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The Evolution of Alzheimer's Disease: Progress Over Decades

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Tucson Osteopathic Medical Foundation
Silver Anniversary Meeting
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Disclosures

- I am a “Baby Boomer” (one of 78 million)
- I am a geriatrician. *About half of my patients have cognitive impairment/dementia.*
- My favorite group are “super seniors”
- Both of my grandmother’s had AD
- I believe that progress has been made in AD and *there is hope for the future!*
- I believe every day above ground is a great day!

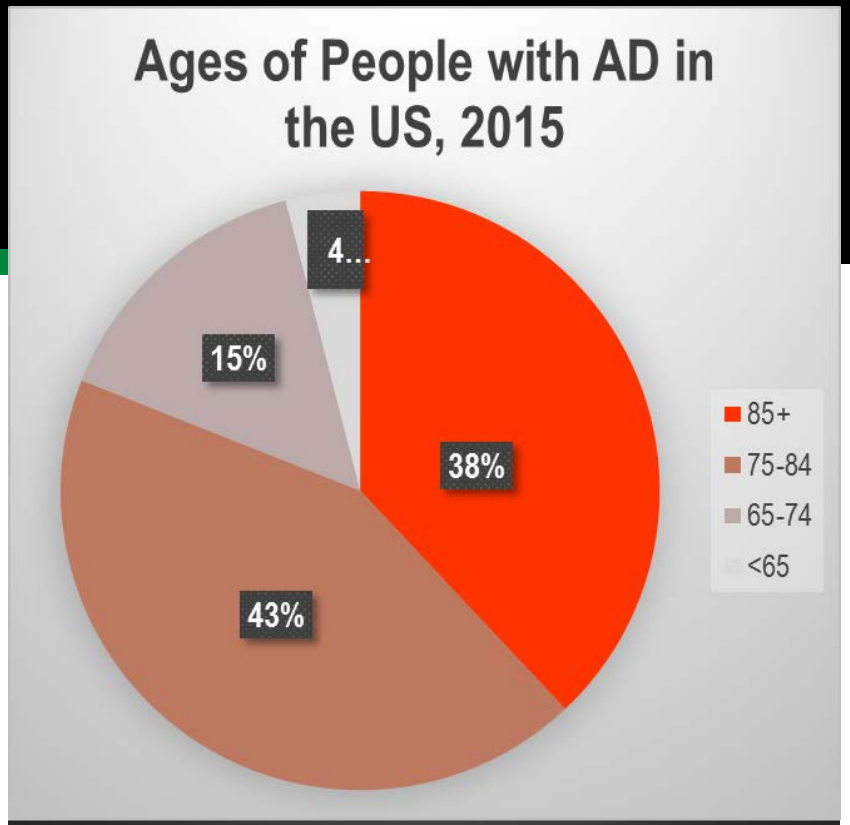
Objectives

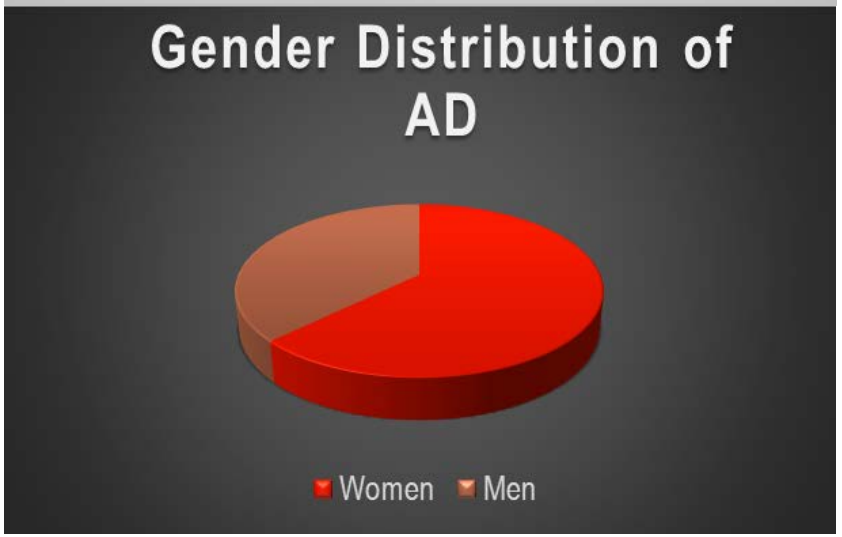
- Explore how the understanding of AD and dementia has changed in medicine
  (Major Milestones)
- Discuss advances in treatment and diagnosis of AD
- Review the Medicare Annual Wellness Visit
  Assessment of Cognition in Primary Care

Did You Know? Prevalence

- 5.3 million Americans with AD
- 5.1 million are age 65 and older
- 3.2 million women, 1.9 million men
- 1 in 9 people age 65 and older (11%) have AD
- 1 in 3 of people age 85 and older (32%) have AD

- 2015 Alzheimer's disease facts and figures. Available at: http://www.alz.org/downloads/Facts_Figures_2015.pdf





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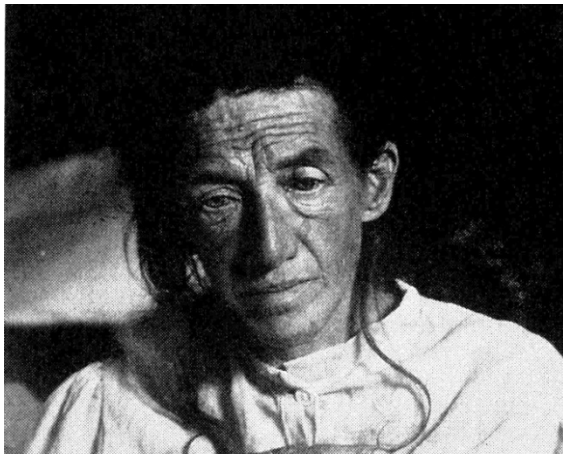
First Discovery: 1906-1960

- 1906 - Alois Alzheimer first described “a peculiar disease” with his patient, Auguste D
- 1952 – DSM 1 – Chronic Brain Syndrome with Senile Disease
- 1968 - Researchers develop the first validated measurement scale for assessing cognitive and functional decline in older adults



Modern Research Era: 1970-1979

- 1974 - Establishment of National Institute on Aging (NIA)
- 1976 - Neurologist Robert Katzman identified AD as the most common cause of dementia

NIH National Institute on Aging

Awareness and Momentum: 1980-1989

- 1980 - Formation of the Alzheimer's Association with Mr. J.H Stone as founding president
  - DSM III - Organic Brain Disorders/Organic Brain Syndromes
- 1983 - Congress designated November as National AD Month
- 1984 - Researchers George Glenner and Cai'ne Wong identified beta-amyloid
- 1983-84 - NINCDS-ADRDA criteria established for the clinical diagnosis of AD (Diagnosis Based on Clinical Judgement)

Awareness and Momentum: 1980-1989

- 1986 - Researchers discover that tau protein is a key component of tangles

- 1987 - The Alzheimer's Association assists the NIA and Warner-Lambert Pharmaceutical Company (now Pfizer) in launching and recruiting participants for clinical trials of tacrine - first drug specifically targeting symptoms of AD

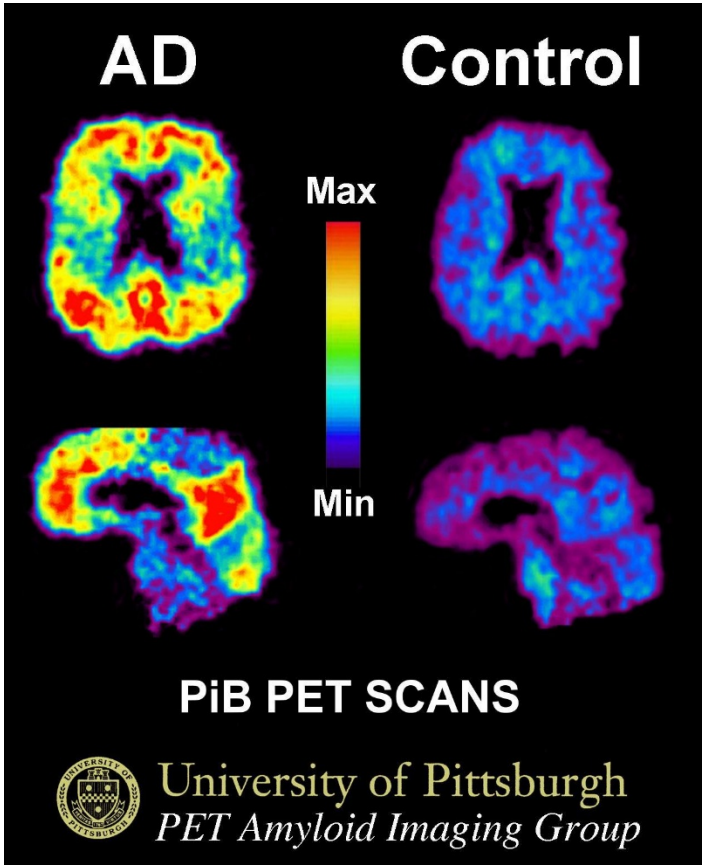
- 1989 – Texas Council on Alzheimer’s Disease and Related Disorders (TCADRD) established

Treatment Emerged: 1990-1999

- 1993 - First AD risk factor gene- APOE-e4, identified. The Food and Drug Administration (FDA) approved tacrine (Cognex) as the first approved Alzheimer's drug
- 1994 - President Ronald Reagan announced his diagnosis of AD. The first World Alzheimer's Day (WAD) launched on September 21
- 1995 - First transgenic mouse model announced
- 1999 - "Alzheimer's vaccine" successful in mice nationwide study to establish standards for obtaining and interpreting brain images

Progress and Hope: 2000-2009

- 2003 - National AD genetic study begins
- 2004 - First report on an imaging agent called Pittsburgh Compound B (PIB), a major potential breakthrough in disease monitoring and early detection
- 2004 - AD Neuroimaging Initiative- nationwide study to establish standards for obtaining and interpreting brain images
- 2005 - Alzheimer's and Dementia journal launched
- - Texas appropriation for AD Research with founding of TARCC



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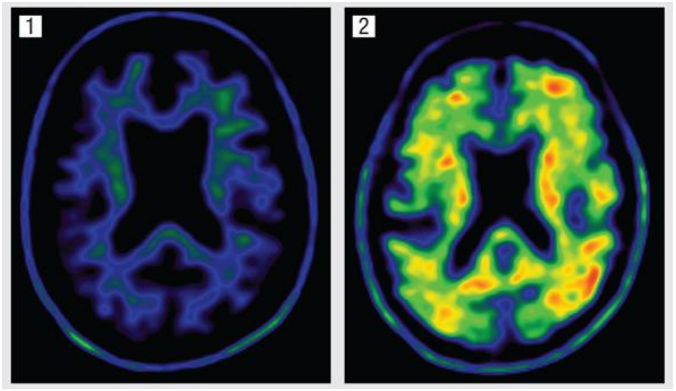
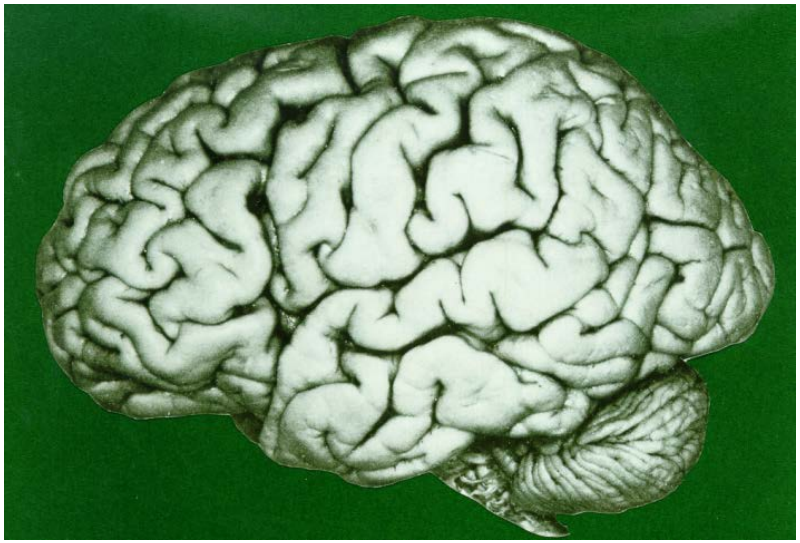
Setting a National Agenda: 2010-2019

- 2010 - AD clinical database established and TrialMatch was launched
- 2011 - President Obama signed the National Alzheimer's Project Act (NAPA) into law
- 2011 – NIA & Alzheimer's Association Workgroup new criteria and guideline for AD diagnosis developed (THREE stages of AD: preclinical, MCI, AD & Biomarkers included, notably in CSF and neuroimaging)
- 2012 - FDA approved a Florbetapir F18- new radiopharmaceutical agent to assist clinicians in detecting causes of cognitive impairment other than Alzheimer's disease
- 2014 - DSM 5 – Neurocognitive Disorder (Mild/Major)

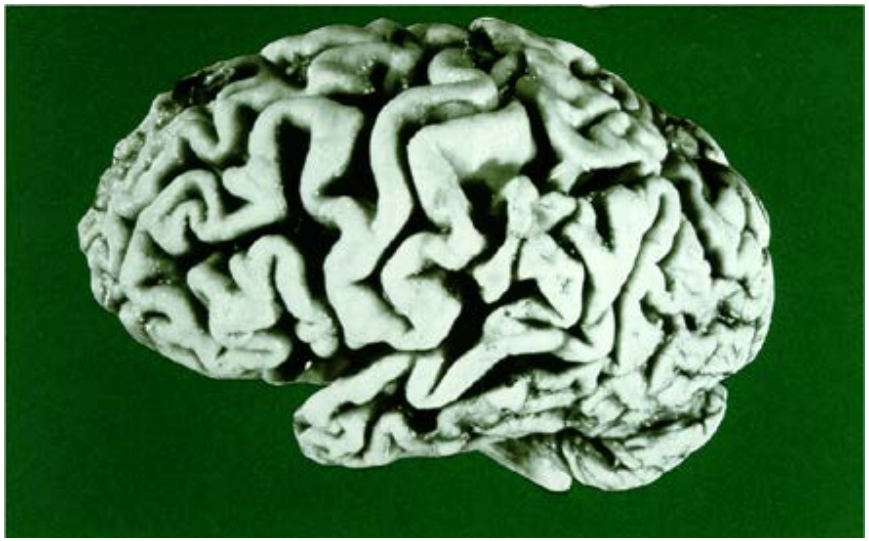


The Evolution of Alzheimer's Disease: Advances in Diagnosis & Treatment

- Normal Aging



- Abnormal Aging



Normal aging

- Age-related forgetfulness is normal
  - Misplacing keys, glasses, etc.
  - Forgetting names of acquaintances
  - Occasionally forgetting an appointment
  - Forgetting the reason for entering a room
- People with age-related forgetfulness can still:
  - Function independently and pursue normal activities
  - Recall incidents of forgetfulness
  - Find their way to familiar places
  - Hold a conversation with no difficulty
  - Behave appropriately

Memory loss and aging. Available at: http://www.helpguide.org/life/prevent_memory_loss.htm.

Normal Aging

- *65 – 75 years of age*: no significant changes in major domains of cognitive functioning
- **≥ *75 years of age***: decline in processing speed, word finding, semantic memory, episodic memory and procedural memory – vocabulary not affected
- **≥ *85 years of age***: decline is even greater
- Level of decline correlated with:
  - Education
  - General physical health
  - Age

Small B J et al. J Gerontol B Psychol Sci Soc Sci 2010;geronb.gbq093

Abnormal Aging

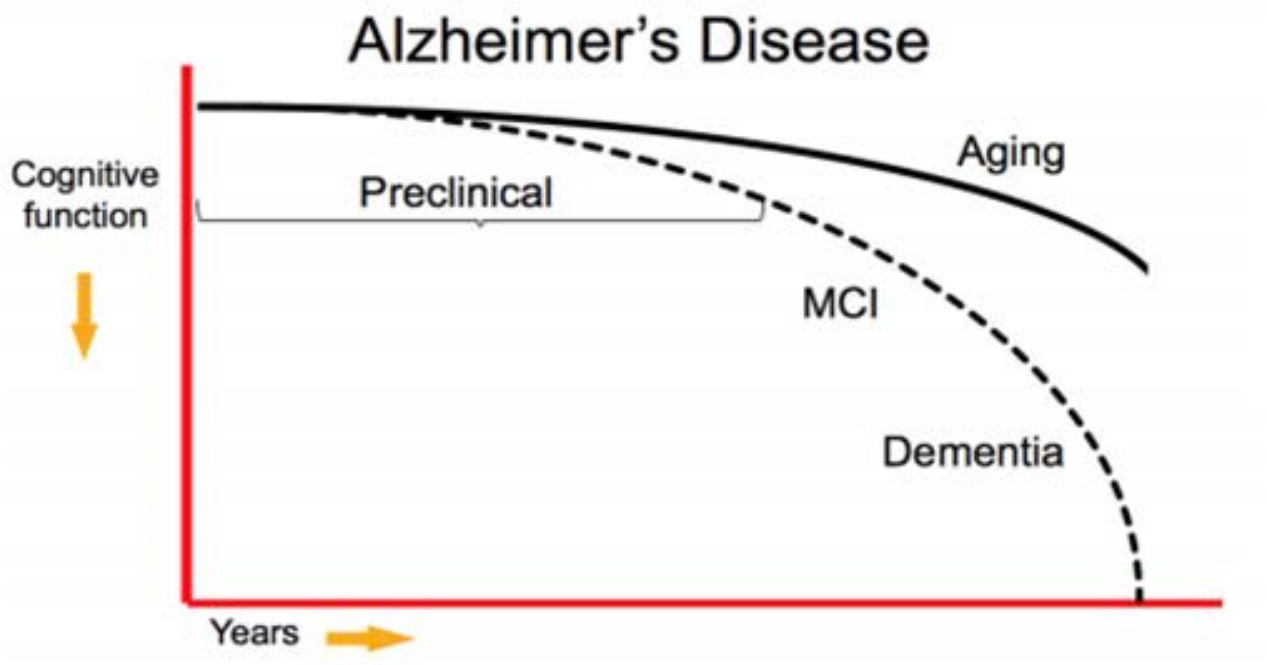
- Troublesome signs
  - Being repetitive and not just for emphasis
  - Not recalling that conversations or events ever took place
  - Difficulty with appointments and time frames
  - Losing established abilities

Person may not realize that there is a memory problem

The 3 Stages of Alzheimer's Disease

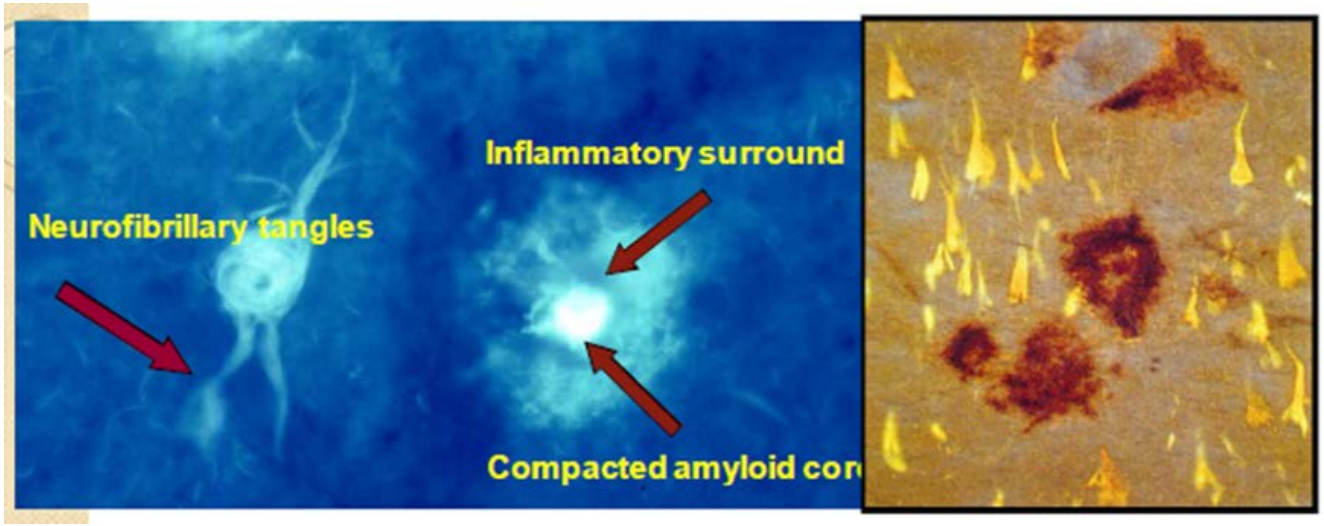
- Preclinical: must have measurable changes in brain (MRI, PET), CSF, or blood before any cognitive symptoms present
- MCI Due to AD (Prodromal AD in IWG terminology)
  - Single domain impaired, usually memory, below expected for age and education
  - Measurable changes in brain (MRI, PET), CSF, or blood
- Dementia Due to AD
  - 2 domains impaired
  - Biomarkers show amyloid accumulation in brain
  - Biomarkers showing brain injury or degeneration

Model of Clinical Trajectory of AD



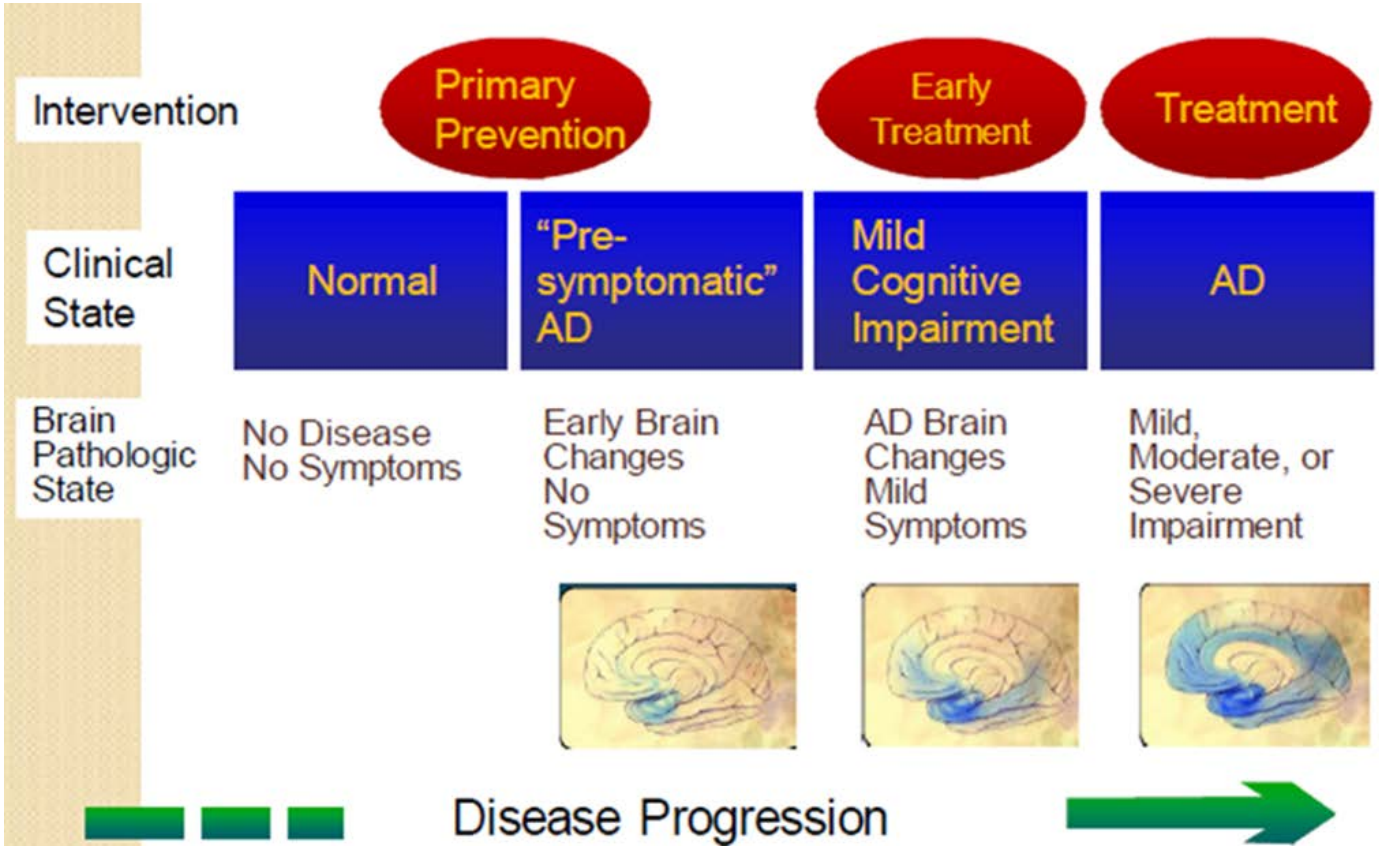
Preclinical Alzheimer's Disease Workgroup. Criteria for Preclinical Alzheimer's Disease, Alzheimer's Association- NIH, June 2010

Defining AD Pathology: Neurofibrillary Tangles & Amyloid (Neuritic) Plaques

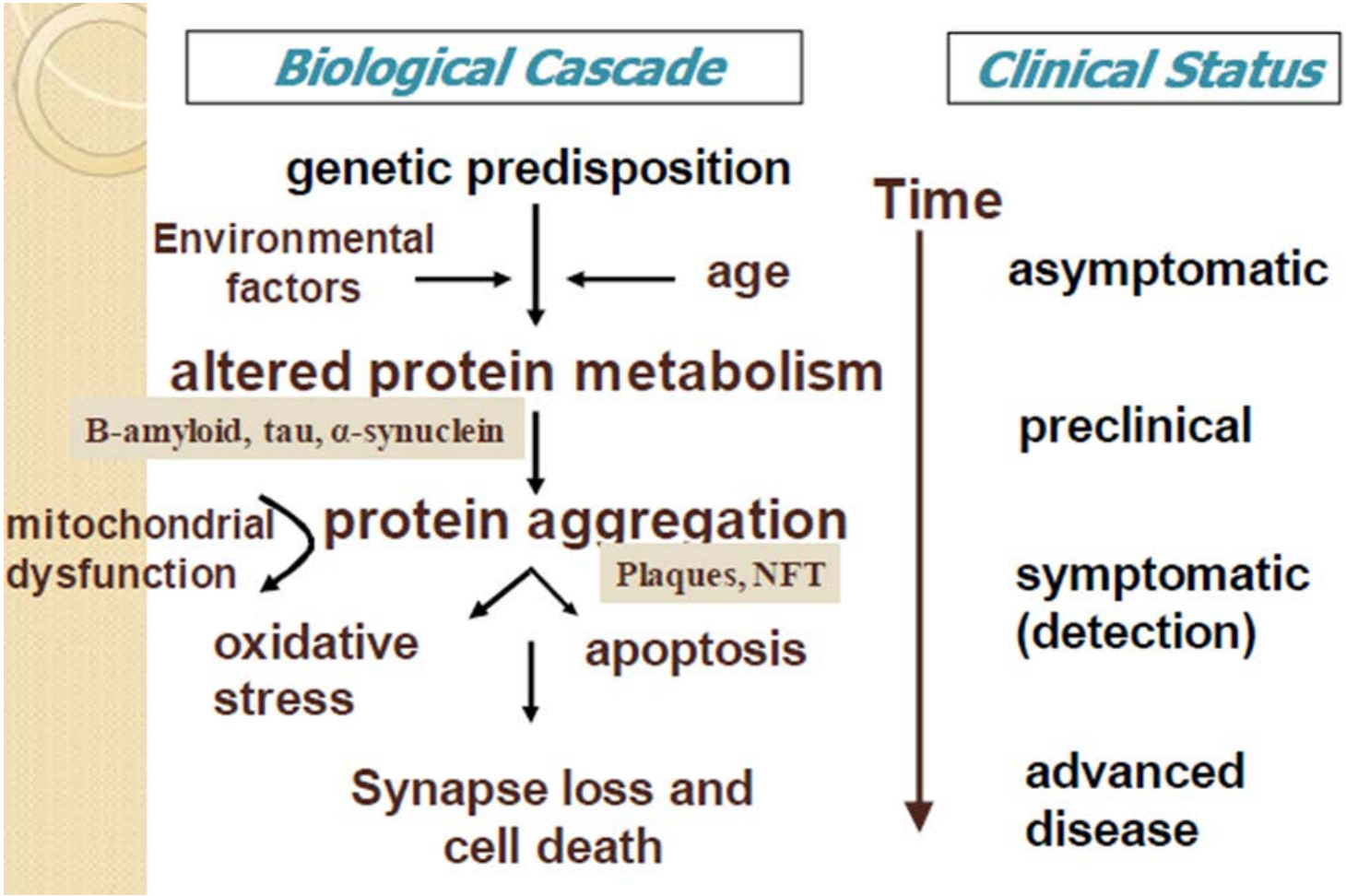


- The inflammation consists of distorted/degenerating synaptic processes, activated microglia, and astrocytic processes
- Plaques and tangles do not appear everywhere in brain, but only in certain areas, especially those involved in thinking and memory
- Also: inflammation, oxidative stress, nerve cell death, loss of neurotransmitters that communicate with other nerve cells, atrophy

Alzheimer's Disease: A Continuum of Pathological & Clinical Progression



Mechanisms in Neurodegeneration



Mild Cognitive Impairment/ Mild Neurocognitive Disorder (NCD)

- Mild NCD: Evidence of modest cognitive decline, but decline does NOT interfere with everyday activities
- MCI patients typically have no trouble with ADL functioning but struggle with executive functioning.

Criteria for Mild Cognitive Impairment (MCI)

European consensus[1]	Peterson[2]	NIA 2011 guidelines
• Cognitive complaint • Decline in cognitive function relative to previous abilities in the past year • Cognitive disorders as evidenced by clinical evaluation • Absence of major repercussions on daily life • Absence of dementia	• Memory complaint • Impaired memory function for age and education • Preserved cognitive function • Intact ADL • Not demented	• Cognitive complaint • Impairment in at least one cognitive domains • Intact ADL • Not demented

[1]Portet F, et al. Mild cognitive impairment (MCI) in medical practice: a critical review of the concept and new diagnostic procedure. Report of the MCI Working Group of the European Consortium on Alzheimer's Disease. J Neurol Neurosurg Psychiatry 2006;77:714-18.
[2]Peterson RC, et al. Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985-92.
[3]Albert MS, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dementia 2011;7:270-9.

Dementia/ Major Neurocognitive Disorder (NCD) Diagnostic Criteria

A. Evidence of significant cognitive decline from prior level of performance or in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor or social cognition) based on:
   1. Concern of individual, knowledgeable informant, or clinician that there has been decline
   2. Modest impairment in cognitive performance from neuropsychological or clinical assessment

B. Interference with daily IADLs/ADLs

C. Rule out delirium

D. Deficits not caused by other mental disorders

Alzheimer's Disease/ NCD due to AD Diagnostic Criteria

- Major or Mild NCD
- Insidious onset and gradual progression
- Meet criteria of possible or probable
- No other medical cause
- Probable Major NCD if both 1 and 2 met, otherwise possible Major NCD:
  1. Positive genetic mutation or family history
  2. All of the following:
     a. Decline in memory and learning plus 1 other cognitive domain
     b. Insidious, gradual with brief plateaus
     c. No mixed etiology

Alzheimer's Disease / NCD due to AD

- Prevalence – 11% age 65 and above, 32% age 85 and above;60-80% dementia cases
- Development and Course
  - Progressive neurodegenerative brain disorder
  - 10-20 years
- Genetic & Risk Factors
  - AGE!!!
  - Family History
  - ApoE gene (late-onset AD)
  - Mutations of APP, presenilin 1 & presinilin 2
  - MCI
  - Cardiovascular Disease
  - Education
  - Social and Cognitive Engagement
  - Traumatic Brain Injury (TBI)

2015 Alzheimer's disease facts and figures. Available at: http://www.alz.org/downloads/Facts_Figures_2015.pdf

Diagnosis: History and physical

Pertinent information to gather from history

- *What changes in memory/behavior have taken place?*
  - Aphasia, apraxia, agnosia, anomia
  - Onset, duration, and progression of these changes?
  - Decline from usual activities?
  - Neuropsychiatric symptoms
  - Current and new medications
  - Sleep disturbance
- *Are there any relevant comorbidities?*
  - Seizures, diabetes, CVAs, hypertension, HLD, TBI, depression
- Obtain history from family/close friend

Pertinent components of physical exam & testing

- ADL (Katz)/ IADL functioning (Lawton-Brody)
- Focused neurological evaluation: frontal release signs, Extrapyramidal signs, lateralization
- Alcoholism screen: CAGE ≥2 cutoff
- Depression test: Geriatric Depression Scale (GDS)
- Neurosyphilis screen: VDRL/RPR in HIV+ patients
- Laboratory studies: CBC, CMP, B_{12}/folate, methylmalonic acid, homocysteine, TSH
- Diagnostic studies: brain imaging (MRI, CT, PET scans)
- In-depth cognitive evaluation

Additional Diagnostics

A. Changes in structural or functional brain imaging
   1. Volumetric MRI – atrophy of hippocampus, basal & lateral temporal lobes, medial parietal cortex
   2. Single Photon Emission CT (SPECT) – decreased blood flow in parietal and/or temporal regions
   3. Positron Emission Tomography (PET) Scan – decreased glucose metabolism in parietal and/or temporal regions
   4. AV45 or Amyvid – Increased PET imaging of amyloid

B. Spinal fluid analysis
   1. Low CSF amyloid-beta 42, and/or elevated CSF total tau or phosphor-tau

C. Genetics
   1. Presence of an autosomal dominant gene mutation

      (APP, Presenilin 1, Presenilin 2)

Making the Diagnosis of AD

- No longer a diagnosis of exclusion!
- Indifference, denial or lack of concern is common (confusion with “normal aging”)
- Anecdotes help make the diagnosis
- Biomarkers developing for general use; expensive, not yet covered by Medicare or 3rd party insurance.
- Evidence-based diagnosis guidelines

Treatment initiation

- Symptomatic treatment of dementia
- What is the patient's/family's goal?
- Is pharmacologic therapy acceptable/affordable?
- Pharmacologic options
  - Cholinesterase inhibitors (CHEI's)are the standard of care for Alzheimer's disease
    - Rivastigmine tartrate : for mild to moderate Alzheimer's disease
    - Galantamine : for mild to moderate Alzheimer's disease
    - Donepezil: for mild, moderate to severe Alzheimer's disease
  - NMDA receptor antagonist
    - Memantine: for moderate to severe Alzheimer's disease
  - Combination NMDA/CHEI
    - Memantine/Donepezil: for moderate to severe Alzheimer's disease

Treatment initiation

- Treatment of comorbidities
  - Diabetes
  - Hypertension
  - Hypothyroidism
  - Hyperlipidemia
  - CHD
  - CKD
  - COPD

Comorbidities

Coexisting Condition	Percentage of People with Alzheimer's Disease and Other Dementias Who Also Had Coexisiting Medical Condition
Coronary Heart Disease	30%
Diabetes	29%
Congestive Heart Failure	22%
Chronic Kidney Disease	17%
Chronic Obstructive Pulmonary Disease	17%
Stroke	14%
Cancer	9%

Created from unpublished data from the National 20% Sample Medicare Fee-for Service Beneficiaries for 2009.

Behavioral and Psychological Symptoms of Dementia

- Apathy
- Depression
- Anxiety
- Agitation
- Psychosis
- Sleep Disturbance
- Dis-inhibition/Perseveration

Principles of management BPSD

- Dementia drugs reduce BPSD
- Look for avoidable triggers
- Some behaviors may need medications eg antidepressants, antipsychotics, anxiolytics
- The risk/benefit ratio of antipsychotic meds is controversial
- Sleep disturbance and anxiety should try to be managed nonpharmacologically
- Engagement in activities

Holmes etal Neurology 2004:63:214-219;
Doody etal Neurology 2001; Schneider etal NEJM 2006;355(15):1525-1538

Overview of AD Therapies

- Symptomatic Improvement (cognitive and behavioral)
  - Current medications (donepezil, galantamine, rivastigmine, memantine)
- Non-specific therapies
  - Antioxidants, anti-inflammatory agents, others
  - None so far successful
- Specific therapies
  - Anti-amyloid therapy
  - Anti-neurofibrillary tangle strategies (“anti-tau”)
  - Neurotrophins
  - APOE modifiers (make E4 act like E3?)
  - Others?
    - Genetics-guided interventions: stem cells? Transformed cells? Virus vectors with appropriate therapy?

Anti-Amyloid Mechanisms in AD Medications

- Enzyme inhibitors:
  - Beta secretase inhibitors (in trials)
  - Gamma secretase inhibitors in modulators
    - (failed trials thus far; toxicity)
- Passive immunotherapy
  - Monocional antibodies (some have failed; several others in trials)
  - Immunoglobulin G (trial failed)
- Active immunotherapy (“vaccine”)
  - Immunize with beta amyloid or a fragment of it
  - Several types under evaluation or entering trials
- Anti-aggregation compounds
  - None successful so far

Dementia Prevention Objectives

- Identify presymptomatic persons at elevated risks
- Take action (public health measures) to prevent dementia or significantly delay onset, e.g., exercise, diet
- Treat asymptomatic persons with disease-modifying medications to delay onset of symptoms in dementia
- Prior prevention trials either negative (Ginkgo GEM trial; DeKosky et al, 2009) or stopped for toxicity (ADAPT, NSAIDs; WHIMS (estrogen, estradiol)
- Barring breakthrough in design, such studies will take years to complete
- Regulatory agencies are easing the restrictions to allow more rapid answers to emerge
- Several prevention trials underway currently

Current Prevention Initiatives

- API (Alzheimer Prevention Initiative)
  - PS I families in Antioquia, Columbia (F. Lopera) (crenezumab)
  - APOE e4/e4 carriers, Arizona (BACE inhibitor, and an active vaccine CAD 106)
- DIAN (Dominantly Inherited Alzheimer Network)
  - Familial, early-onset AD (North America) (solanezumab and gantenuramab)
- A4 (Anti-Amyloid Treatment in Asymptomatic Alzheimer's)
  - Normal subjects with positive amyloid scans, 2 years
  - Primary outcome: cognition; B-amyloid, hippocampal atrophy (solanezumab)
- A5 (similar to design A4, using BACE inhibitor)
- AD-4833/TOMM40
  - Pioglitazone prevention trial
- MAPT, FINGER, others
  - 3 year follow-up, requirements for frailty, cardiovascular risks; interventions: food supplements, nutritional, strength and aerobic exercise, cognitive training, socialization, management of metabolic & vascular risk factors

Disease-Modifying Mechanisms: The Key to Slowing or Preventing AD

- Medications that slow primary pathology of amyloid plaques, formation of neurofibrillary tangles, inflammation, and other mechanisms
- Lifestyle changes associated with lowering risk of AD: exercise, diet, cognitive activity
- Prevention starts with midlife health activities

Nonpharmacologic considerations

- Address behavioral issues with caregiver and patient, providing information on specific community resources to aid in each situation, wherever possible.
  - Home safety/ Firearms
  - Driving
  - Finances
  - Medication management
  - Living arrangements
- Discuss advanced care planning.
  - Advanced directive/Medical Power of Attorney/OOH-DNR
  - Durable Power of Attorney
  - Artificial Nutrition and Hydration (ANH)
- Prepare caregivers/families that decline is inevitable.[1]
  - Slow progression: loss of <2 MMSE points/year
  - Intermediate progression: loss of 2-4 MMSE points/year
  - Rapid progression: loss of ≥5 MMSE points/year

[1]Doody R, et al. A method for estimating progression rates in Alzheimer disease. Arch Neurol 2001;58:449-54

Caring for the caregiver!!!!

Educational intervention

- Provide information about the disease.
- Provide information about community resources (legal assistance, respite care, financial issues, etc).
- Demonstrate how to effectively respond to symptoms of the disease.

Supportive intervention

- Suggest support groups for caregivers (professionally or peer-led).
- Alzheimer's Association
- Direct caregiver to helpful websites.

Psychotherapy

- If available and necessary, recommend visiting a trained therapy professional who can teach skills, such as self-monitoring, problem-solving, time management, and re-engagement in hobbies/enjoyable activities.

Sörensen, S, et al. How effective are interventions with caregivers? An updated meta-analysis. Gerontologist 2002;42:356-72.

Medicare Annual Wellness Visit (AWV)

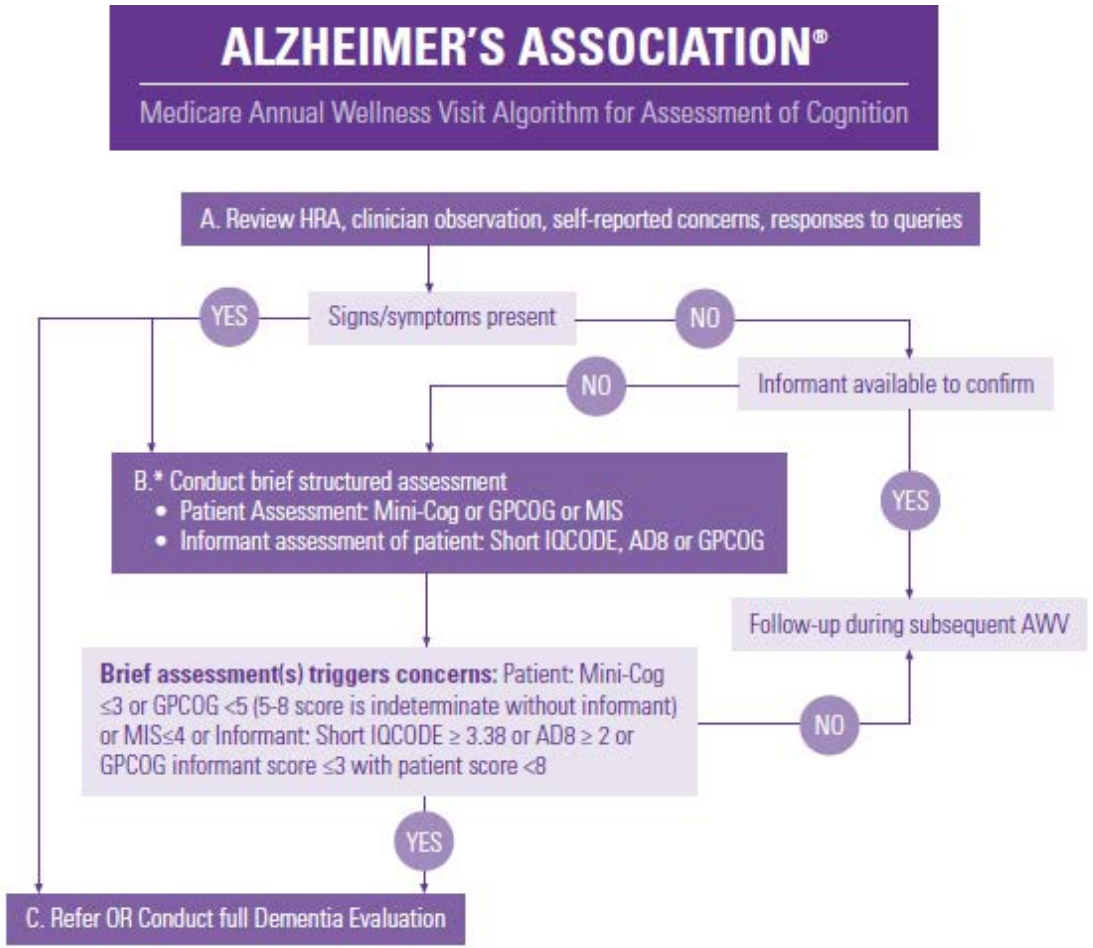
- ACA 2010 added AWV effective 1/2011
- Components of AWV: HRA, ht, wt, BMI, BP measurements; Review of medical and family hx; Assessment to detect cognitive impairment; Establishment of list of current medical providers, medications & schedule for future preventive services
- During 1st AWV only: screened for depression & functional difficulties
- CMS: the AWV requires detection of cognitive impairment by "assessment of an individual's cognitive function by direct observation, with due consideration of information obtained by way of patient report, concerns raised by family members, friends, caretakers or others"
- CMS: "No nationally recognized screening tool for detection of cognitive impairments at present time…"

Alzheimer's Association: Cognitive Assessment Toolkit

- Medicare Annual Wellness Visit Algorithm for Assessment of Cognition
- 3 Validated Patient Assessment Tools:
  - GPCOG, MIS and Mini-Cog
- 3 Validated Informant Assessment of Patient Tools:
  - Short IQCODE, AD8 and GPCOG
- "Alzheimer's Association Recommendations for Operationalizing the Detection of Cognitive Impairment During the Medical Annual Wellness Visit in a Primary Care Setting"

Alz & Dementia 9(2013) 141-150

Alzheimer's Association: Medicare Annual Wellness Visit Algorithm for Assessment of Cognition



* No one tool is recognized as the best brief assessment to determine if a full dementia evaluation is needed. Some providers repeat patient assessment with an alternate tool (e.g., SLUMS, or MoCA) to confirm initial findings before referral or initiation of full dementia evaluation.

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Patient Assessment Tools

GPCOP, MIS and Mini-Cog

- Requires 5 minutes or less
- Validated in primary care or community setting
- Easily administered by medical staff members
- Relatively free from educational, language and/or cultural bias
- Use by clinicians without payment for copyrights

Screening tool	Areas assessed	Time to administer	Who can administer	Specificity	Sensitivity
MoCA: Montreal Cognitive **Assessment (cutoff point ≥** 26)	Attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation	10 min	Clinician	87%	100%
Mini-cog	Recall and visuospatial abilities	2-4 min	Clinician	89%	76%
MMSE: Mini Mental State Exam (cutoff point = 25)	Orientation, registration/recall, attention and calculation, and language	10 min	Clinician	84%	76%
SLUMS: St. Louis University Mental Status exam	Orientation, registration/recall, remote memory, visuospatial skills, attention, abstraction, and executive function	7 min	Clinician?	98%	98%
IQCODE (informant questionnaire for cognitive decline in the elderly) - short	Informant based: executive functions, cultural experience	6-10 min	Anyone	>75%	>75%
Clock drawing test	Visuospatial abilities, executive functions, semantic processing, global and diffuse cognitive abilities	1-2min	Clinician	77%	87%
General practitioner assessment of cognition (GPCOG)	Similarities with mini-cog, recall, executive function, visuospatial abilities, orientation.	6 min	Clinician	86%	85%
MIS: Memory impairment screen (cutoff point ≤ 5)	Subjective memory loss	10 min	Clinician	98%	45%
AD8	Orientation, recall, executive function, and interest in activities	1-3 min	Anyone	86%	85%

Should We Screen or Assess for Cognitive Impairment?

Yes

- It is important to know
- Early detection allows better outcomes (not proven to USPSTF)
- Able to plan early (vigilance about overseeing finances)
- Avoiding domestic and driving accidents
- Living arrangements
- Sense of uncertainty removed from family and from patient (assuming workup is completed)

Should We Screen or Assess for Cognitive Impairment?

No

- Benefits not proven
- Potentially increases costs for care, for positive and false positive cases
- Increased time/ cost for providers
- Increases anxiety/fear/avoidance by patients and families

Alzheimer's Association App

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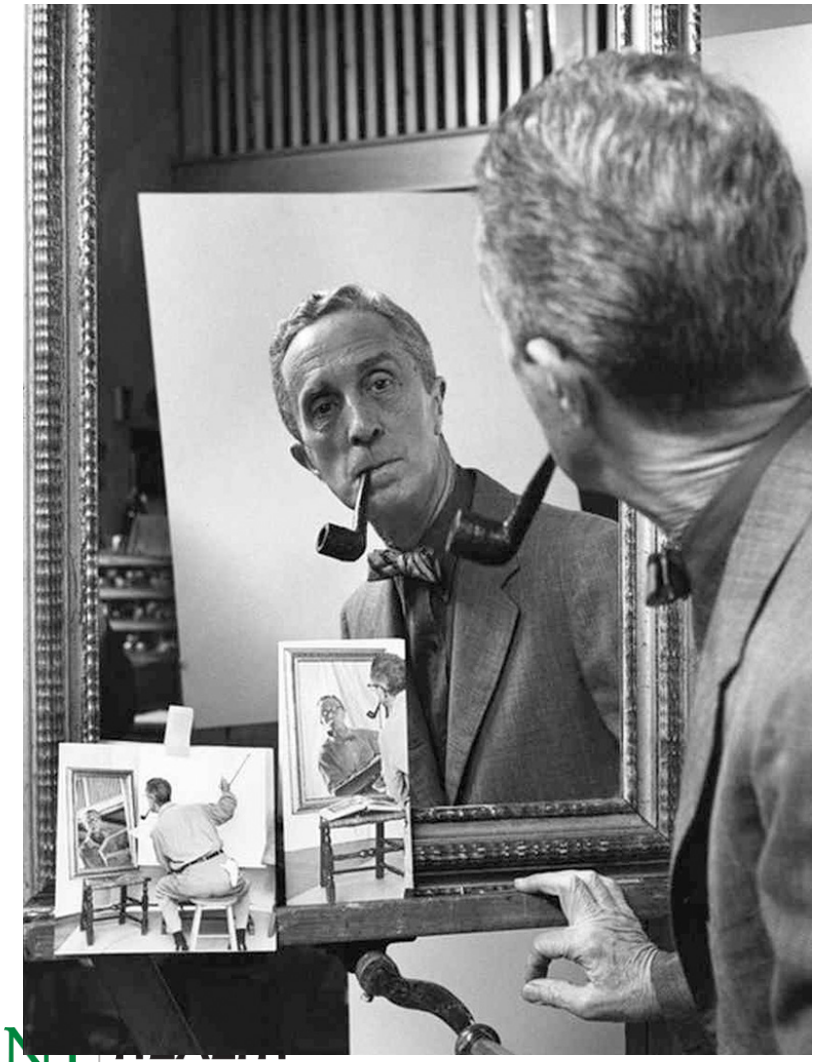
Notable Celebrities Diagnosed with Alzheimer's



- Norman Rockwell
  (1894-1978)
  One of the most famous American painters, became well known for his illustrations on the cover of the Saturday Evening Post.

Notable Celebrities Diagnosed with Alzheimer's

- **Ronald Reagan**
  (1911 – 2004)
  Actor appearing in more than 50 films and served as president of the Screen Actor's Guild. He served two terms as governor of California, then served two terms as U.S. President, beginning in 1980.

Notable Celebrities Diagnosed with Alzheimer's

- **Sugar Ray Robinson**
  (1921-1989)
  Recognized as one of the greatest boxers in history, he held the welterweight and middleweight title belts, and finished with a final record of 173 wins, 19 losses and 2 draws.

Notable Celebrities Diagnosed with Alzheimer's

- **Charlton Heston**
  (1923 – 2008)
  Oscar-winning film actor known for portraying historic and heroic roles. He championed the cause of civil rights with Dr. Martin Luther King, and was awarded the Presidential Medal of Freedom in 2003.

Notable Celebrities Diagnosed with Alzheimer's

- **Glen Campbell**
  (1936 –)
  Country singer and guitarist, has released more than 70 albums, has sold 45 million records and accumulated 12 RIAA Gold albums, 4 Platinum albums and 1 Double-Platinum album, and a historical win of four Grammy's in 1967

Notable Celebrities Diagnosed with Alzheimer's

- **Pat Summitt**
  (1952 –)
  Coached the Tennessee Lady Vols basketball team an amazing 8 NCAA championships and retired with a record of 1,098-208.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