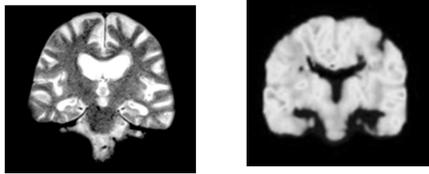


Neuro-ophthalmic Manifestations of Alzheimer's Disease



Leonard V. Messner, OD, FAAO
 Professor of Optometry
 Vice President for Strategy & Institutional
 Advancement
 Illinois College of Optometry



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Disclosure Statement:

Neuro-ophthalmic Manifestations of Alzheimer's Disease

Leonard V. Messner, OD

- King Devick Technologies (board of directors)
- Heidelberg Engineering (professional advisory board)
- Horizon Therapeutics (professional advisory board)

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Key Points

- Types of dementia
- Pathophysiology of Alzheimer's Disease (AD)
- Non-ocular findings with AD
- Neuro-ophthalmic findings with AD
- Management

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Definition of Dementia

- Dementia is a loss of brain function that occurs with certain diseases. It affects memory, thinking, language, judgment, and behavior.

US National Library of Medicine-2015

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Common Types of Dementia

- Alzheimer's disease (60-80%)
- Vascular dementia
- Dementia with Lewy bodies
- Frontotemporal lobular degeneration
- Mixed dementia
- Parkinson's disease
- Creutzfeldt-Jakob disease
- Normal pressure hydrocephalus

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Common Types of Dementia

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- Normal pressure hydrocephalus

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Alois Alzheimer, MD (1906)



- South-West German Psychiatrists' Meeting presentation on pre and post-mortem findings of Auguste Deter - *"On a Peculiar Disease of the Cerebral Cortex"*

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Alzheimer's Disease

- Progressive dementia with loss of neurons and the presence of two main microscopic neuropathological hallmarks: extracellular amyloid plaques and intracellular neurofibrillary tangles

Gheorghita M, et al. *Rom J Psychopharmacol* 2010

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Epidemiology of Alzheimer's Disease (AD)

- 96% > 65 years
- 5th leading cause of death > 65 years
- 5.2 million Americans with AD (24 million world-wide)
- Increasing incidence and prevalence (est. American prevalence of 13.8M by 2050)

Reitz C, et al. *Nat Rev Neurol* 2011

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Risk Factors for AD

- Older age
- Genetics (APOE4 allele)
- Prior history of TBI

DeKoskey ST AAN SCC 2015

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APOE & AD

ALLELE FREQUENCY:

	normal population:	in AD:
E2	7%	7%
E3	79%	40-50%
E4	14%	40-50%

- APOE4
 - Impaired sequestration of cholesterol (atherosclerosis)
 - Impaired glucose transport to the brain (type 3 diabetes)
 - Impaired removal of β amyloid (Alzheimer's disease)
 - Allele frequency is twice as high in Africans/African Americans as compared to Caucasians

DeKoskey ST AAN SCC 2015

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Increased Risk of AD with APOE4 & TBI

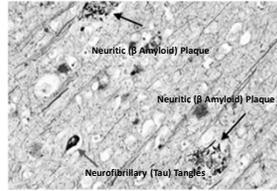
- 2 fold increase of AD with APOE4 alone
- 10 fold increase in AD with APOE4 & history of TBI

Schmmechel DE et al. *Proc Natl Acad Sci* 1993

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Pathology of AD (Beta-Amyloid Cascade Hypothesis)

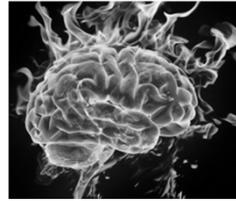
- Mitochondrial dysfunction (cytochrome oxidase pathway)
- Up-regulation of amyloid precursor protein (APP)
- Extracellular β -amyloid neuritic plaques
- Intracellular neurofibrillary tau tangles



Gheorghita M, et al. *Rom J Psychopharmacol* 2010
Photo credit: Daniel Pearl, MD Mt Sinai J Med 2010

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Brain Under Attack!



- Extracellular neuritic plaques activate microglia & astrocytes

↑
Upregulation of
Complement molecules,
pro-inflammatory cytokines
& other inflammatory mediators

- Progressive neurodegeneration
- ? Role of anti-inflammatory agents

Meraz-Rios M, et al. *Front Integr Neurosci* 2013

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Clinical Presentation of AD (non-ocular)

- Early:
 - Difficulty remembering names and recent events
 - Apathy and depression
 - Problems with vision and sense of smell
- Later:
 - Impaired judgment, disorientation, confusion, behavior changes, difficulty walking, speaking, swallowing → death (pathology/degeneration of bulbar structures)

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Staging of Alzheimer's Disease

1. Preclinical Alzheimer's Disease (AD risk state)
2. Prodromal AD / Mild Cognitive Impairment
3. Dementia due to Alzheimer's Disease

National Institute on Aging & Alzheimer's Association 2010

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Stage 1: Preclinical AD (Asymptomatic with Positive Biomarkers)

- Accumulation of CNS $A\beta$
 - CSF analysis
 - Brain imaging (PET scan)
- Marker of neuronal injury
 - Accumulation of tau within CSF
 - Abnormal brain glucose metabolism (PET scan)
- Subtle cognitive changes

National Institute on Aging & Alzheimer's Association 2010

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Stage 2: Prodromal AD / Mild Cognitive Impairment (MCI)

- Evidence of CNS biomarkers
- Evidence of early cognitive decline

National Institute on Aging & Alzheimer's Association 2010

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Stage 3: Dementia due to AD

- Mild
- Moderate
- Severe

National Institute on Aging & Alzheimer's Association 2010

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Mild Dementia due to AD

- Impaired short-term memory
- Impaired problem solving abilities (e.g. math/numbers, judgment tasks)
- Difficulty with thought organization and expression
- Unfamiliarity with environment
- Personality changes (e.g. irritability & anger)

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Moderate Dementia due to AD

- Increasingly poor judgment and confusion
- Increased memory problems - inability to remember vital personal information (e.g. inability to remember phone number, address, etc. with repetition of familiar stories)
- Increased need for assistance with daily living activities (e.g. bathing, grooming, bladder and bowel function)
- Progressive personality and behavioral changes (e.g. suspicion of others, late-day agitation, outbursts of aggression)

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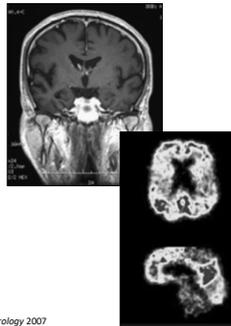
Severe Dementia due to AD

- Loss of ability to respond to environment
- Inability to communicate
- Loss of motor control & mobility
- Loss of bulbar function (e.g. difficulty with swallowing, bladder/bowel control & breathing)

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CNS Biomarkers for Prodromal AD / MCI

- Medial temporal lobe atrophy on MRI
- CSF abnormalities (β -amyloid, phosphorylated tau)
- Temporoparietal hypometabolism on 18 F-fluorodeoxyglucose PET
- Positivity on amyloid ligand imaging with PET

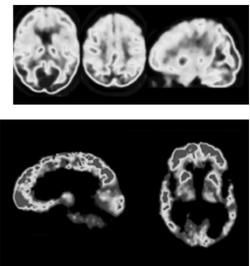


Dubois B, et al. Lancet Neurology 2007

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Brain PET in AD

- FDG-PET
 - Decreased cortical metabolism of glucose with AD
- Amyloid PET
 - Increased signal associated with uptake of amyloid ligand



Marcus C, et al. Clin Nucl Med 2014

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Preliminary Results of IDEAS Study

- Amyloid PET allows for more accurate detection or exclusion of AD as compared to metabolic imaging and/or CSF analysis
 - Pre-scan diagnosis of AD with positive aPET associated with 99% accuracy of AD
 - Pre-scan diagnosis of non-AD with negative aPET associated with 99% accuracy of non-AD
 - Pre-scan diagnosis of non-AD with positive aPET associated re-assessment as AD in 60% of cases
 - Pre-scan diagnosis of AD with negative aPET associated with exclusion of AD in 54% of cases

Alzheimer's Association International Conference (London) 2017

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FDA NEWS RELEASE FDA Clears First Blood Test Used in Diagnosing Alzheimer's Disease

New Test Provides Less Invasive Option, Reduces Reliance on PET Scans and Increases Diagnosis Accessibility

- Lumipulse G pTau217/beta-amyloid 1-42 ratio
- Blood biomarker for beta amyloid 1-42 in patients with cognitive impairment
- 92%PPV & 97%NPV (benchmarked to PET/CSF analysis)
- Reduced need for PET/CSF Dx of AD

FDA press release 5/16/25

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Ocular Manifestations of Alzheimer's Disease



The NEW ENGLAND
JOURNAL of MEDICINE

Vol. 313 No. 8

OPTIC NEUROPATHY IN ALZHEIMER'S DISEASE — HINTON ET AL.

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OPTIC-NERVE DEGENERATION IN ALZHEIMER'S DISEASE

DAVID R. HINTON, M.D., ALFREDO A. SADUN, M.D., PH.D., JANET C. BLANKS, PH.D.,
AND CAROL A. MILLER, M.D.

Abstract Alzheimer's disease is a dementing disorder of unknown cause in which there is degeneration of neuronal subpopulations in the central nervous system. In postmortem studies, we found widespread axonal degeneration in the optic nerves of 8 of 10 patients with Alzheimer's disease. The retinas of four of the patients were also examined histologically, and three had a reduction in the number of ganglion cells and in the thickness of the nerve-fiber layer. There was no retinal neurofibrillary degeneration or amyloid angiopathy, which

are typically seen in the brains of patients with Alzheimer's disease. The changes we observed in the patients with Alzheimer's disease were clearly distinguishable from the findings in 10 age-matched controls and represent a sensory-system degeneration that occurs in Alzheimer's disease. Study of the retina in patients with this disease may be helpful diagnostically, and isolation of the affected ganglion cells may facilitate molecular analysis of the disorder. (N Engl J Med 1986; 315:485-7.)

- 1986 study post mortem study of optic nerves in patients with AD
- Wide-spread axonal degeneration in 8/10 optic nerves
- Specificity for larger M-cell degeneration
- Thinning of RNFL and retinal ganglion cells

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Neuro-ophthalmic Findings with AD

- Functional
 - Visual Dysfunction (contrast sensitivity / low contrast acuity)
 - Visual-motor dysfunction (abnormal saccades)
- Structural (OCT)
 - RNFL/GCC thinning

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What's the
Evidence?



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Visual Dysfunction

Reduced Contrast Sensitivity / Low Contrast Acuity with Alzheimer's Disease



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Visual Dysfunction in Alzheimer's Disease: Relation to Normal Aging (Cronin-Golomb A, et al. *Ann Neurol* 1991)

- Impaired contrast sensitivity (particularly at low spatial frequencies) with AD vs. healthy elderly controls
- Implication of disease involving primary and association visual cortex vs. retina/optic nerve

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Vision in Aging & Dementia (Bassi CJ, et al. *Optom Vis Sci* 1993)

- Study of visual deficits in patients with AD (N = 10) other dementias (N = 10) age-matched controls (N = 11) & young controls (N = 10)
- Assessment of color vision (D-15), contrast sensitivity (Pelli-Robson) & stereo acuity (RANDOT)
- Low spatial frequency contrast sensitivity deficits most specific for AD vs. other visual measures

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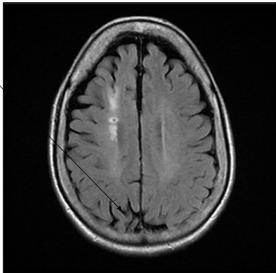
Visual Contrast Sensitivity in Alzheimer's Disease, Mild Cognitive Impairment, and Older Adults with Cognitive Complaints (Risacher SL, et al. *Neurobiol Aging* 2013)

- Contrast sensitivity (frequency doubling technology) assessment in individuals with with AD (n = 10), mild cognitive impairment (n = 28), cognitive complaints (n = 20) & healthy controls (n = 29)
- CS evaluation as a function of cognitive performance
- Reduced contrast sensitivity specific for AD and parallels the course of cognitive impairment with AD

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Posterior Cortical Atrophy (Benson's Syndrome)

- Approx. 5% of AD patients (earlier age of onset)
- Preserved cognitive function
- Beta amyloid/tau infiltration & atrophy of visual cortex
 - Progressive vision loss (without obvious clinical correlation)
 - Difficulty reading / inability to follow printed words
 - Photophobia
 - Problems with depth perception
 - Hemianopic field loss / Visual neglect
 - Difficulty with visual processing (recognition of familiar objects/faces)
 - Image confabulation (hallucinatory palinopsia)



Benson DF, et al. *Arch Neurol* 1988

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Visual-motor Dysfunction with AD

↓

Impaired Saccades

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Types of Saccades

- Voluntary - FEF
- Predictive - DLPFC, FEF
- Memory - DLPFC, FEF
- Reflex - Parietal
- Antisaccade - DLPFC, FEF- direct eyes away from a target



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Challenges to Brain

- Saccades must be fast (300-500 deg/sec, up to 900-100 deg/sec) and brief (100-200 msec)
- Saccades must be accurate
- Saccade-generating “burst neurons” in the brainstem must discharge vigorously
- Prone to malfunction in neurodegenerative disease & TBI

Slide courtesy of Janet Rucker, MD

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Visual-motor Dysfunction with AD: Impaired Saccades

- Impaired eye tracking while reading with AD vs. age-matched controls (Fernandez G, et al. *Invest Ophthalmol Vis Sci* 2013)
- Impaired microsaccades with mild cognitive impairment & AD (Kapoula Z, et al. *Age (Dodr)* 2014)
- Impaired antisaccades with amnesic mild cognitive impairment & AD→impaired executive function (Peltsch A, et al. *Eur J Neurosci* 2014)
- Abnormal “reading saccades” with AD suggesting disease of pre-frontal cortex (Fernandez G, et al. *J Integr Neurosci* 2015)

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BRAIN

Impaired eye movements in post-concussion syndrome indicate suboptimal brain function beyond the influence of depression, malingering or intellectual ability

Marcus H. Heitger,^{1,2} Richard D. Jones,^{1,3,4} A. D. Macleod,⁴ Deborah L. Snell,⁵ Chris M. Frampton¹ and Tim J. Anderson^{1,5,6}

- Prospective analysis of 36 PCS subjects vs. healthy controls
- PCS associated with worsening of anti-saccades, self-paced saccades, memory-guided sequences & smooth pursuits
- Eye movement dysfunction showed higher correlation with symptom load as compared to neuro-psych testing
- Biological substrate for concussion-related symptoms

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Neurology. 2011 Apr 26;76(17):1456-62.
The King-Devick test as a determinant of head trauma and concussion in boxers and MMA fighters
Galletta KM, Baven J, Allen M, Madala F, Delicata D, Tomany AT, Brasas CC, Maguire MG, Messner LV, Devick S, Galetta SL, Balcer LJ
Department of Neurology, University of Pennsylvania School of Medicine

- Postfight K-D scores (n = 39 participants) were significantly higher (worse) for those with head trauma during the match (59.1 ± 7.4 vs 41.0 ± 6.7 seconds, $p < 0.0001$, Wilcoxon rank sum test)
- Those with loss of consciousness showed the greatest worsening from prefight to postfight. Worse postfight K-D scores ($r(s) = -0.79$, $p = 0.0001$) and greater worsening of scores ($r(s) = 0.90$, $p < 0.0001$) correlated well with postfight MACE scores
- Worsening of K-D scores by ≥ 5 seconds was a distinguishing characteristic noted only among participants with head trauma
- High levels of test-retest reliability were observed (intraclass correlation coefficient 0.97 [95% confidence interval 0.90-1.0])

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ORIGINAL ARTICLE

Screening Utility of the King-Devick Test in Mild Cognitive Impairment and Alzheimer Disease Dementia

Kristin M. Galetta, MD*†‡, Kimberly R. Chapman, BA,‡, Maritza D. Essis, MS,‡, Michael L. Alocco, PhD,‡, Danielle Gillard, BA,‡, Eric Steinberg, NP,‡, Diane Dixon,§, Brent Martin, MS,§, Christine E. Chaitson, MPH,§§, Neil W. Konoll, MD,‡¶¶,§§, Yorghos Tripodis, PhD,***††, Lara J. Balcer, MD, MScE,†† and Robert A. Stern, PhD,‡†††

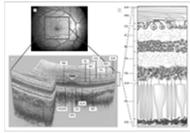
- Comparison of K-D test performance among individuals with MCI (N = 39), AD (N = 32) and healthy controls (N = 135)
- Increased testing time for MCI & AD vs. controls
- Results suggest utilization of K-D as effective screening test for MCI & AD

Galetta KM, et al. *Alzheimer Dis Assoc Disord* 2016

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Ocular Structural Changes with AD

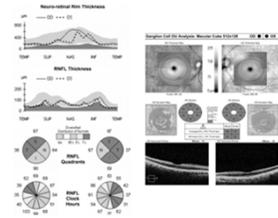
OCT Findings



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OCT Findings in AD

- RNFL & paramacular thinning in AD vs. controls (Polo V, et al. *Eye* 2014)
- RNFL thinning (superior quadrant selectivity with mild cognitive impairment/early AD) parallels dementia progression in AD (Liu D, et al. *BMC Neurol* 2015)
- RNFL and superior retinal thickness/GCL thinning (Cunha JP, et al. *Graefes Arch Clin Exp Ophthalmol* 2017)



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Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 6 (2010) 162–170

Alzheimer's
&
Dementia

Retinal Imaging Retinal thickness in Alzheimer's disease: A systematic review and meta-analysis

Jurre den Haan^{a,b}, Frank D. Verbraak^{c,d}, Pieter Jelle Visser^{e,f}, Femke H. Bouwman^g

- Meta-analysis of 25 studies involving 887 AD patients, 216 MCI patients and 864 health controls
- AD & MCI patients had thinner RNFL ($p < 0.0001$) & macular thickness ($p = 0.0001$) as compared to healthy controls

den Haan J, et al. *Alzheimer's & Dementia* 2017

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OCT Angiography in AD

- Enlargement of foveal avascular zone (FAZ) in patients with pre-clinical AD vs. health controls
- Reduction in retinal vascular density in patients with AD vs. Health controls



O'Bryhim BE, et al. *JAMA Ophthalmol* 2018
Zabel P, et al. *IOVS* 2019

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Pharmacotherapy for AD

- Cholinesterase inhibitors
 - NMDA antagonists
 - A β sequestration agents / disease modifying therapy
- } 6-12 month delay of symptoms

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Cholinesterase Inhibitors

- Donepezil (Aricept)
 - All stages
- Galantamine (Razadyne)
 - Mild-moderate AD
- Rivastigmine (Exelon)
 - Mild-moderate AD

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U.S. News HEALTH
Home Hospitals Doctors Health Insurance Nursing Homes Diets Health & Wellness

Drug & Alcohol Rehab
rehabilitation-center.org/Rehab
We Have Immediate Availability. Affordable & Private. High Success.

Dementia Meds May Lead to Harmful Weight Loss: Study

HealthDay | Aug 3, 2015 | 12:00 p.m. EDT

HealthDay
By Robert Freed, HealthDay Reporter

MONDAY, Aug. 3, 2015 (HealthDay News) — A class of drugs widely used to treat dementia — called cholinesterase inhibitors — could cause harmful weight loss in some patients, a new study suggests.

These medications include Aricept (donepezil), Razadyne (galantamine) and Exelon (rivastigmine).

"Our study provides evidence in a large, real-world population that cholinesterase inhibitors may contribute to clinically significant weight loss in a substantial proportion of older adults with dementia," study lead author Dr. Meera Sheffrin, a genetics fellow in the School of Medicine, at

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NMDA Antagonists

- Memantine (Namenda)
 - Moderate to severe AD
 - Alone or in combo with cholinesterase inhibitors
- Namzeric (Namenda/Aricept combo)

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Disease Modifying Therapy

- Lecanemab (Lequemi™)
- Donanemab (Kisunla™)

} MCI / early AD

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Alzheimer's Association Applauds CMS Decision to Cover PET Imaging for Alzheimer's Disease Diagnosis

October 13, 2023
Email: media@alz.org

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— Association encourages regional MACs to ensure no delays —

CHICAGO, Oct. 13, 2023 — A valuable Alzheimer's disease diagnostic tool will now be more accessible across the country thanks to a policy change today by the Centers for Medicare & Medicaid Services (CMS). The Alzheimer's Association applauds CMS for taking action to expand coverage of brain amyloid positron emission tomography (PET) imaging for the diagnosis of Alzheimer's disease. In issuing its new policy, CMS said the specific details of the coverage will be made by the Medicare Administrative Contractors (MACs). The Alzheimer's Association urges

Alzheimer's Association, October 13, 2023

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Non-pharmacologic Therapy

- Exercise → increase in brain-derived neurotrophic factor (BDNF)
 - Released from astrocytes → repair of adjacent neurons ("brain fertilizer")
- Mediterranean diet
- Turmeric (curcumin)
 - Improved cognitive function
 - Degradation of plaques (animal models)

Mishra S, et al. *Ann Indian Acad Neurol* 2008

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- Management

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Thank you!

