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Biogen Alzheimer's Education

Current Concepts in Alzheimer's Disease

Contents

Learning objectives

1. Understand mechanisms and types of Alzheimer's disease
2. Identify risk and protective factors
3. Gain knowledge of the diagnostic pathway and stages of Alzheimer's disease
4. Be aware of current treatment options and diagnostic guidelines

Introduction to Alzheimer's disease

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Alzheimer’s disease

Multifactorial and heterogeneous neurodegenerative disorder[1]

Most common cause of dementia, and account for 60–80% of dementia cases[2]

Leading cause of disability and morbidity in the elderly[2]

Neuronal and synaptic failure are common features and play a pivotal role in cognitive dysfunction[1]

No disease-modifying drug available, treatment is symptomatic only

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AD, Alzheimer's disease

1. Kazim SF, Iqbal K. Mol Neurodegener 2016;11:50; 2, Alzheimer’s Association. Alzheimers Dement 2018;14:367–429

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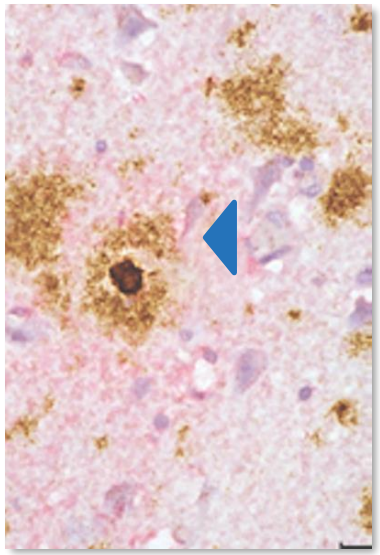
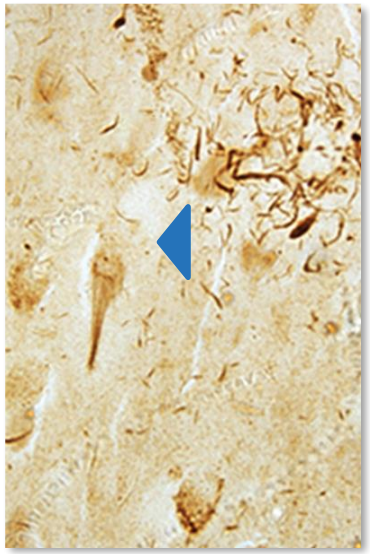
Alzheimer’s disease pathology begins 15–20 years before clinical presentation

-20 years **-15 years** **Onset of disease**

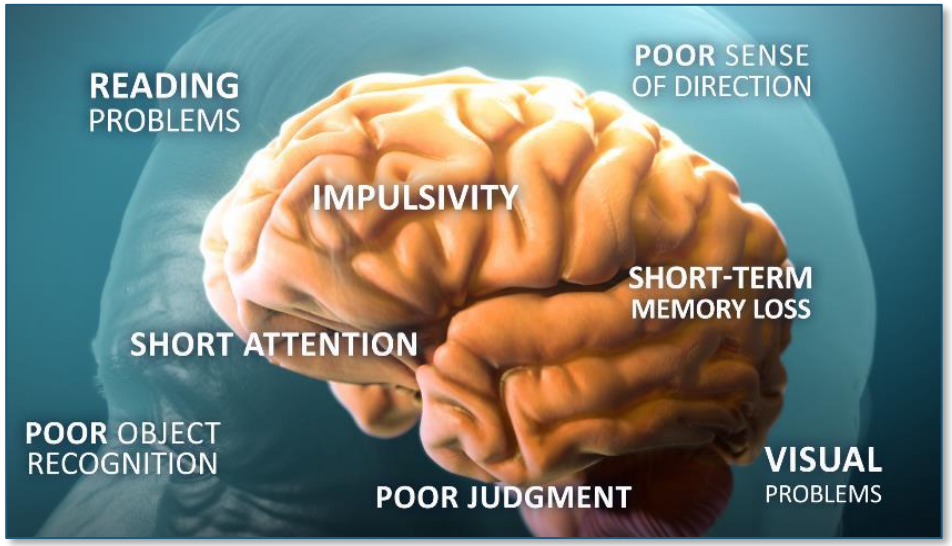
Aβ[1]



Tau[2]



Symptoms across stages



Aβ, amyloid beta; AD, Alzheimer's disease

1. Mathur R, et al. PLoS One 2015;10:e0118463; 2. Day RJ, et al. PLoS One 2015;10:e0132637;
3. Jack CR, et al. Alzheimers Dement 2018;14:535–562; 4. Bateman RJ, et al. N Engl J Med 2012;367:795–804

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Risk and protective factors

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Non-modifiable risk factors: Genetic factors

Individuals with close relatives with AD are up to two times more likely to develop the disease[1]

Monogenic AD: Associated with mutations in the ***APP***, ***PSEN1***, and ***PSEN2*** genes directly involved in amyloid processing[2,3]

Sporadic AD: **ε4 of *APOE*** is one gene associated with risk[3]

AD, Alzheimer's disease; ApoE ε4, apolipoprotein E ε4; APP, amyloid beta precursor protein; PSEN, presenilin

1.. Loy CT, et al. Lancet 2014;383:828–840; 2. Karch CM, Goate AM. Biol Psychiatry 2015;77:43–51; 3. Pilotti A et al. Biomed Res Int 2013;2013:689591

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Modifiable risk factors

Education

Vascular risk factors

Cardiovascular disease

Systemic inflammation

Neuropsychiatric conditions

Roberts R, et al. Clin Geriatr Med 2013;29:10

Alzheimer’s disease pathology

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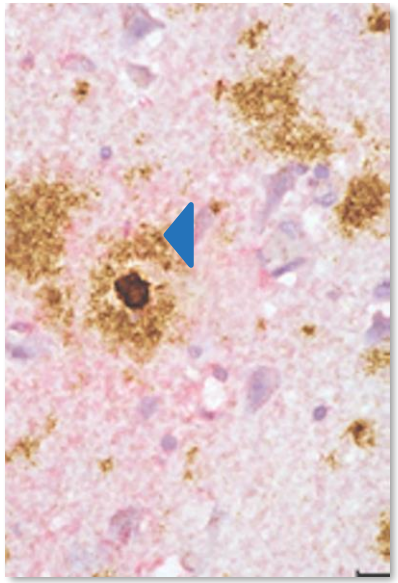
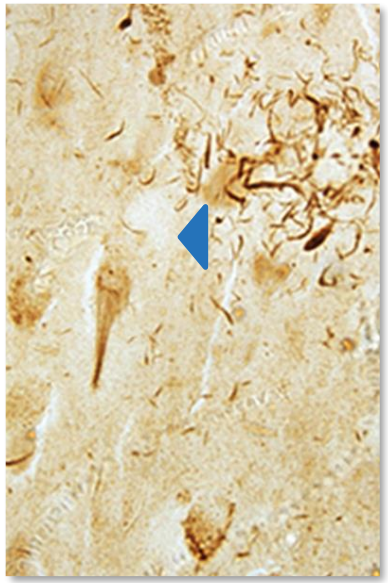
Key neuropathologic hallmarks of Alzheimer's disease[1]

- Amyloid β plaques
- NFTs (aggregates of phosphorylated-tau protein)
- Glial responses
- Synaptic and neuronal loss

Aβ[2]



Tau[3]



Diagnostic criteria depend on distribution Aβ plaques and NFTs

Aβ, amyloid beta; AD, Alzheimer's disease; NFT, neurofibrillary tangle

1. Serrano-Pozo A, et al. Cold Spring Harb Perspect Med 2011;1:a006189; 2. Mathur R, et al. PLoS One 2015;10:e0118463; 3. Day RJ, et al. PLoS One 2015;10:e0132637

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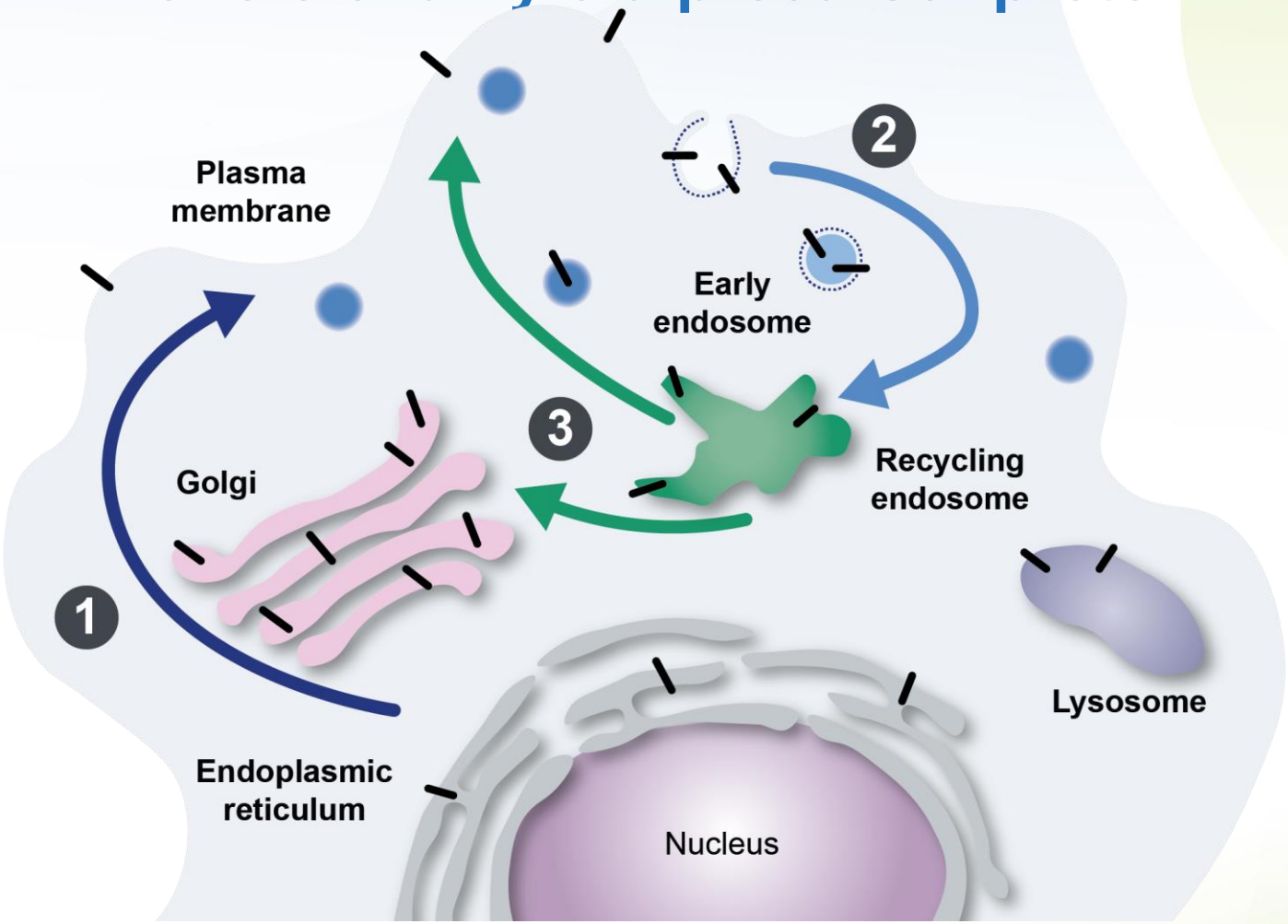
The role of amyloid precursor protein



Step 1: APP molecules mature through the constitutive secretory pathway;

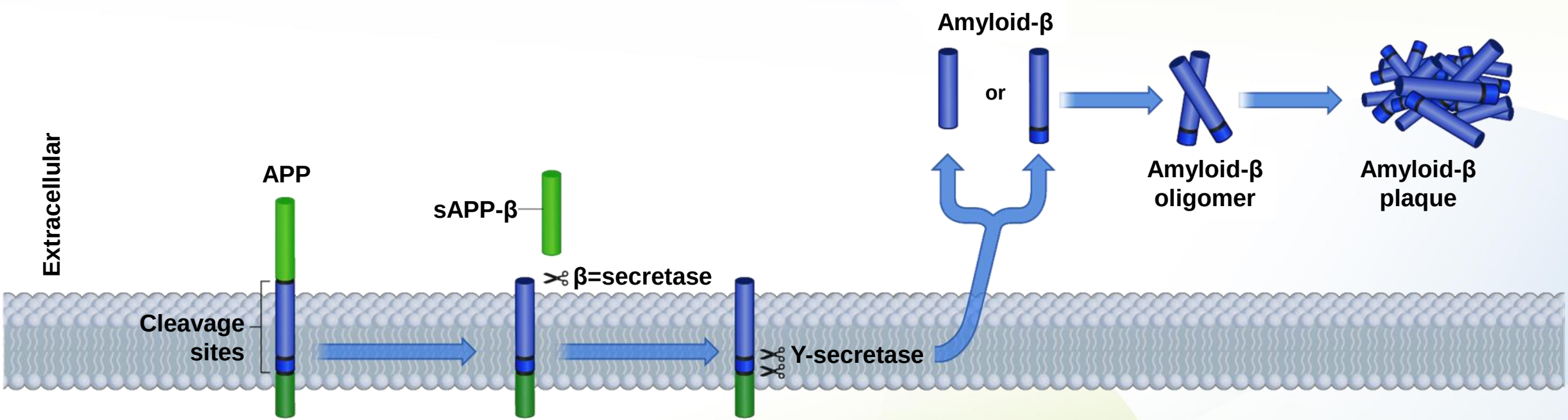
Step 2: APP is rapidly internalized;

Step 3: APP is trafficked through endocytic and recycling compartments back to the cell surface or degraded in the lysosome

Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid precursor protein; CSF, cerebrospinal fluid
Image adapted from: Thinakaran G, Koo EH. J Biol Chem 2008;283:29615–29619

Aβ in Alzheimer's disease pathology

In AD, Aβ clearance is reduced, leading to aggregation into oligomers, which further aggregate into fibrils and plaques[1]



Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid beta precursor protein; sAPP, soluble amyloid beta precursor protein

1. Sadigh-Eteghad S, et al. Med Princ Pract 2015;24:1–10

Image adapted from: Makin S. Nature 2018;559:S4–S7

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Pathologic changes associated with Aβ deposition

Aβ forms soluble oligomers and insoluble amyloid fibrils, which are the main **constituents of amyloid plaques** (mainly Aβ42) and **cerebral amyloid angiopathy** (primarily Aβ40)[1]

Aβ could trigger other downstream processes, in particular tau aggregation, which mediate neurodegeneration[2]

Progressive Aβ deposition is followed by surrounding neuritic and glial cytopathology in brain regions serving cognition, including memory[3]

Aβ deposition is also responsible for microglial activation, contributes to enhanced inflammation by NF-κB stimulation, and regulates the ERK and MAPK pathways[4]

Aβ, amyloid beta; AD, Alzheimer's disease; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B

1. Serrano-Pozo A, et al. Cold Spring Harb Perspect Med 2011;1:a006189; 2. Musiek ES, Holtzman DM. Nat Neurosci 2015;18:800–806; 3. Selkoe DJ, Hardy J. EMBO Mol Med 2016;8:595–608; 4. Ridolfi E, et al. Clin Dev Immunol 2013;2013:939786

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Role of tau in AD pathology

Tau is a brain-specific, axon-enriched, microtubule-associated protein (**t-tau**)[1] generated by neurons[2]

Disruption of this equilibrium may lead to an accumulation of abnormal **p-tau**, which aggregates and form **NFTs**[3]

Changes in levels of t-tau and p-tau can occur years before the onset dementia[4]

Changes in **t-tau can reflect neuronal degeneration**, while the level of **p-tau correlates with NFT load**[4]

AD, Alzheimer's disease; NFT, neurofibrillary tangle; p-tau, phosphorylated-tau; t-tau, total-tau

1. Bloom GS. JAMA Neurol 2014;71:505–508; 2. Buèe L et al. Brain Res Brain Res Rev 2000;33:95–130;
3. Martin L et al. Ageing Res Rev 2013;12:39–49; 4. Blennow K. Neurol Ther 2017;6:S15–S24

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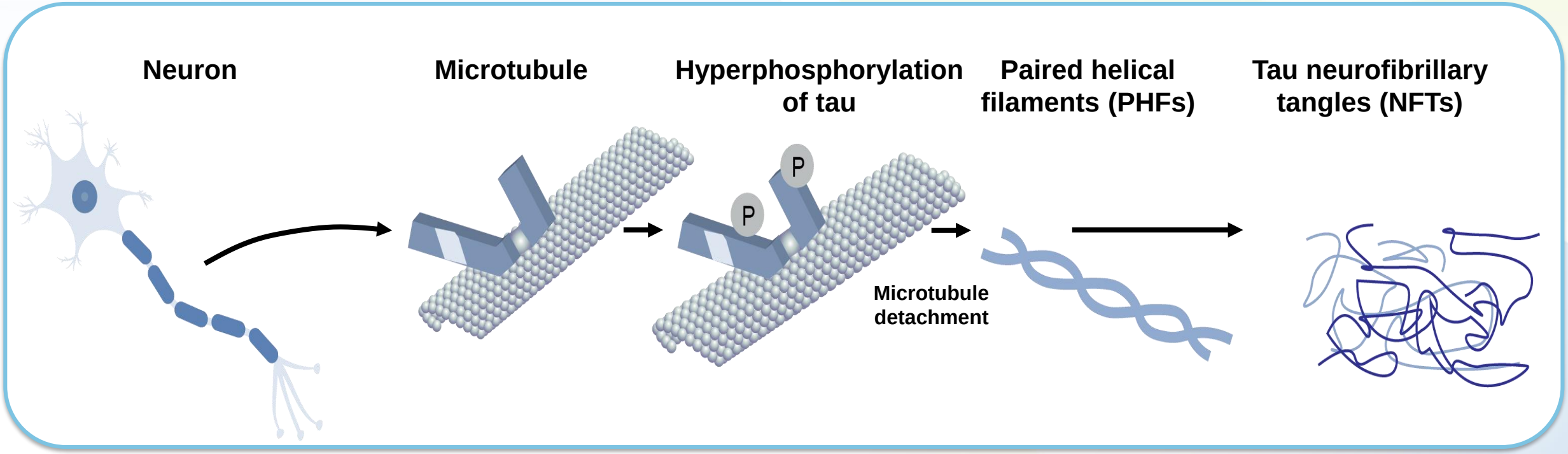
The formation of NFTs



Aβ, amyloid beta; AD, Alzheimer's disease; FTD, frontotemporal dementia; NFT, neurofibrillary tangle

1. Wegmann S, et al. EMBO J 2018;37:e98049; 2. Lim S, et al. Comput Struct Biotechnol J 2014;12:7–13; 3. Gendron TF, Petrucelli L. Mol Neurodegener 2009;4:13
Image from: https://www.abcam.com/neuroscience/untangle-tau (Accessed November 20, 2018)

Cerebrovascular disease and Alzheimer's disease (1/2)

CVD:

- Induces Aβ deposition and affects the age of onset of sporadic AD.[1]
- Exacerbates cognitive impairment and increases the likelihood of clinical dementia symptoms[2]

Aβ deposition has been shown to cause cerebrovascular degeneration,[1,2] while vascular lesions are directly involved in AD pathogenesis[2]

CVD also impairs Aβ clearance and may disturb homeostasis between Aβ production and clearance, thereby contributing to Aβ burden[2]

Aβ, amyloid beta; AD, Alzheimer's disease; BBB, blood-brain barrier; CVD, cerebrovascular disease

1. Lee CW, et al. Curr Alzheimer Res 2014;11:4–10; 2. Saito S, Ihara M.Curr Opin Psychiatry 2016;29:168–173;

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Cerebrovascular disease and Alzheimer's disease (2/2)

One of the mechanisms linking CVD to AD is **decreased cerebral blood flow**.[1]

- Cerebral hypoperfusion causes BBB dysfunction leading to oxidative stress, mitochondrial dysfunction, neuroinflammation, and reduced cerebral perfusion, which accelerates neurodegeneration[2]

Limited evidence **has shown that CVD also has an influence on tau pathology** [3,4]

Aβ, amyloid beta; AD, Alzheimer's disease; BBB, blood-brain barrier; CVD, cerebrovascular disease

1. Saito S, Ihara M.Curr Opin Psychiatry 2016;29:168–173; 2.. Di Marco LY, et al. Neurobiol Dis 2015;82:593–606;
3. Iliff JJ, et al. J Neurosci 2014;34:16180–16193; 4. Nation DA, et al. JAMA Neurol 2015;72:546–553

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Etiologic hypothesis of Alzheimer's disease

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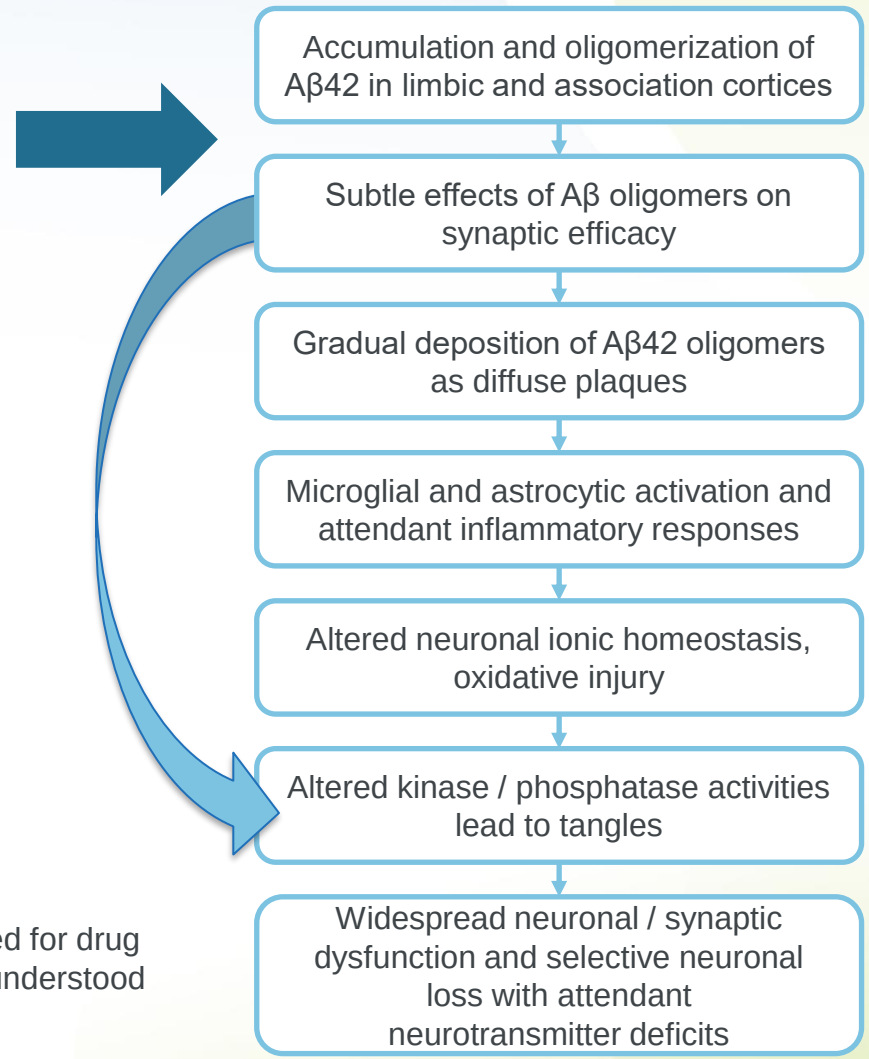
The amyloid cascade hypothesis

Dominantly inherited (missense mutations in the *APP*, *PSEN1,* or *PSEN2* genes)

Trisomy 21

- ↑ relative Aβ42 production throughout life



Non-dominant forms of AD – including sporadic AD (failure of Aβ clearance)

- Gradually rising Aβ42 levels in the brain

Cognitive symptoms and eventually dementia

NB this is the current working hypothesis used for drug discovery, but the mechanisms are not fully understood

Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid beta precursor protein; PSEN, presenilin
Adapted from: Selkoe DJ, Hardy J. EMBO Mol Med 2016;8:595–608

Role of cholinergic pathway

Loss of cholinergic activity is commonly observed in the brains of patients with AD[1]

Cholinergic depletions affects cognition[2]

As opposed to directly causing AD or affecting hippocampal learning, it may reduce the ability of the brain to compensate for the accumulation of risk factors[2]

Aβ, amyloid beta; Ach, acetylcholine; AChEI, acetylcholinesterase inhibitors; AD, Alzheimer's disease

1. Perry EK, et al. Lancet 1981;2:149; 2. Craig L, et al. Neurosci Biobehav Rev 2011;35:1397–1409

Alzheimer’s disease continuum

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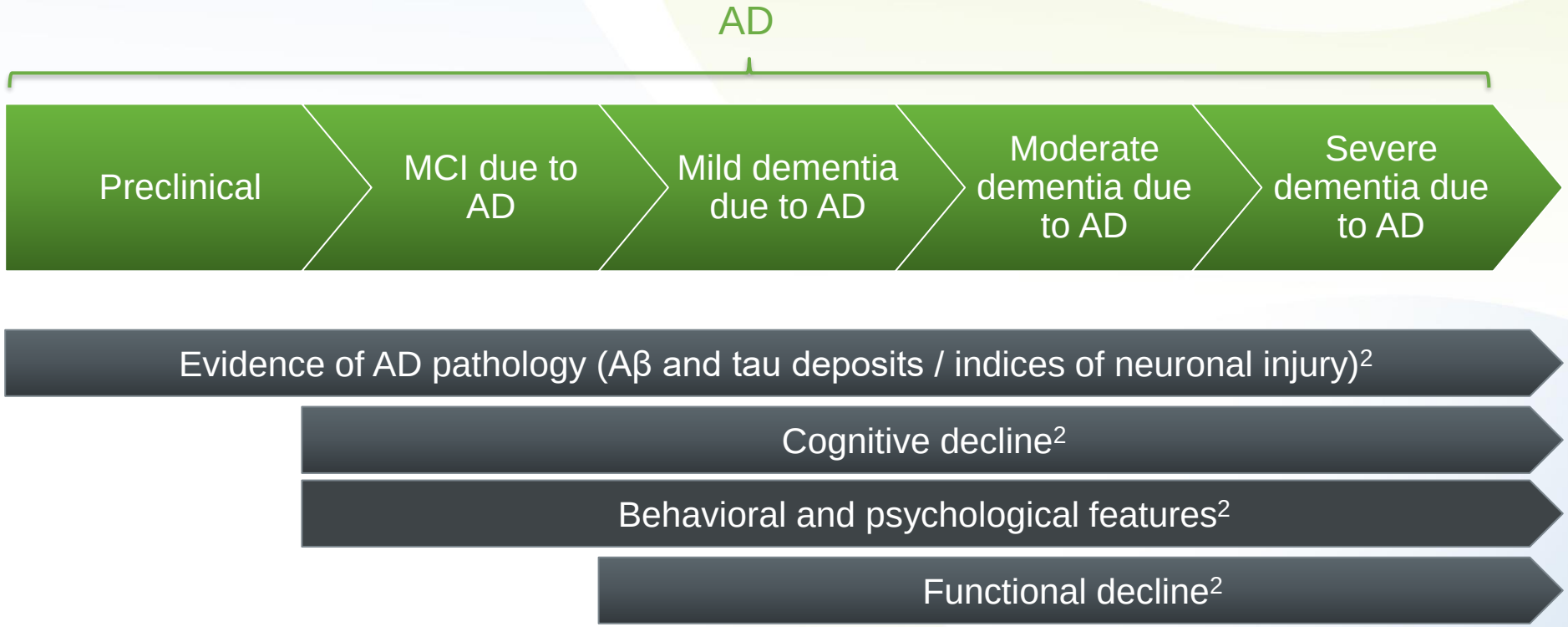
The Alzheimer's disease continuum

AD continuum definition from the NIA-AA[1]



Aβ, amyloid beta; AD, Alzheimer's disease; IWG-2, International Working Group 2; MCI, mild cognitive impairment; NIA-AA, National Institute on Aging—Alzheimer's Association guidelines

1. McKhann et al. Alzheimers Dement 2011; 7:263-9; 2. Albert MS, et al. Alzheimers Dement 2011;7:270–279

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Differentiating between the most common dementia etiologies (1/4)

	Pathology	Symptoms	Diagnostic considerations
Alzheimer's disease	• 50% involve solely Alzheimer's pathology • Patients with mixed pathology are referred to as mixed dementia with AD pathology	• Early: Difficulty remembering recent conversations, names, or events (episodic memory) • Later: Impaired communication, disorientation, confusion, poor judgment, difficulty speaking, etc.	Progressive disease that begins well before clinical symptoms emerge

AD, Alzheimer's disease

2018 Alzheimer's disease facts and figures. Available from: https://www.alz.org/media/Documents/facts-and-figures-2018-r.pdf (Accessed November 10, 2018)

Differentiating between the most common dementia etiologies (2/4)

	Pathology	Symptoms	Diagnostic considerations
Vascular dementia/ mixed	• Less common as a sole cause of dementia than AD • Caused by blood vessel damage leading to infarcts in the brain • Very common as a mixed pathology in older patients with AD/mixed dementia	• Impaired judgment or ability to make decisions, plan, or organize	Coexists with AD pathology

2018 Alzheimer's disease facts and figures. Available from: https://www.alz.org/media/Documents/facts-and-figures-2018-r.pdf (Accessed November 10, 2018)

Differentiating between the most common dementia etiologies (3/4)

	Pathology	Symptoms	Diagnostic considerations
Lewy body	• Lewy bodies (abnormal aggregations of protein alpha-synuclein in neurons) develop and affect the cortex	• More likely to have initial or early symptoms of sleep disturbances, hallucinations, and slowness, gait imbalance or other Parkinsonian movement features (may occur in the absence of significant memory impairment)	Coexists with AD pathology

2018 Alzheimer's disease facts and figures. Available from: https://www.alz.org/media/Documents/facts-and-figures-2018-r.pdf (Accessed November 10, 2018)

Differentiating between the most common dementia etiologies (4/4)

	Pathology	Symptoms	Diagnostic considerations
frontotemporal dementia	• Frontal and temporal lobe atrophy later in disease	• Marked changes in personality and behaviors and/or difficulty producing language • Memory is typically spared in the early stages	Most develop symptoms at a younger age than AD

2018 Alzheimer's disease facts and figures. Available from: https://www.alz.org/media/Documents/facts-and-figures-2018-r.pdf (Accessed November 10, 2018)

Diagnostic pathway

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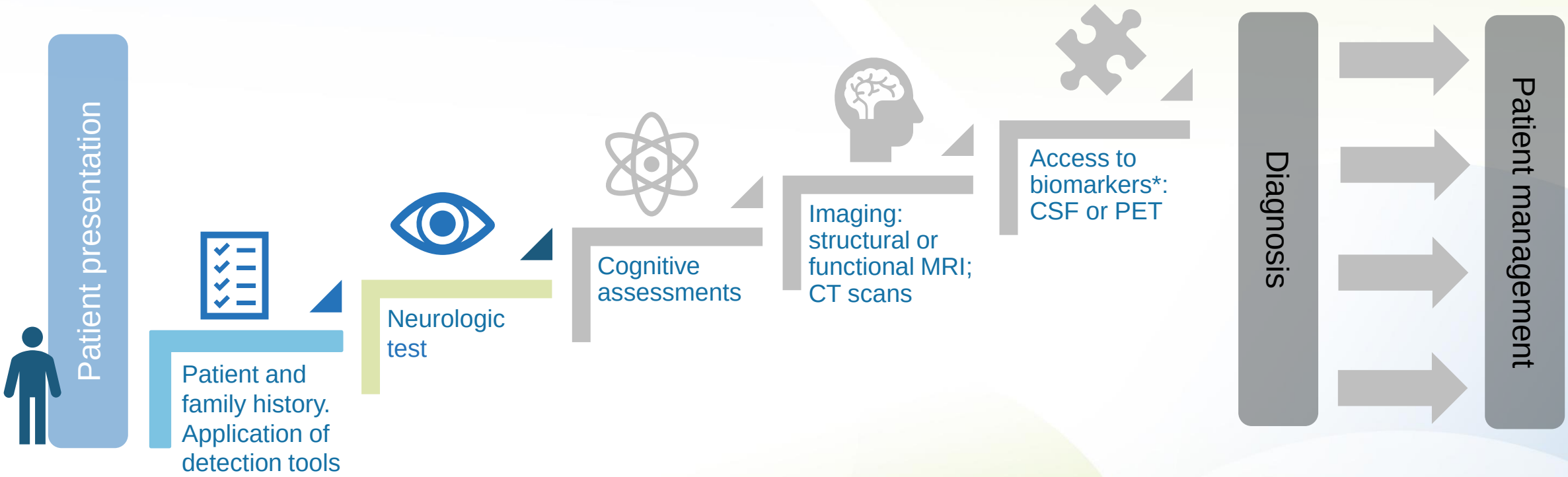
The patient journey



*In some regions available in tertiary care clinics when necessary or under research studies

CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography

Clinical assessment: Overview

- History[1,2]
- Neurologic examination[3]
- Cognitive functioning (office-based, objective, self-report, informant report)[1,2]
- Assessment of functional independence[2]
- Neuropsychiatric assessment[1,2]
- Laboratory tests (to rule out reversible causes of cognitive impairment)[2]
- Neuroimaging (to rule out other causes and to help rule in AD as cause)[1]

AD, Alzheimer's disease

1. McKhann GM, et al. Alzheimers Dement 2011;7:263–269; 2. Galvin JE, Sadowsky CH. J Am Board Fam Med 2012;25:367–382; 3. Cooper S, Greene JD. J Neurol Neurosurg Psychiatry 2005;76:v15–v24

Use of comprehensive cognitive assessments

Objective assessment of a person's cognitive status

Identify the presence or absence of cognitive deficits

Identify the nature and extent of any deficits

Support a diagnosis

Monitor change over time

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Galvin JE, Sadowsky CH. J Am Board Fam Med 2012;25:367–382

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Cognitive Testing: Tests Involvement of Various Cognitive Domains

Cognitive Domain	MMSE	MoCA
Orientation	Yes	Yes
Memory – Learning/Delayed recall	Yes	Yes
Attention	Yes	Yes
Language	Yes	Yes
Visuospatial	Yes	Yes
Executive Function	Yes	Yes

Tang-Wai DF. 7th Canadian Conference on Dementia, October 2013

Neuropsychological Testing: Detailed Assessment of Specific Cognitive Domains

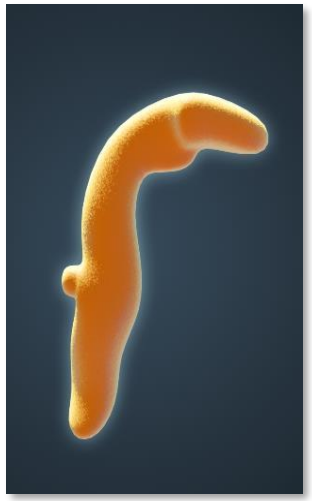
Cognitive Domain	Examples of Specific Neuropsychological Test
Orientation	
Memory – Learning/Delayed recall	Logical (story) memory, California adult verbal learning test (CVLT), Free-cued recall
Attention	Reverse digit span, letter cancellation
Language	Boston Naming Test, Token Test (comprehension)
Visuospatial	Rey-O complex figure, block design
Executive Function	Wisconsin card sorting, Stroop, Trails making Test

Tang-Wai DF. 7th Canadian Conference on Dementia, October 2013

Imaging: Available diagnostic technologies

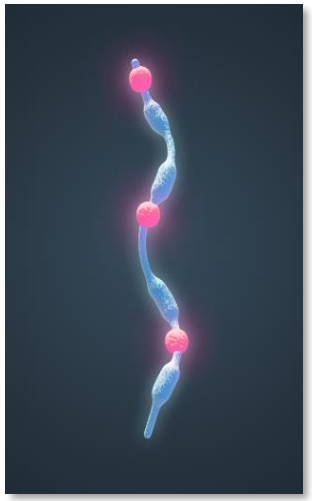
Aβ

- CSF Aβ42 and Aβ42/Aβ40
- Amyloid PET[1,2]



Tau

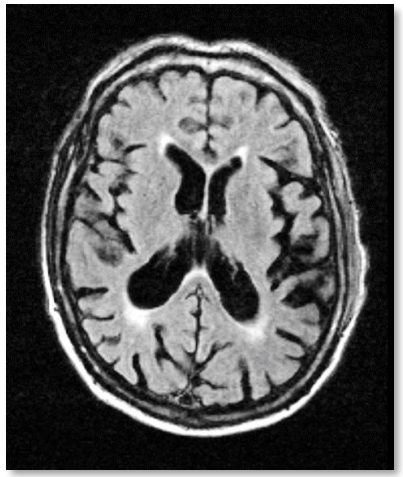
- CSF p-tau and t-tau
- Tau PET[1,2]



Non-specific imaging modalities

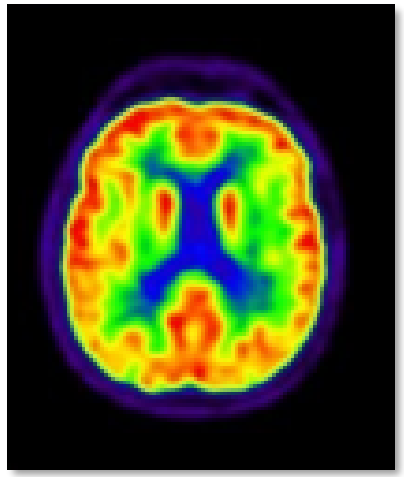
Structure

- MRI*[1,3]



Metabolism

- FDG-PET[1,4]



The NIA-AA criteria state that for diagnosis of Alzheimer's disease, markers of amyloid and tau must be present[1]

*MRI cannot be used to diagnose Alzheimer's disease, only to exclude differential diagnoses

Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; FDG-PET, fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; NIA-AA, National Institute on Aging—Alzheimer's Association guidelines; p-tau, phosphorylated-tau; t-tau; total-tau; PET, positron emission tomography

1. Jack CR, et al. Alzheimers Dement 2018;14:535–562; 2. Images from: Understanding Alzheimer's Disease. Available from: https://www.youtube.com/watch?v=jBvWadjjwXs (Accessed November 6, 2018); 3. Image provided by Scheltens P, presented at ADI 2017; 4. Image provided by Scheltens P, presented at AAIC 2017

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Structural neuroimaging in Alzheimer's disease

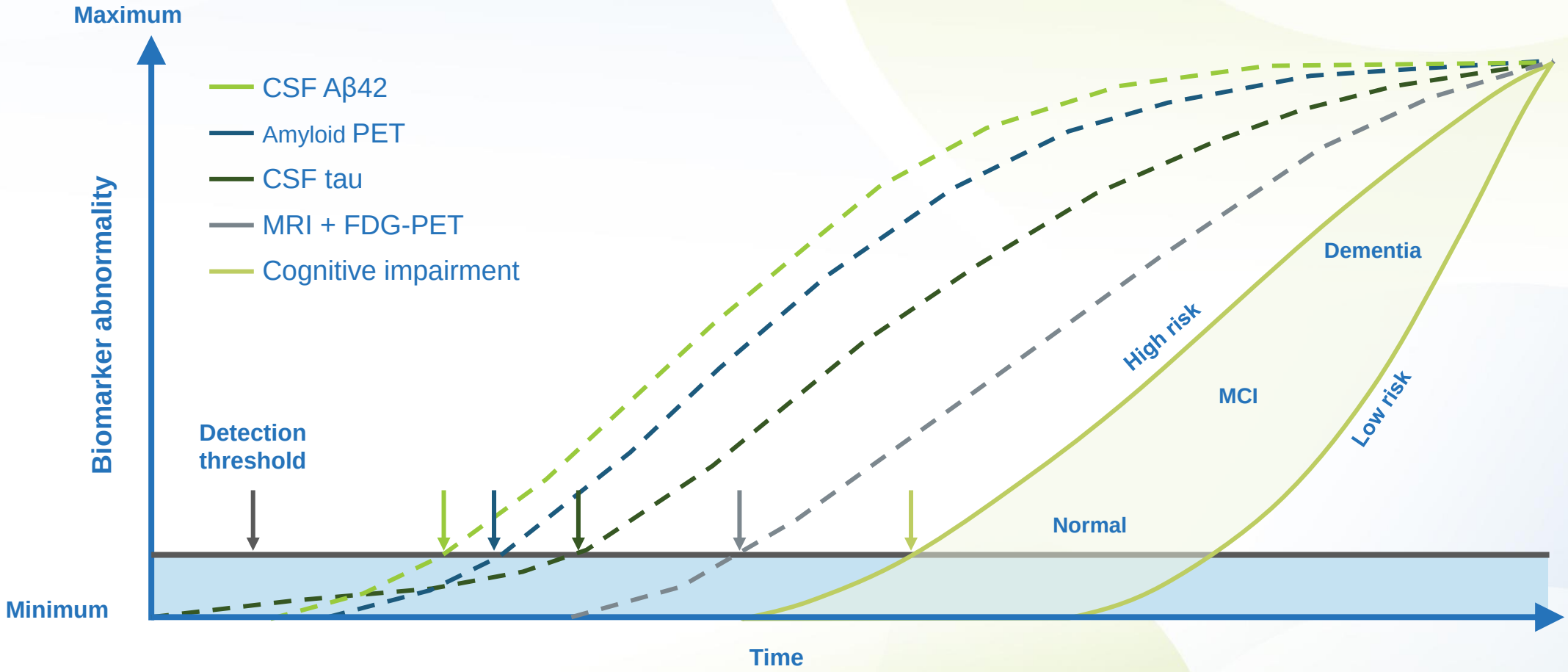
- Use in combination with clinical assessment to establish a diagnosis[1,2]
- Shifted from focusing on exclusion of other pathology to inclusion of features to support a diagnosis, e.g. hippocampal volume[1]
- MRI is the imaging modality of choice in diagnostic guidelines/recommendations,[3–6] although a high-resolution CT scan can also be used

NIA-AA neurodegenerative markers of AD: atrophy observed on structural MRI, increased CSF tau, hypometabolism on [^{18}F]-fluorodeoxyglucose-PET, or positive tau PET[7]

AD, Alzheimer's disease; CSF, cerebrospinal fluid; CT, computed tomography; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NIA-AA, National Institute on Aging—Alzheimer's Association guidelines; PET, positron emission tomography

1. Harper L, et al. J Neurol Neurosurg Psychiatry 2014;85:692–698; 2. Sheikh-Bahei N, et al. J Alzheimers Dis Rep 2017;1:71–88; 3. Sperling RA, et al. Alzheimers Dement 2011;7:280–292; 4. Hort J, et al. Eur J Neurol 2010;17:1236–248;
5. NCC for Mental Health. Dementia: The NICE-SCIE Guideline on Supporting People with Dementia and Their Carers in Health and Social Care (National Clinical Practice Guideline). British Psychological Society and RCPsych Publications; 2007;
6. CCCDTD5 Canadian Consensus, *In Press 2020;* 7. Jack Jr CR, et al. Alzheimers Dement 2018;14:535–562

Use of Biomarkers: Changes precede cognitive changes[1,2]



Aβ, amyloid-beta; AD, Alzheimer's Disease; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography

1. Selkoe D & Hardy J. EMBO Mol Med 2016; 8:595-608; 2. Jack CR et al. Lancet Neurol 12:207-16.

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Utilizing core pathophysiologic biomarkers of Alzheimer's disease

Modality	Analyte	Abnormality	Pathology
MRI[1]	Regional anatomy	↓ hippocampal volume, temporal and parietal atrophy, and global brain atrophy[2]	Neurodegeneration
CSF[1]	Aβ42	↓ concentration	Brain amyloidosis
CSF[1]	Total-tau / phosphorylated-tau	↑ concentration	Neurodegeneration / aggregated tau[3]
PET[1]	^{11}C-Pittsburgh compound B, ^{18}F ligands*	↑ cortical uptake	Brain amyloidosis
PET[1]	^{18}F-fluorodeoxyglucose (FDG)	↓ metabolism in posterior cingulate-precuneus and temporoparietal cortex	Neurodegeneration

*No tau PET tracers currently approved

Aβ, amyloid beta; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography

1. Frisoni GB, et al. Neurobiol Aging 2017;52:119–131; 2. Frisoni GB, et al. Nat Rev Neurol 2010;6:67–77; 3. Jack Jr CR, et al. Alzheimers Dement 2018;14:535–562

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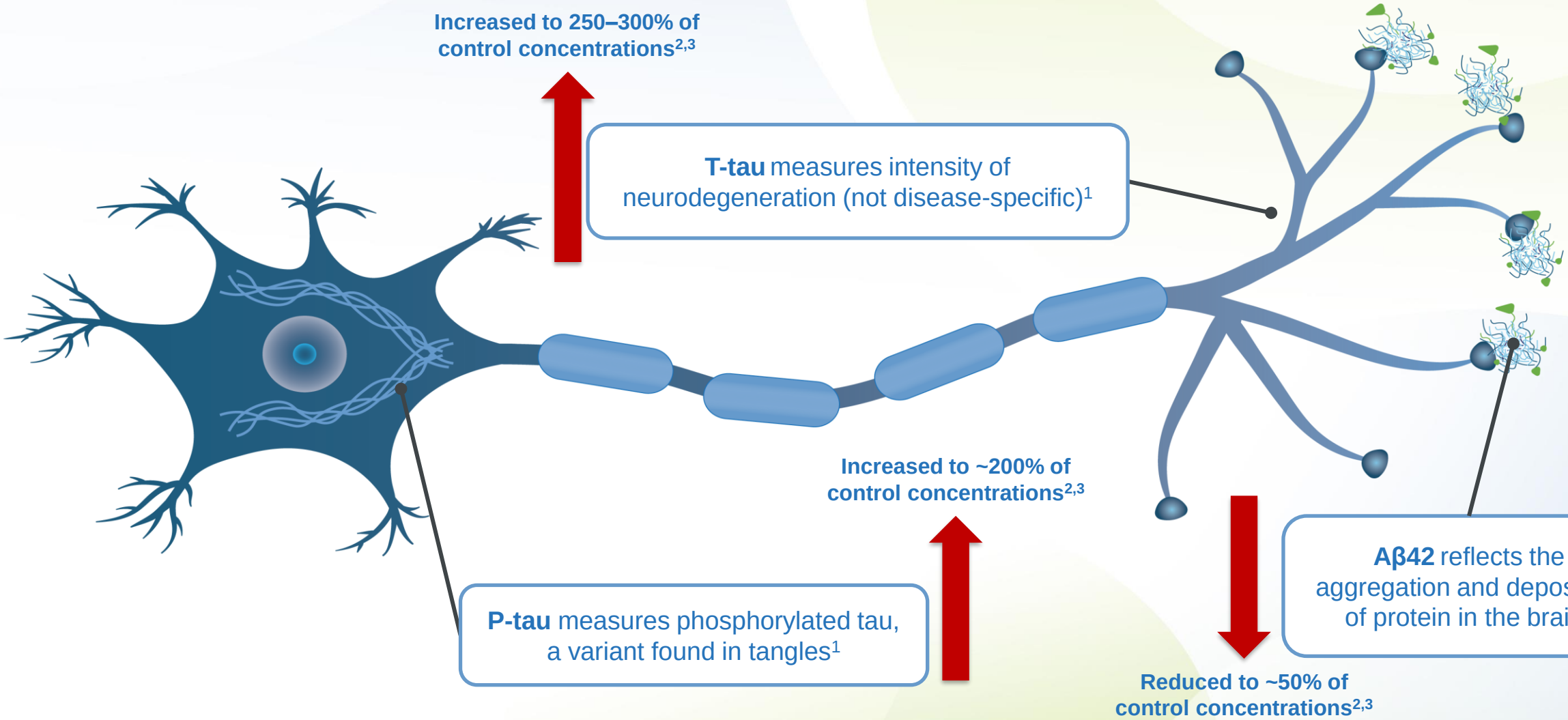
Core CSF biomarkers in Alzheimer's disease

Increased to 250–300% of control concentrations[2,3]

T-tau measures intensity of neurodegeneration (not disease-specific)[1]



Increased to ~200% of control concentrations[2,3]

P-tau measures phosphorylated tau, a variant found in tangles[1]

Aβ42 reflects the aggregation and deposition of protein in the brain[1]

Reduced to ~50% of control concentrations[2,3]

Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; p-tau, phosphorylated-tau; t-tau, total-tau

1. Blennow K, Zetterberg H. J Intern Med 2018;284:643–663; 2. Blennow K, et al. Alzheimers Dement 2015;11:58–69;
3. Olsson B, et al. Lancet Neurol 2016;15:673–684

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Ethical considerations of biomarker-based diagnosis

Diagnosing patients with AD before treatments are available has ethical considerations[1,2]

- Potential benefits of an early diagnosis e.g. financial pre-planning, need to be weighed against:
  - The certainty of the results[1]
  - The potential psychological impact to patients and family[3]
  - Legal implications e.g. disability, insurance, and criminal law[2,4]

- Use of a validated diagnostic test is important:[5]
  - Poor sensitivity might result in false reassurance and exclusion of treatments or access to clinical trials
  - Poor accuracy can result in over-diagnosis, causing unnecessary anxiety, over-treatment, and inappropriate inclusion in clinical trials

AD, Alzheimer's disease

1. Sperling R, et al. Alzheimers Dement 2011;7:280–292; 2. Arias JJ, Karlawish J. Neurology 2014;82:725–729; 3. Grill J, et al. Neurodegener Dis Manag 2013;3:43–51; 4. Preston J, et al. AMA J Ethics 2016;18:1207–1217; 5. Frisoni GB, et al. Lancet Neurol 2017;16:661–676

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Types of Alzheimer's disease

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Comparison between familial and sporadic Alzheimer's disease

	Familial	Sporadic
Age of onset[1]	Usually <60 years	Usually >60 years* *sporadic atypical cases can be early onset
Proportion of AD cases[1,2]	1-6%	99%
Cause[1,4]	Generally monogenic or atypical causes	Genetic and environmental factors
Family history[3]	Can occur with a positive family history	Can occur with a positive family history
Clinical symptoms[3]	• Gradual decline in cognitive function • Inability to retain recently acquired information, impairment in a number of cognitive domains, difficulty at work or in social situations and changes in mood, etc.	

AD, Alzheimer's disease; ApoE ε4, apolipoprotein E ε4; APP, amyloid beta precursor protein; PSEN, presenilin

1. Kazim SF, Iqbal K. Mol Neurodegener 2016;11:50; 2. Bird TD. Genetics Med 2008; 10: 231-9.
3. Bekris LM, et al. J Geriatr Psychiatry Neurol 2010;23:213–227; 4. Dubois B, et al. Lancet Neurol 2010;9:1118–1127

Alzheimer’s disease clinical spectrum

Typical AD[1]

- Early significant and progressive episodic memory deficits that remains dominant in the later stages of the disease
- Followed by, or associated with, other cognitive impairments and neuropsychiatric changes

Mixed AD[1]

- Fulfil the diagnostic criteria for typical AD
- Also present with clinical and brain imaging / biological evidence of other comorbid disorders e.g. cerebrovascular disease or Lewy body dementia

Atypical AD[1]

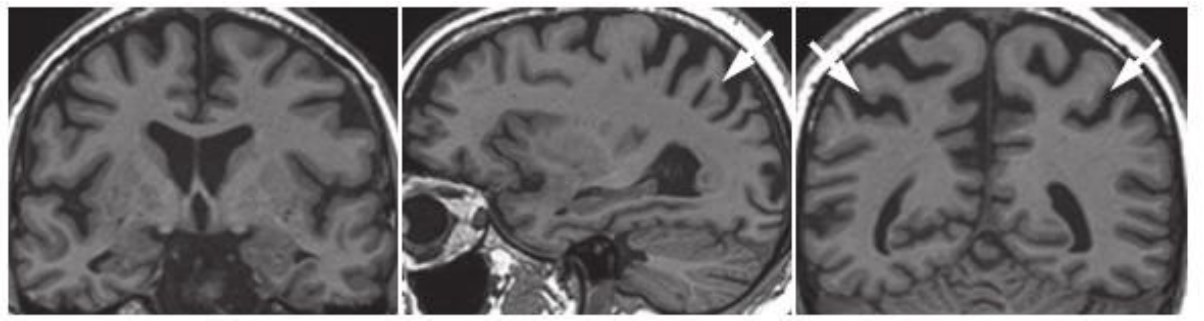
- Less common and well-characterized clinical phenotypes of the disease that occur with Alzheimer's pathology
- Examples: primary progressive non-fluent aphasia, logopenic aphasia, frontal variant of AD, and posterior cortical atrophy

AD, Alzheimer's disease; CSF, cerebrospinal fluid

Dubois B, et al. Lancet Neurol 2010;9:1118–1127

Pathologic hallmarks of atypical variants of Alzheimer's disease (1/3)

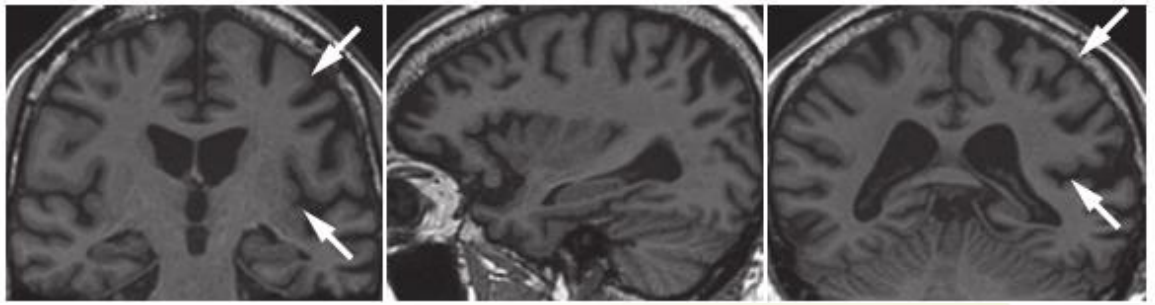
	Characteristics	Pathologic findings
Posterior cortical atrophy (PCA)	• Progressive form of AD • Characterized by prominent disorders of **higher visual processing** affecting both dorsal and ventral streams, which cause Balint's syndrome, alexia, and visual agnosia[1,2]	• **Aβ plaques** and **NFTs** most frequent[2] • Aβ plaques are variable, while NFTs are relatively increased in the occipital lobe, temporoparietal junction, and posterior cingulate[3]



Aβ, amyloid beta; AD, Alzheimer's disease; 1. McMonagle P, et al. Neurology 2006;66:331–338; 2. Tang-Wai DF, et al. Neurology 2004;63:1168–1674; 3. Warren JD, et al. Nat Rev Neurol 2012;8:451–464;

Pathologic hallmarks of atypical variants of Alzheimer's disease (2/3)

	Characteristics	Pathologic findings
Logopenic variant primary progressive aphasia	• Predominantly **language-based form of AD** • Patients report word-finding difficulties, abnormal speech patterns, or a deterioration in spelling[1,2] • Characterized by prolonged word-finding pauses (anomia) and impaired auditory verbal short-term memory	• Aβ plaque deposition is similar to typical AD, while NFTs are relatively increased in left perisylvian cortices[3] • The profile of atrophy is variable[3]



Aβ, amyloid beta; AD, Alzheimer's disease; NFT, neurofibrillary tangle

1. Mesulam MM. Ann Neurol 1987;22:533–534; 2. Mesulam MM, et al. Ann Neurol 2003;54 Suppl 5:S11–S14;
3. Woodward M, et al. Int J Geriatr Psychiatry 2010;25:732–738

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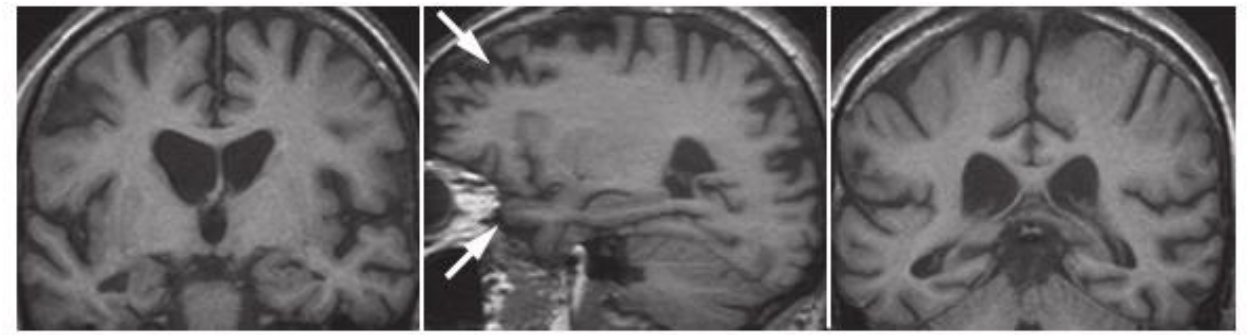
Pathologic hallmarks of atypical variants of Alzheimer's disease (3/3)

	Characteristics	Pathologic findings
Frontal variant AD	• Characterized by **impairments of behaviour and executive functions**[3] • Frequent **psychiatric symptoms** and impaired ADL vs. typical AD at a comparable disease stage[1]	• Aβ plaques are variable, whereas NFTs are increased in the frontal lobe[2]



Aβ, amyloid beta; AD, Alzheimer's disease; ADL, activities of daily living; NFT, neurofibrillary tangle;

1. Warren JD, et al. Nat Rev Neurol 2012;8:451–464; 2. Woodward M, et al. Int J Geriatr Psychiatry 2010;25:732–738

Pharmacologic and non-pharmacologic interventions in Alzheimer's disease

Overview of currently available symptomatic pharmacologic treatments for Alzheimer's disease*

Class	Generic	Indication	MoA
Acetylcholinesterase inhibitors (AChEIs)[1]	Donepezil hydrochloride	All stages of AD	Reversibly inhibits acetylcholinesterase enhancing cholinergic transmission[2]
	Rivastigmine	Mild-to-moderate AD dementia	
	Galantamine	Mild-to-moderate AD dementia	
NMDA receptor antagonist	Memantine	Moderate-to-severe AD dementia	Reversibly inhibits NMDA receptors thereby preventing glutamate excitotoxicity[3]

*Refer to the Product Monograph for specific guidance and treatment indications

AD, Alzheimer's disease; MoA, mechanism of action; NMDA, N-methyl-D-aspartate

1. Alzheimer's Association: Medications for Memory Loss. Available from: https://www.alz.org/alzheimers-dementia/treatments/medications-for-memory (Accessed November 20, 2018). 2. Birks J, Harvey RJ. Cochrane Database Syst Rev 2018;6:CD001190; Exelon Product Monograph. Available from: https://www.novartis.ca/sites/www.novartis.ca/files/exelon_scrip_e.pdf (Accessed 10 December 2018); 3. Ebixa Product Information. Available from: https://www.lundbeck.com/upload/ca/en/files/pdf/pm/Ebixa.pdf (Accessed November 20, 2018)

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Symptomatic treatment: Cholinesterase inhibitors

Block the enzyme[1] acetylcholinesterase

- No observed differences in efficacy between agents
- Adverse events including abdominal pain, anorexia, nausea, vomiting, and diarrhea[1]
- Meta-analyses show benefits in cognitive function, activities of daily living, and clinician-rated global clinical state in mild-to-moderate AD[2-4]

AChEIs showed promise in stabilizing memory impairment, however the lack of impact on underlying disease pathology has shifted the focus toward other targets (e.g. tau & Aβ)[5]

AD, Alzheimer's disease

1. Birks J. Cochrane Database Syst Rev 2006;1:CD005593; 2. Birks J, Harvey RJ. Cochrane Database Syst Rev 2018;6:CD001190; 3. Birks J, et al. Cochrane Database Syst Rev 2015;9:CD001191; 4. Loy C, Schneider L. Cochrane Database Syst Rev 2006;1:CD001747; 4. Craig L, et al. Neurosci Biobehav Rev 2011;35:1397–1409

Alzheimer's Disease Neuroimaging Initiative

WHAT

- The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a longitudinal, multicenter study designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of AD
- Currently composed of 4 studies: ADNI 1, ADNI GO, ADNI 2, ADNI 3

GOALS

- To detect AD at the earliest possible stage and identify ways to track progression with biomarkers
- To support advances in AD intervention, prevention, and treatment through new diagnostic methods as early as possible
- To continually administer ADNI's innovative data-access policy

AD, Alzheimer's disease; MCI, mild cognitive impairment; PET, positron emission tomography

Alzheimer's Disease Neuroimaging Initiative. Available from: http://adni.loni.usc.edu/about/ (Accessed November 20, 2018)

The FINGER study: Multidomain intervention to prevent cognitive decline in at-risk elderly people

Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)[1]

- **A 2-year, randomized controlled trial to assess a multidomain approach to prevent cognitive decline in at-risk elderly people from the general population (N=1260)**

Intervention: Healthy diet, increased physical activity, cognitive training, and vascular risk management

There are multiple FINGER-like studies being initiated around the world (eg US POINTER, CAN-THUMBS UP)[2, 3]

CAN-THUMBS UP: Canadian Aging and Neurodegeneration Prevention Therapy Study Using Multidimensional Interventions for Brain Support – Unified Platform

1. Ngandu T, et al. Lancet 2015;385:2255–2263; 2. Alzheimer's Association. Available from: https://alz.org/us-pointer/overview.asp (Accessed January 31, 2019);

3. https://ccna-ccnv.ca/news/canadas-largest-dementia-research-network-the-canadian-consortium-on-neurodegeneration-in-aging-enters-its-second-phase/. Accessed June 2020

Key Takeaways (1 of 2)

Risk factors for AD include non-modifiable genetic factors and modifiable risk factors

Amyloid β plaques, NFTs (aggregates of phosphorylated-tau protein), glial responses, synaptic and neuronal loss are the pathological hallmarks of AD

The patient journey to diagnosis includes clinical assessment including neurologic and cognitive assessments, imaging, and when available, biomarkers

AD, Alzheimer's disease; MCI, mild cognitive impairment; NFT, neurofibrillary tangles

Key Takeaways (2 of 2)

There is currently no disease-modifying drug available, current treatment is symptomatic only

There is ongoing research on neuroimaging and development of biomarkers, new therapeutic interventions and multidomain strategies for prevention

AD, Alzheimer's disease; MCI, mild cognitive impairment; NFT, neurofibrillary tangles

Back-up slides

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An introduction to the pathogenesis of Alzheimer's disease

Proposed background video to be embedded in the PowerPoint as a brief introduction to the pathogenesis of AD:
https://www.youtube.com/watch?v=jBvWadjjwXs

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AD, Alzheimer's disease

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