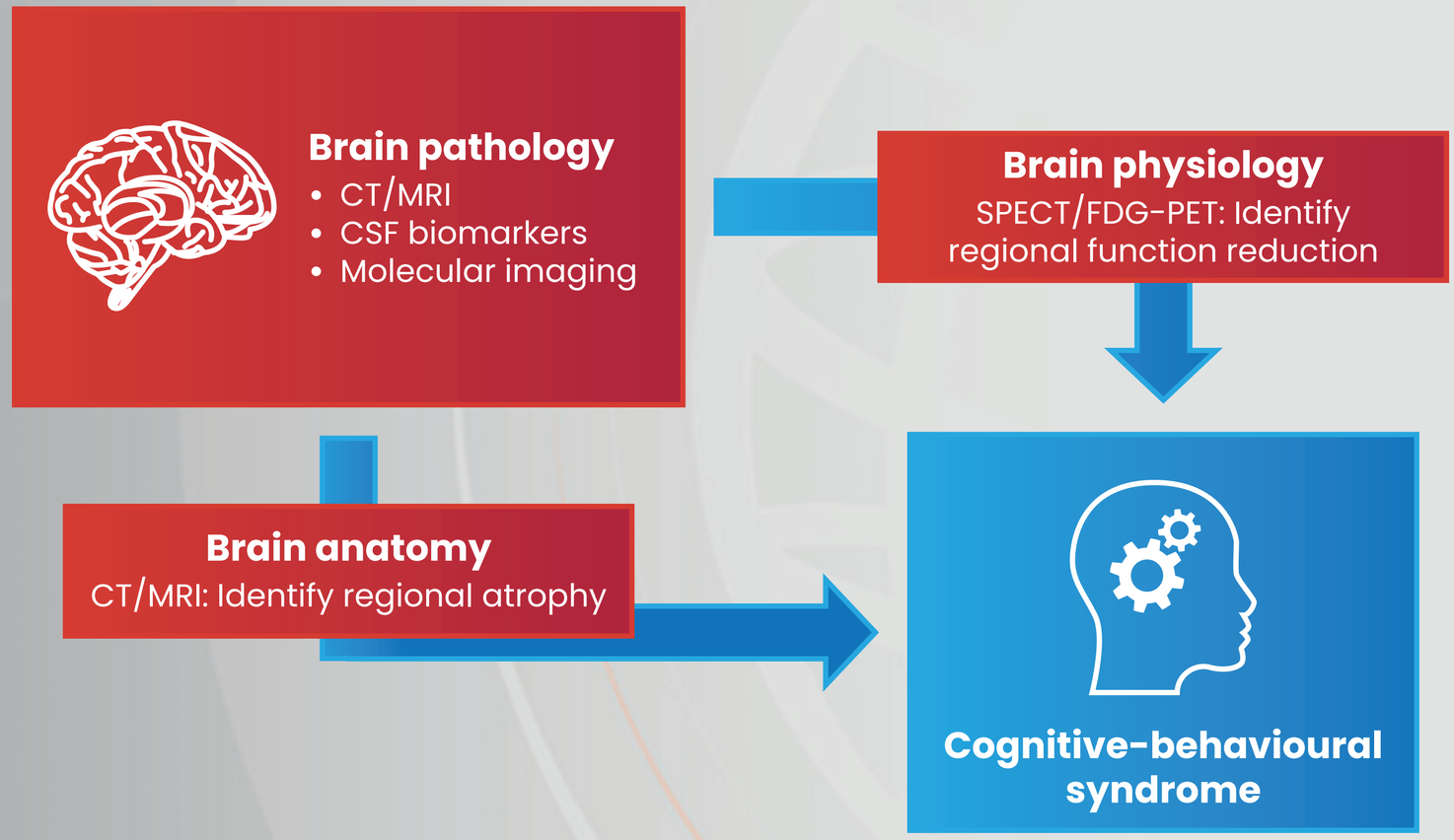
Evaluating neurodegenerative disease



Aβ, beta amyloid; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computerized tomography.

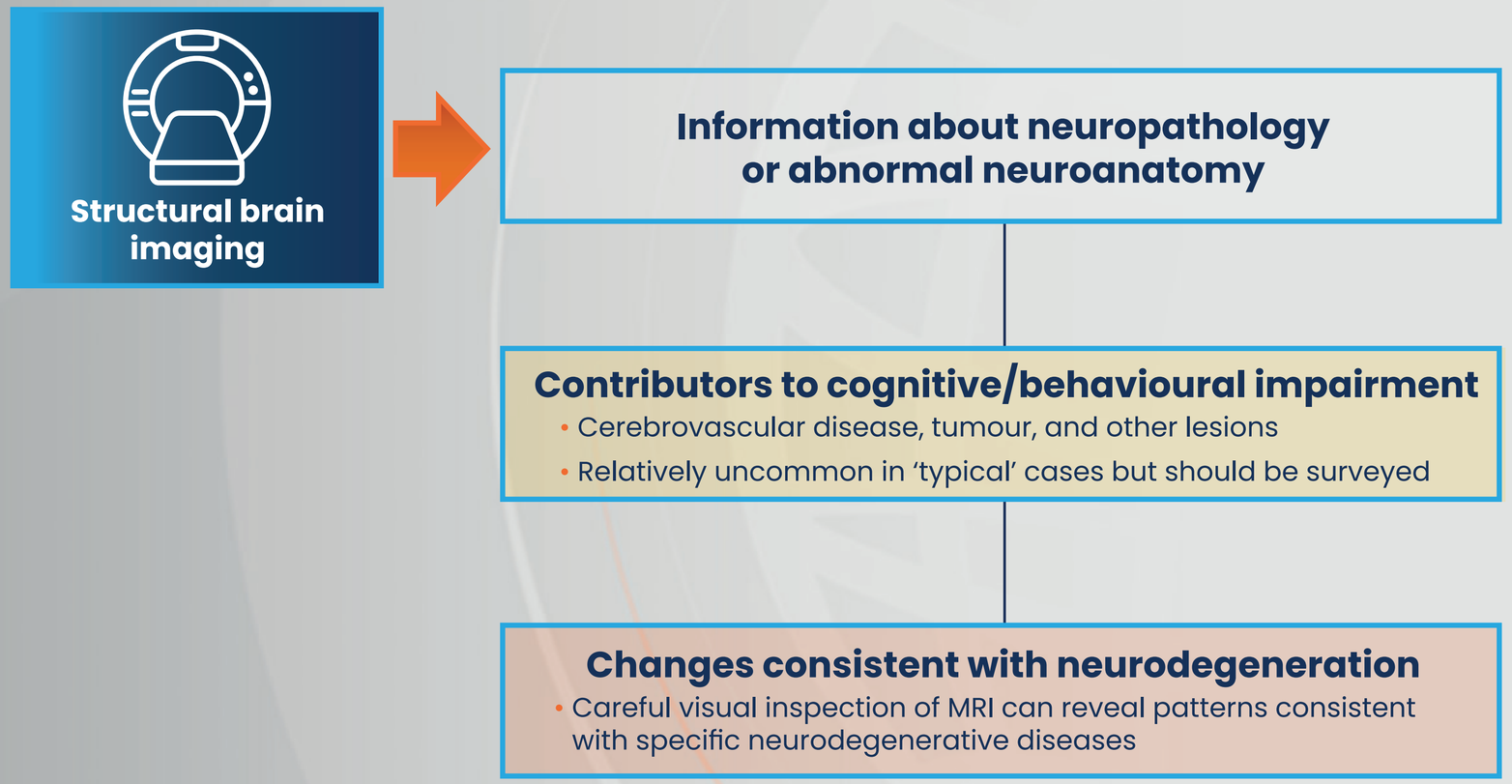
Wong B, et al. *Neurodegener Dis Manag.* 2019;9:217–39.

Evaluating neurodegenerative disease



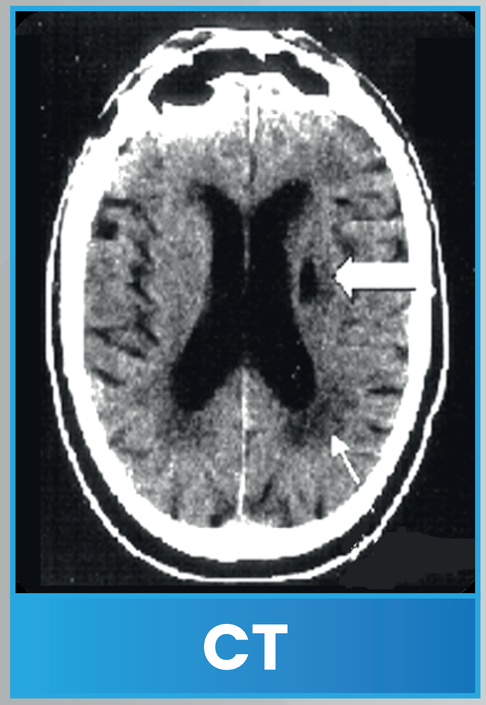
Byrne A, Prichard J. *Prog Neurol Psychiatry.* 2018;22:31–5.

Evaluating neurodegenerative disease

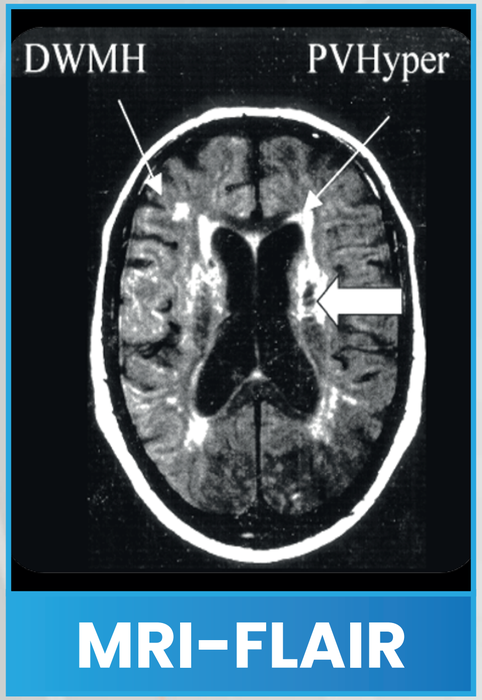


Koran ME. Neuroimaging and Alzheimer's Disease. 2019
Available at: https://practicalneurology.com/articles/2019-nov-dec/neuroimaging-and-alzheimers-disease (accessed 25 March 2021).

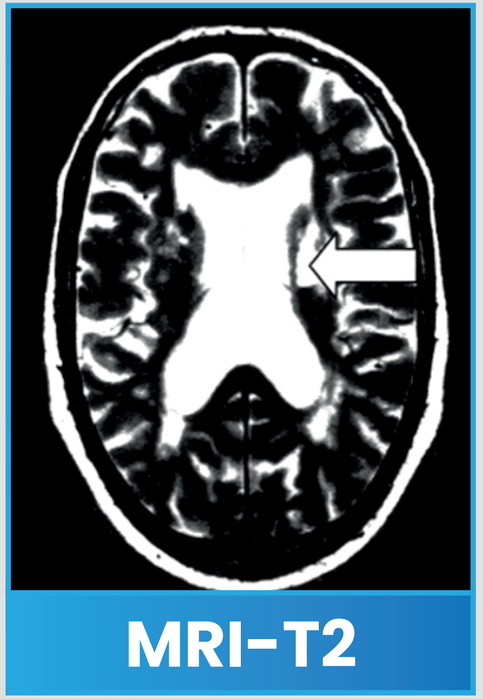
Cerebrovascular disease



CT



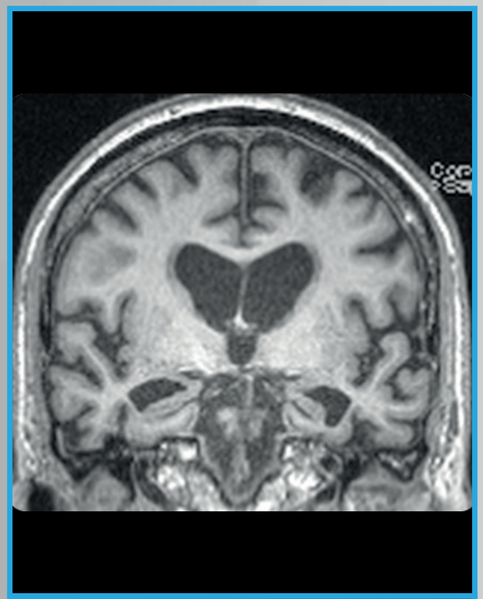
MRI-FLAIR



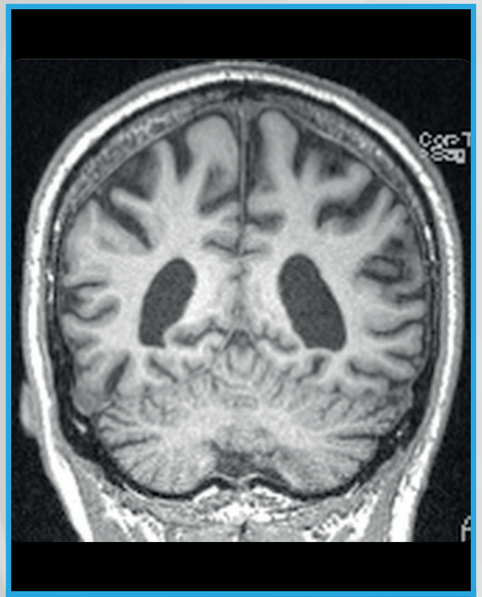
MRI-T2

DWMH, deep white matter hyperintensities; FLAIR, fluid-attenuated inversion recovery; PVHyper, periventricular hyperintensity.
Images provided courtesy of Dr Dickerson.

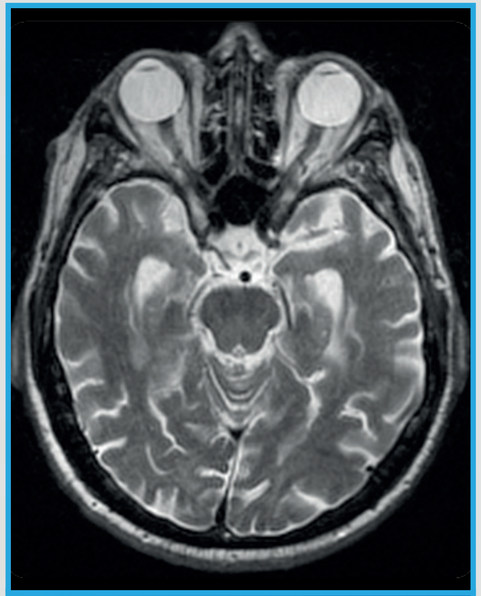
Alzheimer's disease



Hippocampal atrophy



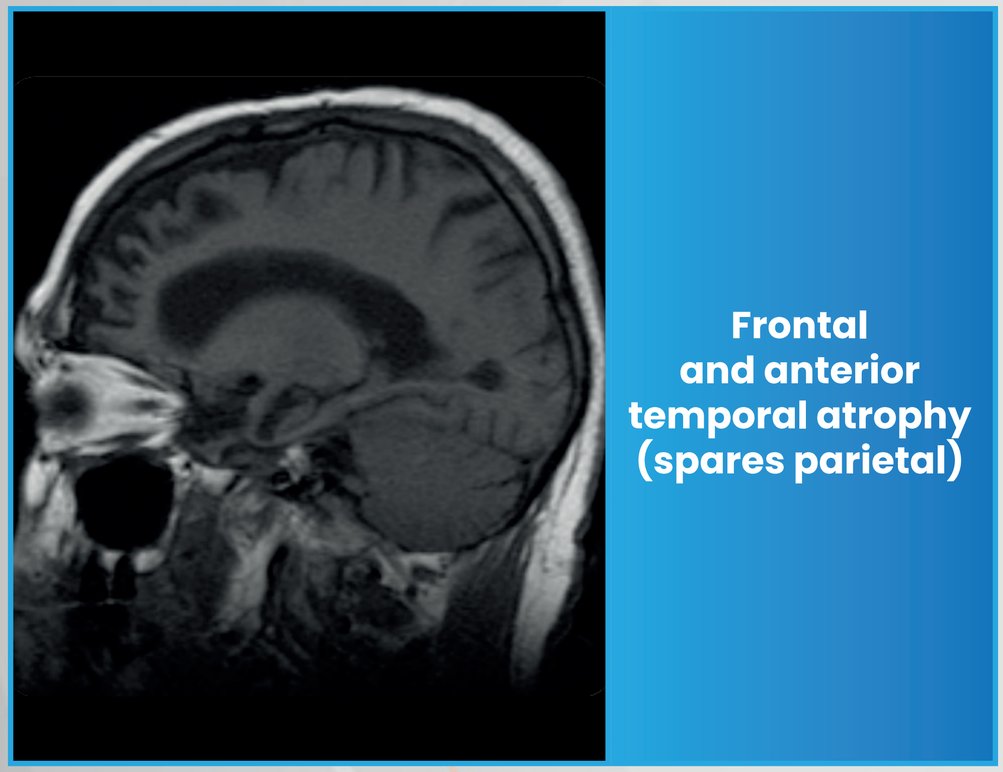
Temporoparietal atrophy



Hippocampal and lateral temporal atrophy

Images provided courtesy of Dr Dickerson.

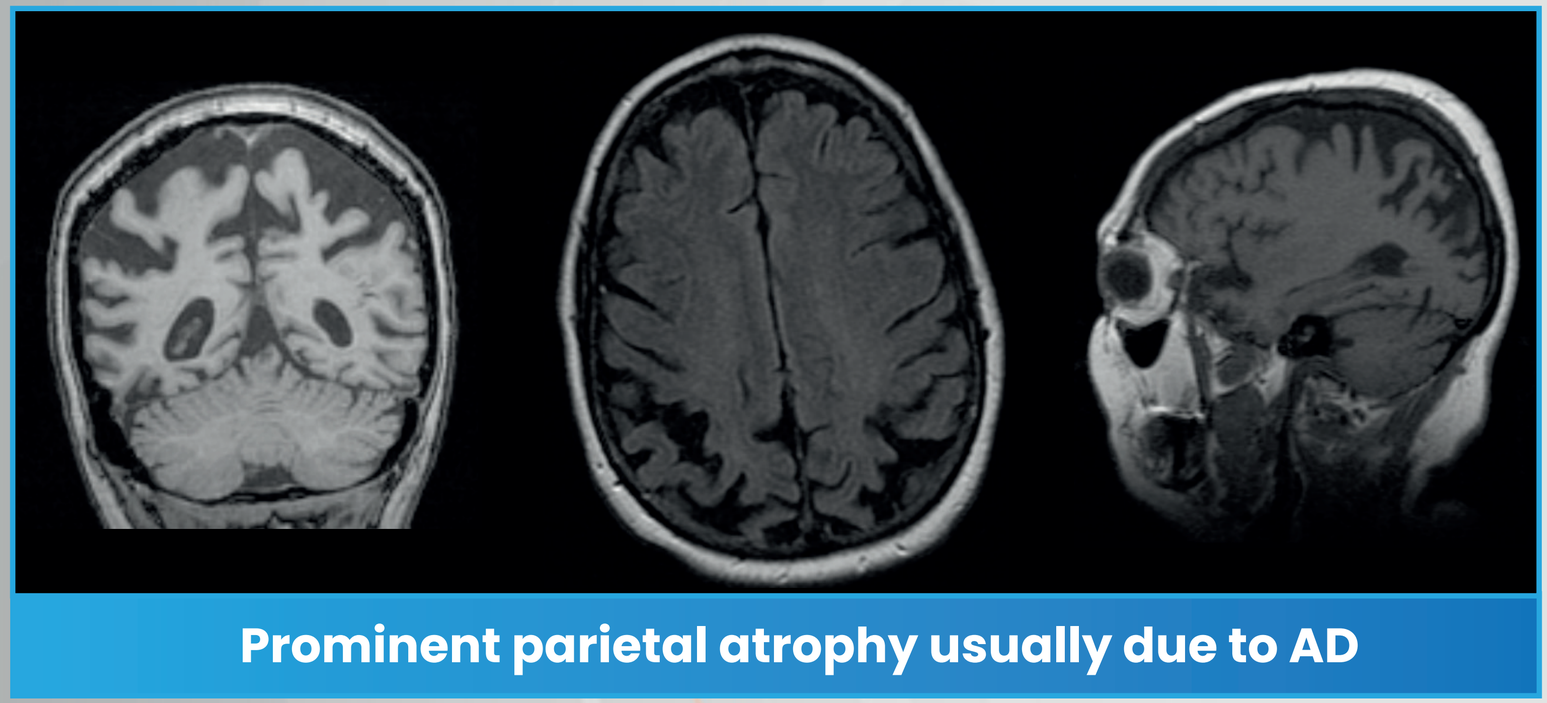
Frontotemporal lobar degeneration



Frontal and anterior temporal atrophy (spares parietal)

Image provided courtesy of Dr Dickerson.

Posterior cortical atrophy syndrome



Prominent parietal atrophy usually due to AD

AD, Alzheimer's disease.
Images provided courtesy of Dr Dickerson.

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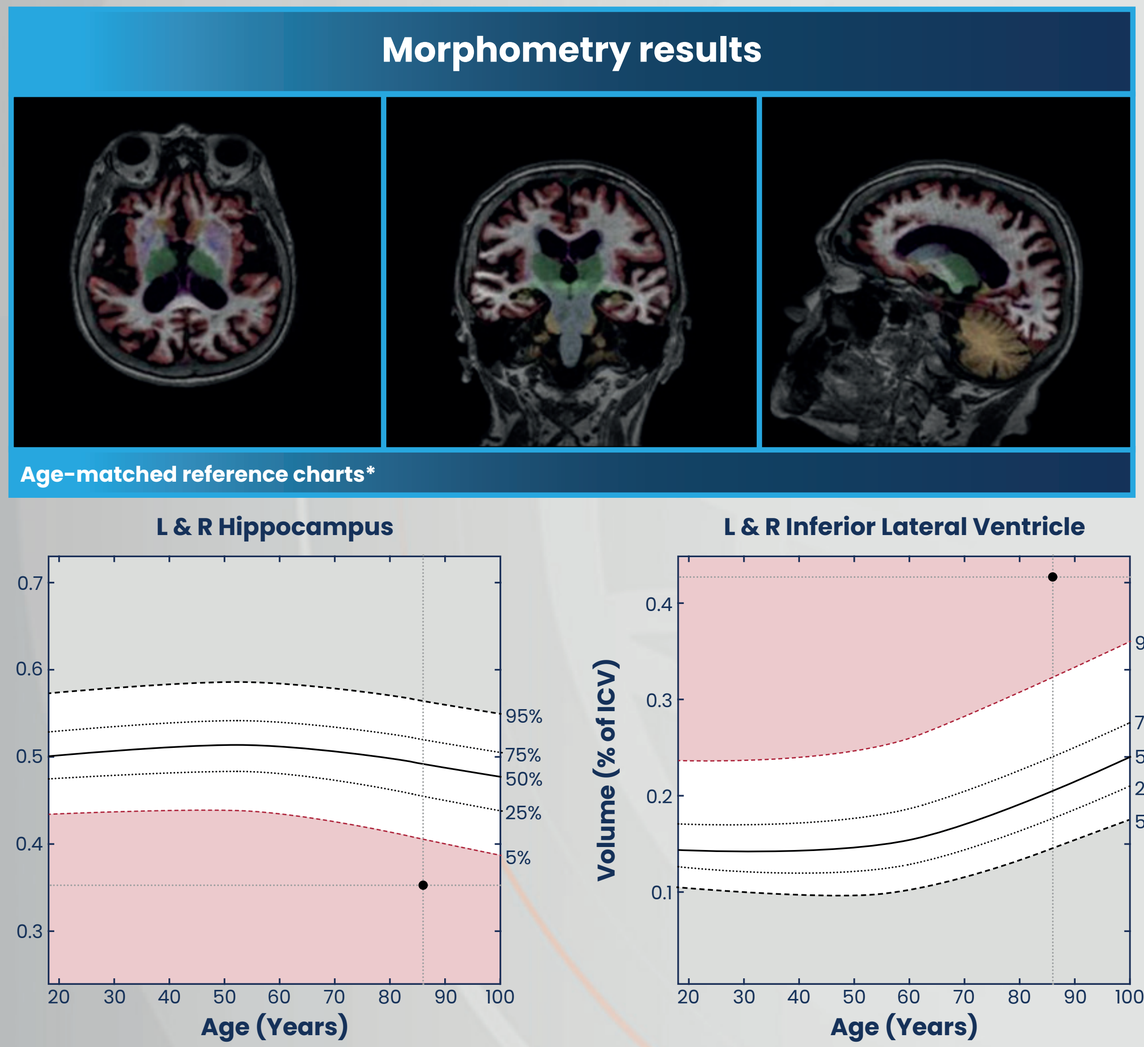
Volumetric analysis in the clinic

Morphometry results

Brain Structure	Volume (cm^3)	% of ICV (5%-95% Normative Percentile*)	Normative Percentile*
Hippocampi	4.76	0.35 (0.41-0.56)	<5
Lateral Ventricles	62.19	4.60 (1.89-4.78)	92
Inferior Lateral Ventricles	5.76	0.43 (0.15-0.32)	>95

Images provided courtesy of Dr Dickerson.

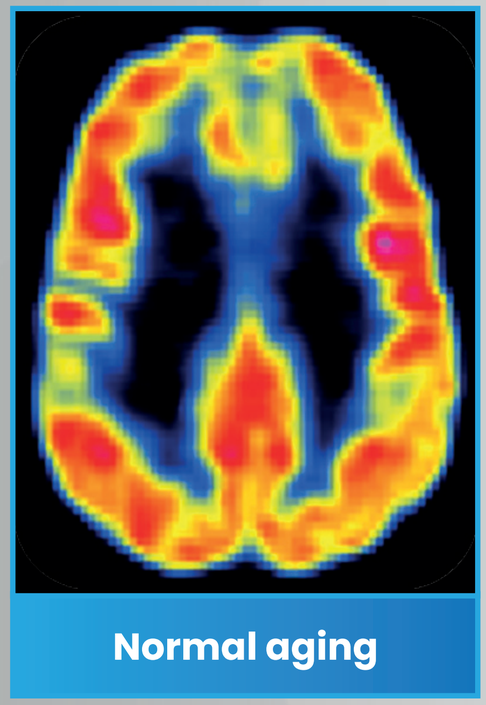
Volumetric analysis in the clinic



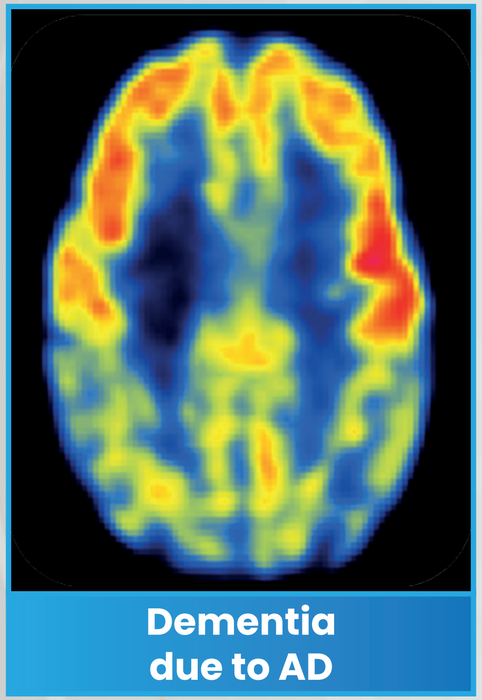
*Charts and normative values are provided for reference purposes only. The FDA has not approved their use for diagnostic purposes.

Images provided courtesy of Dr Dickerson.

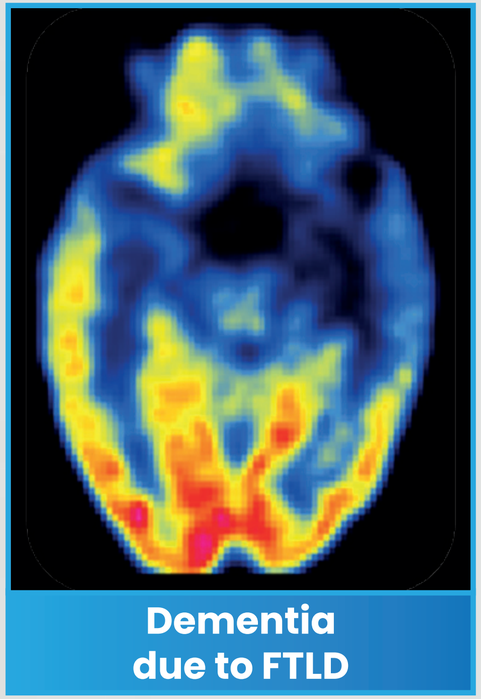
FDG-PET: glucose metabolism



Normal aging



Dementia due to AD



Dementia due to FTLD

Images provided courtesy of Dr Dickerson.

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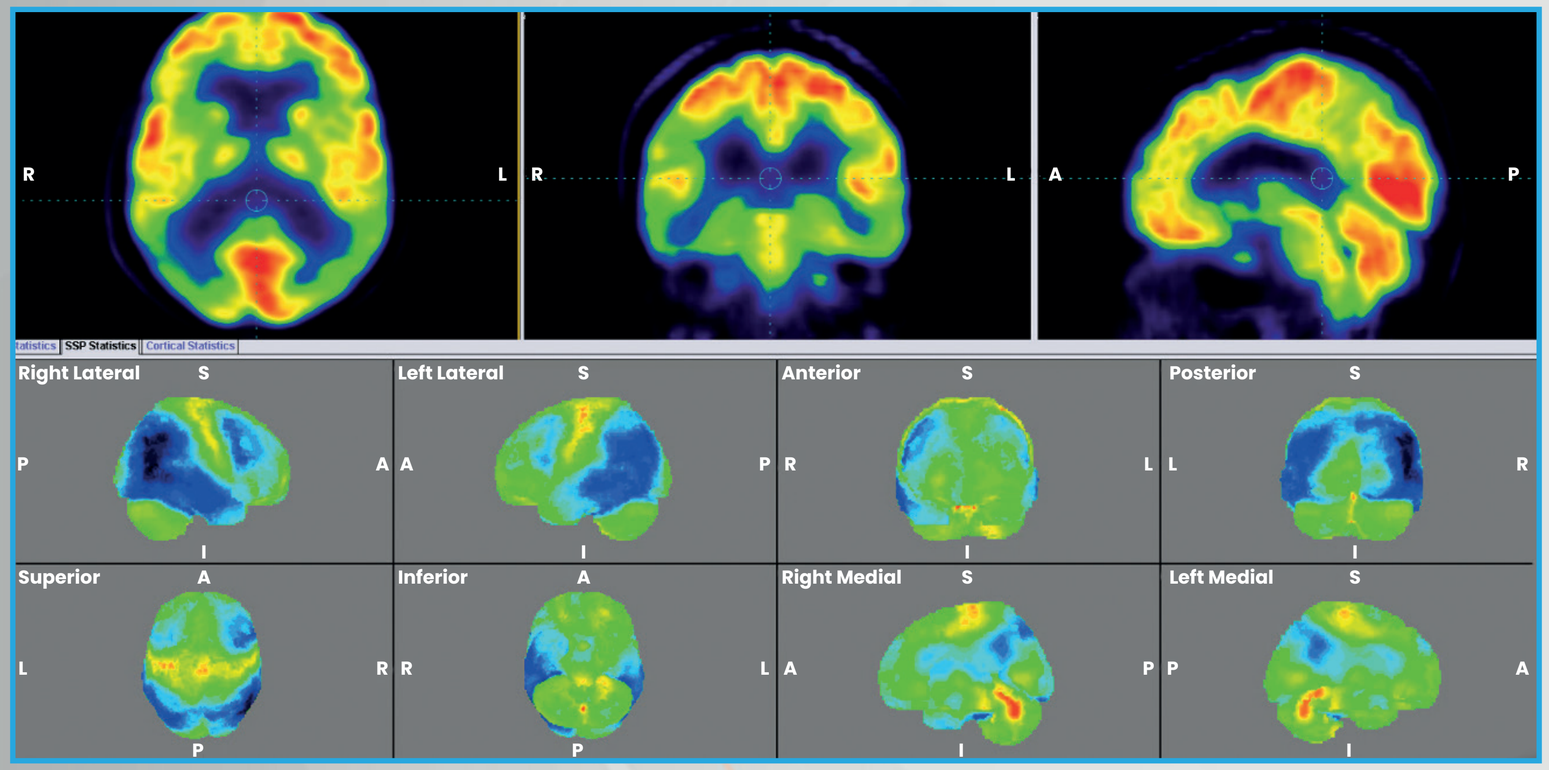
Bilateral temporoparietal and PCC hypometabolism (likely AD)



PCC, posterior cingulate cortex.
Images provided courtesy of Dr Dickerson.

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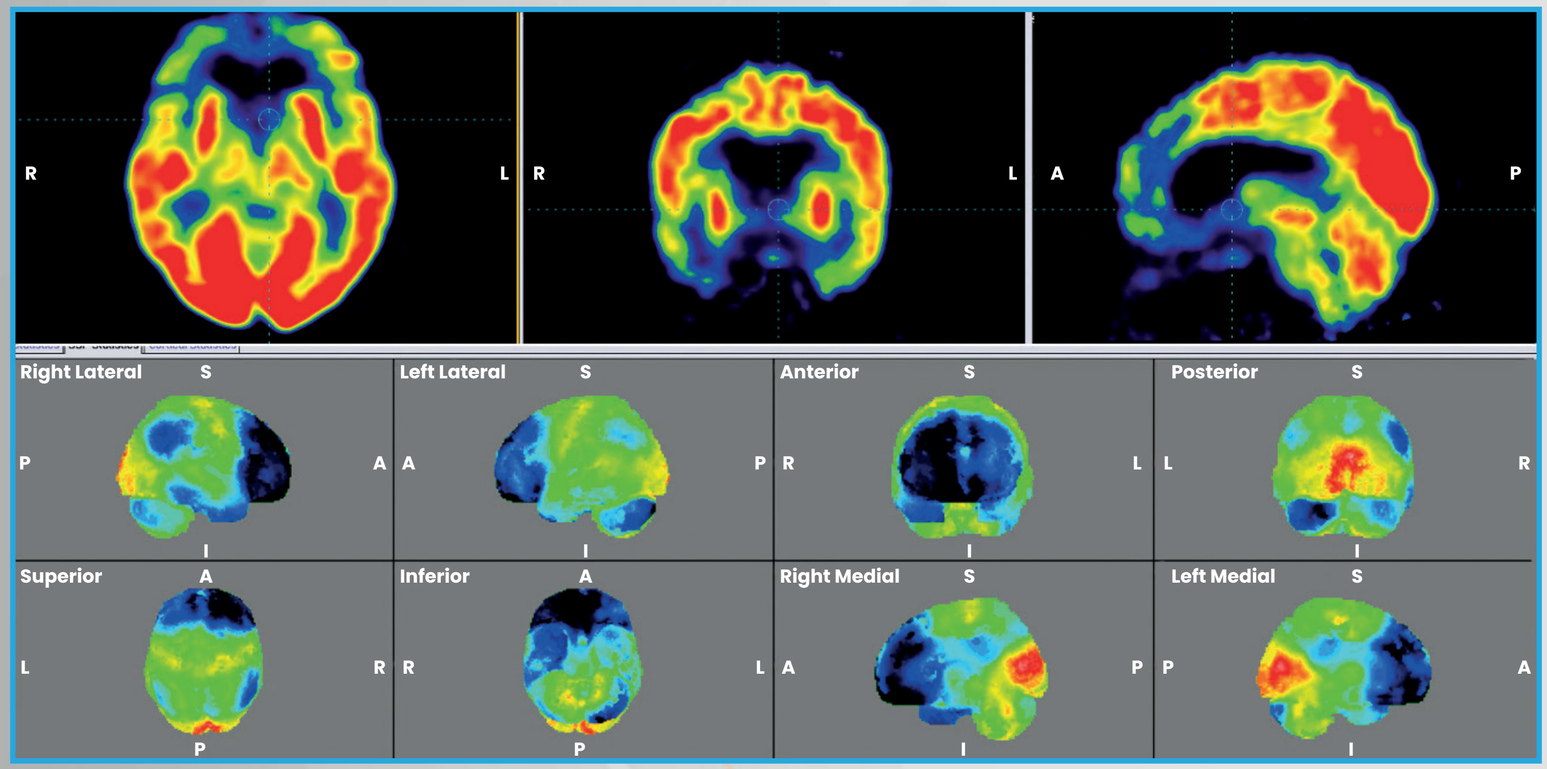
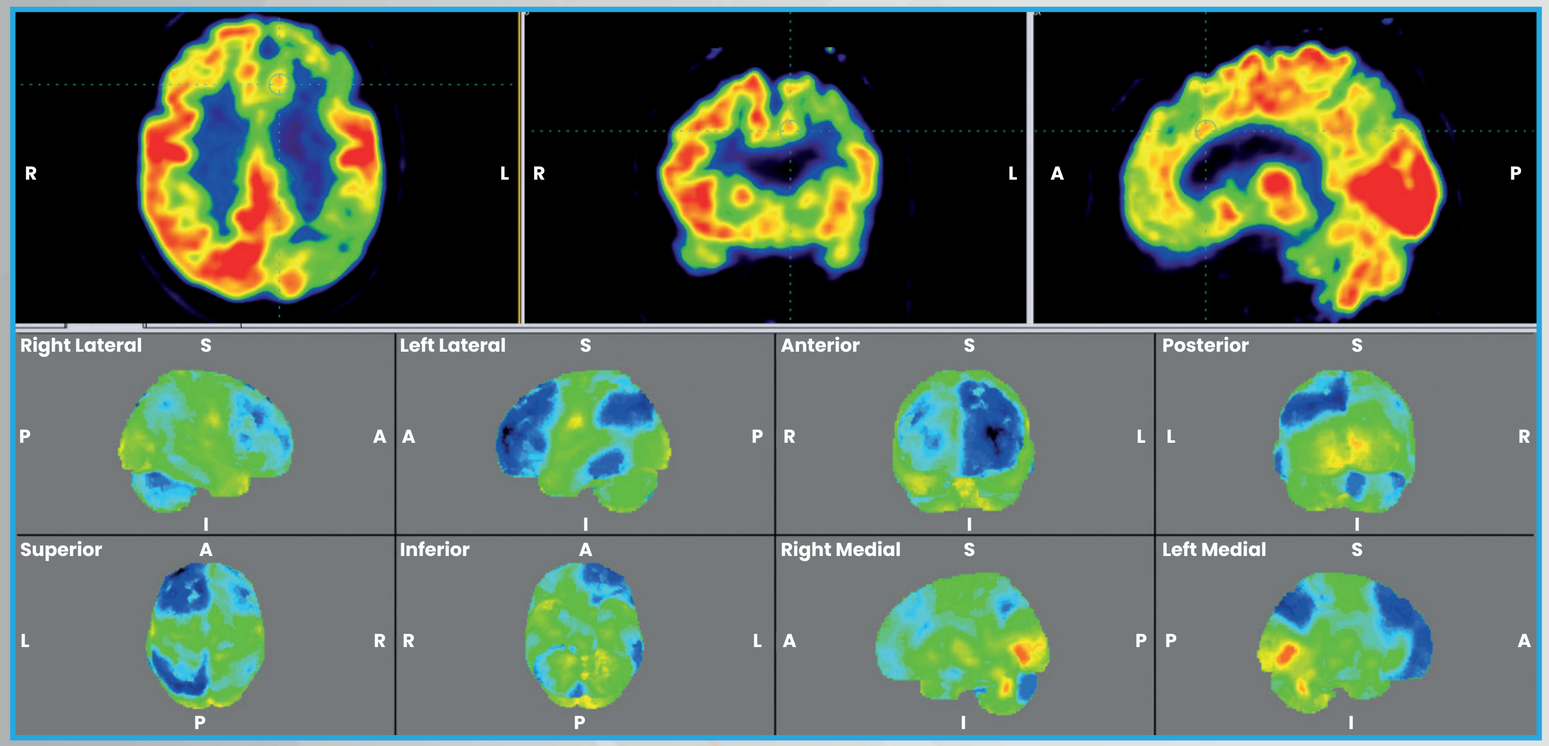
Bilateral frontal and anterior temporal hypometabolism (likely FTLD)



Images provided courtesy of Dr Dickerson.

Asymmetric frontal and temporoparietal hypometabolism (difficult to interpret)



Images provided courtesy of Dr Dickerson.

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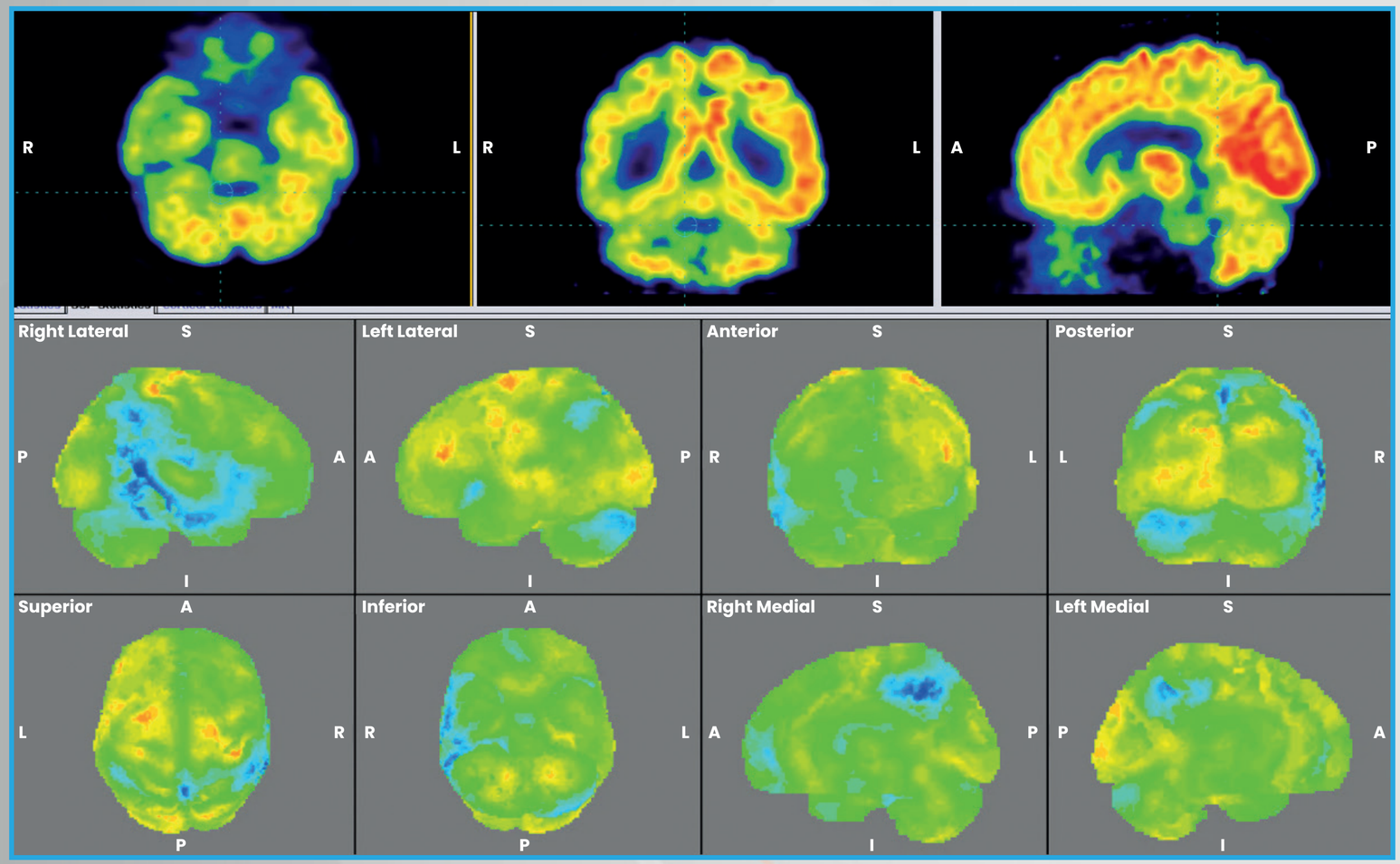
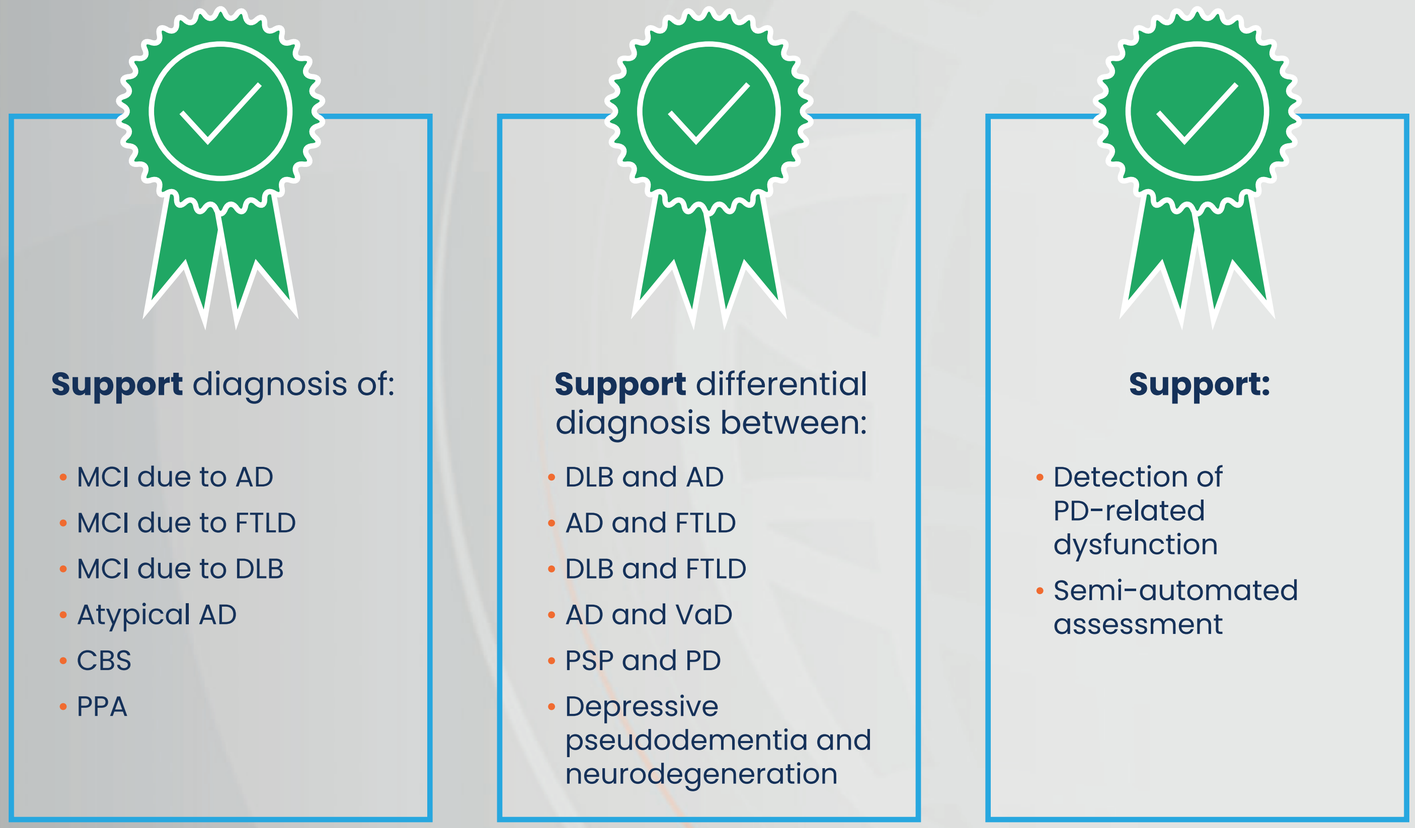
Subtle asymmetric temporoparietal hypometabolism (difficult to interpret)



Images provided courtesy of Dr Dickerson.

EANM and EAN recommendations for FDG-PET



Support diagnosis of:

- MCI due to AD
- MCI due to FTLD
- MCI due to DLB
- Atypical AD
- CBS
- PPA

Support differential diagnosis between:

- DLB and AD
- AD and FTLD
- DLB and FTLD
- AD and VaD
- PSP and PD
- Depressive pseudodementia and neurodegeneration

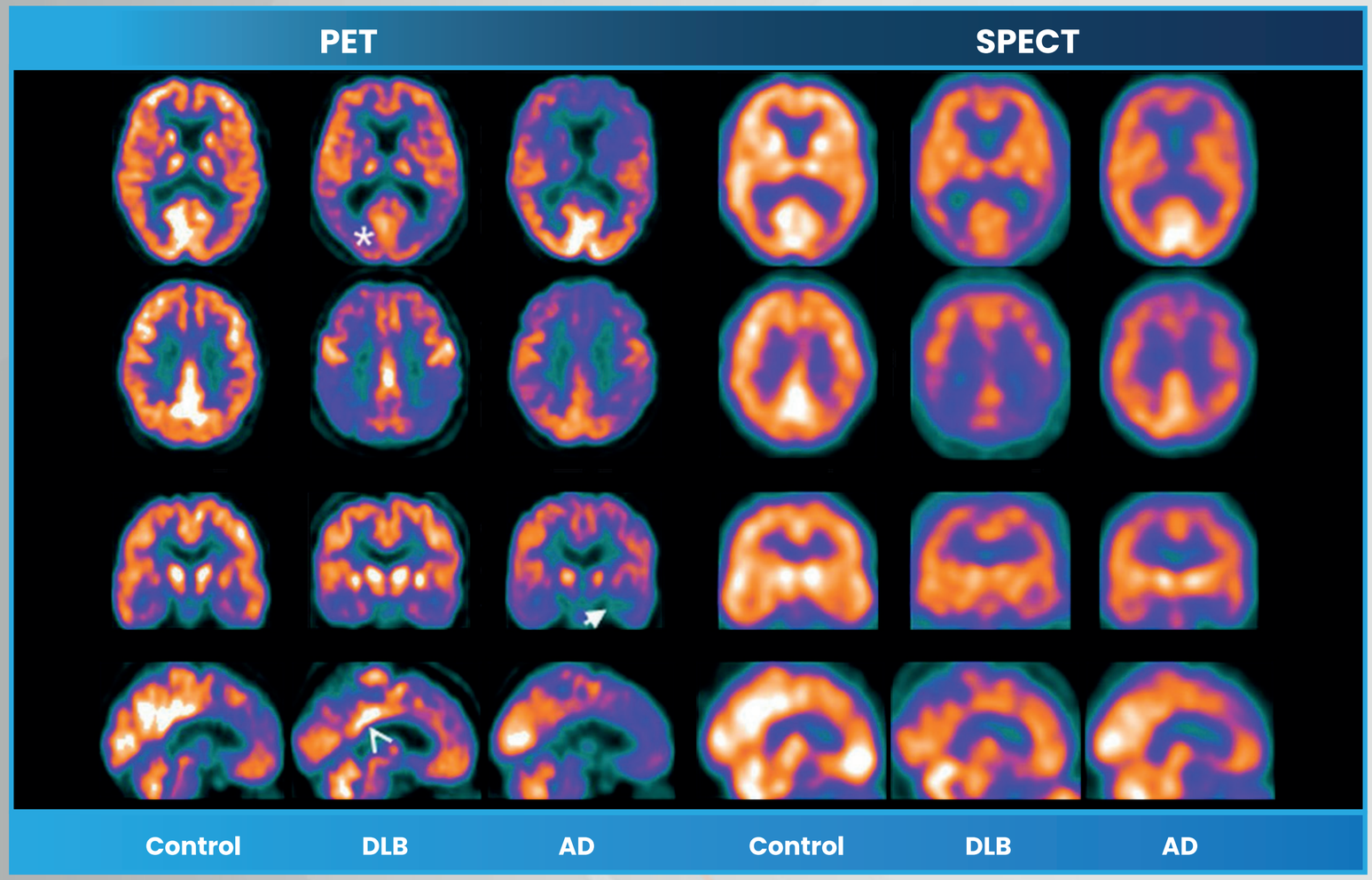
Support:

- Detection of PD-related dysfunction
- Semi-automated assessment

CBS, corticobasal syndrome; DLB, dementia with Lewy bodies; EAN, European Academy of Neurology; EANM, European Association of Nuclear Medicine; PD, Parkinson's disease; PPA, primary progressive aphasia; PSP, progressive supranuclear palsy; VaD, vascular dementia.

Nobili F, et al. *Eur J Neurol.* 2018;25:1201–17.

Cingulate island sign and occipital hypometabolism in DLB

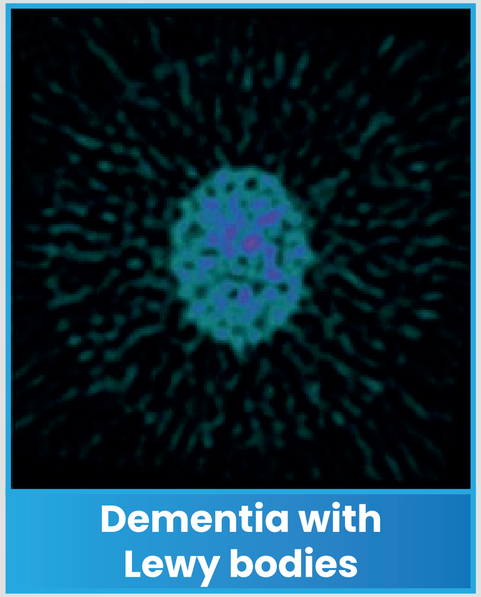


Example of ^{18}F-FDG PET and SPECT scans for AD, DLB, and control. Medial temporal loss in AD (arrow) and occipital lobe reduction (asterisk) and posterior cingulate island sign (arrowhead) in DLB are shown.

Dopamine transporter (DAT) SPECT in DLB

Essential tremor

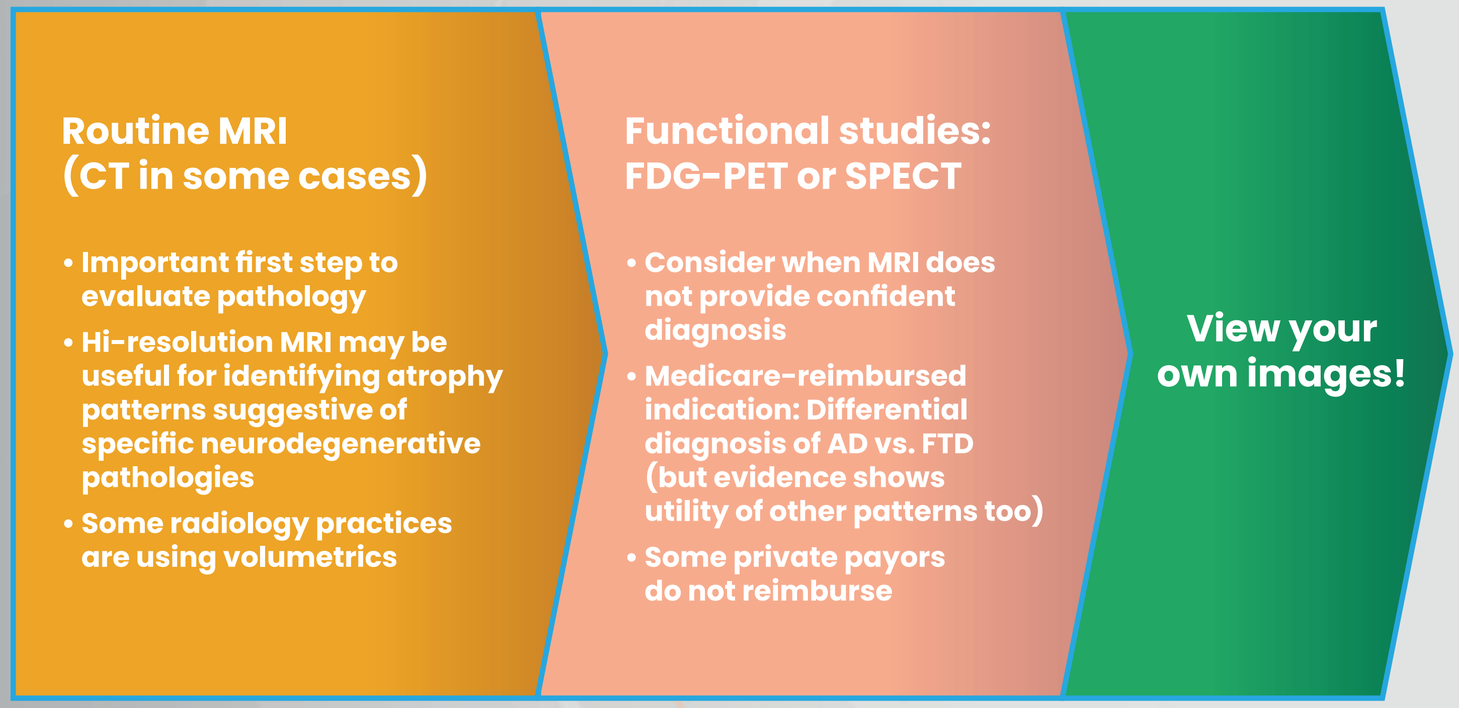
Parkinson's disease



Dementia with Lewy bodies

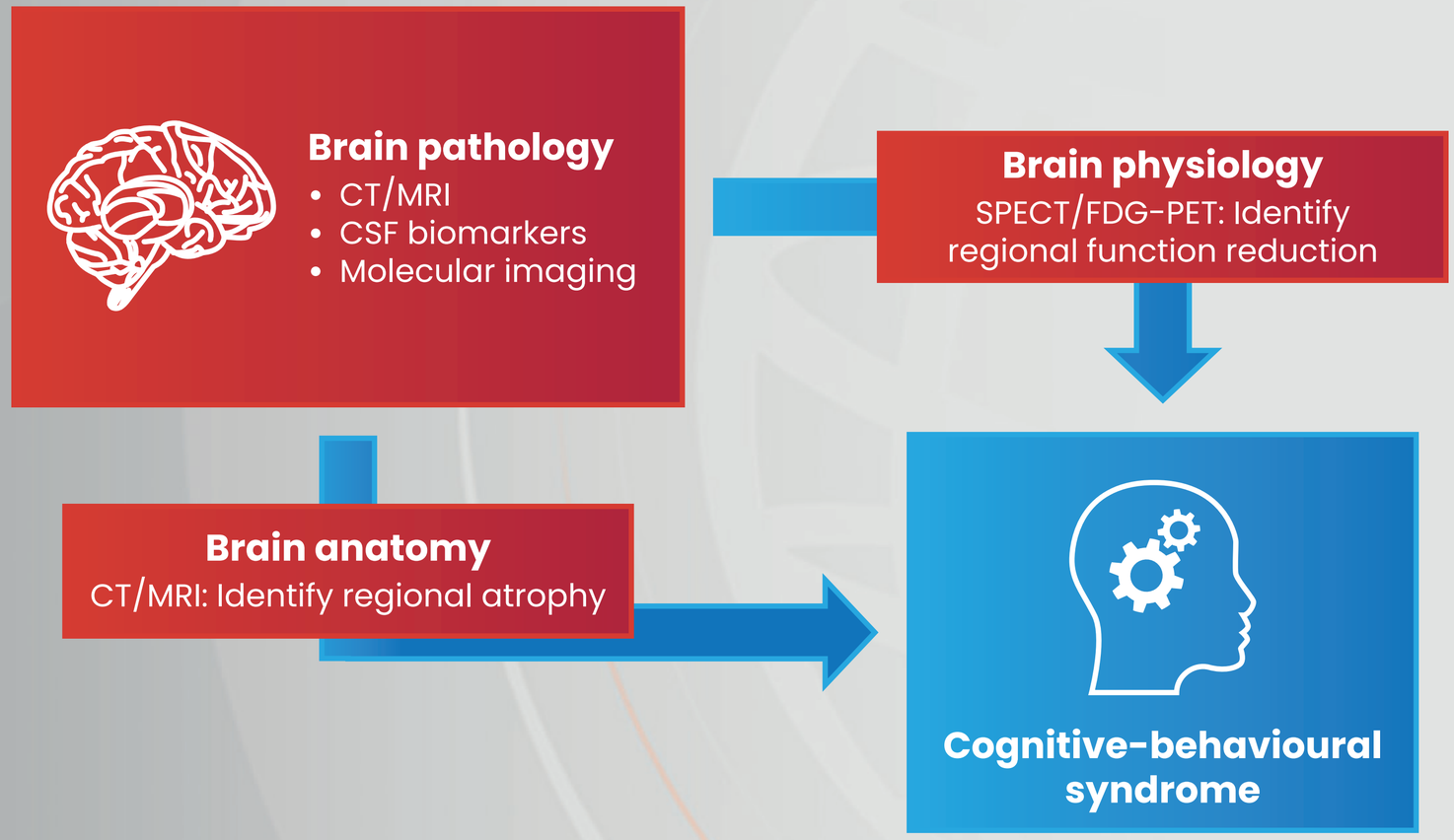
DAT, dopamine active transporter.

Roles of structural and functional brain imaging in dementia clinical practice



What are the recent advances in neuroimaging technologies and how can they be implemented in practice?

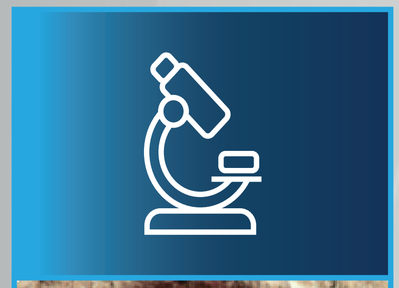
Roles of imaging and biomarkers in dementia



CSF, cerebrospinal fluid; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computerised tomography.

Byrne A, Prichard J. *Prog Neurol Psychiatry.* 2018;22:31–5.

In vivo molecular biomarkers of AD neuropathology

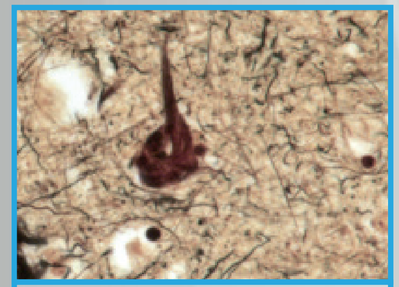


Amyloid plaque

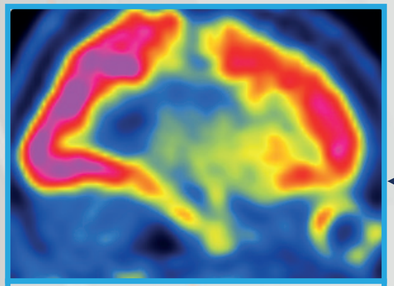
Amyloid PET

CSF collection
(usually reimbursed)

(not yet reimbursed)



Tau tangle



Tau PET

AD, Alzheimer's disease.
Images provided courtesy of Dr Dickerson.

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NIA-AA 2011 MCI criteria

Diagnostic category	Biomarker-driven probability of AD aetiology	Aβ (PET or CSF)	Evidence of neuronal injury (tau, FDG, sMRI)
MCI-core clinical criteria	Uninformative	Conflicting/indeterminate/untested	
MCI due to AD: intermediate likelihood	Intermediate	Positive	Untested
		Untested	Positive
MCI due to AD: high likelihood	Highest	Positive	Positive
MCI: unlikely due to AD	Lowest	Negative	Negative

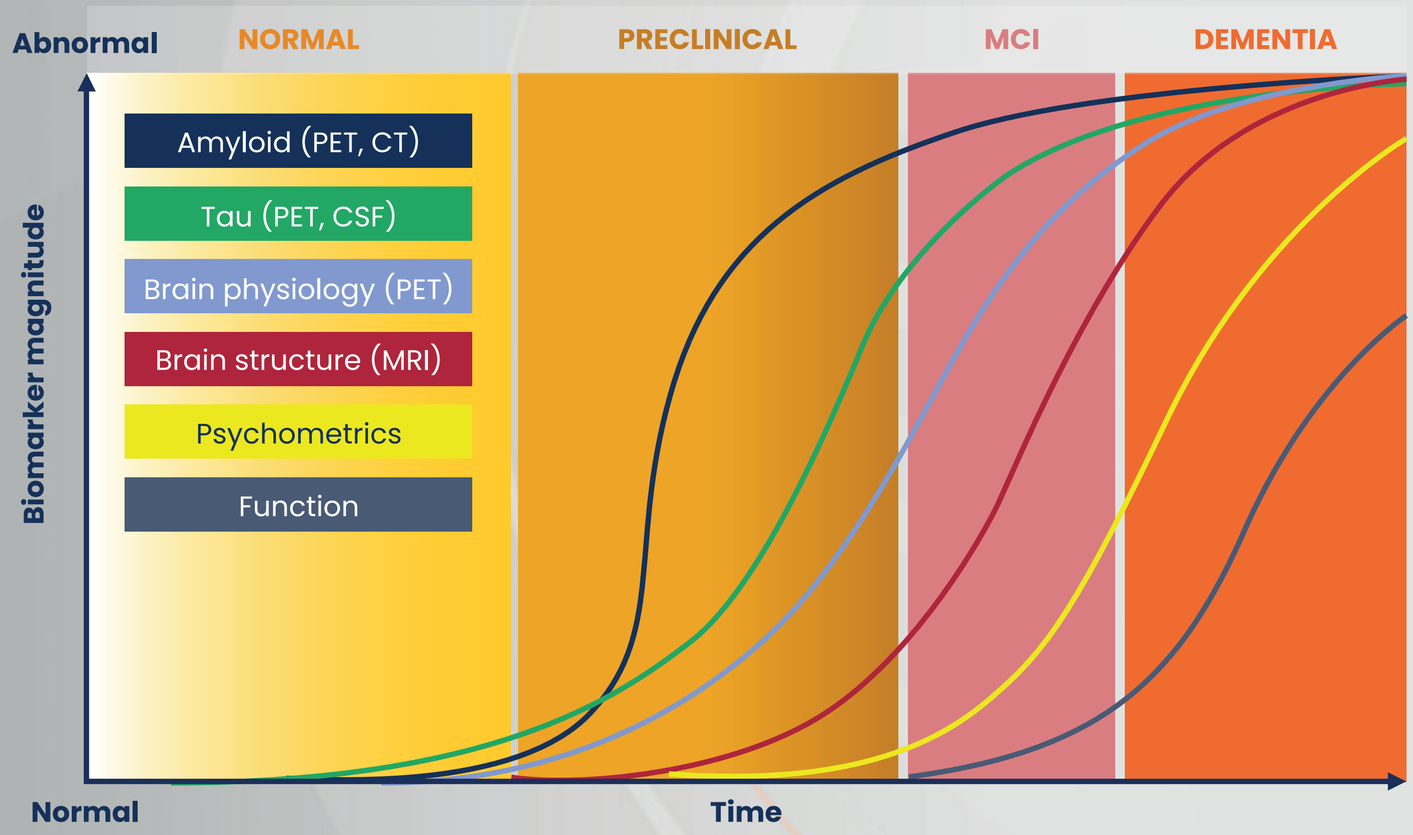
Aβ, amyloid beta; MCI, mild cognitive impairment; NIA-AA, National Institute on Aging-Alzheimer's Association; sMRI, structural MRI.
Albert MS, et al. *Alzheimers Dement.* 2011;7:270–9.

NIA-AA 2011 Alzheimer's disease criteria

Diagnostic category	Biomarker-driven probability of AD aetiology	Aβ (PET or CSF)	Evidence of neuronal injury (tau, FDG, sMRI)
Probable AD dementia based on clinical criteria	Uninformative	Unavailable/conflicting/indeterminate	
With 3 levels of AD pathophysiological process	• Intermediate • Intermediate • High	• Unavailable/indeterminate • Positive • Positive	• Positive • Unavailable/indeterminate • Positive
Dementia unlikely due to AD	Lowest	Negative	Negative

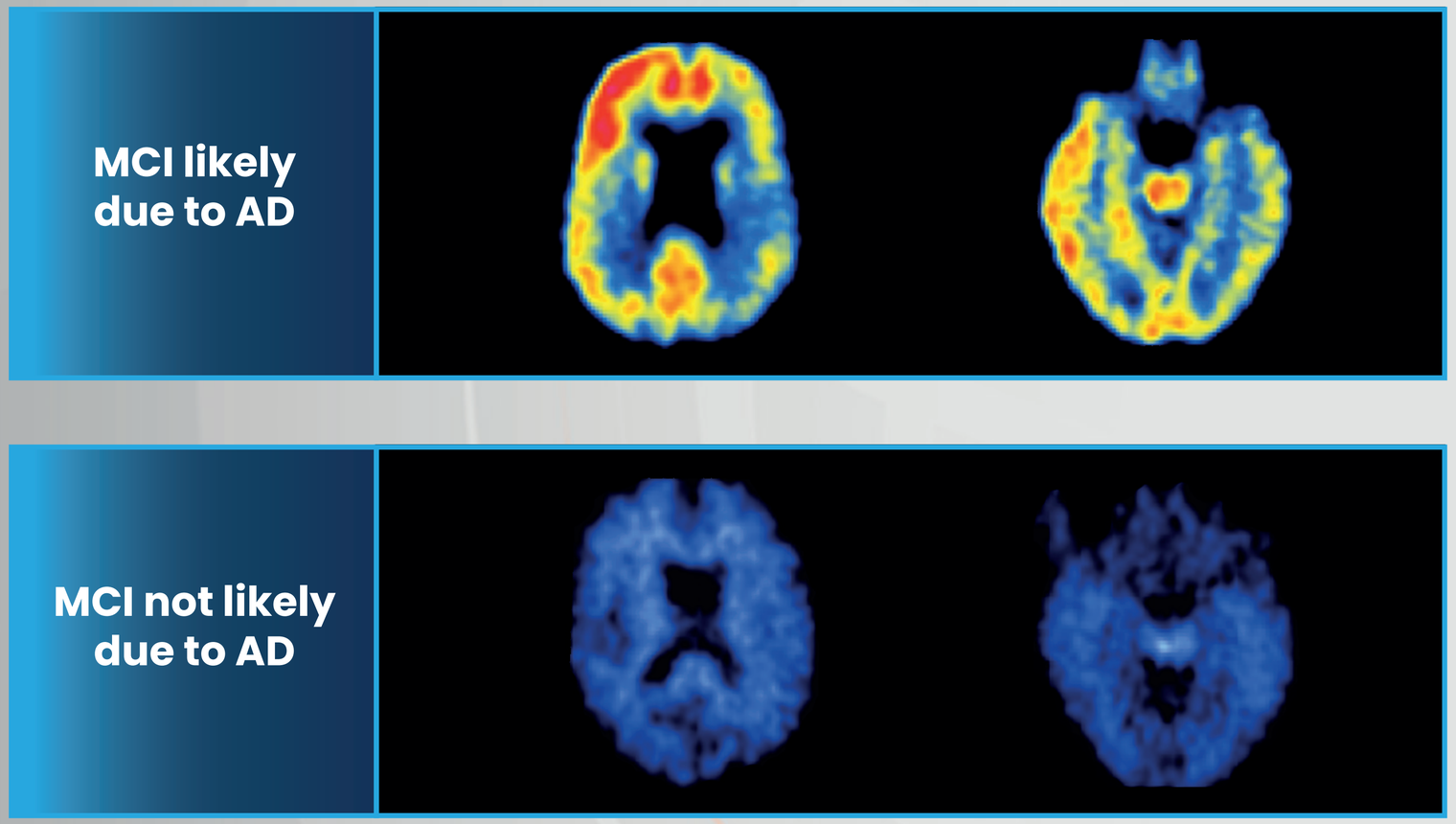
McKhann GM, et al. *Alzheimers Dement.* 2011;7:263–69.

Biomarker cascade through the AD continuum



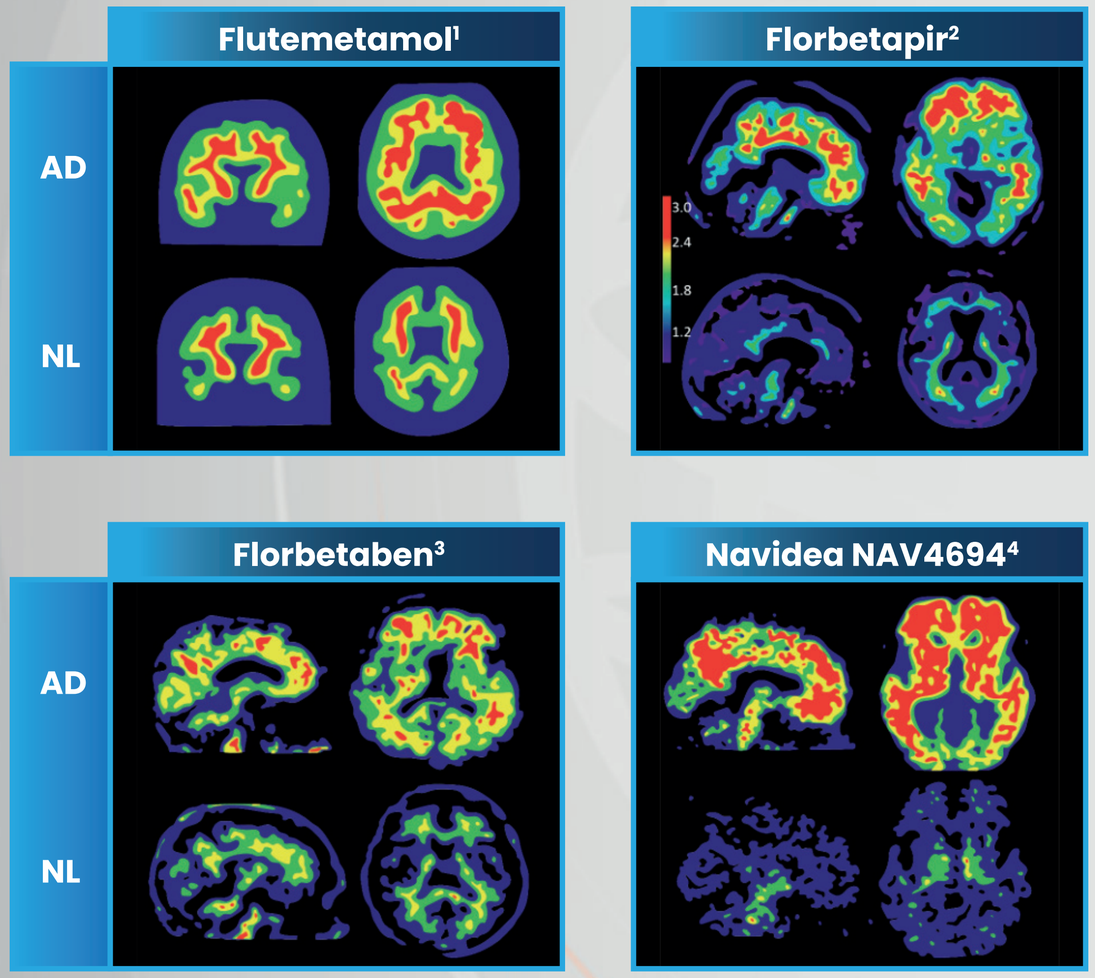
Adapted from Jack CR Jr, et al. *Lancet Neurol.* 2010:9:119–28.

Amyloid imaging with PET (PIB)



PIB, Pittsburgh Compound B.
Images provided courtesy of Dr Dickerson.

^{18}F amyloid imaging tracers



NL, Control.
Adapted from: 1. Vandenberghe R, et al. *Ann Neurol.* 2010;68:319–29; 2. Wong DF, et al. *J Nucl Med.* 2010;51:913–20; 3. Barthel H, et al. *Lancet Neurol.* 2011;10:424–35.
4. Chen K, et al. *Alzheimers Dement.* 2012;8(4 suppl):P14(abstract IC-P-011).

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Amyloid imaging correlates with amyloid pathology

Neurodegenerative disorder	^{18}F-AV-45 PET		Amyloid staining (4G8 antibody)	
	Visual read	AV45 SUVr	Amyloid burden (Quant IHC; %)	Neuropathologic diagnosis
MCI	1	1.08	0.0	Normal brain
Dem	0	0.87	0.2	Tangles only
PDD	3	1.15	3.6	AD with cortical Lewy bodies
Dem	4	1.42	5.4	AD
Dem	4	1.33	7.9	AD
Dem	4	1.67	8.6	AD

Dem, dementia; IHC, immunohistochemistry; PDD, Parkinson's disease dementia; SUVr, standard uptake value ratio.
Fleisher AS. *Neurology.* 2009;74(9, suppl 2);abstract 1165AAN1OD1; Clark CM et al. *JAMA.* 2011;305:275–83.

Amyloid imaging taskforce: Appropriate criteria for use

Cognitive complaint with objectively confirmed impairment

Performed only after full standard workup

- Structured clinical evaluation with objective neurocognitive testing
- Structural brain imaging
- Relevant laboratory tests

AD diagnosis possible but uncertain

Knowledge of Aβ pathology would increase diagnostic certainty and alter management

Ordered by a dementia expert

- Specialty training and ≥25% dementia practice
- Geriatric/behavioural psychiatry and neurology

Aβ, beta amyloid.

Johnson KA, et al. *Alzheimers Dement.* 2013;9:e1-e16; Johnson KA, et al. *J Nucl Med.* 2013;54:1011–3.

Amyloid imaging taskforce: Inappropriate use

Evaluation of individuals without cognitive complaints

- Preclinical AD may become an indication for amyloid imaging if preventive treatments prove effective

When standard recommended clinical diagnostic testing has not been ordered for initial assessment

As a stand-alone diagnostic for AD dementia

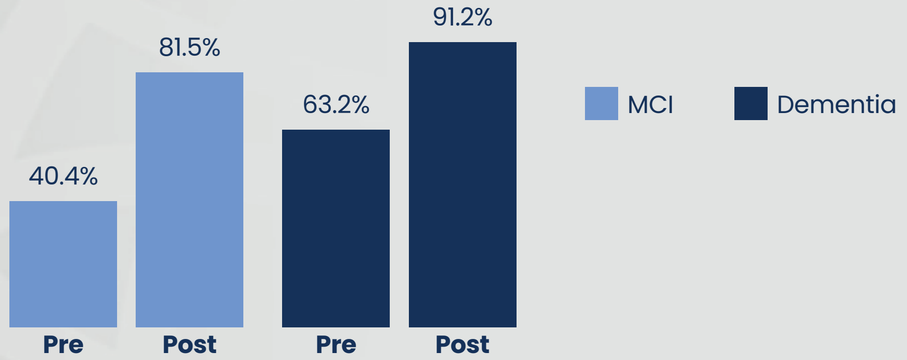
To assess disease progression

Johnson KA, et al. *Alzheimers Dement.* 2013;9:e1–e16.

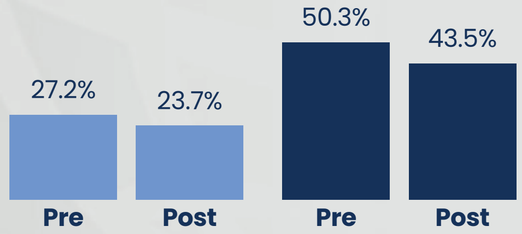
Amyloid PET results alter clinical management

Longitudinal study assessing change in management pre- and post-amyloid PET in 11,409 patients with MCI or dementia treated by 946 dementia specialists

Increased use of AD medication with positive PET scan ($p<0.001$)



Decreased use of AD medication with negative PET scan ($p<0.01$)



Rabinovici GD, et al. *JAMA*. 2019;321:1287–94.

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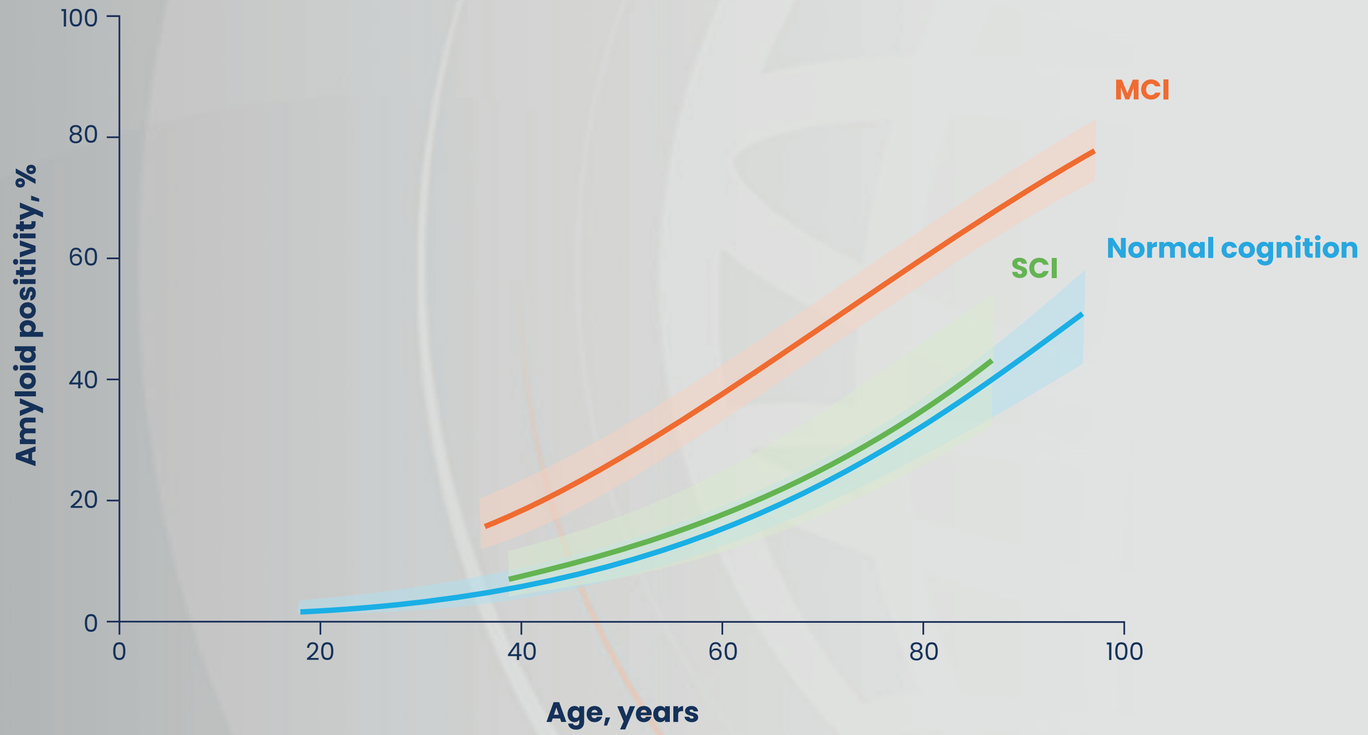
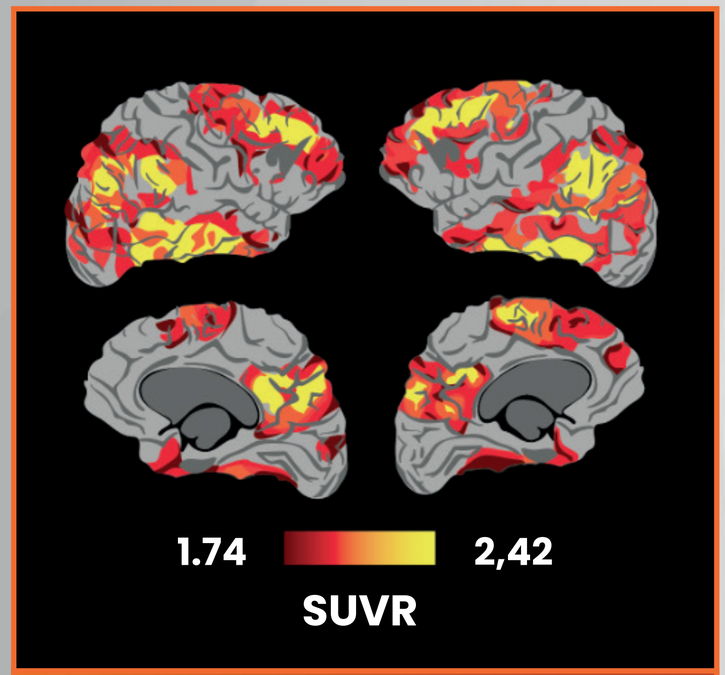
Amyloid positivity percentage increases with age and is more prevalent in patients with MCI

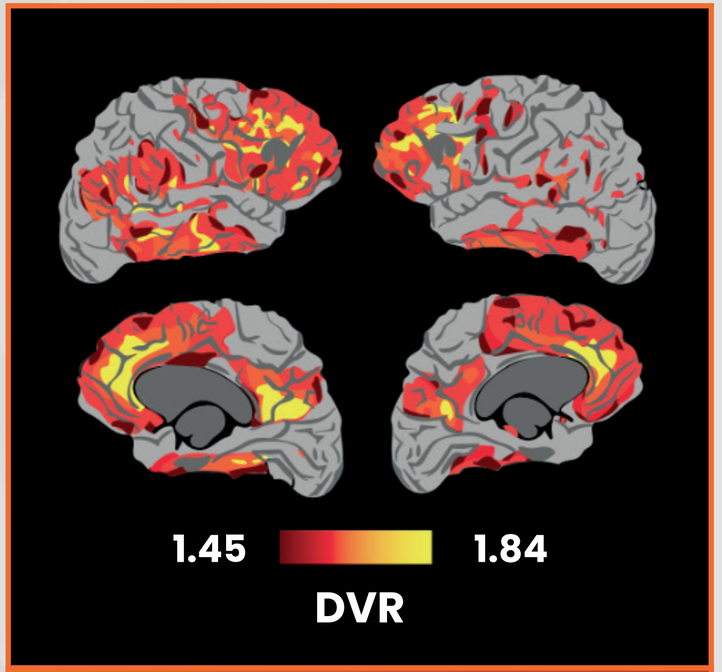


SCI, subjective cognitive impairment.
Adapted from: Jansen WJ, et al. *JAMA*. 2015;313:1924–38.

Typical AD dementia on PET



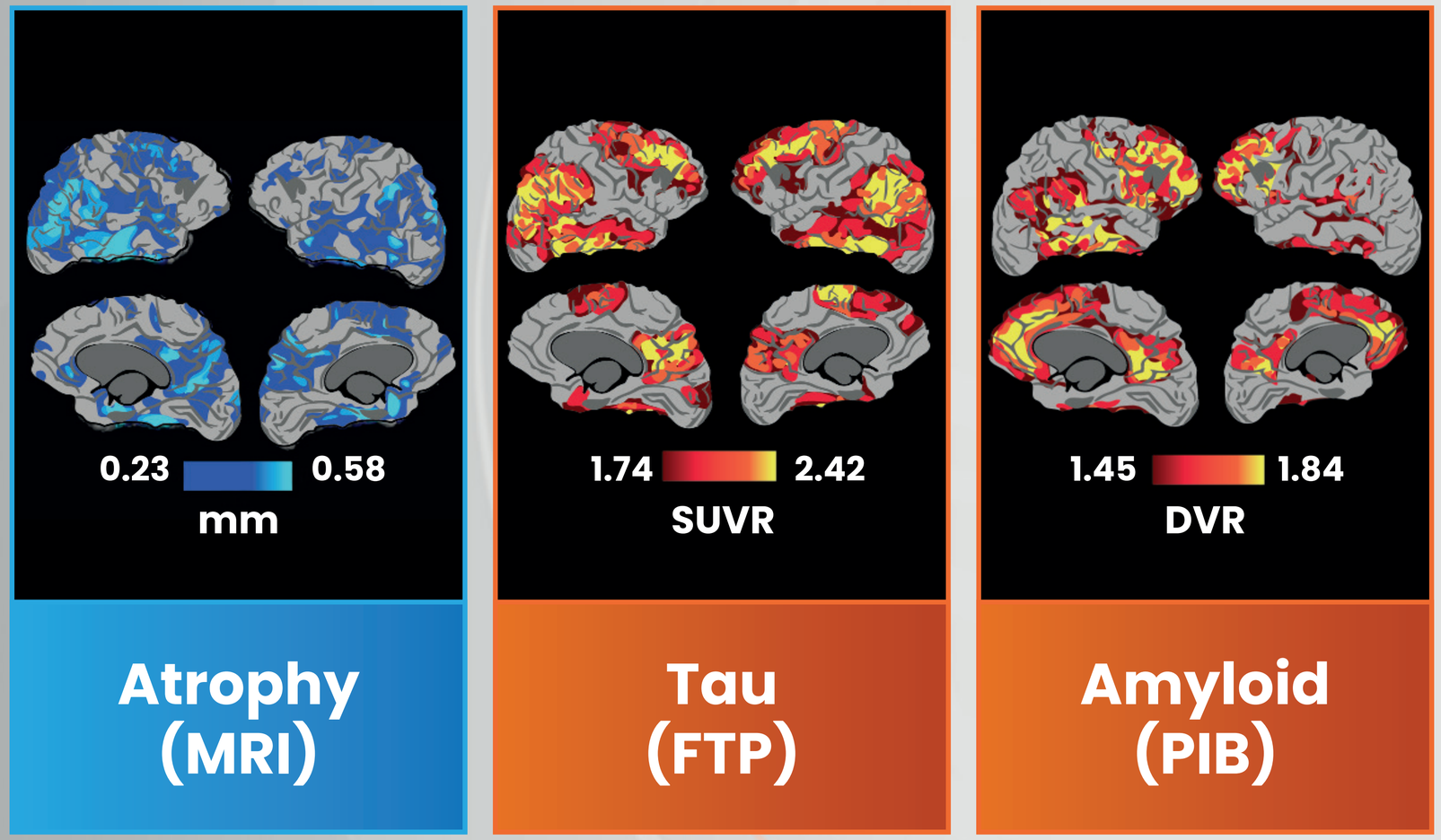
Tau
(FTP)



Amyloid
(PIB)

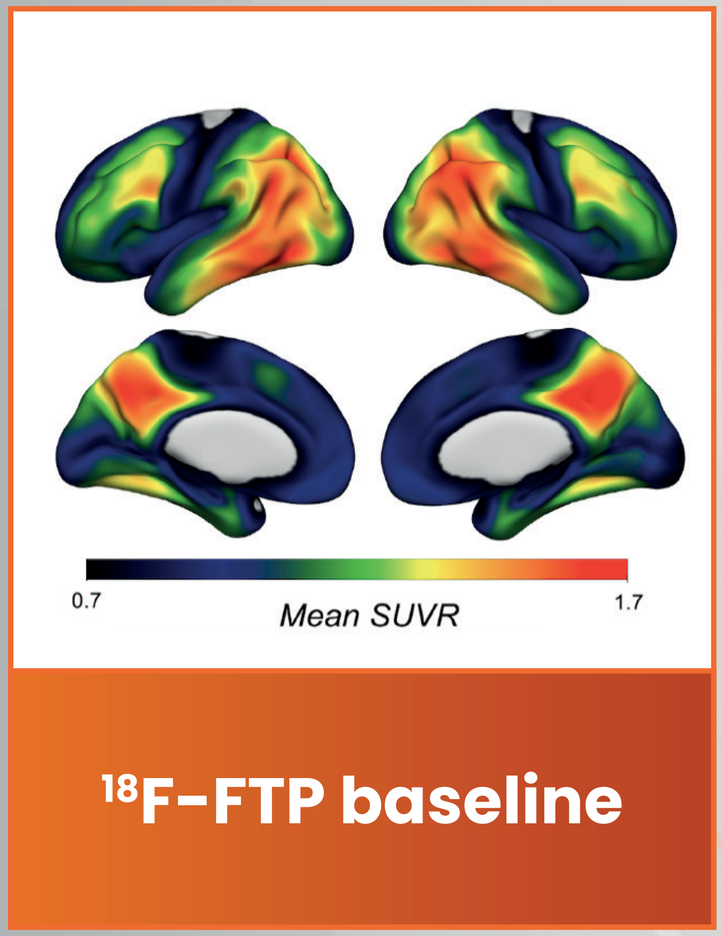
DVR, distribution volume ratio; FTP, flortaucipir.
Adapted from: Xia C, et al. *JAMA Neurol.* 2017;74:427–510.

Brain atrophy with AD dementia on MRI

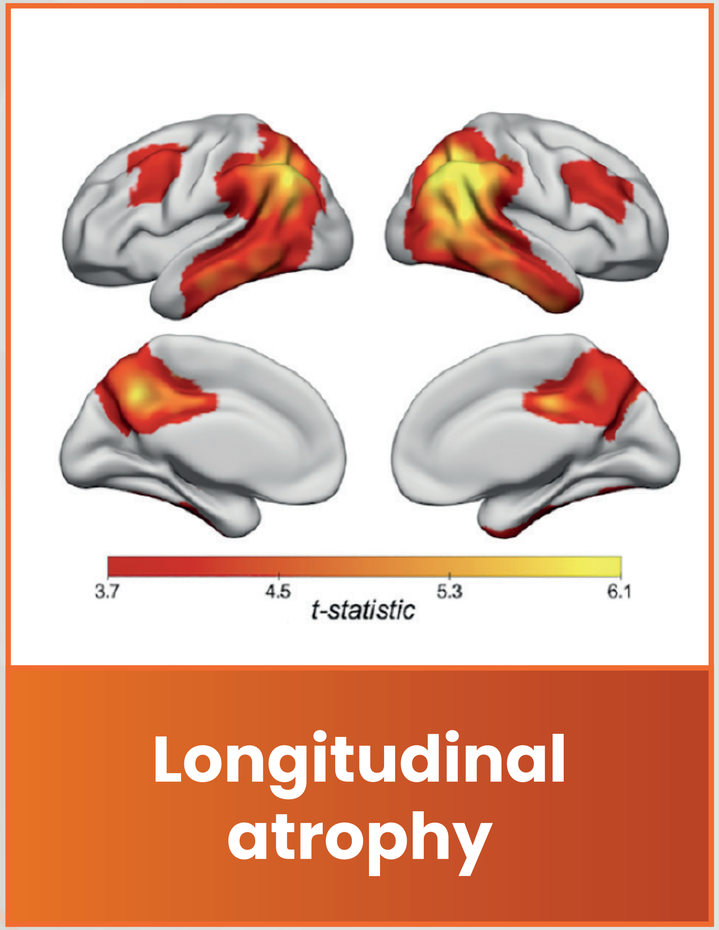


Adapted from: Xia C, et al. *JAMA Neurol.* 2017;74:427–510.

Tau PET uptake pattern corresponds with atrophy on MRI in AD

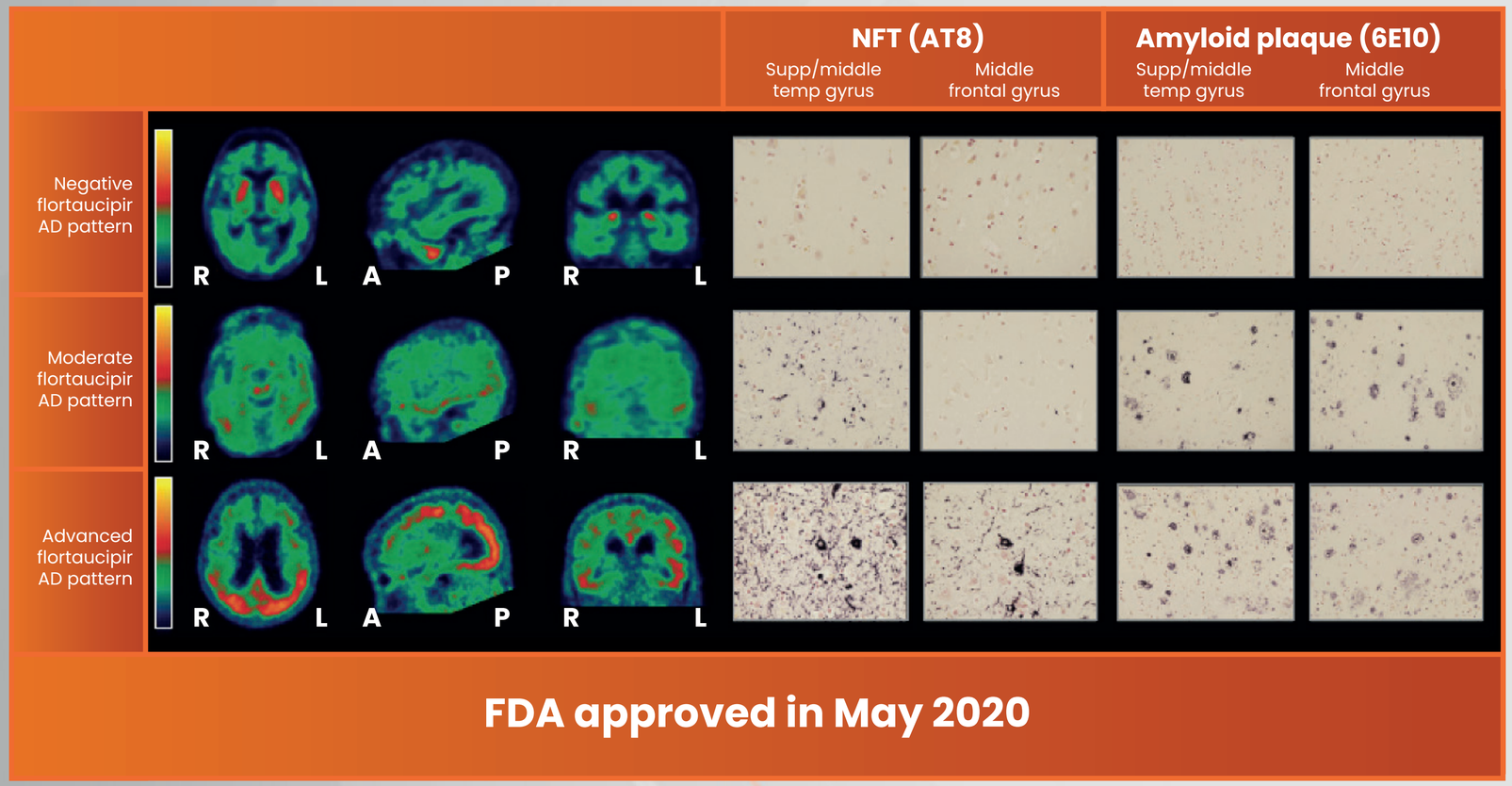


^{18}F-FTP baseline



Longitudinal atrophy

^{18}F-FTP uptake correlates with NFT pathology with high sensitivity in AD



A, anterior; FDA, Food and Drug Administration; L, left; NFT, neurofibrillary tangle; P, posterior; R, right.

CSF markers in AD

Reduced in AD

Elevated in AD and other disorders

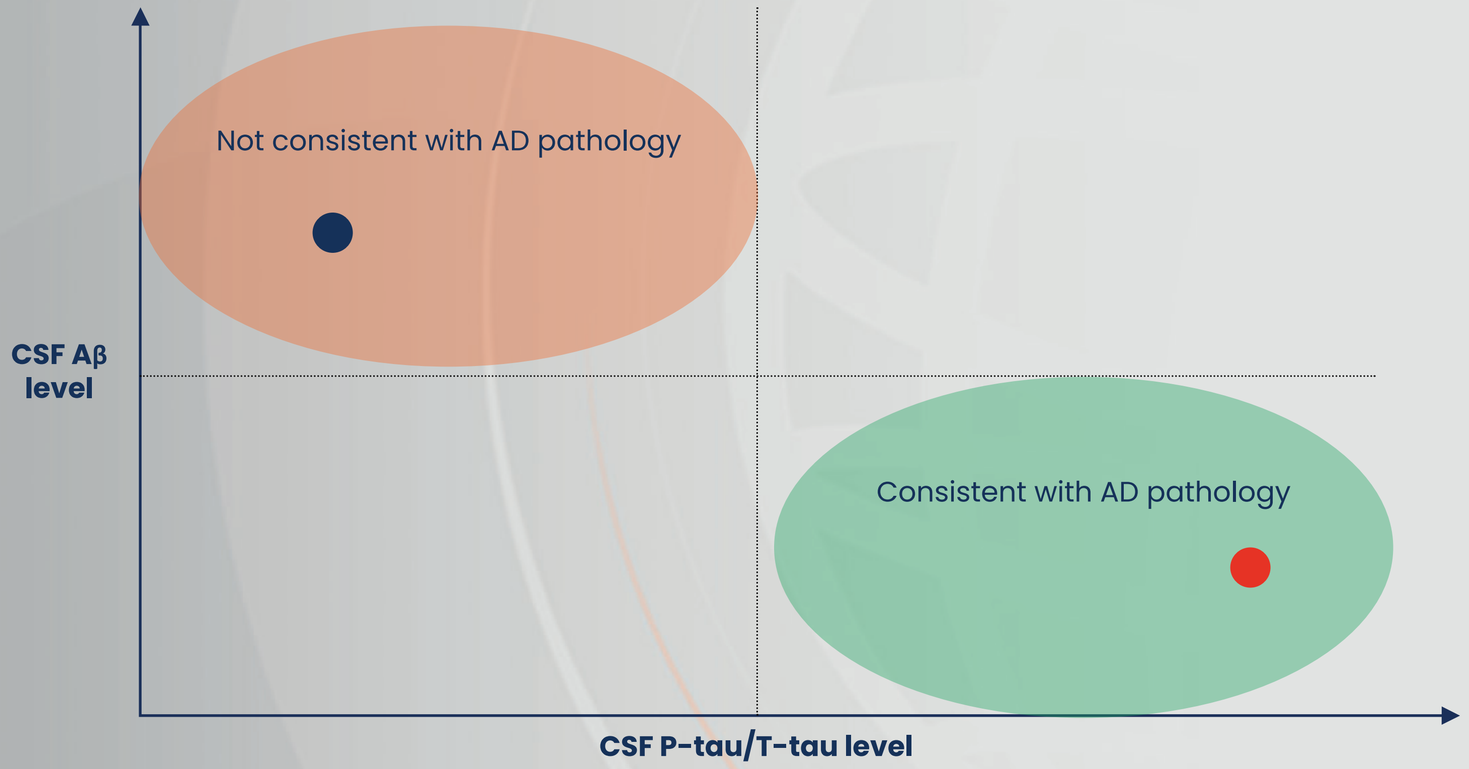
Elevated only in AD

…and in other disorders in the future?

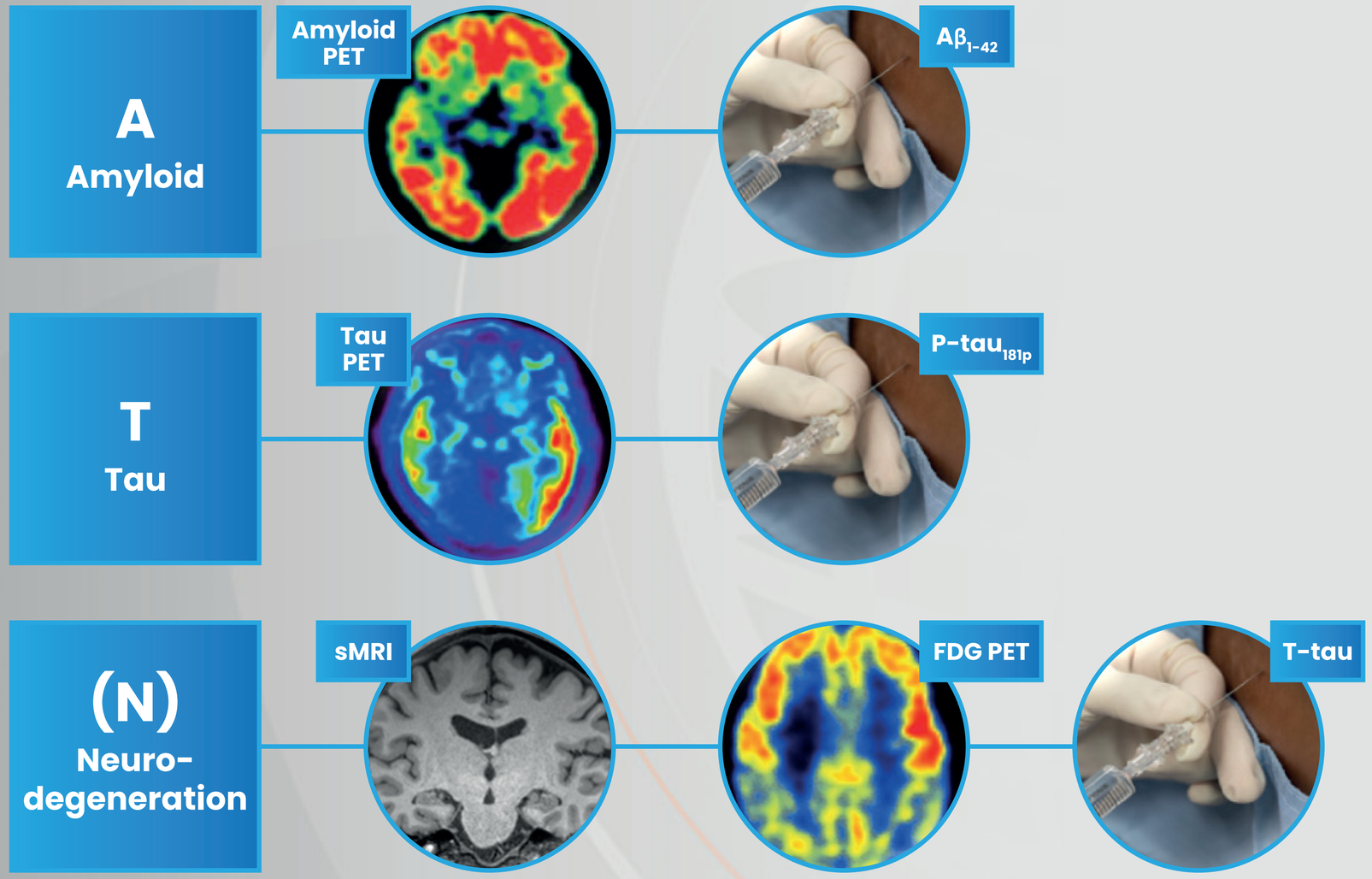
- Frontotemporal dementia
- Dementia with Lewy bodies
- Parkinson's disease
- Amyotrophic lateral sclerosis

P-tau, phosphorylated tau; T-tau, total tau.
Jack CR Jr, et al. *Alzheimers Dement.* 2018;14:535–62.

Cerebrospinal fluid markers



Moving to a biological definition of AD



Jack CR Jr, et al. *Alzheimers Dement.* 2018;14:535–62.
Images provided courtesy of Dr Dickerson.

Roles of molecular imaging and CSF biomarkers in dementia clinical practice

Amyloid PET

- Specific guidance for appropriate use
- May be less useful in older adults
- Reimbursed in VA settings only at present

Tau PET

- Appropriate use criteria in development
- Not yet reimbursed, distribution network in process

AD CSF biomarkers

- Available via LP and usually reimbursed

LP, lumbar puncture; VA, Veterans Affairs.

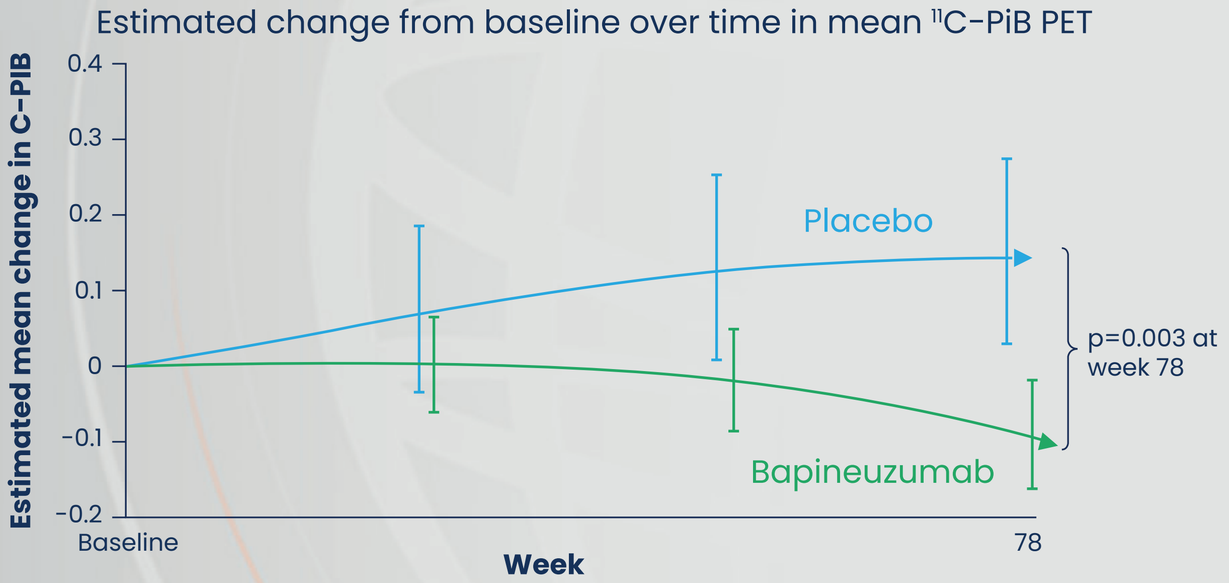
What is the role of neuroimaging biomarkers for patient diagnosis, selection and monitoring in Alzheimer's disease?

Why patient selection matters

- Phase III studies of the anti-Aβ monoclonal antibody bapineuzumab in patients with AD
- Patient selection based on MRI and clinical scores

No clinical benefit with anti-Aβ treatment

BUT... about 14% of the treatment cohort did not have Aβ in the brain



Aβ, amyloid beta; AD, Alzheimer's disease; C-PIB, Pittsburgh Compound B; MRI, magnetic resonance imaging.

Rinne JO, et al. *Lancet Neurol.* 2010;9:363–72; Salloway S, et al. *N Engl J Med.* 2014;370:322–33.

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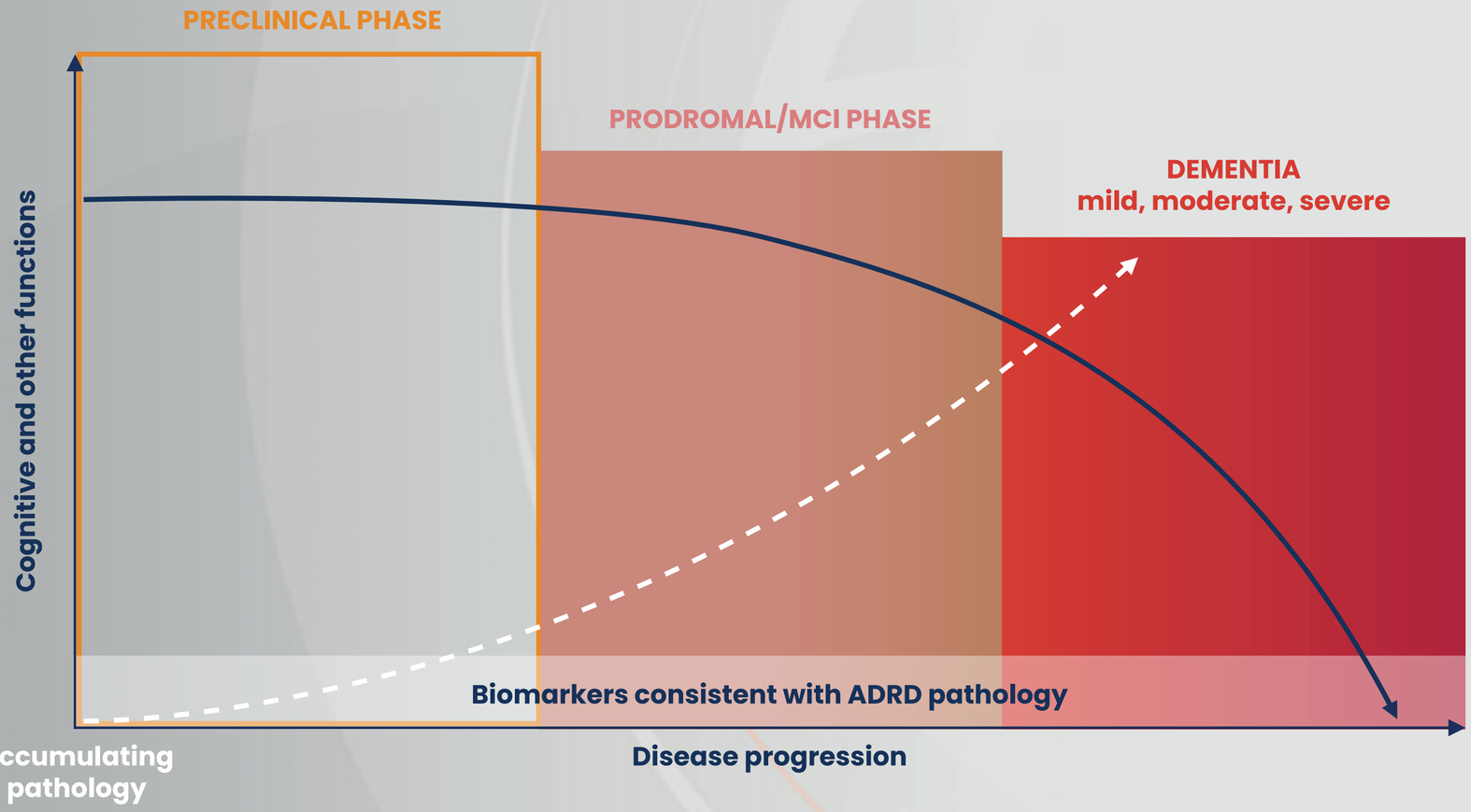
Clinical trials in prodromal or mild AD dementia: Biomarkers in studies of potential disease-modifying interventions



ADRD, AD-related dementias; MCI, mild cognitive impairment.
Adapted from Wong B, et al. *Neurodegener Dis Manag.* 2019;9:217–39.

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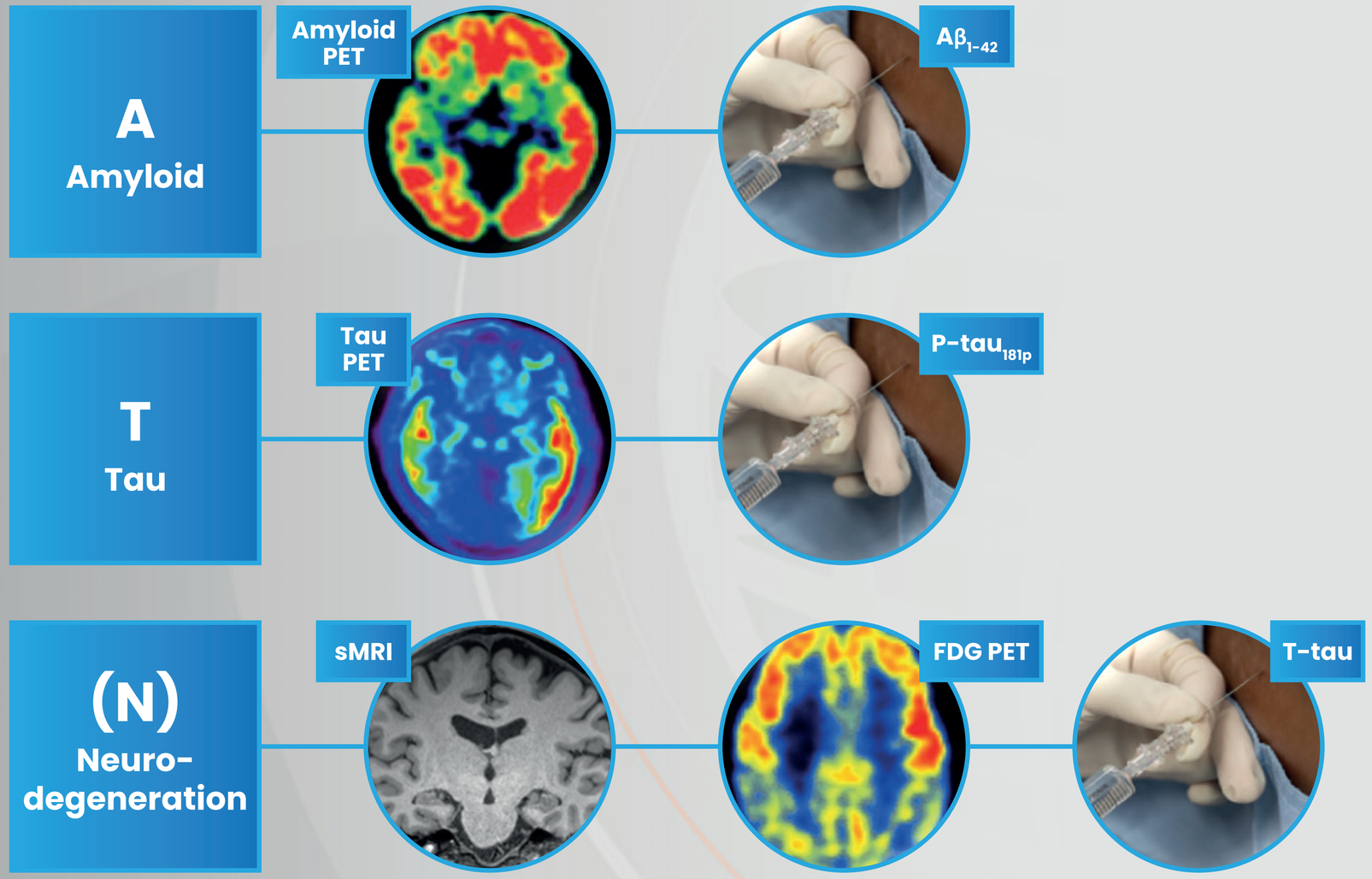
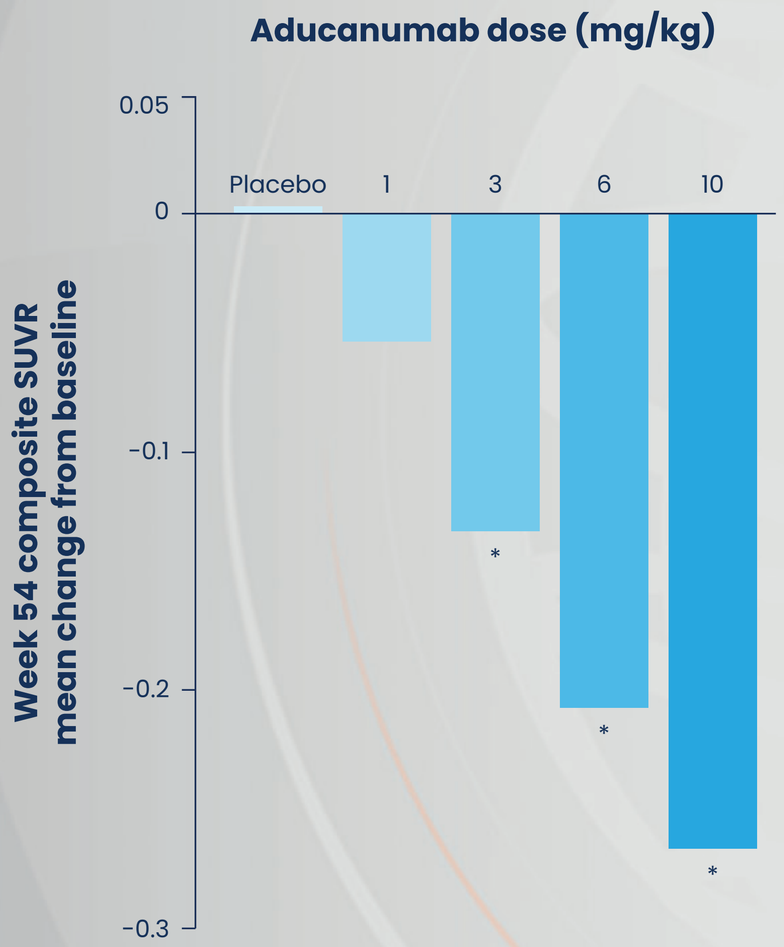
Moving to a biological definition of AD



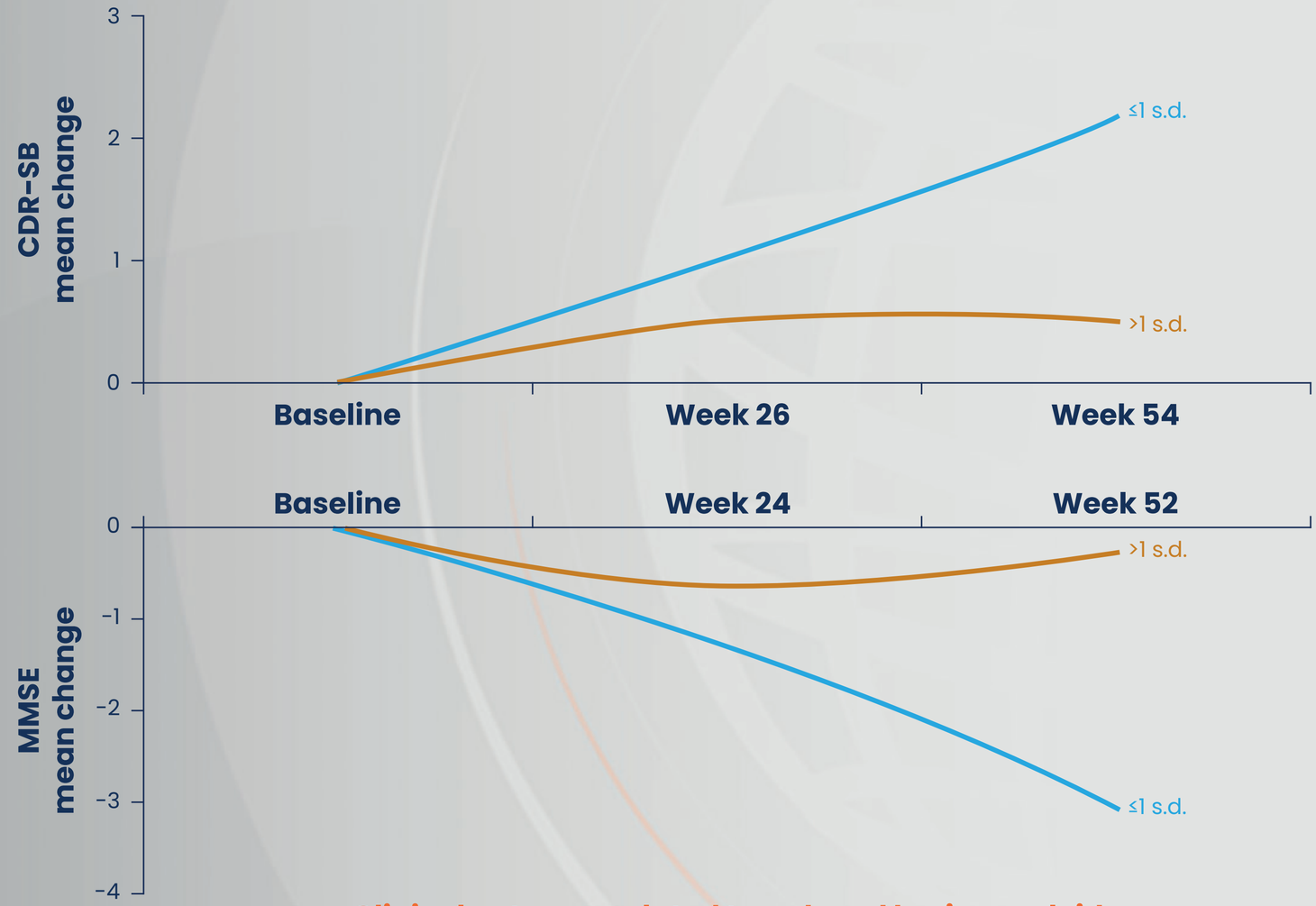
FDG, fluorodeoxyglucose; P-tau, phosphorylated tau; PET, positron emission tomography; sMRI, structural magnetic resonance imaging; T-tau, total tau.
Jack CR Jr, et al. *Alzheimers Dement.* 2018;14:535–62.

Aducanumab phase Ib amyloid PET outcomes



*Dose response p<0.001 based on a linear contrast test. *Post hoc* analysis showed that those aducanumab-treated patients who showed amyloid plaque reduction, as measured by SUVR score, 1 s.d. unit relative to placebo-treated patients after one year of treatment experienced a stabilization of clinical decline on both CDR-SB and MMSE scores.
CDR-SB, Clinical Dementia Rating Scale Sum of Boxes; MMSE, Mini-Mental State Examination; s.d., standard deviation; SUVR, standardized uptake value ratio.
Sevigny J, et al. *Nature.* 2016;537:50–6.

Aducanumab phase Ib amyloid clinical outcomes



Clinical outcome related to reduced brain amyloid

Sevigny J, et al. *Nature.* 2016;537:50–6.

Aducanumab phase III clinical outcomes

EMERGE 1,638 patients dosed	**Placebo** (n=548)	**Low dose** (n=543)	**High dose** (n=547)
Discontinued treatment (%)	**15.0**	**19.9**	**23.9**
Adverse event	2.9	7.6	8.4
Consent withdrawn	1.1	4.1	3.3
Death	0.9	0	0.9
Other*	8.4	7.3	8.6
Withdrawn from study (%)	**7.1**	**9.9**	**12.1**
Adverse event	1.8	2.0	3.3
Consent withdrawn	1.5	5.2	4.0
Death	0.9	0	1.1
Other*	0.9	2.0	1.8
Completed placebo-controlled period (%)	**50.2**	**50.5**	**52.1**

*Includes study visit burden, site terminated by sponsor and other.

Haeberlain SB, et al. Biogen Presentation AAT-AD/PD, Vienna, Austria. April 2020.
Available at: https://investors.biogen.com/static-files/f91e95d9-2fce-46ce-9115-0628cfe96e83 (accessed April 2021).

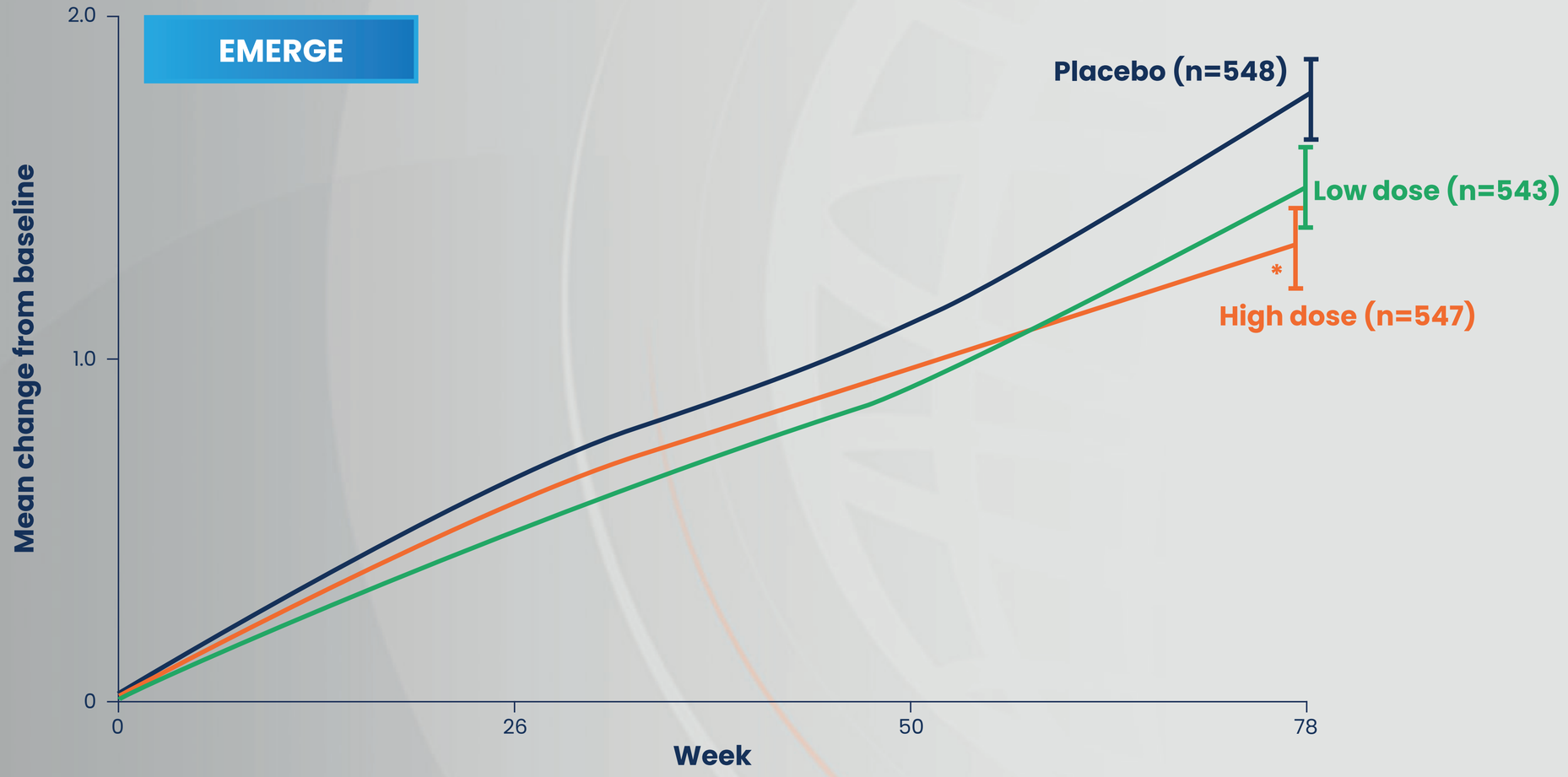
Aducanumab phase III clinical outcomes

ENGAGE 1,647 patients dosed	**Placebo** (n=545)	**Low dose** (n=547)	**High dose** (n=555)
Discontinued treatment (%)	**17.6**	**19.2**	**26.7**
Adverse event	4.8	7.9	11.5
Consent withdrawn	2.6	2.0	2.7
Death	0	0.5	0.2
Other*	8.7	7.4	10.9
Withdrawn from study (%)	**10.6**	**11.0**	**14.1**
Adverse event	2.9	4.2	4.7
Consent withdrawn	3.9	2.6	4.1
Death	0	0.5	0.4
Other*	2.2	1.6	3.6
Completed placebo-controlled period (%)	**58.5**	**57.4**	**49.5**

*Includes study visit burden, site terminated by sponsor and other.

Haeberlain SB, et al. Biogen Presentation AAT-AD/PD, Vienna, Austria. April 2020.
Available at: https://investors.biogen.com/static-files/f91e95d9-2fce-46ce-9115-0628cfe96e83 (accessed April 2021).

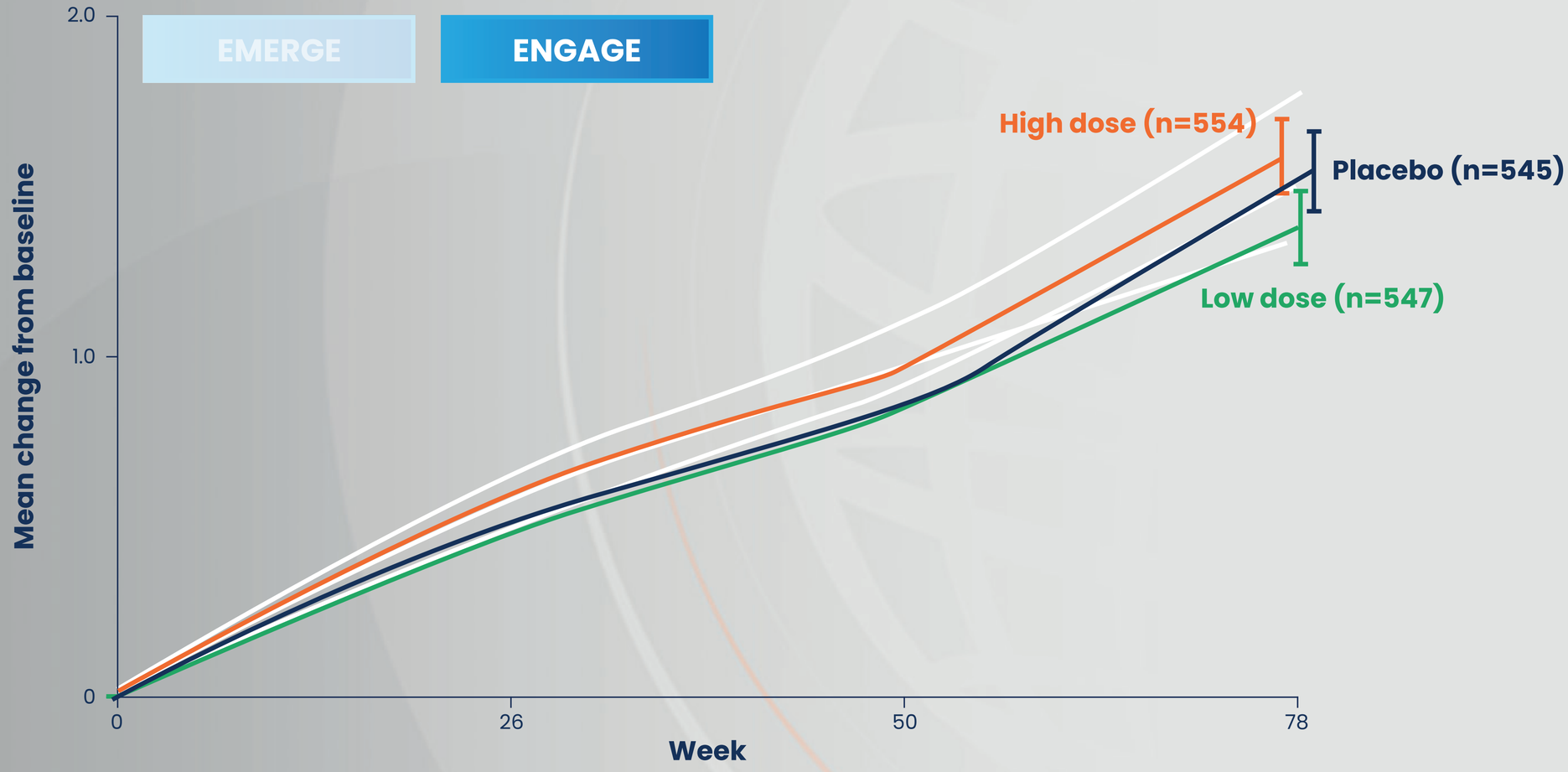
Aducanumab phase III clinical outcomes: CDR-SB



*p<0.05 vs placebo.

Haeberlain SB, et al. Biogen Presentation AAT-AD/PD, Vienna, Austria. April 2020. Available at: https://investors.biogen.com/static-files/f91e95d9-2fce-46ce-9115-0628cfe96e83 (accessed April 2021).

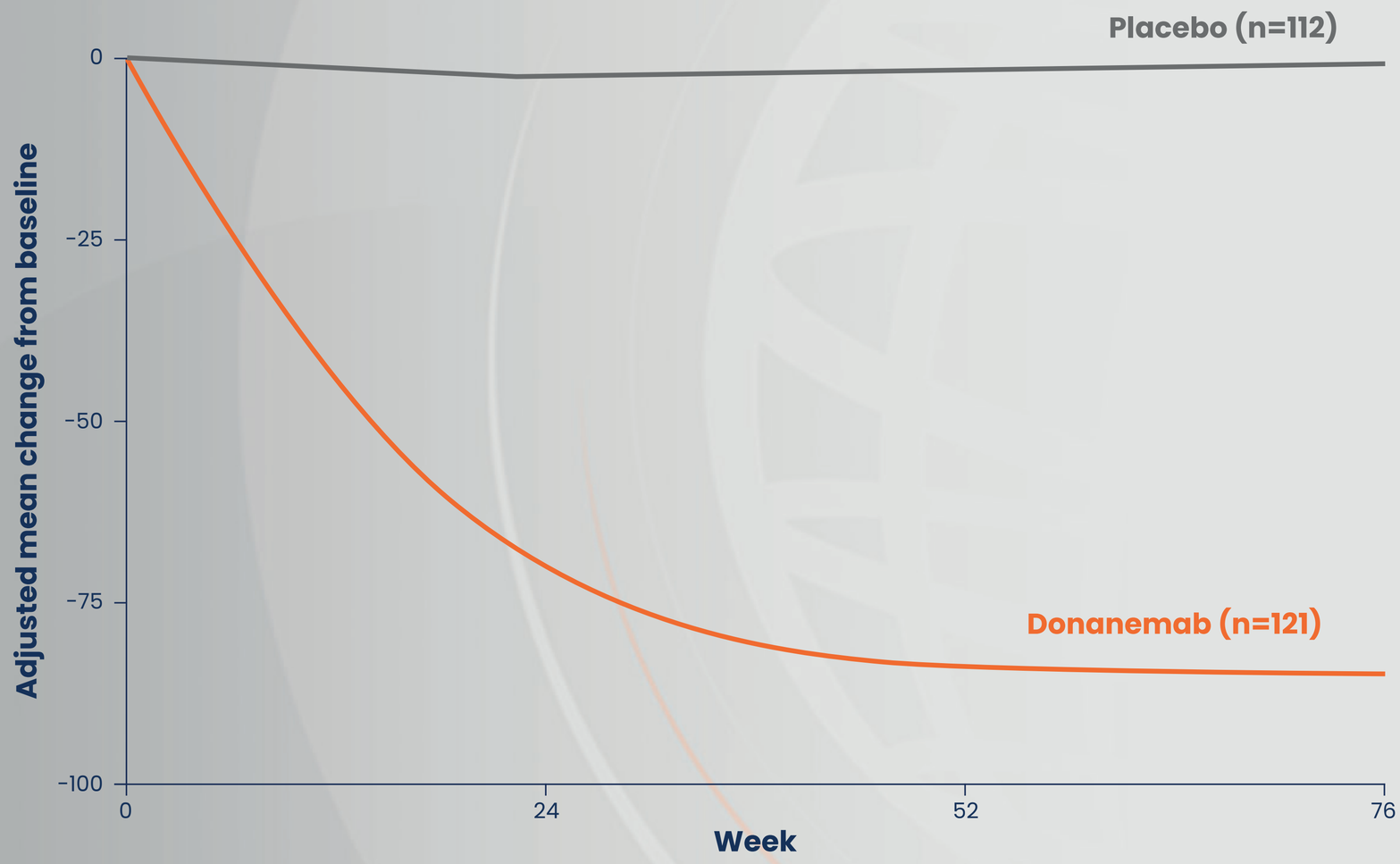
Aducanumab phase III clinical outcomes: CDR-SB



*p<0.05 vs placebo.

Haeberlain SB, et al. Biogen Presentation AAT-AD/PD, Vienna, Austria. April 2020. Available at: https://investors.biogen.com/static-files/f91e95d9-2fce-46ce-9115-0628cfe96e83 (accessed April 2021).

Donanemab phase II amyloid plaque level by florbetapir PET



Mintun MA, et al. *N Engl J Med.* 2021;384:1691–704.

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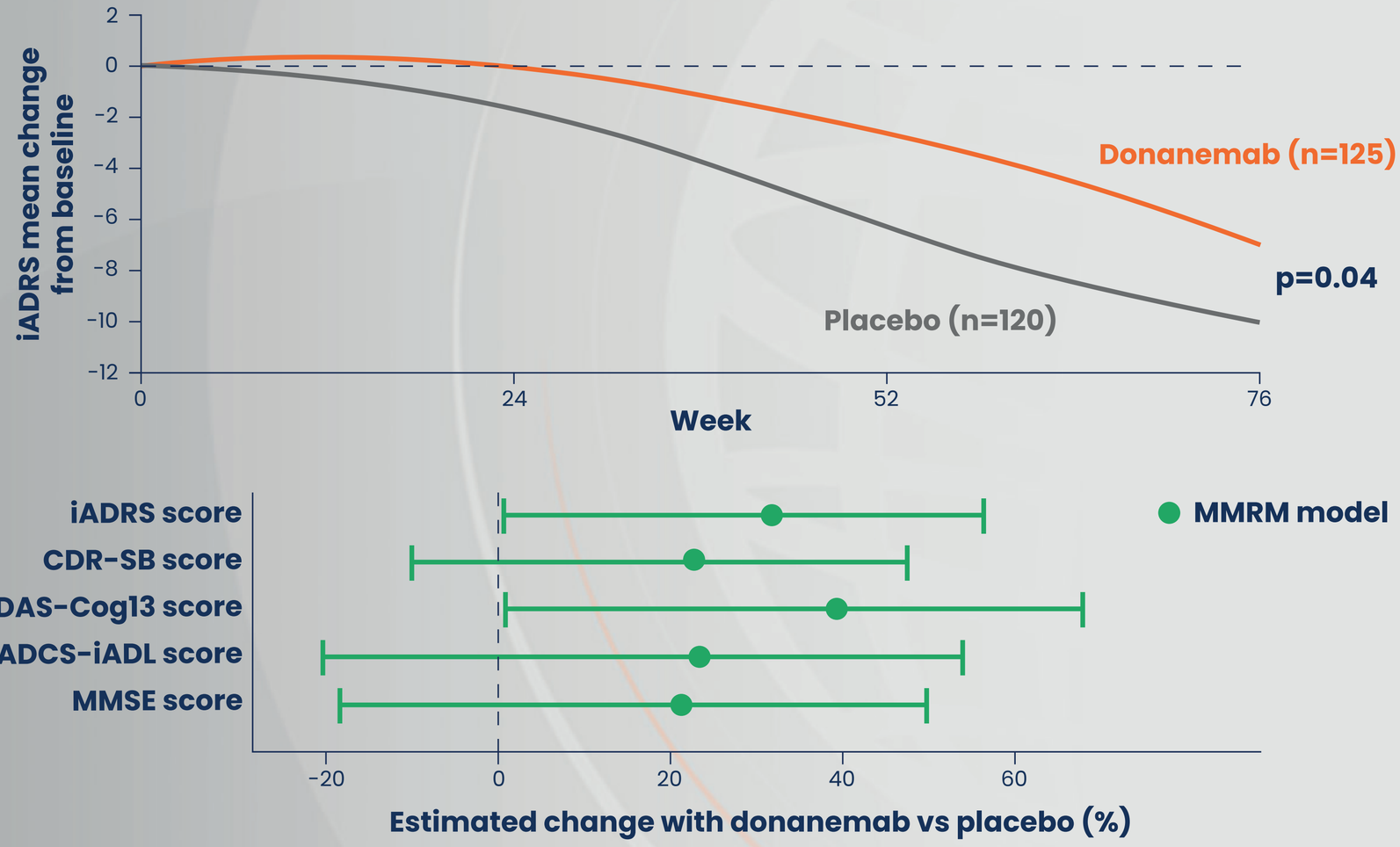
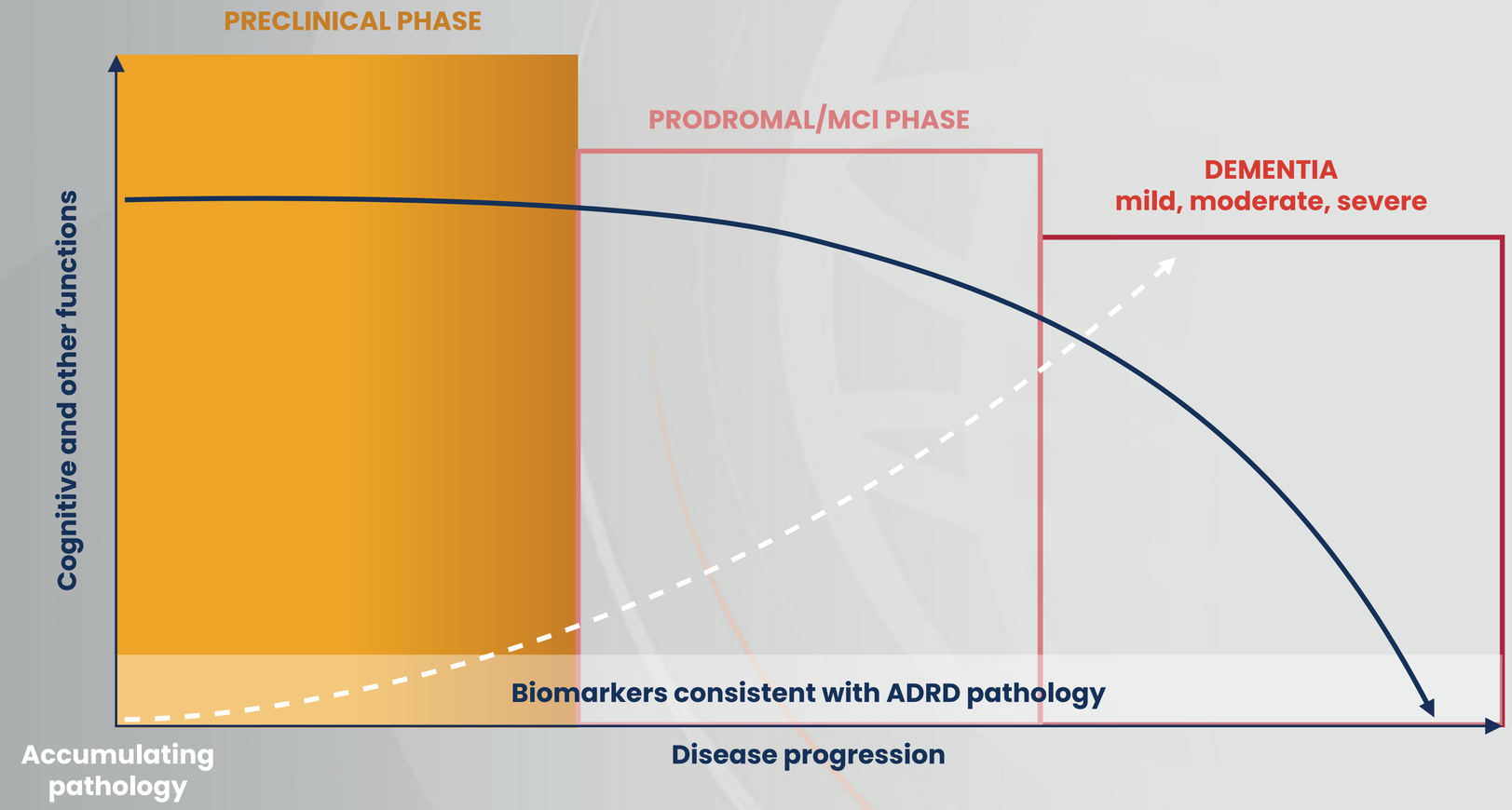
Donanemab phase II clinical outcomes



ADAS-Cog13, Alzheimer's Disease Assessment Scale 13-item cognitive subscale; ADCS-iADL, Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Inventory; iADRS, integrated Alzheimer's Disease Rating Scale; MMRM, mixed model for repeated measures.

Mintun MA, et al. *N Engl J Med.* 2021;384:1691–704.

The continuum of neurodegenerative dementias: Separating the illness from the disease using biomarkers



Adapted from Wong B, et al. *Neurodegener Dis Manag.* 2019;9:217–39.

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Preclinical Alzheimer's disease

No cognitive impairment on testing (possible subjective impairment)

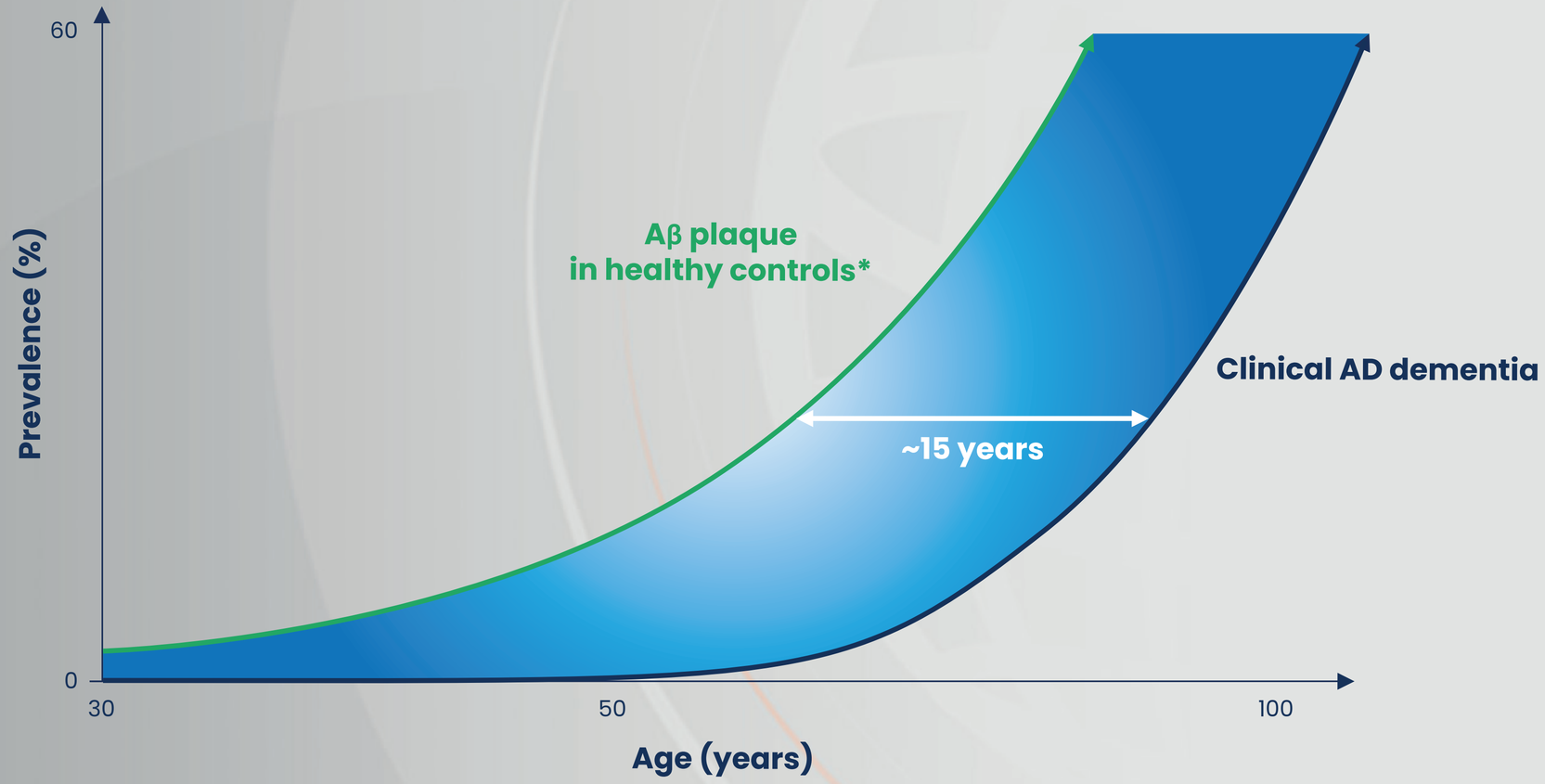
No functional impairment

Biomarker evidence of AD

- Amyloid[1]
- Amyloid and tau[2]

1. Sperling RA, et al. *Alzheimers Dement.* 2011;7:280–92; 2. Jack CR Jr, et al. *Alzheimers Dement.* 2018;14:535–62.

Preclinical Alzheimer's disease



*Data obtained at post-mortem from cognitively unimpaired subjects.
Rowe CC, et al. *Neurobiol Aging.* 2010;31:1275–83.

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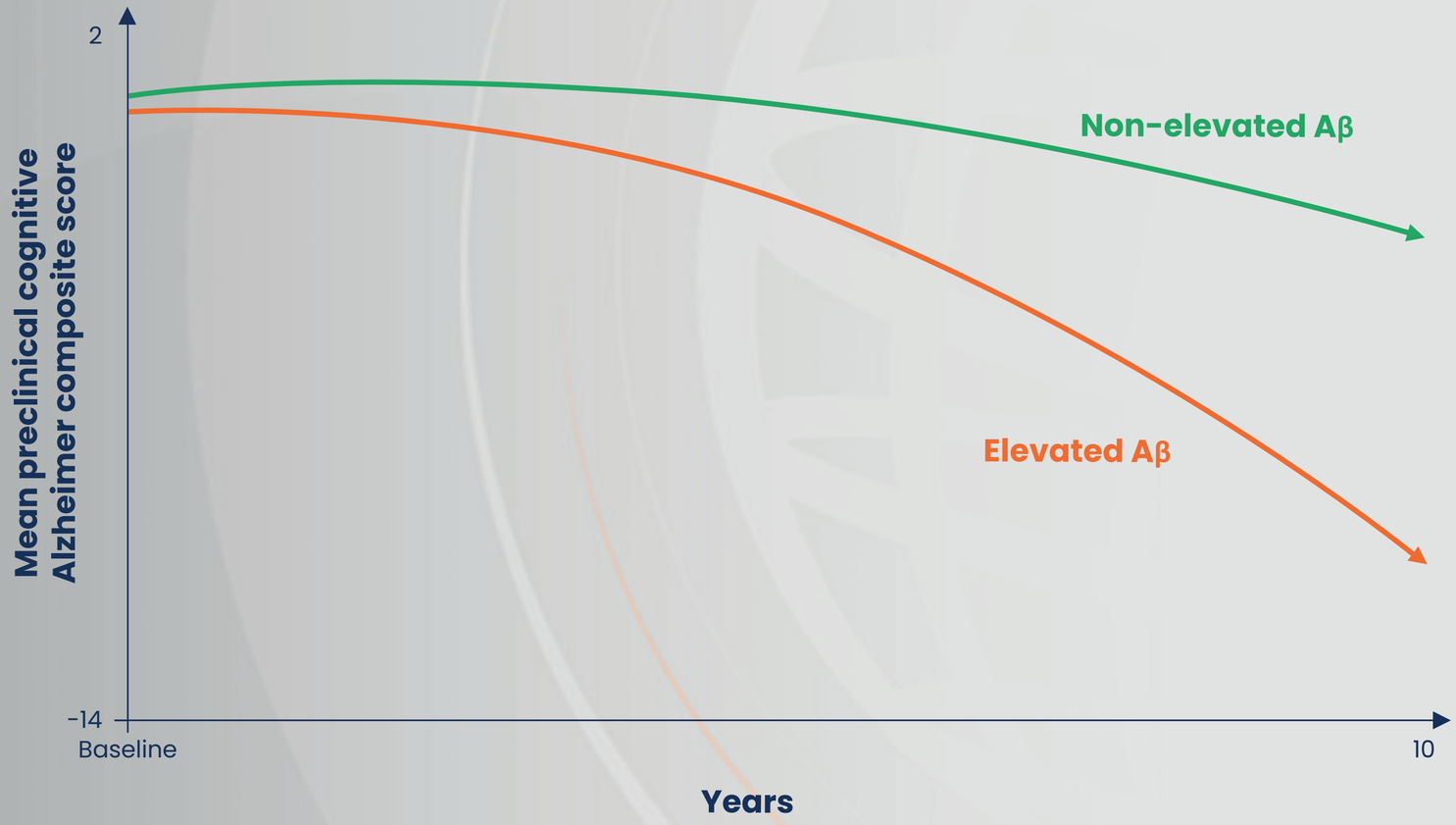
Amyloid-related cognitive decline in older adults (ADNI)



ADNI, Alzheimer's Disease Neuroimaging Initiative.
Donohue MC, et al. *JAMA.* 2017;317:2305–16.

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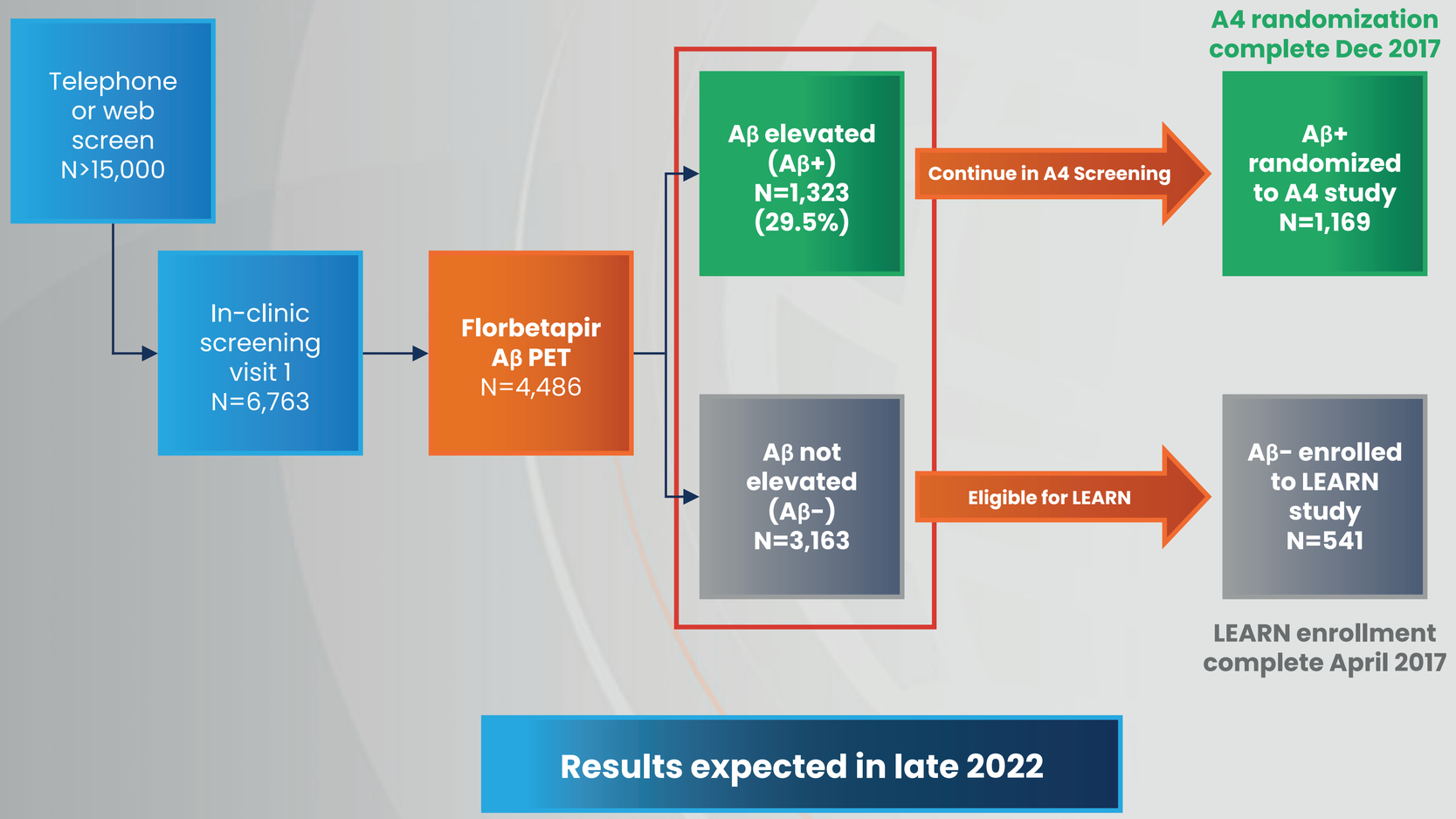
Anti-amyloid treatment in asymptomatic AD (A4, solanezumab): Screening results



Aβ, beta amyloid; AD, Alzheimer's disease.
Courtesy of Reisa Sperling, MD.

Envisioning future practice in the era of disease-modifying therapies for AD and ADRD

Symptomatic patients
Prodromal/very mild dementia stage

- Disease-specific biomarkers (screen then definitive)
- DMT treatment
- Close clinical, imaging and biomarker monitoring

Patients with preclinical disease

- Stratify risk by family history, polygenic markers
- Blood biomarker screening
- Definitive biomarker screening
- DMT treatment
- Close clinical, imaging and biomarker monitoring

DMT, disease-modifying therapy.