Alzheimer’s & Cognitive Impairment:
You already told us that story!

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Alzheimer’s Association
OVERVIEW

• Impact of AD & New Framework
• Revised diagnostic criteria
  • Impact new criteria might have on clinical medicine over the next several years
• Current status/direction of Alzheimer’s research
• Screening for cognitive impairment in the primary care setting – tools used and value
Prevalence of Alzheimer’s Disease

• There are an estimated 5.4 million Americans with Alzheimer’s disease (AD) in 2011.
  – This figure includes the 5.2 million people aged 65 and older.
  – Twenty-two percent of older people with AD are dually eligible.
Progression of Alzheimer’s

- Most people survive an average of four to eight years after an Alzheimer’s diagnosis, but some live as long as 20 years with the disease.
- On average, 40 percent of a person’s years with Alzheimer’s are spent in the most severe stage of the disease – longer than any other stage.
- Four percent of the general population will be admitted to a nursing home by age 80. But, for people with Alzheimer’s, 75 percent will be admitted to a nursing home by age 80.
Alzheimer’s and Mortality

• Alzheimer’s is the 6th leading cause of death across all ages and the 5th leading cause of death for those aged 65 and older.

• Alzheimer’s is the only cause of death among the top 10 in America without a way to prevent, cure or even slow its progression.

• Deaths from Alzheimer’s increased 66 percent between 2000 and 2008, while deaths from other major diseases decreased.

Change in the Number of Deaths Between 2000 and 2008

- Breast Cancer -3%
- Prostate Cancer -8%
- Heart Disease -13%
- Stroke -20%
- HIV -29%

Based on preliminary 2008 mortality data
2011 Cost of Alzheimer’s

Total: $183 Billion
Medicare and Medicaid: $130 Billion
Alzheimer’s Disease
Public Policy Efforts
National Alzheimer's Project Act (NAPA)

Largest legislative victory in many years for the Alzheimer's cause

**GOAL:** To create a coordinated national plan to overcome the Alzheimer's crisis and will ensure the coordination and evaluation of all national efforts in Alzheimer's research, clinical care, institutional, and home- and community-based programs and their outcomes.

**GOAL:** Prevent and Effectively Treat Alzheimer's Disease by 2025
• Advisory Council created on Alzheimer's Research, Care and Services mandated by the National Alzheimer's Project Act.
• The council advises the U. S. department of Health and Human Services in its development of a national plan for AD and related dementias.
• January 2012: First draft of the plan made public.
• DRAFT can be found at http://www.alz.org/join_the_cause_federal_update.asp
February 7, 2012
President Obama: We Can’t Wait!
• $50M 2012 for Research
• $80M 2013 for Research
• $26M 2013 for Care/Support

The Washington Post

Obama administration proposes raise for Alzheimer’s research, some now and some next year

By Associated Press, Updated: Tuesday, February 7, 11:19 A

WASHINGTON — The Obama administration is increasing spending on Alzheimer’s disease by 2025.
Modernizing the Diagnosis of Alzheimer’s Disease
Modernizing the Dx of Alzheimer’s Disease Based on a Continuum

<table>
<thead>
<tr>
<th>Normal</th>
<th>Pre-clinical</th>
<th>MCI</th>
<th>Alz dementia</th>
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<tbody>
<tr>
<td>No apparent symptoms; Biological/pathological changes occurring</td>
<td>Subjective problem in memory or another domain, informant corroborated and measurable on tests; normal overall cognition and ADLs</td>
<td>Clear deficits in 2 or more core cognitive domains; ADLs affected</td>
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Revised Dx of Alzheimer’s Dementia

• Cognitive and behavioral symptoms that impair an individual’s ability to function independently (not changed).

• Diagnostic certainty might be improved by incorporation of certain biomarker tests.
  – CSF, vMRI, amyloid imaging

• Reliability of these tests in everyday medical practice still needs to be tested.
Table 1
Summary of clinical and cognitive evaluation for MCI due to AD

Establish clinical and cognitive criteria
Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time)
Objective evidence of Impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains)
Preservation of independence in functional abilities
Not demented
Examine etiology of MCI consistent with AD pathophysiological process
Rule out vascular, traumatic, medical causes of cognitive decline, where possible
Provide evidence of longitudinal decline in cognition, when feasible
Report history consistent with AD genetic factors, where relevant
Mild Cognitive Impairment Due to AD

- Mild changes in memory and thinking abilities, not impairment that compromises independence/everyday activities.
- Challenge is distinguishing individuals with MCI who will develop Alzheimer’s dementia from those who do not.
- Criteria focus on the added benefit of biomarkers to help increase diagnostic accuracy in research settings.
• Proposed approaches are for research.
• Changes that may indicate very earliest signs of disease.
• Create standards for data collection; Can “preclinical” stage be defined?
• Experimental criteria call for measurement of blood and cerebrospinal fluid, vMRI and neuroimaging.
Preclinical AD Staging Framework

Stage 1
Asymptomatic amyloidosis
- High PET amyloid tracer retention
- Low CSF Aβ_{1-42}

Stage 2
Amyloidosis + Neurodegeneration
- Neuronal dysfunction on FDG-PET/fMRI
- High CSF tau/p-tau
- Cortical thinning/Hippocampal atrophy on sMRI

Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for MCI

MCI → AD dementia

Session 10: Cognitive Impairment
Modernizing the Dx of Alzheimer’s Disease Based on a Continuum

Normal | Pre-clinical | MCI | Alz dementia

- Research setting
- Early stages – no symptoms
- Biological markers
- Need validation

- Research setting
- Early stages – mild symptoms
- Biological markers
- Need validation

- Clinical setting
  Similar to criteria used today
  Use of biological markers supports diagnosis on other criteria
Operational Approach to Preclinical AD

An Operational Approach to NIA-AA Criteria for Preclinical Alzheimer’s Disease
Annals of Neurology Oct 2011

Clifford R. Jack, Jr., MD,*¹ David S. Knopman, MD,*²,³ Stephen D. Weigand, MS,⁴ Heather J. Wiste, BA,⁴ Prashanthi Vennum, PhD,¹ Val Lowe, MD,¹ Kejal Kantarci, MD,¹ Jeffrey L. Gunter, PhD,¹ Matthew L. Senjem, MS,¹ Robert J. Ivnik, PhD, LP,⁵ Rosebud O. Roberts, MBBCh,⁶ Walter A. Rocca, MD, MPH,²,⁶ Bradley F. Boeve, MD,²,⁶ Ronald C. Petersen, MD, PhD,²,³,⁶

• Pittsburgh compound B positron emission tomography (PET) imaging as biomarker of cerebral amyloidosis.

• 18fluorodeoxyglucose PET imaging and hippocampal volume as biomarkers of neurodegeneration.
• A group of 42 clinically diagnosed AD subjects was used to create imaging biomarker cut-points.
• A group of 450 cognitively normal (CN) subjects from a population based sample was used to develop cognitive cut-points and to assess population frequencies of the different preclinical AD stages using different cut-point criteria.
• The new criteria subdivide the preclinical phase of AD into stages 1-3.

• To classify CN subjects, two additional categories were needed.

• **Stage 0 denotes subjects with normal AD biomarkers and no evidence of subtle cognitive impairment.**

• **Suspected Non-AD Pathophysiology (SNAP) denotes subjects with normal amyloid.**
RECOMMENDATIONS:

• **Stage 0 denotes subjects with normal AD biomarkers and no evidence of subtle cognitive impairment.**

• **Suspected Non-AD Pathophysiology (SNAP) denotes subjects with normal amyloid**
  - 43% of our sample was classified as stage 0
  - 16% stage 1
  - 12% stage 2
  - 3% stage 3
  - 23% SNAP. (vascular pathology and synucleinopathy)

• 97% CN accounted for
Degrees of Prevention

1º Prevention

Preclinical

[Accumulation Pathology]

2º Prevention

MCI

3º Prevention

Dementia

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Urgency

- Studies to prove (or disprove) these hypotheses, this may take more than a decade.
- Need to estimate the likelihood and timeframe of progression to AD to weigh risk/benefit ratio of potential disease-modifying treatment in normal individuals.
- Secondary prevention trials in preclinical populations already in planning stages:
Future “Prevention” Trials

• OPAL: Opportunity for the Prevention of AD
  – Selection criteria is TOMM40, ND
  – Intervention TBA

• API: Alzheimer’s Prevention Initiative
  – Selection criteria undetermined
  – Intervention underdetermined

• DIAN: Dominantly Inherited Alz Network
  – No intervention at this time

• A4: Anti-Amyloid Treatment in Asymptomatic AD
  – Intervention undetermined
PET Amyloid Imaging: Pending Approval

PET Amyloid Imaging:
- AV-45 (Florbetapir, Avid)
- F18 Flutemetamol (GEHC)
- BAY 94-9172 (Florbetaben, Bayer)

US FDA Approval pending:
- To rule out the presence of amyloid in the brain
Amyloid PET Imaging: Pending Approval

- AV45 – Autopsy Study, 35 people with AD
- Amyloid load correlated with amyloid pathology at autopsy
Amyloid PET Imaging: Pending Approval

JAMA, 2011

**RED** = maximum uptake

**VIOLET** = minimum uptake
Appropriate Use Criteria are needed:

• Alzheimer’s Association and Society for Nuclear Medicine created a taskforce to develop Appropriate Use Criteria.
• Who should receive the scan?
• What does it mean?
• Who should NOT receive this scan?
• What should physicians know about this?
Accumulation of tau in the brain starts in the entorhinal cortex (EC) which functions as a hub in the brain’s network for memory and navigation.

The EC is the main interface between the brain’s memory center (the hippocampus) and the outer layers of the brain (the neocortex).
Trans-Synaptic Spread of Tau Pathology \textit{In Vivo}

Li Liu$^1$, Valerie Drouet$^1$, Jessica W. Wu$^1$, Menno P. Witter$^2$, Scott A. Small$^3$, Catherine Clelland$^1$, Karen Duff$^{1,*}$

• Article demonstrated that tau pathology initiating in the EC can spread to other synaptically connected brain areas as the mice age.

• This supports the idea that AD progresses via an anatomical cascade as opposed to individual events occurring in differentially vulnerable regions.

• Thus, this mouse model provides a model in which the spatial and temporal propagation of the disease can be predicted, and correlative functional outcomes can now be tested.
The Alzheimer’s Association strongly supported the inclusion of detection of cognitive impairment in the new Medicare Annual Wellness visit in the ACA. We are currently participating in the CMS/NIA workgroup on implementing this provision.
Cognitive Screening:

Annual Wellness Visit

• The Alzheimer’s Association convened a panel of experts to review available tools for detection of cognitive impairment.

• The workgroup plans to make recommendations and work with the provider community to implement best practices.

• Further, the Association is developing a clinical “decision tree” which will help providers choose the best tool, based on their practice patterns and patient demographics.
SUMMARY

• Alzheimer’s disease – 21st century health epidemic
• National Alzheimer’s Project Act: GOAL is 2025!
• Update on Current Research Trends
  – Establishing a modern Dx for Alzheimer’s disease
  – Future “Prevention” Trials
  – Pending Imaging Agent Approval
  – Medicare Wellness Cognitive Screen