Mileposts in Memory Loss: The Role of Biomarkers in Alzheimer’s Disease (AD)

Beau Ances MD, PhD, MSc, FANA, FAAN
Daniel J Brennan MD Professor of Neurology
Washington University in Saint Louis

Neurology Grand Rounds
October 19, 2018
Beau M. Ances, MD, PhD, MSc

Disclosure of Interest

National Institute of Nursing Research (NINR) (R01NR014449 and R01NR015738)

National Institute of Aging (U01AG052564, R01AG052550, 1R01AG057680)

National Institute of Mental Health (NIMH) (R01MH118031)

WUSTL Institute for Clinical and Translational Science (ICTS)

Clinical Trials
National Institute of Aging (NIA) (RC2AG036535)-Alzheimer’s Disease Neuroimaging Initiative (ADNI)

Consultant
None

Speakers Bureau
None

Alzheimer’s Association

Dr. Ances owns no stocks or equity in any pharmaceutical company
Objectives

• Introduction
  • Epidemiology and statistics

• AD biomarkers in the **clinical** and **research** arenas
  • Genetics
  • Clinical Dementia Rating (CDR) scale
  • Cerebrospinal fluid (CSF) amyloid and tau evaluations
  • Positron emission tomography (PET)
  • Magnetic resonance imaging (MRI) using resting state functional connectivity

• Timeline of biomarkers changes during AD
  • Healthy aging vs. preclinical AD
  • Symptomatic AD

• The **next generation of AD clinical trial**- early intervention
A 72 year old Caucasian female presents with cognitive changes.

For the past few years she has noted some very mild memory issues. She notes that she is repeatedly misplacing objects (i.e. car keys), occasionally missing appointments with friends, repeating words during a conversation, and forgetting the names of casual acquaintances.

She is still able to drive, manage her personal finances, and can operate home appliances (e.g. lawnmower).
“I Am Getting More Forgetful”- Part 2

Past Medical History: Hypertension

Family history: Mother and uncle died of “some kind of memory problem” at ~80 years old

Meds: Quinapril

Exam: Female who is sitting in no apparent distress
Cranial nerves: Intact 2-12
Motor: Normal tone and bulk, 5/5 throughout
Sensory: Diminished sensation below the knees
Reflexes: 2+ upper extremities, 2+ patellar, 1+ at ankles
Coordination/ Gait: Normal
The AD Tsunami

It's the only cause of death in the top 10 in America that CANNOT BE PREVENTED, CURED OR SLOWED.

Almost two thirds of Americans with Alzheimer’s disease are women.

1 in 3 seniors dies with Alzheimer’s or another dementia.

6: Alzheimer’s disease is the 6th leading cause of death in the United States.

[Diagram showing: Only 45% of people with Alzheimer’s disease or their caregivers report being told of their diagnosis. More than 90% of people with the four most common types of cancer have been told of their diagnosis.]

By 2050, these costs could rise as high as $1.1 trillion.

In 2015, Alzheimer’s and other dementias will cost the nation $226 billion.
Hidden Costs of Dementia: Effects on Caregiver and Society

In 2014, 15.7 million family and friends provided 17.9 billion hours of unpaid care to those with Alzheimer’s and other dementias care valued at $217.7 billion.

In fact, due to the physical and emotional toll of caregiving, Alzheimer’s and dementia caregivers had $9.7 billion in additional health care costs of their own in 2014.

Nearly 60% of Alzheimer’s and dementia caregivers rate the emotional stress of caregiving as high or very high; about 40% suffer from depression.

One in five of older female dementia caregivers has high depressive symptoms, twice the rate seen in caregivers of people with other disorders, an NIA-funded study showed.

In the clinic, we are often treating at least two individuals:

• Patient
• Caregiver/family member(s)
Hallmarks of AD Pathology: Amyloid and Tau

- Amyloid plaques
- Tau tangles

- Definitive diagnosis of AD is made at autopsy
AD Consists of Preclinical and Symptomatic Stages

<table>
<thead>
<tr>
<th></th>
<th>Normal Aging</th>
<th>Preclinical AD</th>
<th>Symptomatic AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amyloid Plaques</strong></td>
<td>None or a few diffuse plaques</td>
<td>Many plaques (diffuse &gt; neuritic)</td>
<td>Many plaques (diffuse &gt; neuritic)</td>
</tr>
<tr>
<td>in neocortex</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Tau Tangles</strong></td>
<td>Few to many (increases w/age)</td>
<td>Many</td>
<td>Many</td>
</tr>
<tr>
<td>in entorhinal cortex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and hippocampus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cell loss</strong></td>
<td>None</td>
<td>Little to none</td>
<td>Substantial (30%-60%)</td>
</tr>
<tr>
<td>in entorhinal cortex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical diagnosis</strong></td>
<td>Normal, CDR 0</td>
<td>Normal, CDR 0</td>
<td>Very mild dementia or MCI, CDR 0.5</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Pathological diagnosis</strong></td>
<td>Normal</td>
<td>AD</td>
<td>AD</td>
</tr>
</tbody>
</table>

AD Biomarkers
Genetic Biomarkers for Evaluating AD in the Research Setting

- Family history increases risk for developing AD
- Presence of one apolipoprotein ε4 (APOE4) allele increases AD risk by 4 fold and 2 APOE ε4 alleles increases AD risk by 12 fold.
- Genetic mutations account for 1-3% of all AD worldwide. Most common mutations are amyloid precursor protein (APP), presenilin 1 and 2 (PSEN1 and PSEN2).
- Down syndrome (APP triplicate) is associated with increased risk of AD.
Clinical and Neuropsychological Performance Testing for Evaluating AD in the Clinical Setting

**Clinical Dementia Rating (CDR) Scale**

<table>
<thead>
<tr>
<th>Impairment</th>
<th>None</th>
<th>Questionable</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Memory</strong></td>
<td>No memory loss or slight inconsistent forgetfulness</td>
<td>Consistent slight forgetfulness; partial recollection of events; &quot;benign&quot; forgetfulness</td>
<td>Moderate memory loss; more marked for recent events; defined interference with everyday activities</td>
<td>Severe memory loss; only highly learned material retained; new material rapidly lost</td>
<td>Severe memory loss; only fragments remain</td>
</tr>
<tr>
<td><strong>Orientation</strong></td>
<td>Fully oriented</td>
<td>Fully oriented except for slight difficulty with time relationships</td>
<td>Moderate difficulty with time relationships; oriented to place of examination; may have geographic disorientation elsewhere</td>
<td>Severe difficulty with time relationships; usually disoriented to time, often to place</td>
<td>Oriented to person only</td>
</tr>
<tr>
<td><strong>Judgement &amp; Problem Solving</strong></td>
<td>Solves everyday problems and handles business and financial affairs well; judgement good in relation to past performances</td>
<td>Slight impairment in solving problems, similarities and differences</td>
<td>Moderate difficulty in handling problems, similarities and differences; social judgement usually maintained</td>
<td>Severe impairment in handling problems, similarities and differences; social judgement usually impaired</td>
<td>Unable to make judgements or solve problems</td>
</tr>
<tr>
<td><strong>Community Affairs</strong></td>
<td>Independent function at usual level in job, shopping, volunteer and social groups</td>
<td>Slight impairment in these activities</td>
<td>Mild but definite impairment of function at home; more difficult tasks abandoned; more complicated hobbies and interests abandoned</td>
<td>No pretense of independent function outside home</td>
<td>Appears well enough to be taken to functions outside the family home</td>
</tr>
<tr>
<td><strong>Homes &amp; Hobbies</strong></td>
<td>Life at home, hobbies and intellectual interests well maintained</td>
<td>Life at home, hobbies and intellectual interests slightly impaired</td>
<td>Requires assistance in dressing, hygiene, keeping of personal effects</td>
<td>Requires much help with personal care; frequent incontinence</td>
<td></td>
</tr>
<tr>
<td><strong>Personal Care</strong></td>
<td>Full capable of self-care</td>
<td>Needs prompting</td>
<td></td>
<td></td>
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- Scored in relation to the previous usual level of the patient
- Baseline and annual repeat testing can establish important trends in cognitive health

**Montreal Cognitive Assessment (MoCA)**

- Can be easily administered in the clinic
- Can be used with other neuropsychological testing to evaluate changes in cognition over time.

The patient is CDR 0 and scores a 26 on the MoCA
### Lumbar Puncture (LP) to Obtain CSF for Evaluating AD in the Clinical Setting

The spinal cord ends at L2

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
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<tbody>
<tr>
<td>Safe and easy procedure to perform</td>
<td>Invasive and requires trained expert</td>
</tr>
<tr>
<td>Reimbursed by insurance</td>
<td>Samples the entire brain and spinal cord</td>
</tr>
<tr>
<td>Can assist in differentiating AD from other neurodegenerative disease</td>
<td>Should be collected in the AM, fasting, and specific tubes</td>
</tr>
<tr>
<td>Spinal fluid is quickly replenished within a few hours</td>
<td>Results can vary depending on assay lot used</td>
</tr>
</tbody>
</table>
Amyloid PET for Evaluating AD in the Research Setting

Histology - Thioflavin T

Amyloid Plaques

Amyloid PET Imaging

PET Imaging - [\(^{11}\text{C}\)]6-OH-BTA-1 (PIB)

PET amyloid imaging is approved by the FDA but not compensated by insurance
Amyloid PET Correlates With Pathology

Clark et al., *JAMA*, 2011
Tau PET for Evaluating AD in the Research Setting

AV 1451

PET tau imaging is not approved by the FDA but is being used in clinical trials.
Quantitative Measurements of MRI Brain Volumes for Evaluating AD in the **Clinical** Setting
The Restless Brain: Resting State Functional Connectivity for Evaluating AD in the Research Setting

- The brain has high metabolic activity even at rest.
- Scans can be added to existing MRI protocols

Raichle, *Brain Connectivity*, 2011
Hypothetical Timelines for AD Biomarkers

Sperling et al., *Alz and Dem*, 2011; Alberts et al., *Alz and Dem*, 2011
National Institute of Aging (NIA) Stages of Preclinical AD

Stage 0 - cognitively normal and no biomarker evidence

Amyloid
Stage 1
Asymptomatic amyloidosis
- High PET amyloid tracer retention
- Low CSF Aβ₁₋₄₂

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

Neurodegeneration
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

Sperling et al., Alz and Dem, 2011
Albert et al., Alz and Dem, 2011
Are There Differences Between Healthy Aging and Preclinical AD?

Jack et al., Neurology, 2016
CSF Ab42 is Abnormal in Cognitively Normal Individuals With Preclinical AD

- Our patient has diminished CSF Ab42 (389 pg/mL), elevated CSF t-tau (612 pg/mL), and has elevated PET amyloid deposition (SUVR > 0.18)
CSF tau/Ab42 Ratio Predicts Progression to Symptomatic AD Over 5 years

Hansson et al., Lancet Neurol., 2006
Plasma Aβ42/40 Could Be a Potential Biomarker in Preclinical AD

- Using Stable Isotope Labeling Kinetics (SILK) Plasma Aβ42/40 values have been validated in additional cross sectional and longitudinal samples
- Plasma Aβ42/40 is related to amyloid PET scans and CSF Aβ42.

Ovod et al., Alz Dementia, 2017
Amyloid PET is Abnormal in Cognitively Normal Individuals With Preclinical AD

Figure 1: Illustration of biomarker staging of Alzheimer’s disease

Three elderly individuals are placed in order from left to right by use of our proposed biomarker staging scheme. (A) A cognitively normal individual with no evidence of Aβ on PET amyloid imaging with PiB and no evidence of atrophy on MRI. (B) A cognitively normal individual who has no evidence of neurodegenerative atrophy on MRI, but has significant Aβ deposition on PET amyloid imaging. (C) An individual who has dementia and a clinical diagnosis of Alzheimer's disease, a positive PET amyloid imaging study, and neurodegenerative atrophy on MRI.

Aβ=β-amyloid. PiB=Pittsburgh compound B.

Resting State Functional Connectivity is Different in Healthy Aging Compared to Preclinical AD

- Many studies overestimate the effects of aging
Stroop Intra-Individual Variability is a Preclinical Biomarker of AD and Correlates with Resting State Functional Connectivity

Duchek et al. *Neuropsychology*, 2009

Duchek et al., *Neuropsychology*, 2013
Effects of APOE ε4 in Preclinical AD on Resting State Functional Connectivity

Butt et al., under preparation
Effects of APOE ε4 on Biomarkers in Preclinical AD

Butt et al., under preparation
Biomarkers in Symptomatic AD

- Amyloid Abnormalities
- tau Abnormalities
- Cognitive Dysfunction

Healthy Aging

NIA0 | NIA1 | NIA2 | NIA3
---|---|---|---
CDR0 | CDR0.5 | CDR1

Time

Symptomatic AD
CSF Aβ42 and Tau Can Identify Symptomatic AD Patients in the Clinical Setting

CSF Aβ42:
Sensitivity: 70-100%
Specificity: 40-90%

CSF Tau:
Sensitivity: 40-85%
Specificity: 65-85%

Sunderland et al., JAMA, 2003
Amyloid PET Imaging is Abnormal in Symptomatic AD Compared to Healthy Controls in the Research Setting

Bouallegue et al., Journal of Alzheimer’s Disease, 2018

<table>
<thead>
<tr>
<th>Metric</th>
<th>ADAS-cog</th>
<th>Amyloid PET (8 regional SUVRs)</th>
<th>FDG PET (8 regional SUVRs)</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>71%</td>
<td>76%</td>
<td>71%</td>
<td>74%</td>
</tr>
<tr>
<td>Specificity</td>
<td>73%</td>
<td>71%</td>
<td>66%</td>
<td>78%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>72%</td>
<td>72%</td>
<td>67%</td>
<td>77%</td>
</tr>
<tr>
<td>PPV</td>
<td>52%</td>
<td>52%</td>
<td>47%</td>
<td>58%</td>
</tr>
<tr>
<td>NPV</td>
<td>86%</td>
<td>87%</td>
<td>84%</td>
<td>88%</td>
</tr>
</tbody>
</table>

PPV, positive predictive value; NPV, negative predictive value.

Bouallegue et al., Journal of Alzheimer’s Disease, 2018
Tau PET Imaging in Abnormal in Symptomatic AD Patients in the Research Setting

Brier et al. Science Translational Medicine, 2016
Tau PET is Abnormal in Symptomatic AD Patients

Gordon et al., Brain, 2016
Progression of Tau PET Cortical Signature in Symptomatic AD

- β-Amyloid interacts with hippocampal and cortical tauopathy to affect neurodegeneration.
- In the absence of Aβ, hippocampal tau deposition may be insufficient for the neurodegenerative process that leads to AD.

Wang et al., JAMA Neurology, 2016
Tau PET Discriminates AD From Other Neurodegenerative Diseases

Sensitivity: 89.9%
Specificity: 90.6%

Ossenkoppele et al., JAMA, 2018
Resting State Functional Connectivity is Abnormal in Symptomatic AD

Sensitivity = 85%
Specificity = 77%

Greicius et al., PNAS, 2004
Intra and Inter-Network Resting State Functional Connections Are Affected in Symptomatic AD

Medial Temporal Atrophy (Hippocampus) Occurs in Symptomatic AD Patients

Sensitivity: 88%
Specificity: 96%


Vemuri et al., *Neurology*, 2009
Longitudinal Changes in Biomarkers in AD Converters

Molecular

Psychometric

Structural

Roe et al., *Brain*, 2018
Effects of APOE on Amyloid PET in Converters to Symptomatic AD

Roe et al., *Brain*, 2018
Spatial Topography of Neuroimaging Biomarkers in AD

Brier and Ances, *Brain Connectivity*, 2014
Proposed Timeline for Biomarkers in Autosomal Dominant Alzheimer’s Disease (ADAD)

Bateman et al., *NEJM*, 2011
Longitudinal Changes in Biomarkers in ADAD

McDade et al., *Neurology*, 2018
Loss of Intra-Network Resting State Functional Connectivity in ADAD is Similar to LOAD

M- CDR 0= 30  
M+ CDR 0= 25  
M+ CDR 0.5 =12  
M+ CDR ≥ 1= 7  

sAD CDR 0= 300  
sAD CDR 0.5 =62  
sAD CDR ≥ 1= 10

Thomas et al., JAMA Neurol, 2014
The Spatial Topography of ADAD is Similar But Accelerated When Compared to LOAD

Strain et al., to be submitted
Resting State Functional Connectivity Signature Compared to Other Biomarkers in ADAD

Smith et al., to be submitted
The Importance of Preclinical AD Diagnosis

Diagram A: Preclinical Treatment
- Normal: Normal aging
- Severe Impaired: AD
- Cognitive Function: Normal, Mildly Impaired, Demented
- Time: Cognitively Normal, Mildly Impaired, Demented
- Green arrow: "Prevention"

Diagram D: Late Treatment
- Normal: Normal aging
- Severe Impaired: AD
- Cognitive Function: Normal, Mildly Impaired, Demented
- Time: Cognitively Normal, Mildly Impaired, Demented
- Green arrow: "Uncertain Outcome"

Diagram C: Early Treatment
- Normal: Normal aging
- Severe Impaired: AD
- Cognitive Function: Normal, Mildly Impaired, Demented
- Time: Cognitively Normal, Mildly Impaired, Demented
- Green arrows: "Halt Progression", "Delay Progression"
How Early Should We Go? Imaging Biomarkers May Be Theragnostic For Prevention and Treatment Trials in AD

- **Primary Prevention**
  - Delay onset of AD pathology
  - Decrease Aβ production
  - Prevent tangle formation

- **Secondary prevention**
  - Delay onset of cognitive impairment in individuals with evidence of pathology
  - Decrease accumulated Aβ burden
  - Decrease neurodegeneration with anti-tau or neuroprotective agents

- **Tertiary prevention and treatment**
  - Delay onset or progression of dementia
  - Neuroprotection-prevent neuronal loss
  - Enhance function of remaining neurons
  - Neurotransmitter repletion

Clinical disease stage:
- No pathology
- Preclinical
- MCI
- Dementia

Abnormal vs Normal
The New World of Biomarkers for AD

1) Diagnostic criteria for AD diagnosis has changed in research setting. CSF and neuroimaging (MRI and PET) biomarkers can assist in the diagnosis of preclinical AD.
2) Biomarkers can start to tease apart “healthy” aging from preclinical AD.
3) Biomarkers are leading to a paradigm shift from “cure” to “prevention”. We are now intervening in cognitively normal individuals with preclinical AD to prevent neurodegeneration and possible development of AD.
4) Potential use of biomarkers in design/evaluation of clinical trials include:
   a) target engagement
   b) inclusion criteria (confirm and enrich samples for presence of therapeutic target)
   c) surrogate outcome measures (ATN)
      1) Amyloid = CSF Ab42, PET amyloid imaging
      2) Tau = CSF t-tau, PET tau imaging
      3) Neurodegeneration = CSF p-tau, brain atrophy (MRI)

Our patient has preclinical AD (NIA Stage 2/3) and could be a candidate for early initiation of novel amyloid or tau reducing therapies
Acknowledgements

♦ Knight Alzheimer’s Disease Research Center
  • John Morris MD
  • David Holtzman MD
  • Tammie Benzinger MD, PhD
  • Randall Bateman MD
  • Anne Fagan PhD
  • Chengie Xiong PhD
  • Suzanne Schindler MD, PhD
  • Gregg Day MD
  • John McCarthy PhD
  • Ari Stern PhD
  • Todd Kuffner PhD
  • Dave Balota PhD
  • Jan Duchek PhD
  • Carlos Cruchaga, PhD
  • Rick Perrin MD, PhD
  • Brian Gordon PhD
  • Virginia Buckles PhD
  • Krista Mulder PhD
  • Betsy Grant PhD

♦ Ances Neuroimaging Laboratory
  • Jeremy Strain PhD
  • Sarah Cooley PhD
  • Patrick Luckett PhD
  • Julie Wisch PhD
  • Omar Butt MD, PhD
  • Liz Westerhaus MS
  • Dimtre Tomov
  • Regina Thompson
  • Brittany Nelson
  • John Doyle
  • Anna Boerwinkle
  • Jamie Navid
  • Collin Kilgore
Thank you!

Ances Neuroimaging Laboratory
at Washington University in St. Louis

http://neuro.wustl.edu/research/researchlabs/anceslaboratory.html

Please contact me with questions or if interested in collaborating:
bances@wustl.edu (314) 747- 8423