Evaluation and Treatment of Mild Cognitive Impairment and Dementia:

For the Primary Care Physician

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Dementia (Major Neurocognitive Disorder)

Fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)

DSM-5 Criteria for Dementia

- Evidence from history and clinical assessment that indicates a significant cognitive impairment in at least 1 of the following cognitive domains:
  - Executive functioning
  - Learning and memory
  - Language
  - Complex attention
  - Perceptual-motor function
  - Social cognition
- The impairment must be acquired and represent a significant decline from a previous level of functioning
- The cognitive deficits must interfere with independence in everyday activities
- The disturbances are not occurring exclusively during the course of delirium
- The cognitive deficits are not better explained by another mental disorder

Emmady PD, Schoo C, Tadi P. Major Neurocognitive Disorder (Dementia) [Updated 2022 Nov 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557444/

MCI (Mild Neurocognitive Disorder)

Fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)

DSM-5 Criteria for MCI

- Evidence from history and clinical assessment that indicates a mild cognitive impairment in at least 1 of the following cognitive domains:
  - Executive functioning
  - Learning and memory
  - Language
  - Complex attention
  - Perceptual-motor function
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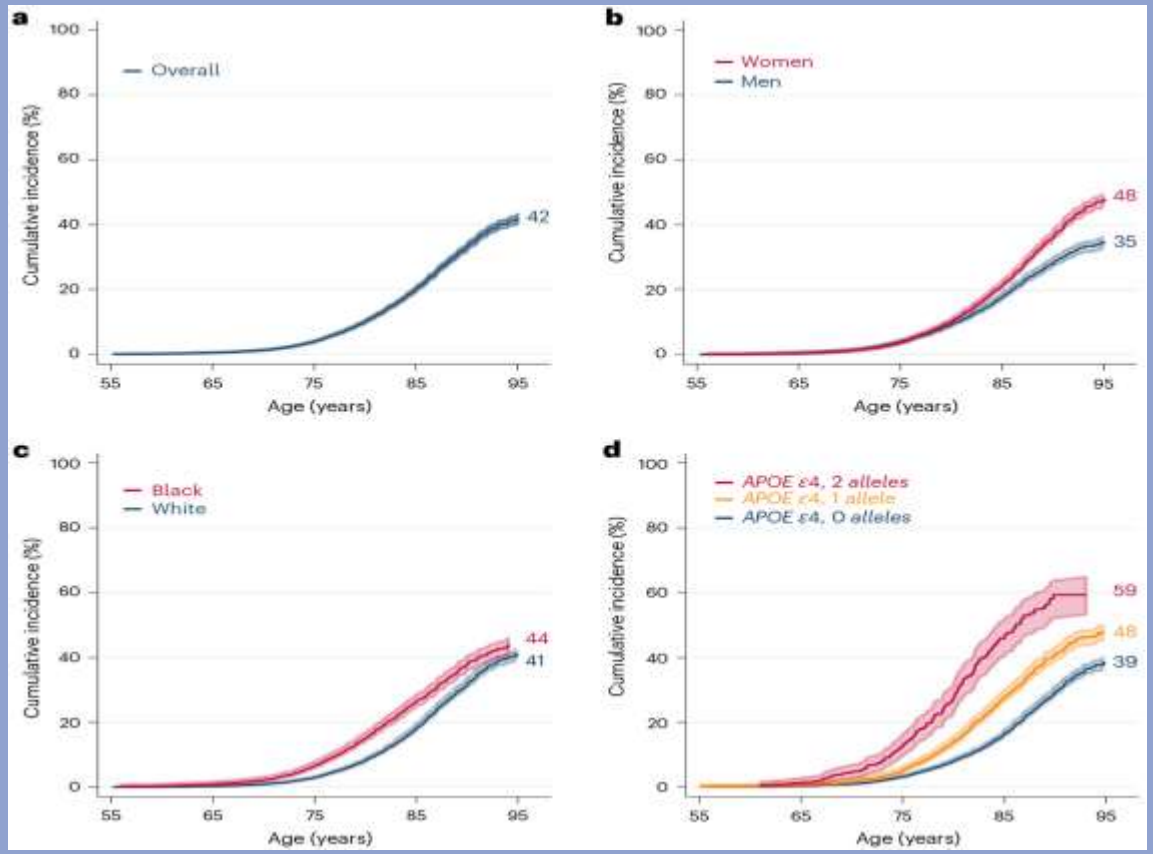
- The impairment must be acquired and represent a decline from a previous level of functioning
- The cognitive deficits do not interfere with independence in everyday activities
- The disturbances are not occurring exclusively during the course of delirium
- The cognitive deficits are not better explained by another mental disorder

Emmady PD, Schoo C, Tadi P. Major Neurocognitive Disorder (Dementia) [Updated 2022 Nov 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557444/



Fang M, Hu J, Weiss J, Knopman DS, Albert M, Windham BG, Walker KA, Sharrett AR, Gottesman RF, Lutsey PL, Mosley T, Selvin E, Coresh J. Lifetime risk and projected burden of dementia. Nat Med. 2025 Mar;31(3):772-776. doi: 10.1038/s41591-024-03340-9. Epub 2025 Jan 13. PMID: 39806070; PMCID: PMC12305800.

Prevalence based on age

Overall **dementia** prevalence based on age

70-79:	5%
80-89:	24%
>90:	37%

Alzheimer's prevalence based on age

70-79:	2%
80-89:	18%
>90:	30%

Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, Burke JR, Hurd MD, Potter GG, Rodgers WL, Steffens DC, Willis RJ, Wallace RB. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. 2007;29(1-2):125-32. doi: 10.1159/000109998. Epub 2007 Oct 29. PMID: 17975326; PMCID: PMC2705925.

JAMA Network™

From: **Estimating the Prevalence of Dementia and Mild Cognitive Impairment in the US: The 2016 Health and Retirement Study Harmonized Cognitive Assessment Protocol Project**

JAMA Neurol. 2022;79(12):1242-1249. doi:10.1001/jamaneurol.2022.3543

Table 2. Group Differences in Prevalence of Dementia and Mild Cognitive Impairment (MCI) Among Harmonized Cognitive Assessment Protocol (HCAP) Participants

		Dementia			MCI		
Variable	Total	Observed No.	%[a] (95% CI)	OR[b] (95% CI)	Observed No.	%[a] (95% CI)	OR[b] (95% CI)
Overall	3496	393	10 (9-11)	NA	804	22 (20-24)	NA
Age group, y							
65-69	821	25	3 (1-4)	1 [Reference]	186	22 (18-25)	1 [Reference]
70-74	667	31	4 (2-6)	1.4 (0.8-2.7)	138	20 (17-24)	0.9 (0.7-1.3)
75-79	844	76	9 (6-11)	3.3 (1.8-5.8)	194	21 (18-24)	1.0 (0.7-1.3)
80-84	611	105	18 (14-22)	7.6 (4.3-13.3)	156	25 (21-29)	1.2 (0.9-1.7)
85-89	345	84	26 (20-31)	11.9 (6.7-21.2)	78	22 (17-27)	1.0 (0.7-1.5)
≥90	208	72	35 (28-43)	18.8 (10.3-34.4)	52	27 (20-35)	1.4 (0.9-2.1)
Sex[c]							
Female	2095	243	10 (9-11)	1.1 (0.8-1.4)	474	22 (19-24)	0.9 (0.8-1.2)
Male	1401	150	10 (8-11)	1 [Reference]	330	22 (20-25)	1 [Reference]
Race and ethnicity[c,d]							
Black	551	63	15 (10-19)	1.8 (1.2-2.7)	126	22 (17-27)	1.0 (0.8-1.4)
Hispanic	382	43	10 (7-13)	1.1 (0.7-1.7)	112	28 (22-34)	1.4 (1.0-2.0)
White	2484	264	11 (10-13)	1 [Reference]	566	23 (21-25)	1 [Reference]
Other[e]	79	12	26 (13-39)	3.3 (1.4-7.6)	26	45 (30-59)	2.7 (1.5-5.1)
Educational attainment[c]							
<High school	715	111	13 (10-16)	1.6 (1.1-2.3)	214	30 (25-34)	1.6 (1.2-2.2)
High school	1166	128	9 (7-11)	1.0 (0.7-1.4)	234	19 (16-21)	0.9 (0.7-1.2)
Some college	764	65	9 (6-11)	0.9 (0.6-1.4)	170	23 (19-26)	1.1 (0.8-1.5)
≥College degree	851	89	9 (7-11)	1 [Reference]	186	21 (17-24)	1 [Reference]

Abbreviations: NA, not applicable; OR, odds ratio.

[a] Indicates prevalence of dementia or MCI in variable category, estimated with sampling weights.

[b] ORs estimated with sampling weights.

[c] Marginal prevalence estimates for sex, race and ethnicity, and educational attainment reflect adjustment for age.

[d] Race and ethnicity data were gathered via self-report at the time of first interview and are considered to be markers of exposure to evolving systems of racism, not as a proxy for genetic variation or any other biological variable. Race was self-selected by participants at the time of the first interview from a list of options defined by the 2000 US Census criteria.

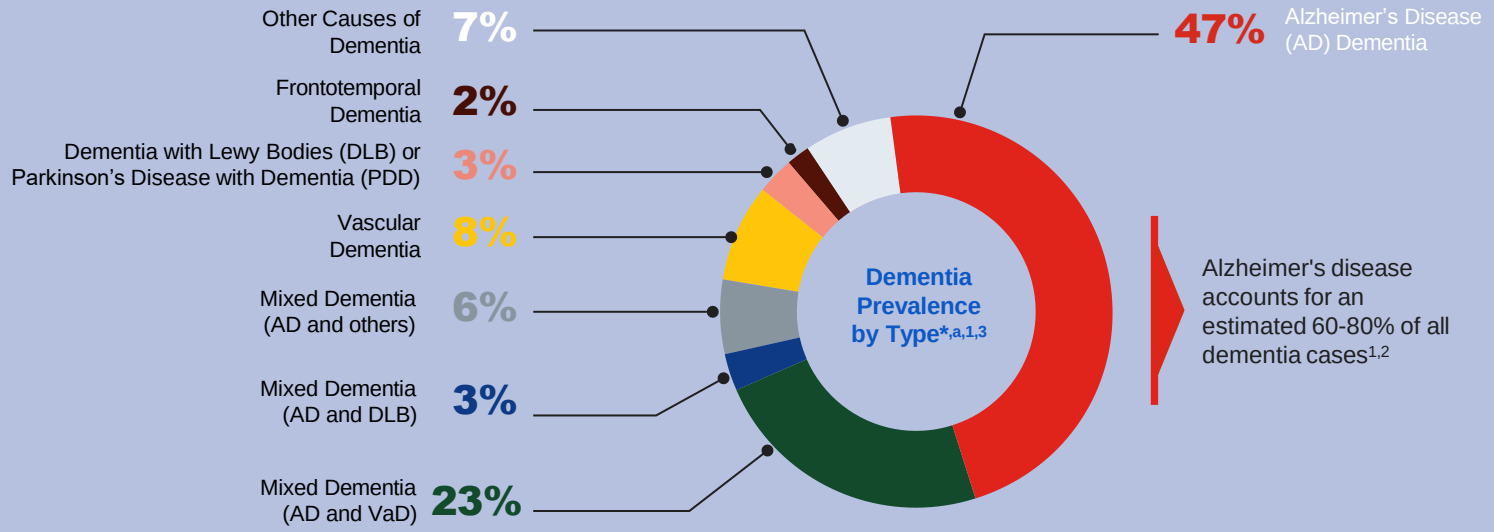
[e] Other includes a pooled group of participants who identified as American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, or another self-described race, consolidated due to small sample sizes and risk of identification.

Dementia types

Alzheimer's Dementia	**50-70%**
Vascular Dementia	**10-15%**
Mixed Dementia	**10-15%**
Lewy Body Dementia	**5%**
Frontotemporal Dementia1-	**2%**
Parkinson's Dementia	**1-2%**
Others:	1%

Normal Pressure Hydrocephalus, Primary Progressive Aphasia, Posterior Cortical Atrophy, Cerebral Amyloid Angiopathy, Chronic Traumatic Encephalopathy, Huntington's, Alcohol-Induced (WKS), Corticobasal Degeneration, Progressive Supranuclear Palsy, Multi-Systems Atrophy, Creutzfeldt-Jakob Disease (CJD)

Alzheimer's Disease is the Most Common Form of Clinical Dementia



- An estimated 6.9 million Americans over age 65 are living with Alzheimer's dementia in 2024[3]
- This number could grow to 13.8 million by 2060[3]
- In 2021, Alzheimer's was the fifth-leading cause of death in the US[3]

*Percentages do not total 100 due to rounding; [a]Patients were ≥70 years old.

AD=Alzheimer's Disease; DLB=Dementia with Lewy Bodies; VaD=Vascular Dementia.

1. Hsiung GY. *In: Atlas of Alzheimer's Disease, Feldman HH (ed).* 2007;27-40. 2. Erkkinen MG, et al. *Cold Spring Harb Perspect Biol*. 2018;10(4):a033118. 3. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2024;20(5):1-149.

Economic Burden of Dementia

- $700,000 for 70 yo person with AD, 3 x more the someone without AD
  - Medicare/Medicaid
  - Personal expenses
  - Lost earnings/unpaid care
- 2019 US annual cost estimate was $500 billion
- $1.5 trillion by 2050
- Long term care ranges from 50k to 100K a year

National Academies of Sciences, Engineering, and Medicine; Division of Behavioral and Social Sciences and Education; Board on Behavioral, Cognitive, and Sensory Sciences; Committee on the Decadal Survey of Behavioral and Social Science Research on Alzheimer's Disease and Alzheimer's Disease-Related Dementias.
Washington (DC): National Academies Press (US); 2021 Jul 26.

Caregiver Burden

- 63% are women
- 48 % family members
- 58 % are 35-64 years old
- 52 % fully employed
- 31 hours per week on average spent care giving
- 2-4 x more likely to have or develop significant medical illness
- 2-4 times more likely to develop anxiety and or depression

2024 Alzheimer's Disease Facts and Figures Report: Executive Summary.*Alzhiemer's and Dementia*,Volume 20, May 2024.Wiley Press

Alzheimer's

Clinical Features:

Typical onset >65

Autosomal dominant, APP, PSEN1, PSEN2, AD associated with Down's

Cardinal symptoms: memory impairment, executive functioning and problem solving, visuospatial impairment, word-finding

Other signs/symptoms: apraxia, olfactory dysfunction, sleep disturbances, seizures.

Atypical presentations:

- **Posterior Cortical Atrophy: >90% due to AD),**
- **Primary Progressive Aphasia, Logopenic type: ~33% due to AD**

Clinical Course:

Preclinical (asymptomatic with AD pathology) -> Mild Cognitive Impairment -> Dementia (mild, moderate, severe)

Life expectancy: 3-20yrs, average 8-10yrs.

D. Luke Fischer MD PhD. Alzheimer disease. In: Lewis SL, Editor-in-Chief. MedLink Neurology. San Diego: MedLink, LLC. Available at www.medlink.com. Updated: January 8, 2025.

Vascular Cognitive Impairment (VCI) / Vascular Dementia

- Definition
  - Mixed dementia, most common cause of dementia by autopsy
  - Comorbid with AD, DLB , PD and FTD
  - Pure Vascular Dementia 8%
- Core features
  - Executive dysfunction
  - Working memory
  - Gait
  - Pseudobulbar palsy / dysarthria
  - Focal neurological deficits
- Pathology
  - Subcortical vascular disease / WMD
  - Cortical strokes
  - Lacunar strokes
  - CAA
  - Microhemorrages
  - Embolic
  - Enlarged perivascular spaces, ischemic injury, inflammatory response

Linda A Hershey MD PhD FAAN FANA. Vascular cognitive impairment. In: Lewis SL, Editor-in-Chief. MedLink Neurology. San Diego: MedLink, LLC. Available at www.medlink.com. Updated: October 22, 2025.

Dementia with Lewy Bodies

- Second most common dementia
- 1 year rule : dementia← →parkinsonism
- Core features
  - Parkinsonism
  - Executive and visual spatial dysfunction
  - Waxing and waning
  - Visual hallucinations
  - REM sleep behavior disorder
- Pathology
  - Synucleinopathy
  - Amyloid and Tau
- Diagnostics
  - Synuclein skin biopsy
  - Da T scan
  - EEG

Linda A Hershey MD PhD FAAN FANA, David G Lichter MB ChB FRACP. Dementia with Lewy bodies. In: Lewis SL, Editor-in-Chief. MedLink Neurology. San Diego: MedLink, LLC. Available at www.medlink.com. Updated: April 4, 2025.

Frontotemporal Dementia

- Typically younger, 3rd most common cause of dementia
- Broad category : Behavioral, PPA Semantic, PPA Non-Fluent
- Clinical Features
  - Behavioral: impulsivity, inappropriate
  - Apathy, inert
  - Early loss of sympathy / empathy
  - Stereotypic behaviors
  - Hyperorality
  - Executive dysfunction (spares memory and visual spatial)
- Pathology: Tau, Ubiquitin, TDP-3
- Diagnosis: Clinical, MRI, FDG PET, LP
- 10% autosomal dominant
- Natural progression widely variable

Irina Anna Skylar-Scott MD, Olivia Lu. Frontotemporal dementia. In: Lewis SL, Editor-in-Chief. MedLink Neurology. San Diego: MedLink, LLC. Available at www.medlink.com. Updated: May 23, 2025.

Timely Diagnosis Can Lead to Improved Patient Outcomes

Medical Care

- Timely diagnosis can allow patients to be actively involved in decision-making and may result in higher quality of care[1,2]
- Early therapeutic intervention may slow disease progression[1,2]
- Helps patients maintain cognitive ability and higher levels of function longer[3]

Quality of Life

- Timely diagnosis could allow patients to create advanced directives[1,4]
- Diagnosis of dementia may reduce safety risks for patients and families;[1,5,6] like prevention of motor vehicle accidents or getting lost

Support Services

- Timely diagnosis allows care coordination and early access to support services[7]
- Connecting caregivers with resources resulted in reduced rate of nursing home placement of the patient[6,8]
- Allows for informed decisions and advanced planning, including financial considerations[7]

1. Dubois B, et al. *J Alzheimers Dis*. 2016;49(3):617-631. 2. Rasmussen J, Langerman H. *Degener Neurol Neuromuscul Dis*. 2019;9:123-130. 3. Small GW. *Am J Geriatr Psychiatry*. 2016;24(12):1142-1150. 4. Nasreddine Z, et al. *Neurol Ther*. 2023;12:11-23. 5. Rafii MS, Aisen PS. *Nat Aging*. 2023;3(5):520-531. 6. Livingston G, et al. *Lancet*. 2024;404(10452):572-628. 7. 2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024;20(5):1-149. 8. McCollum L, Karlawish J. *Med Clin North Am*. 2020;104(5):807-825.

Timely Diagnosis of Alzheimer's Disease: An Unmet Need

DIAGNOSED TOO LATE	Diagnosis has been shown to be delayed on average by 2 to 3 years after symptom onset[1,2]
MISDIAGNOSED	Cumulative evidence from both autopsy studies and clinical trials have previously found that 15% to 30% of symptomatic individuals meeting the clinical AD criteria did not have AD-related brain pathology[3]
UNDERDIAGNOSED	• It has been shown that an estimated 75% of dementia cases may be undiagnosed[4] • One study estimated that 8% of older Americans living with MCI receive diagnosis[3]
IMPACT ON TREATMENT	A large, multisite, practice-based study found that physicians changed their treatment for 63.5% of dementia patients[a] based on amyloid PET data[5]

[a]These were primary care patients older than 65 years.
AD=Alzheimer's Disease; MCI=Mild Cognitive Impairment; PET=Positron Emission Tomography.
1. Balasa M, et al. *Neurology.* 2011;76(20):1720-1725. 2. Boise L, et al. *Am J Alz Dis Other Demen*. 1999;14(1):20-26. 3. https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.13809 (Accessed December 5, 2024). 4. Dumas A, et al. *Aging Brain*. 2023;4:100093. 5. Rabinovici GD, et al. *JAMA.* 2019;321(13):1286-1294.

Initial work-up of cognitive impairment

History is the most important part of the evaluation

- **Obtain history from a reliable caregiver**
  - **Establish a timeline of decline**
  - **Assess for daily activity/routine**
  - **Evaluate for a decline from previous level of functioning**
- **Look for symptoms separate from cognitive impairment**
  - **Parkinsonisms: bradykinesia, rigidity, postural instability, tremor**
  - **Hallucinations**
  - **Urinary Incontinence**
  - **Gait instability**
  - **Autonomic Failure**
  - **Gaze Palsy**
  - **Sleep / RBSD**

D. Luke Fischer MD PhD. Alzheimer disease. In: Lewis SL, Editor-in-Chief. MedLink Neurology. San Diego: MedLink, LLC. Available at www.medlink.com. Updated: January 8, 2025.

Objective evaluations in patients with cognitive impairment

Brief cognitive evaluations:
MMSE or MOCA

Laboratory evaluations
B12/MMA, CBC, CMP, TSH / FT4 CMP, RPR, HIV, BBM amyloid/Tau*

Neuroimaging:
MRI preferred over CT
Cerebral atrophy, ventriculomegaly, strokes, ischemic, cerebrovascular disease, microhemorrhages, occult lesions / tumors

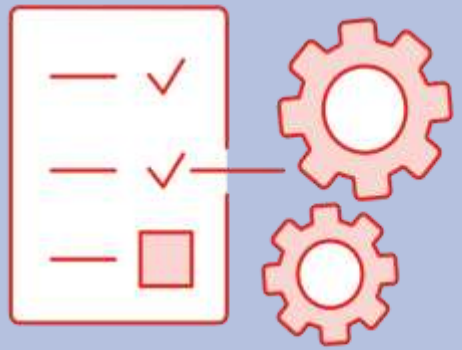
Advanced Neuroimaging:
PET, FDG PET, DaT

Lumbar Puncture:
AD biomarker, Infection, High-volume

Neuropsychologic testing

D. Luke Fischer MD PhD. Alzheimer disease. In: Lewis SL, Editor-in-Chief. MedLink Neurology. San Diego: MedLink, LLC. Available at www.medlink.com. Updated: January 8, 2025.

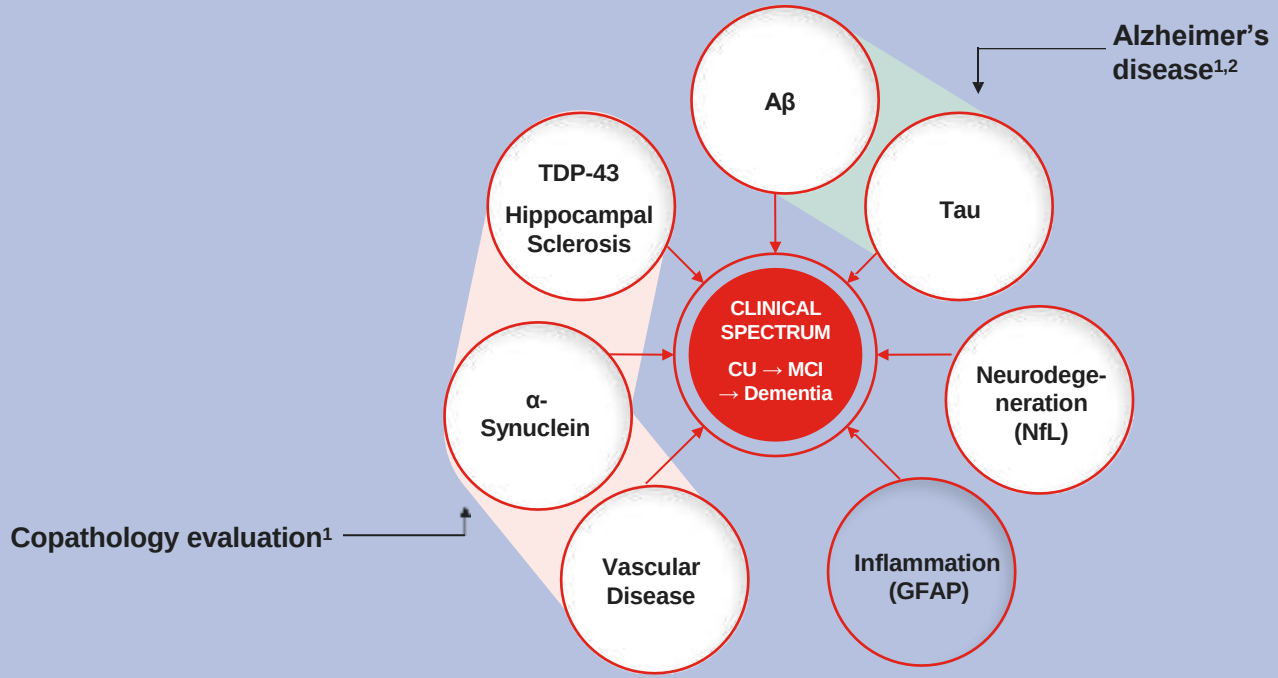
Fundamental Principles From NIA-AA Workgroups



- It is necessary to separate clinical syndrome from biology/etiology
- AD is defined by neuropathology, therefore detection of AD neuropathologic change by biomarkers is equivalent to diagnosing the disease
- AD exists on a continuum
- Symptoms are a result of the disease process and are not necessary to diagnose AD
- Unimpaired individuals with abnormal biomarker tests are at risk for symptoms due to AD
- They are not at risk for a disease they already have
- Clinical syndromes commonly seen with AD may also be caused by disorders other than AD, and therefore clinical presentation alone is not diagnostic of AD
- The same AD biology may result in different phenotypic presentations

AD=Alzheimer's Disease; NIA-AA=US National Institute of Aging – Alzheimer's Association.
Jack CR Jr, et al. *Alzheimers Dement*. 2024;20(8):5143-5169.

Biomarkers Can Assist With Differential Diagnosis[1,2]

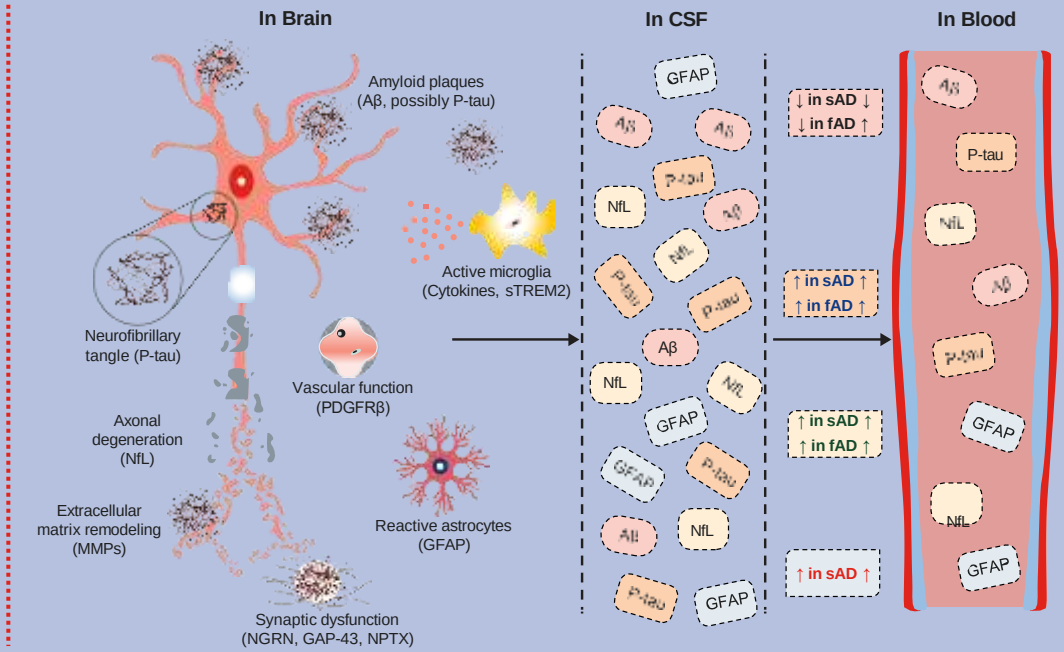


Note: Biomarkers can assist with differential diagnosis when used as an adjunct to other diagnostic evaluations.
Aβ=Amyloid Beta; AD=Alzheimer's disease; CU=Cognitively Unimpaired; GFAP=Glial Fibrillary Acidic Protein; NfL=Neurofilament Light; MCI=Mild Cognitive Impairment; TDP=TAR DNA-Binding Protein.
1. Petersen RC. *Neurology*. 2018;91(9):395-402. 2. Jack CR Jr, et.al. *Alzheimers Dement.* 2024;20(8):5143-5169.

Plasma Biomarkers: Aβ, P-tau, NfL, and GFAP

Detecting brain pathologies in blood can be challenging

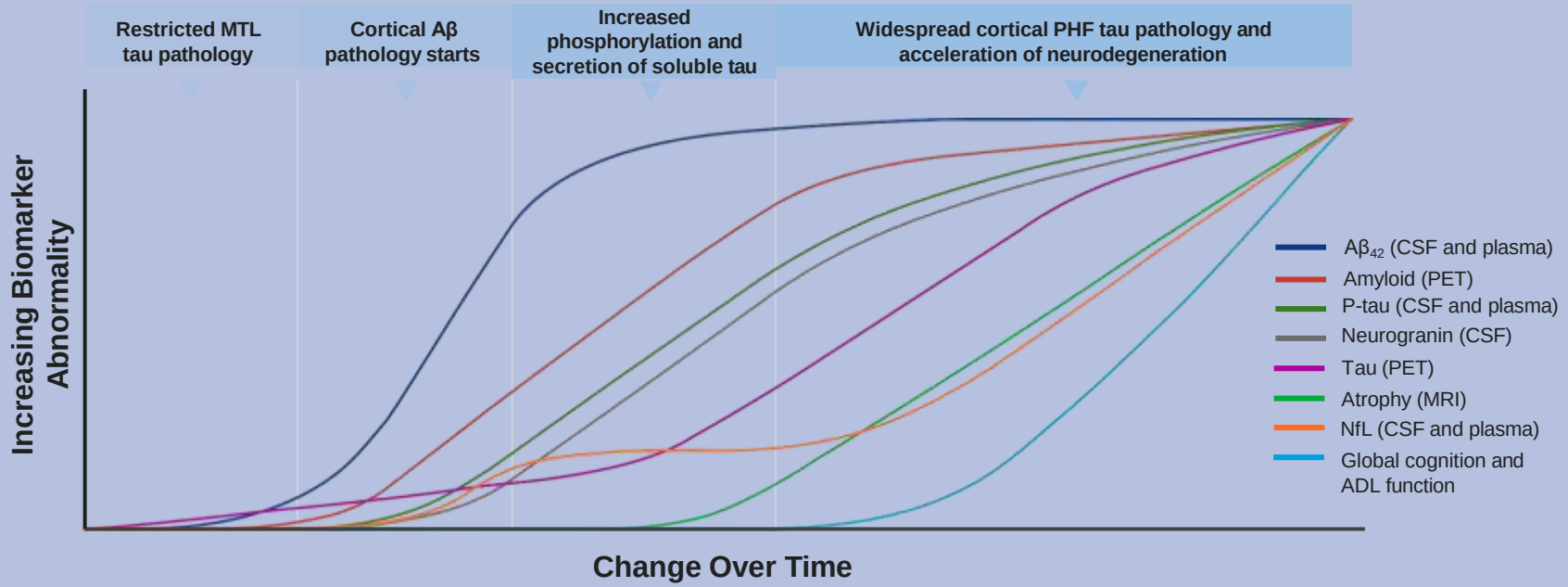
- Plasma Aβ levels are about 20-40 times lower than those in CSF[1,2]
  - Short T1/2, cleared by liver and kidneys[3,4]
- Tau levels in plasma are extremely low[5]
- NfL is made in central and peripheral neurons[6]
- GFAP is expressed in astrocytes and elevated in the plasma of AD patients[7]



Teunissen CE, et al. *The Lancet Neurology*. 2022;21(1):66-77.[8]

Aβ=Amyloid Beta; AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; fAD=Familial AD; GAP=Growth-Associated Protein; GFAP=Glial Fibrillary Acidic Protein; MMP=Matrix Metalloproteinase; NfL=Neurofilament Light Chain; NGRN=Neurogranin; NPTX=Neuronal Pentraxin; PDGFRβ=Platelet Derived Growth Factor Receptor β; pTau=Phosphorylated Tau; sTREM2=Soluble Triggering Receptor Expressed on Myeloid cells 2; sAD=Sporadic AD; T1/2=Half-life.

AD Pathologic Cascade: Biomarker Trajectories



Aβ=Amyloid Beta; AD=Alzheimer's Disease; ADL=Activities of Daily Living; CSF=Cerebrospinal Fluid; MRI=Magnetic Resonance Imaging; MTL=Medial Temporal Lobe; NfL=Neurofilament Light; P-tau=Phosphorylated Tau; PHF=Paired Helical Filament; PET=Positron Emission Tomography.

Hansson O. *Nat Med.* 2021;27:954-963.

AA Workgroup[a]: Advanced Diagnostic Tools

Core Biomarkers

- PET Amyloid/tau imaging
- CSF Aβ/tau concentrations
- Plasma Aβ/tau concentrations

Biomarkers of Non-specific Processes Involved In AD Pathophysiology

- NfL; GFAP
- MRI hippocampal volume or medial temporal atrophy by volumetric measures or visual rating
- FDG-PET imaging

Biomarkers of Non-AD Copathology

- αSyn-SAA
- MRI/CT
- White matter hyperintensity

[a]The AA identified a four-person core leadership group for this effort (i.e., a steering committee) as well as a larger full workgroup.
*α*Syn-SAA=Alpha-Synuclein Seed Amplification Assay; Aβ=Amyloid Beta; AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; CT=Computed Tomography; FDG-PET=Fluorodeoxyglucose PET; GFAP=Glial Fibrillary Acidic Protein; MRI=Magnetic Resonance Imaging; NfL=Neurofilament Light Chain; PET=Positron Emission Tomography.
Jack CR Jr, et al. *Alzheimers Dement*. 2024.

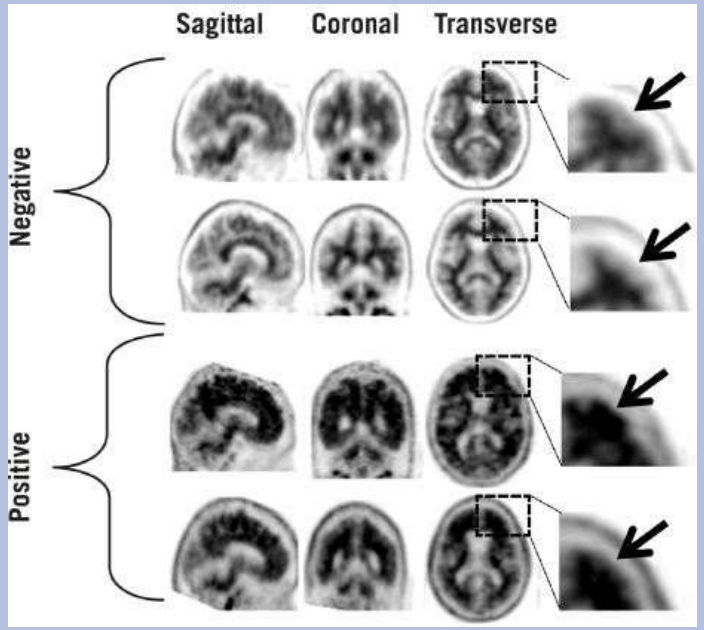
Amyloid PET Imaging Indicates Presence or Absence of Pathological Insoluble Plaques

Negative scan[1-3]

- Indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition
- Reduces the likelihood that a patient's cognitive impairment is due to AD

Positive scan[1-3]

- Indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown that this amount of plaque is present in patients with AD
- May also be present in patients with other types of neurologic conditions, as well as older people with normal cognition



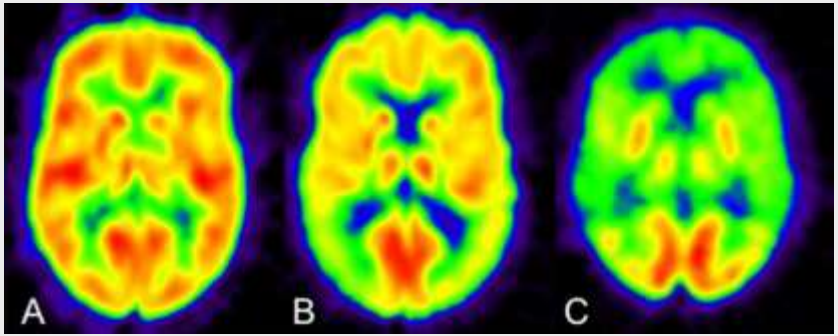
AD=Alzheimer's Disease; PET=Positron Emission Tomography.

1. Florbetapir F 18 injection [USPI]. Indianapolis, IN, USA: Eli Lilly USA LLC, 2019. 2. Florbetaben F 18 injection [USPI]. Warwick, UK: Life Molecular Imaging Ltd, 2021. 3. Flutemetamol F 18 injection [USPI]. Arlington Heights, IL, USA: GE Healthcare, 2020.

FDG-PET: Neurodegeneration

- FDG-PET, as a measure of cerebral glucose metabolism, is a marker of neurodegeneration[1]
- It is useful in AD to detect characteristic regional hypometabolism[1]
- Decreased FDG-PET uptake indicates hypometabolism and impairment of synaptic function in AD[2]
- Hypometabolism is correlated with cognitive impairment along the continuum from preclinical to dementia stages of AD[3]

FDG-PET[1]



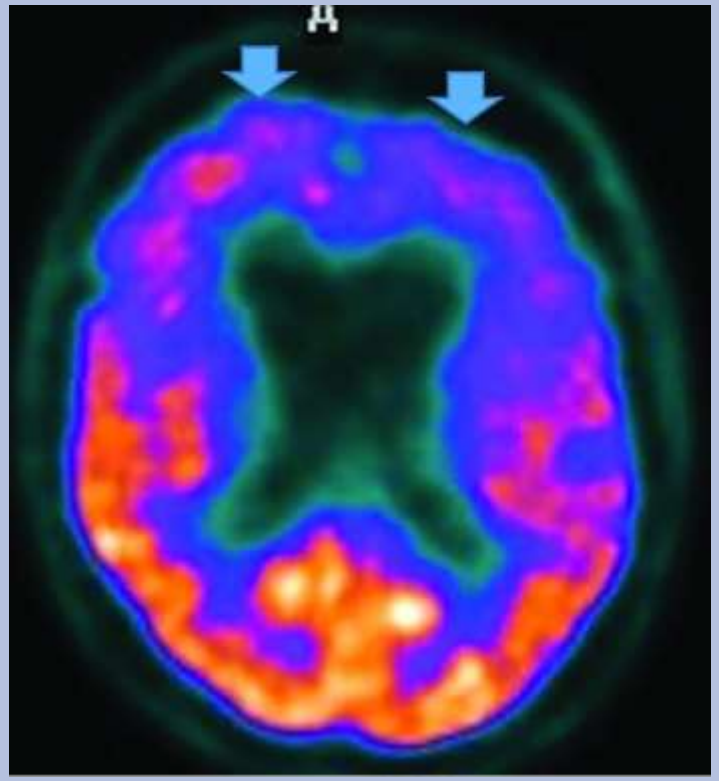
Cognitively normal subject	Patient with suspected early AD	Patient with advanced AD

AD=Alzheimer's Disease; FDG=[18F]-Fluorodeoxyglucose; PET=Positron Emission Tomography.

1. Rice L, Bisdas S. *Eur J Radiol*. 2017;94:16-24. 2. Fessel J. *Alzheimers Dement (N Y)*. 2021;7(1):e12177. 3. Minoshima S, et al. *Ann Neurol*. 1997;42(1):85-94.

FDG PET

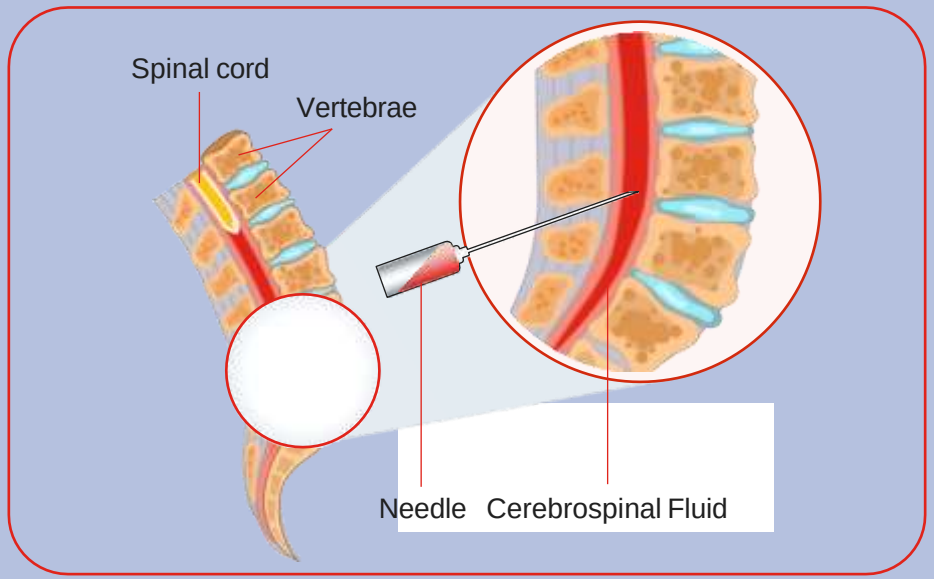
FTD



J.D. Oldan et al. AJNR Am J Neuroradiol 2021;42:998-1007

CSF via Lumbar Puncture

- A lumbar puncture to obtain CSF may be performed **to evaluate AD pathology by measuring the level of markers: $A\beta_{42}$, $A\beta_{42/40}$ ratio, P-tau, and T-tau[1,2]**



Aβ=Amyloid Beta; AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; P-tau=Phosphorylated Tau; T-tau=Total Tau.

1. Shaw LM, et al. *Alzheimers Dement*. 2018;14(11):1505-1521. 2. Hampel H, et al. *Alzheimers Dement.* 2022;18(1):159-177.

CSF Biomarkers: Aβ and Tau (1 of 2)

Measured by quantitative and specific assays[1]

- CSF Aβ results from cleavage of APP to peptides ending at amino acids 37 to 43[2]
- CSF tau consists of proteolytically cleaved fragments, not full-length tau[3]

FDA-Approved Commercially Available Assays

Brand Name (Company)	Pathology Detected: Amyloid/Mixed Pathology	Test Accuracy Data/ Clinical Performance Data (vs. Amyloid PET)	Pathology Detected: Tau/Mixed Pathology	Test Accuracy Data/ Clinical Performance Data
Elecsys® (Roche Diagnostics)[4]	-	-	P-tau181/$A\beta_{42}$ ratio[4]	Sens=91%; Spec=89%[a]
				Sens=88%; Spec=93%[b]
			T-tau/$A\beta_{42}$ ratio[4]	Sens=91%; Spec=89%[a]
				Sens=85%; Spec=94%[b]
Lumipulse® G (Fujirebio)[4]	$A\beta_{42/40}$ ratio	Sens=92%; Spec=84%[b,c]	-	-

Note: This list is not exhaustive. Other assays may be commercially available or for research use only. Product/company names mentioned herein are the trademarks of their respective owners.
[a]Swedish BioFINDER study; [b]Alzheimer's Disease Neuroimaging Initiative study (ADNI); [c] When the categories of 'positive' and 'likely positive' were both considered as positive; when likely positive results were excluded, sensitivity was 92% and specificity was 93%.
Abbreviations and references are listed in the speaker notes.

CSF Biomarkers: Aβ and Tau (2 of 2)

Commercially Available and Laboratory Developed Assays

Brand Name (Company)	Pathology Detected Amyloid/Mixed Pathology	Test Accuracy Data/ Clinical Performance Data (vs. Amyloid PET)	Pathology Detected Tau/Mixed Pathology	Test Accuracy Data/ Clinical performance Data
ADEVL (Mayo Clinic Laboratories)[1,2] Roche Elecys®[1,2]	$A\beta_{42}$[1,2]	Sens=73%; Spec=85%	T- tau[1]	Sens=68%; Spec=83%
			P-tau181[1]	Sens=82%; Spec=76%
	$A\beta_{42/40}$ ratio[1]	Sens=96%; Spec=82%	P-tau/$A\beta_{42}$[1]	Sens=92%; Spec=89%
ADmark® (Athena Diagnostics)[1,3]	$A\beta_{42}$[3]	Sens=93%; Spec=54%	P-tau181[3]	Sens=80%; Spec=80%
	$A\beta_{42}$/T-tau index(ATI)[3]	Sens=72%; Spec=70%		
	$A\beta_{42}$/T-tau ratio and P-tau: ATI<1, P-tau >61 pg/mL[1]	Sens=88%; Spec=82%[a,1]		
Beta-Amyloid 42/40 (Labcorp)[4]	$A\beta_{42/40}$ ratio[4]	Not available	-	-
Euroimmun (Revvity, Inc)[1,5]	$A\beta_{42}$[1]	Sens=83%; Spec=83%	P-tau181[3]	AUC=0.94;PPA=93%;NPA=84%
	$A\beta_{42/40}$ ratio[1]	Sens=97%; Spec=88%		
Lumipulse® G (Fujirebio)[1]	$A\beta_{42}$[1]	Sens=95%; Spec=51%	T-tau[1]	Sens=75%; Spec=83%
			P-tau181[1]	Sens=80%; Spec=83%
			P-tau181/$A\beta_{42}$ ratio[1]	Sens=93%; Spec=89%
TECAN (IBL International)[3,6]	$A\beta_{42}$[6]	Sens=77%; Spec=83%	P-tau181[3]	Sens=87%; Spec=92%
	$A\beta_{42/40}$ ratio[6]	Sens=92%; Spec=94%		
Test accuracy data for assays with agreement/predictive values vs. Amyloid PET				
AMYR (Mayo Clinic Laboratories)[7]	$A\beta_{42/40}$ ratio[7]	Amyloid-PET PPV=96.6% when $A\beta_{42/40}$ ratio is <or=0.058	-	

Note: This list is not exhaustive. Other assays may be commercially available or for research use only. Product/company names mentioned herein are the trademarks of their respective owners.

[a]Gold standard was clinical diagnosis.
Abbreviations and references are listed in the speaker notes

Blood Biomarker Accuracy Recommendations

AA Workgroup[a,1]

Biomarkers used for clinical diagnosis must be proven to be accurate

- Minimum of **90%** accuracy for the identification of moderate/frequent neuritic plaques at autopsy or approved surrogate: amyloid PET or CSF
- Blood-based marker (BBM) assays should have an accuracy equivalent to approved CSF assays
- Plasma P-tau217 assays alone or in combination have accuracy equivalent to approved CSF assays
- BBMs that achieve diagnostic performance **of 90% or better should be considered on equal footing with established PET and CSF biomarkers for diagnosis**

CEOi BBM Workgroup[2]

- Consider a 2-cutoff approach to increase the accuracy of a test for classifying individuals with or without amyloid pathology. This approach should result in intermediate values for no more than **15%-20%** of individuals in a typical clinical population
- **Triaging tests** (to identify individuals with a high likelihood of amyloid pathology but for whom a second test is needed to confirm pathology) should have a **sensitivity of ≥90%** with **specificity of ≥85%** in primary care and ≥75-85%[b] in secondary care depending on the availability of follow-up testing, including <20% intermediate results
- **Confirmatory tests** (to identify individuals with amyloid pathology without the need for a second test) should have >90% sensitivity and specificity and <20% intermediate results

[a]The AA identified a four-person core leadership group for this effort (ie, a steering committee) as well as a larger full workgroup; [b]75%-85% specificity might be acceptable with high capacity for follow-up amyloid PET or CSF testing by dementia specialists. Based on the minimum acceptable standards set by the BBM workgroup, the high-specificity triaging test must achieve a sensitivity of 90% and a specificity of 85%, while the low-specificity triaging test must achieve a sensitivity of 90% and a specificity of 75%.

AA=Alzheimer's Association; BBM=Blood Based Marker; CEOi=The Global CEO Initiative; CSF=Cerebrospinal Fluid; PET=Positron Emission Tomography; P-tau=Phosphorylated Tau.

1. Jack CR Jr, et.al. *Alzheimers Dement.* 2024;20(8):5143-5169. 2. Schindler SE, et al. *Nat Rev Neurol*. 2024;20(7):426-439.

Plasma Biomarkers: Amyloid

Description

- $A\beta_{40}$ is the most common Aβ peptide in the brain (80%-90%)[1]
- $A\beta_{42}$ accounts for 5%-10% of Aβ in the brain[1]
- $A\beta_{42}$ and $A\beta_{40}$ levels are markers of APP metabolism[2]
  - Cleavage of APP by BACE1 and γ-secretase leads to extracellular deposition of Aβ, which then aggregates to form plaques, a key pathological feature of AD[3]

Levels in AD

- Aβ pathology in the brain can be detected by dividing the concentration of aggregation-prone $A\beta_{42}$ by soluble $A\beta_{40}$[3]
  - $A\beta_{42}/A\beta_{40}$ ratio has been found to be lower in patients with AD vs non-AD dementia and vs controls[4]
- $A\beta_{42}/A\beta_{40}$ ratio is reduced by only 8%-20% in plasma compared with 40%-60% in CSF[3,5]
  - This is likely explained by production of Aβ peptides in platelets and other non-cerebral tissues[3]

Timing in AD Pathology

- The change in plasma $A\beta_{42}/A\beta_{40}$ ratio has been observed before positive amyloid Aβ-PET[6]

Diagnostic Accuracy

- A reduction in plasma $A\beta_{42}/A\beta_{40}$ ratio is:
  - Associated with increased amyloid burden within the brain[7,8]
  - Associated with a decline in cognitive performance[7-9]
  - Already detectable during the pre-symptomatic AD stage[5]
- A lower plasma $A\beta_{42}/A\beta_{40}$ ratio has been shown to be associated with positive Aβ-PET[7]
- Plasma $A\beta_{42}/A\beta_{40}$ ratio has been found to be modified by cardiovascular and cerebrovascular factors, potentially limiting the diagnostic and predictive value[4]

Note: 'AD' generally defined in cited references as a diagnosis of confirmed or suspected AD. Assessment informing diagnosis varies by study and may not include pathologic confirmation. Severity of impairment generally not specified.
Abbreviations and references are listed in the speaker notes.

Plasma Biomarkers: Tau

Description

- Tau is essential for axonal microtubule assembly[1]
- Tau phosphorylation leads to development of neurofibrillary tangles[2]
- There are several isoforms of phosphorylated tau (P-tau) associated with AD, including P-tau181,[3,4] P-tau217,[3,4] and P-tau231[4]

Levels in AD

- Increased levels of plasma tau phosphorylated at threonine 181 (P-tau181) and threonine 217 (P-tau217) are reported in patients with AD dementia compared with cognitively unimpaired individuals[5]

Timing in AD Pathology

- The change in plasma P-tau181 is observed to occur before amyloid PET, but after CSF and plasma $A\beta_{42}$[4]
- Plasma levels of P-tau217 start to change at the same time as CSF levels[5]
- Plasma P-tau217 levels increase during the early stages of AD before symptom onset when insoluble tau aggregates were not yet detectable by tau-PET[5]

Diagnostic Accuracy

- Plasma P-tau181[6,7], P-tau 217[6], and P-tau231[7] appear to reflect different stages of tau progression in AD
  - Plasma P-tau181 has been shown to correlate with early Aβ-related tau pathophysiology, so may be useful for disease staging[4]
  - Plasma P-tau231 and P-tau217 better capture the earliest cerebral Aβ changes, before overt Aβ plaque pathology is present[8]
- Plasma P-tau217 performs better than plasma P-tau181 when differentiating patients with neuropathologically confirmed AD from those with no neuropathological evidence of AD[9]
- Plasma P-tau has been shown to be suitable for individualized prediction of cognitive decline in individuals with MCI[7]
  - Plasma P-tau181 correlates with amyloid PET positivity and CSF P-tau181[4]
- Plasma P-tau181 and P-tau217 have shown especially high diagnostic performance for discriminating AD dementia from other neurodegenerative diseases[6]

Note: ‘AD’ generally defined in cited references as a diagnosis of confirmed or suspected AD. Assessment informing diagnosis varies by study and may not include pathologic confirmation. Severity of impairment generally not specified.
Abbreviations and references are listed in the speaker notes.

Recommendations for Clinical Implementation of BBM

BBM Workgroup

BBM test results must be interpreted alongside all clinical data, including medical history and a brief cognitive assessment.

A Triage Tool to Assess DMT Eligibility

- **A preliminary step to identify individuals who may benefit from further,**
  more invasive testing, such as PET scans or CSF analysis
- Age cutoff: ≥55 years in primary care for eligible patients, with no recommended age cutoff in secondary care
- Conduct BBM test in primary or secondary care; consider patient's age and symptoms for AD concern
- Interpret BBM test results to determine next steps for AD or non-AD causes
- **Patients with higher concern for AD and positive BBM test may proceed**
  to secondary care for amyloid confirmation and DMT eligibility[a]
- Secondary care may involve detailed patient history, examination, and cognitive and neuroimaging tests
- Confirmatory biomarker tests follow a positive BBM result to confirm amyloid pathology

A Tool to Confirm Amyloid Pathology

- An evolving scenario in which a BBM test achieves the minimum acceptable performance to confirm amyloid pathology without a follow-up test
- Age cutoff**:** In primary care ≥65 years, when AD is suspected as the etiology of CI
  - No age cutoff recommended when BBM is followed by a careful evaluation by a dementia specialist in secondary care
- **Positive BBM test result identifies amyloid pathology without the need for a second test**
  - In primary care, a positive test means referral to secondary care for assessing DMT eligibility[a]
  - In secondary care, a positive test prompts the determination of ***APOE ε4*** status where applicable
- **A negative result is considered as DMT-ineligible and concurrently evaluated for non-AD causes of cognitive symptoms**

[a]Eligible patients providing informed consent alongside their care partner may be prescribed DMTs.

AD=Alzheimer's Disease; *APOE*=Apolipoprotein; BBM=Blood-Based Marker; CI=Cognitive Impairment; CSF=Cerebrospinal Fluid; DMT=Disease-Modifying Therapy; PET=Positron Emission Tomography.

Mielke MM, et al. *Alzheimers Dement*. 2024;20(11):8216-8224.

Plasma Biomarkers: Commercially Available Assays

Brand Name (Company)	Pathology Detected	Test Accuracy (vs. Amyloid PET)	Test Results
LabCorp ATN (LabCorp)[1]	$A\beta_{42/40}$ ratio[1] P-tau181, NfL	$A\beta_{42/40}$ ratio: Sens=96%; Spec=87%	Normal, AD continuum, Non-AD dementia
PrecivityAD® (C_2N diagnostics)[a,2,3]	$A\beta_{42/40}$ and *APOE*[2,3]	Sens=92%; Spec=77%[2] Combined AUC-ROC=0.90; Accuracy=86%[3]	Positive or negative (Amyloid probability score)
Quest AD Detect® Beta-Amyloid 42/40 Ratio (Quest diagnostics)[4]	$A\beta_{42/40}$[4]	Sens=91%; Spec=76%	Positive, indeterminate, negative
PrecivityAD2™ (C_2N)[5]	%P-tau217, (P-tau/NP-Tau), and $A\beta_{42/40}$ ratio[5]	Sens=88%; Spec=89%[b]	Positive or negative (Amyloid probability score)

Confirmatory test with Sens and Spec~90% equivalent to CSF test[6]

High-specificity triaging test with Sens ≥90% and Spec ≥85%[6]

Low-specificity triaging test with Sens ≥90% and Spec ≥75%[6]

BBM tests with Sens or Spec below CEOi BBM Workgroup criteria or with clinical accuracy status not known[6]

Note: This is not an exhaustive list of all the commercially available plasma biomarker tests. The listed tests are all laboratory-developed tests. Product/company names mentioned herein are the trademarks of their respective owners.

[a]Has received FDA's breakthrough device designation in 2018[7]; [b]Indicates overall sensitivity and specificity of APS2 that combines % P-tau217 and $A\beta_{42/40}$.
Abbreviations and references are listed in the speaker notes.

Genetic Screening: *ApoE ε4*

- Individuals inherit one form of the *APOE* (ε2, ε3, or ε4) from each parent[1]
  - 20%-30% of US population has one or two copies of ε4
  - ~2% of the US population has two copies of ε4
- Inheriting the ε4 form confers a risk of developing AD, but does not guarantee that an individual will develop AD[2-4]
  - "Risk gene", not "deterministic gene"
  - Amyloid PET burden was shown to be greater in cognitively normal *ApoE ε4* carriers compared with noncarriers older than age 70 years
- Inheriting the ε2 form confers protection against AD, but does not guarantee that an individual will not develop AD[4]
- **Commercially available assays from:**
  - LabCorp[5]
  - Quest Diagnostics[6]
  - 23andMe[7]
  - Invitae[9]
  - C_2N Diagnositcs[10]
  - Alzheimer's Organization: Genetic Testing[11]
  - EmpowerDX[12]

AD=Alzheimer's Disease; ApoE=Apolipoprotein E; PET=Positron Emission Tomography.

Effect of *ApoE ε4* on AD Frequency and Age at Onset[8]

	ApoE ε4		
	Noncarrier	**Heterozygous**	**Homozygous**
AD frequency	**20%**	**47%**	**91%**
Mean age of clinical onset (years)	**84**	**76**	**68**

Gharbi-Meliani, A., Dugravot, A., Sabia, S. *et al.* The association of *APOE* ε4 with cognitive function over the adult life course and incidence of dementia: 20 years follow-up of the Whitehall II study. *Alz Res Therapy* **13,** 5 (2021). https://doi.org/10.1186/s13195-020-00740-0

Differentiating Diagnostic Approaches to AD

Alzheimer's Association Working Group vs. International Working Group

Definition and possible implications	AAWG 2024	IWG 2024
Definition of Alzheimer disease	Biological ("AD should be defined biologically not based on a clinical syndrome")	Clinical-biological ("AD is a clinical-biological construct")
Possible implications for the diagnosis in clinical setting	Presence of any abnormal core 1 AD biomarker (i.e., fluid Aβ42/40, p-tau, etc) is sufficient	Presence of objective cognitive deficits and AD biomarkers is needed
	A biomarker-positive cognitively normal person can be diagnosed with AD	A biomarker-positive cognitively normal person cannot be diagnosed with AD[a]
Possible implications in diagnostic disclosure of individual's status	Cognitively normal persons with 1 positive core 1 AD biomarker can be told they have AD	Cognitively normal persons with positive AD biomarker can be told they are at risk for AD[a]
Possible implications for phase 3 preventive clinical trials	Biomarkers could be primary endpoints in clinical trials	Biomarkers cannot be primary end points in clinical trials
	Demonstration of efficacy on clinical parameters may not be necessary	Demonstration of efficacy on clinical parameters is necessary
Clinical Use	AD Biomarkers intended only for symptomatic individuals presently	

[a]Except in the cases fulfilling the requirements for presymptomatic AD.

AAWG=Alzheimer Association Work Group; Aβ=Amyloid Beta; AD=Alzheimer's Disease; IWG=International Working Group; p-tau=Phosphorylated Tau.

Dubois B, et al. *JAMA Neurol*. Published online November 1, 2024.

Blood based markers (BBM)

- p Tau 217
- Amyloid beta 42
- p Tau 181
- NFL
- GFAP

Therriault J, Brum WS, Trudel L, Macedo AC, Bitencourt FV, Martins-Pfeifer CC, Nakouzi M, Pola I, Wong M, Kac PR, Real AP, Witherow C, Karikari TK, Moscoso A, Zimmer ER, Schöll M, Pascoal T, Benedet AL, Ashton NJ, Schindler SE, Zetterberg H, Blennow K, Rosa-Neto P. Blood phosphorylated tau for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol. 2025 Sep;24(9):740-752. doi: 10.1016/S1474-4422(25)00227-3. PMID: 40818474.

AA Workgroup[a]: Implications for Clinicians

- Abnormal Core 1 Biomarker is sufficient for confirming AD pathology in symptomatic individuals
- The integrated biological and clinical staging approach may aid clinical judgement in assessing the contribution of AD to the clinical syndrome
- The development of Core biomarker categories which include fluid and PET biomarkers for amyloid and tau provides greater flexibility to clinicians regarding access to specific biomarkers and their judgment as to which biomarkers is most appropriate
- AD biomarkers used in clinical practice now or in the future may provide greater opportunities for clinicians to make decisions about treatments including therapeutic response and/or duration of treatment

[a]The AA identified a four-person core leadership group for this effort (i.e., a steering committee) as well as a larger full workgroup.
AD=Alzheimer's Disease.
Jack CR Jr, et al. *Alzheimers Dement*. 2024.

AA Workgroup[a]: Intended Uses for AD Biomarkers

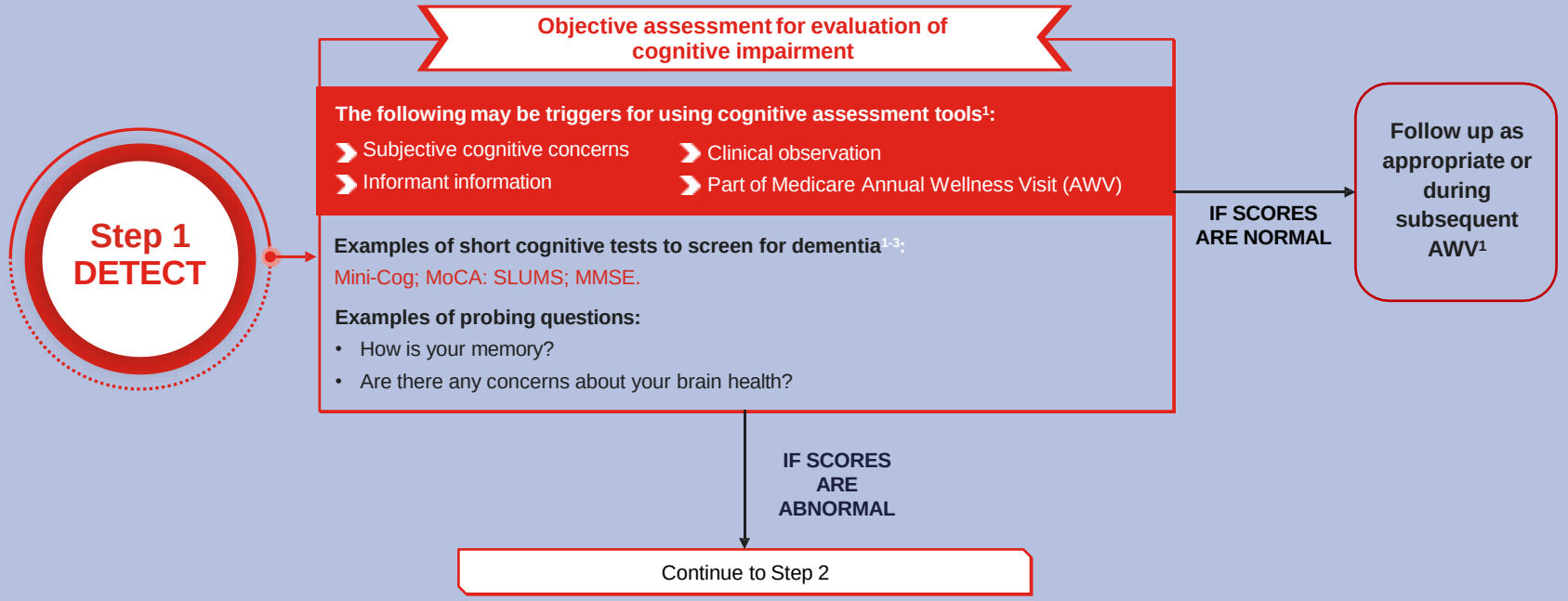
Intended use	CSF	Plasma	Imaging
Diagnosis			
A: (A*β* proteinopathy)	-	-	Amyloid PET
T_1: (phosphorylated and secreted AD tau)	-	p-tau217	-
Hybrid ratios	p-tau181/Aβ42, t-tau/Aβ42, Aβ42/40	%p-tau217	-
Staging, prognosis, as an indicator of biological treatment effect			
A: (A*β* proteinopathy)	-	-	Amyloid PET
T_1: (phosphorylated and secreted AD tau)	-	p-tau217	-
Hybrid ratios	p-tau181/Aβ42, t-tau/Aβ42, Aβ42/40	%p-tau217	-
T_2: (AD tau proteinopathy)	MTBR-tau243, other p-tau forms (eg, p-tau205), non-phosphorylated mid-region tau fragments	MTBR-tau243, other p-tau forms (eg, p-tau205)	Tau PET
N (injury, dysfunction, or degeneration of neuropil)	NfL	NfL	Anatomic MRI, FDG PET
I (inflammation) Astrocytic activation	GFAP	GFAP	-
Identification of copathology			
N (injury, dysfunction, or degeneration of neuropil)	NfL	NfL	Anatomic MRI, FDG PET
V vascular brain injury	-	-	Infarction on MRI or CT, WMH
S α-synuclein	αSyn-SAA	-	

[a]The AA identified a four-person core leadership group for this effort (i.e., a steering committee) as well as a larger full workgroup.

αSyn-SAA=Alphasynuclein Seed Amplification Assay; Aβ=Amyloid Beta; Pathologic Tau, and Neurodegeneration; CSF=Cerebrospinal Fluid; CT=Computed Tomography; FDG=Fluorodeoxyglucose; GFAP=Glial Fibrillary Acidic Protein; MRI=Magnetic Resonance Imaging; MTBR=Microtubule-Binding Region; NFL=Neurofilament Lightchain; PET=Positron Emission Tomography; P-tau=Phosphorylated Tau; T-tau=Total Tau; WMH=White Matter Hyperintensity.

Jack CR Jr, et.al. *Alzheimers Dement*, 2024.

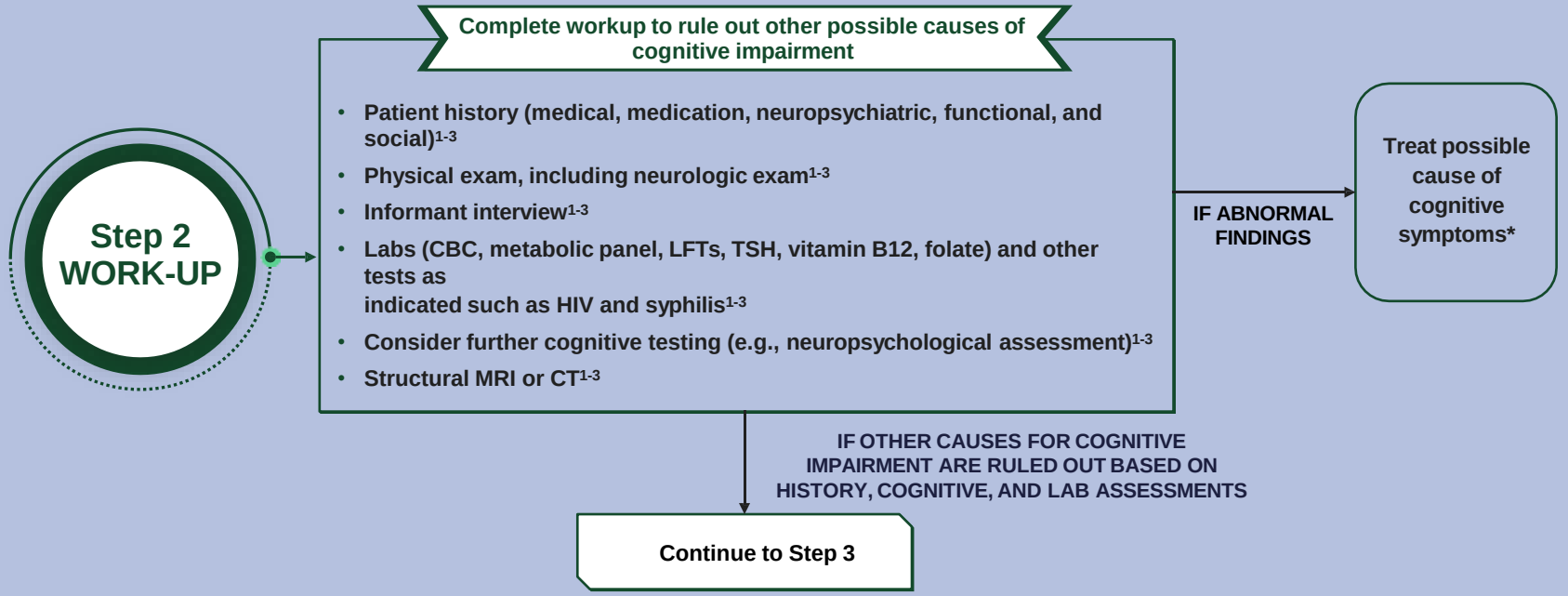
Step 1: A Routine Diagnostic Approach Can Help Determine if AD is a Cause of Cognitive Impairment



AD=Alzheimer's disease; AWV=Annual Wellness Visit; MMSE=Mini-Mental State Exam; MoCA=Montreal Cognitive Assessment; SLUMS=St. Louis University Mental Status.

1. Cordell CB, et al; Medicare Detection of Cognitive Impairment Workgroup. *Alzheimers Dement*. 2013;9(2):141-150. 2. McCollum L, Karlawish J. *Med Clin North Am*. 2020;104(5):807-825. 3. Scharre DW, Trzepacz PT. *Focus*. 2013;11(4):482-500.

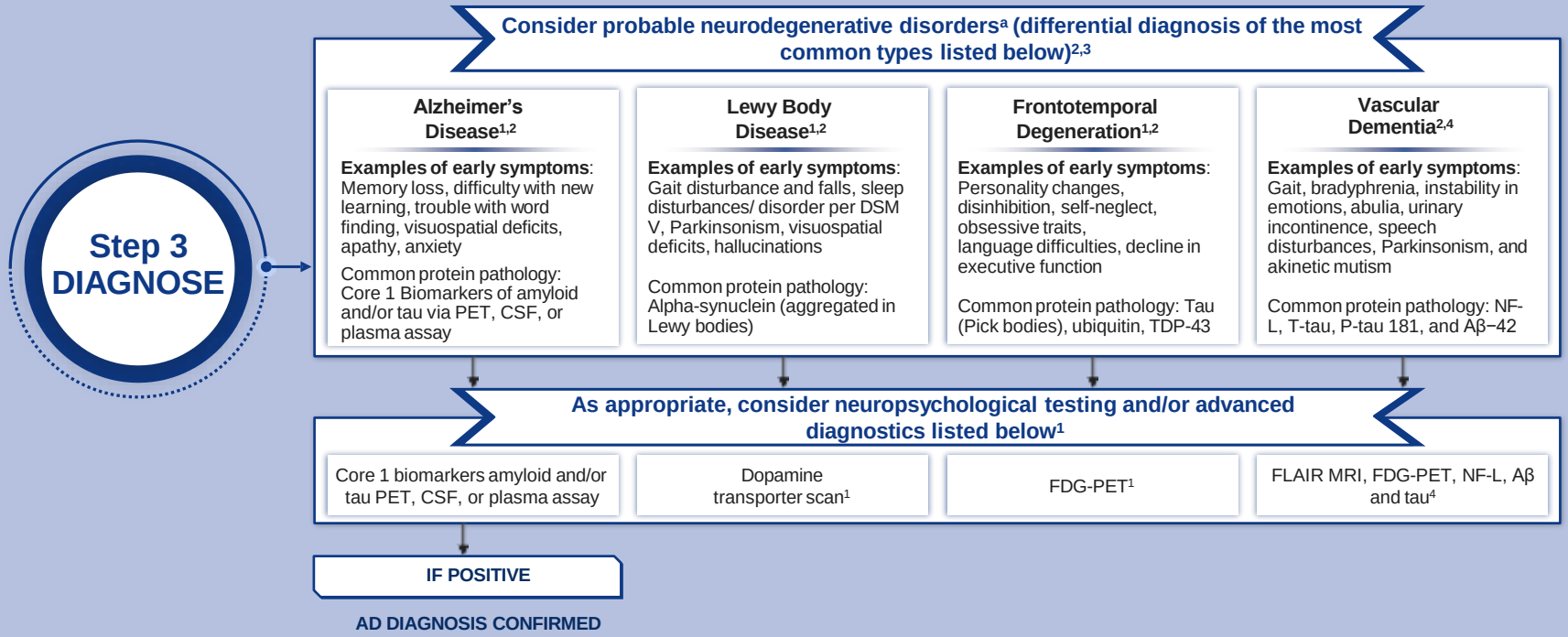
Step 2: Complete Workup to Rule Out Non-Dementia-Related Causes of Cognitive Impairment



*It is possible to have multiple comorbid conditions which contribute to cognitive impairment.
CBC=Complete Blood Count; CT=Computerized Tomography; HIV=Human Immunodeficiency Virus; LFT=Liver Function Test; MRI=Magnetic Resonance Imaging; TSH=Thyroid Stimulating Hormone.

1. Cordell CB, et al; Medicare Detection of Cognitive Impairment Workgroup. *Alzheimers Dement*. 2013;9(2):141-150. 2. Scharre DW, Trzepacz PT. *Focus.* 2013;11(4):482-500. 3. http://www.actonalz.org/sites/default/files/documents/ACT-Provider-ClinicalPracticeTool.pdf (Accessed August 19, 2024).

Step 3: Distinguishing Alzheimer's Disease from Other Neurodegenerative Disorders



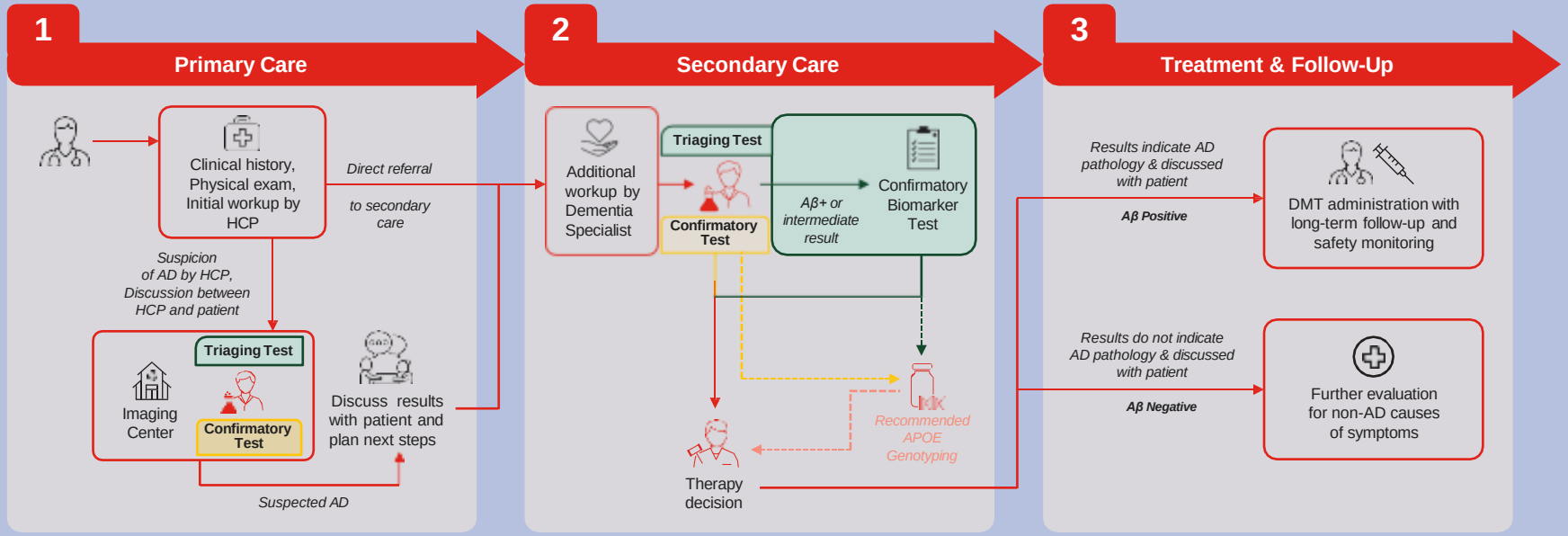
[a]Patient may have more than one neurogenerative disease or disorder.

CSF=Cerebrospinal Fluid; DSM V=Diagnostic and Statistical Manual of Mental Disorders V; FDG-PET=Fluorodeoxyglucose PET; PET=Positron Emission Tomography; TDP-43=TAR DNA-binding Protein 43.

1. Cordell CB et al; Medicare Detection of Cognitive Impairment Workgroup. *Alzheimers Dement.* 2013;9(2):141-150. 2. Scharre DW, Trzecapz PT. *Focus*. 2013;11(4):482-500. 3. McKhann GM, et al. *Alzheimers Dement.* 2011;7(3):263-269. 4. Prajjwal P, et al. *Dis Mon*. 2023;69(5):101557.

Recommended Clinical Implementation Pathways for Use of BBM Tests in AD Diagnosis

BBM Workgroup



AD=Alzheimer's Disease; Aβ=Amyloid Beta; *APOE*=Apolipoprotein E; BBM=Blood-Based Biomarker; DMT=Disease Modifying Therapy; HCP=Healthcare Professional.

Mielke MM, et al. *Alzheimers Dement*. 2024;20(11):8216-8224.

AA Workgroup[a]: Implications for Clinicians

The biologically based diagnosis of AD is meant to assist rather than replace the clinical evaluation of individuals with cognitive impairment

- The clinical use of AD biomarkers is presently intended for the evaluation of symptomatic individuals, not cognitively unimpaired individuals
- The presence of abnormal biomarkers does not preclude the search for other contributors to the clinical symptoms, particularly copathologies
- AD biomarkers are fundamental to making an accurate diagnosis and determining likely contributions to a patient's symptoms. They can be used to determine eligibility for ATTs, counseling, and tailoring medications for symptomatic treatments

[a]The AA identified a four-person core leadership group for this effort (i.e., a steering committee) as well as a larger full workgroup. AD=Alzheimer's Disease; ATTs=Amyloid Targeting Therapies; PET=Positron Emission Tomography.
Jack CR Jr, et al. *Alzheimers Dement*. 2024.

Treatment Strategies

- "Four Legs of the Table"
  - Sleep
  - Nutrition (Protein, ETOH, caffeine, THC)
  - Exercise
  - Social engagement

Mace N, Rabins P. **The *36-Hour Day***: *A Family Guide to Caring for People Who Have Alzheimer Disease and Other Dementias (8th edition).* Johns Hopkins Univ. Press, 2025

Treatment Strategies

- Caregiver Respite
- Educate themselves
- Anticipatory planning
  - Powers of attorney / living will
  - Aging in place vs communities
- Safety
  - Medications
  - Appliances
  - Guns
  - Monitors
  - Elopement

Mace N, Rabins P. **The *36-Hour Day***: *A Family Guide to Caring for People Who Have Alzheimer Disease and Other Dementias (8th edition).* Johns Hopkins Univ. Press, 2025

Which Objective Assessment Tools Might Fit Your Patient Type and Practice?

Test[a]	Description	Time[b]	Considerations
MMSE[1] **(Mini-Mental State Exam)**	A 30-point test that assesses orientation, memory, attention, language, and praxis	7-10 min	• 88.3% sensitive and 86.2% specific for dementia with a cut point of 23/24 or 24/25 • Limited sensitivity and specificity for MCI
MoCA[1,2] **(Montreal Cognitive Assessment)**	A 30-point test that assesses short-term memory, recall, visuospatial abilities, multiple aspects of executive functioning, attention, concentration, working memory, language, and orientation	10 min	• 80%–100% sensitive and 50%–76% specific for MCI using cut point of 25/26
Mini-Cog[1]	A cognitive assessment test that includes 3-item word memory recall and clock drawing	3-4 min	• 76%–100% sensitive and 54%–85.2% specific for dementia • Low sensitivity for MCI • May perform better in low-education populations
SLUMS[3-5] **(Saint Louis University Mental Status Examination)**	11-item, 30-point cognitive screening measure that is easy to administer, assesses several cognitive domains including attention, calculation, immediate and delayed recall, animal naming, abstract thinking, and visuospatial skills in a short amount of time	Approx. 7 min	• Excellent sensitivity and specificity rates in both high and low educated groups (0.92, 0.81, respectively, in a less than high school educated population; and 0.95, 0.76, respectively, in a greater than high school educated population)

[a]Tests are representative only; alternative tools are available and can be used at the discretion of the clinician.
[b]Average times reported; times may vary.

MCI=Mild Cognitive Impairment; min=Minute.

1. McCollum L, Karlawish J. *Med Clin North Am*. 2020;104(5):807-825. 2. Davis DH, et al. *Cochrane Database Syst Rev.* 2021;7(7):CD010775. 3. Yokomizo JE, et al. *Rev Saude Publica*. 2018 Nov 23;52:88. 4. Feliciano L, et al. *Am J Geriatr Psychiatry*. 2013;21(7):623-630. 5. Mueller J, Cammermeyer G. *Alzheimer's Dement*. 2023; 19: 4743–4752.

Pharmacologic Therapy in AD

- **Cholinesterase inhibitors**
  - **Donepezil (Aricept)**
  - **Rivastigmine (Exelon)**
  - **Galantamine (Razadyne)**
- **NMDA antagonist**
  - **Memantine (Namenda)**
- **Combination**
  - **Donepezil / Namenda (Namzaric)**

D. Luke Fischer MD PhD. Alzheimer disease. In: Lewis SL, Editor-in-Chief. MedLink Neurology. San Diego: MedLink, LLC. Available at www.medlink.com. Updated: January 8, 2025.

Notes and suggestions

- Set realistic expectations
- Early improvement may be seen, but disease will progress
- Preserves cognition, behavior and ADLs for longer periods
- Reduces caregiver distress / burden
- Prolongs need for placement
- Off label use in VD, DLBD, FTD, Parkinson's
- "Mild disease"

D. Luke Fischer MD PhD. Alzheimer disease. In: Lewis SL, Editor-in-Chief. MedLink Neurology. San Diego: MedLink, LLC. Available at www.medlink.com. Updated: January 8, 2025.

Consensus recommendations for symptomatic management

- Brepiprazole (Rexulti) FDA+ in AD
- Suvorexant (Belsomra) FDA+in AD
- SSRI's
- Risperidone
- Trazadone
- Quetiapine (Seroquel)
- Pimavanserin (Nuplazid) FDA+ in PD
- Avoid benzodiazepines
- Avoid " Z drugs", TCA's
- Sleep, Nutrition, Exercise, Social engagment

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Disease modifying therapy / Amyloid targeting therapy

- Aducanemab (Aduhelm)
  - IV every 4 weeks
  - no longer commercially available
- Lecanemab (Leqembi)
  - IV q 2 weeks
  - sub q weekly maintenance after 18 months of therapy
  - IV q monthly after 18 months after 18 months of therapy
- Donanemab (Kisunla)
  - IV q monthly

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Disease modifying therapy / Amyloid targeting therapy

- Target amyloid beta protofibrils and plaques
- MCI and mild dementia with Alzheimer's disease (MMSE > 21)
- 27-30% reduction in progression of disease as measurd by CDR-SB
- Generally well tolerated
- ARIA-E and ARIA-H (amyloid related imaging abnormality)
- ApoE profile
- Confirmation of amyloid pathology
- MRI prior to starting, < 4 microbleeds
- Requires frequent MRI monitoring in the first 6 months

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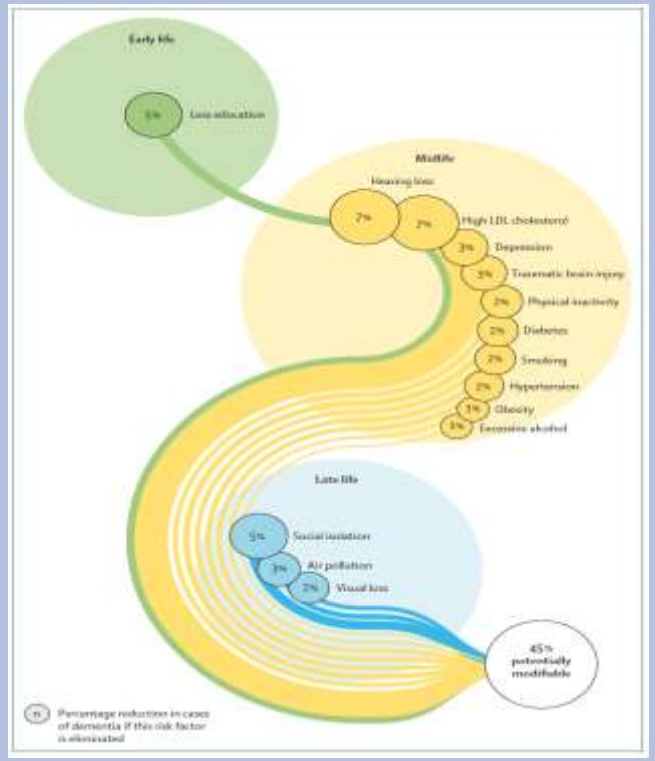
Strategies to reduce incidence of dementia by the Lancet Commission

- Manage Hypertension
- Treat obesity/reduce diabetes risk
- Engage in regular exercise
- Stop smoking
- Improve social/community connection
- Treat depression
- Reduce alcohol consumption
- Make quality education available
- Air pollution
- Treat LDL in midlife
- Helmets /Head protection
- Screening for hearing loss / hearing aids
- Correct vision loss

The Lancet Commissions*: Dementia prevention, intervention and care: 2024* report of the *Lancet* Standing commission. Published online July 31, 2024



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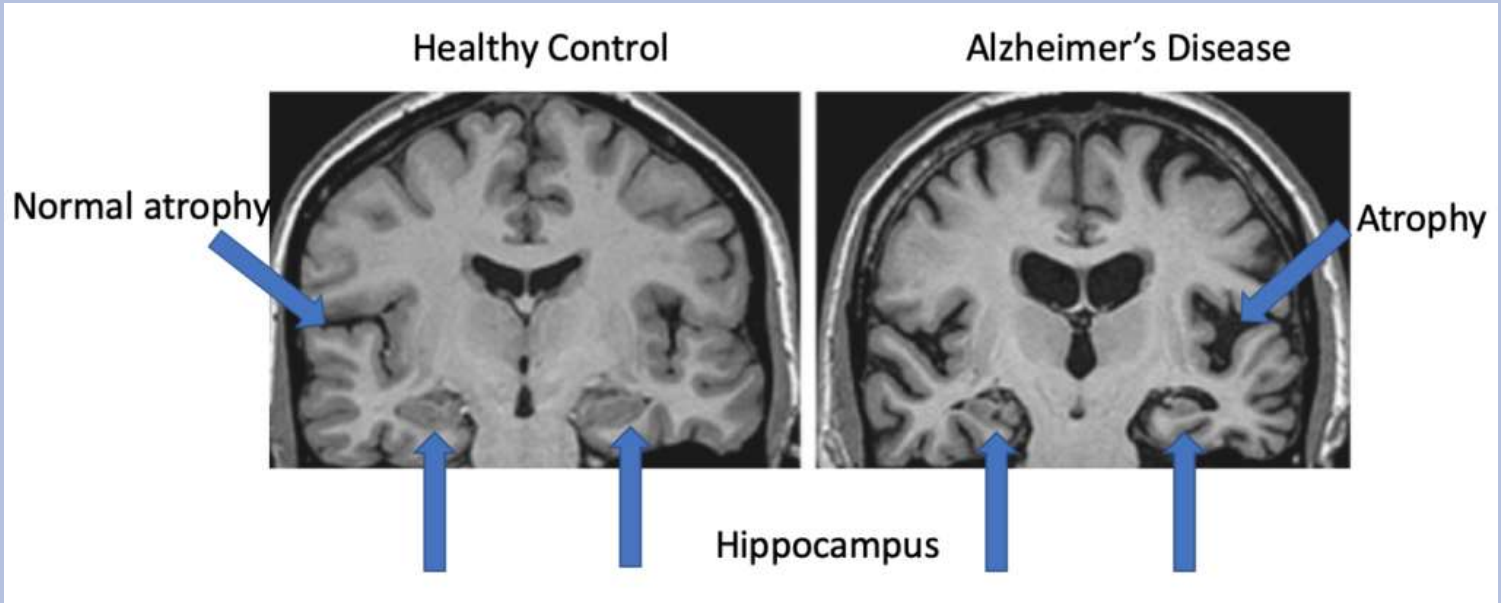
Alzheimer's: MRI



https://dementia.ie/lessons/mri-scan-of-brain-alzheimers-disease/