## 2013 Webinar Series

### State of the Science:

### Dementia Evaluation and Management among Diverse Older Adults and their Families

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Sponsored by Stanford Geriatric Education Center in conjunction with American Geriatrics Society, California Area Health Education Centers, & Community Health Partnership

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## Use of Biomarkers to Distinguish Subtypes of Dementia

Geoffrey A. Kerchner, MD, PhD
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Stanford University School of Medicine

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Jan 23 2013

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State of the Science:
Dementia Evaluation and Management
among Diverse Older Adults and their Families
*2013 WEBINAR SERIES*

## "Use of Biomarkers to Distinguish Subtypes of Dementia"

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## About the Presenter

**Geoffrey A. Kerchner, MD, PhD**
**Assistant Professor of Neurology and Neurological Sciences**
**Stanford Center for Memory Disorders**
**Stanford University School of Medicine**
**Stanford, California, USA**

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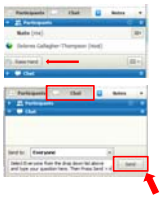
## Q & A

- There will be a Q & A session at the end of the presentation. if you have any questions, please use the "Chat" feature located on the right side of your screen. **Please send your chat to everyone if possible.**
- After the Q and A, We would like to ask each of the participants to answer the short evaluation questionnaire.



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## Use of Biomarkers to Distinguish Subtypes of Dementia

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STATE OF THE SCIENCE:
Dementia Evaluation and Management among Diverse Older Adults and their Families
Stanford Geriatric Education Center Webinar Series – January 23, 2013

## CASE HISTORY

A 57 year-old man presents to clinic complaining of short term memory loss…

## Use of Biomarkers in Dementia

DEFINITION: an easily-observable measurement (e.g., the concentration of a molecule, or size of a brain region) that serves as a proxy for a harder-to-determine biological state (the presence of Alzheimer's disease pathology)

USES:

- Diagnosis (early, accurate)
- Disease Tracking

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## Use of Biomarkers in Dementia

WHY BOTHER?

- Our patients desire a confident diagnosis.
- Newly emerging drugs are more likely to help in the early stages of the disease, before symptoms take hold.
- Using biomarkers as an endpoint in clinical trials, we may be able to gauge a new drug's efficacy more quickly, with fewer patients, and less money.

## Use of Biomarkers in Dementia

AVAILABLE NOW
- CSF amyloid-beta and tau
- Amyloid PET imaging
- Metabolic imaging
- Structural MRI

POSSIBLE FUTURE BIOMARKERS
- High resolution structural MRI
- Functional MRI
- Others

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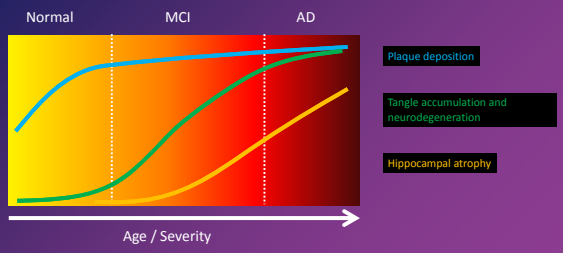
## Hypothetical Timeline




## Biomarkers for Alzheimer's Disease

TWO CATEGORIES:

- Biomarkers of *amyloidosis*
  - CSF amyloid-beta
  - Amyloid PET imaging
- Biomarkers of *neuronal injury*
  - CSF tau
  - FDG-PET
  - Structural MRI

## Biomarkers for Alzheimer's Disease

NEW DIAGNOSTIC CLINICAL CRITERIA
(McKhann et al., 2011; Albert et al., 2011)

Three levels of certainty for "Probable AD" and for "Mild Cognitive Impairment due to AD"

- Uninformative (ie, unavailable, conflicting, or indeterminate)
- Intermediate (ie, one category positive, the other unavailable or indeterminate)
- High (positive results in both categories)

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## Cerebrospinal Fluid Biomarkers

WHAT ARE WE MEASURING?
- Aβ(1-42) peptide
- Total tau protein
- Phospho-tau (Y181)

Tips:
- Use polypropylene tubes (not the ones typically supplied in kits), as Aβ interacts with other plastics
- Commercial labs offer this as a send-out service

## Cerebrospinal Fluid Biomarkers

- In one test, you can obtain two biomarkers
  - CSF amyloid-beta – a marker of *amyloidosis*
  - CSF tau and phospho-tau – markers of *neuronal injury*
- CSF Aβ *declines* in AD
  - Equivalent to a positive amyloid PET scan
  - Shares same high sensitivity but questionable specificity as amyloid imaging
- CSF tau *rises* in AD
  - Probably reflects neuronal death
  - Nonspecific – also goes up in other neurodegenerative conditions, notably CJD

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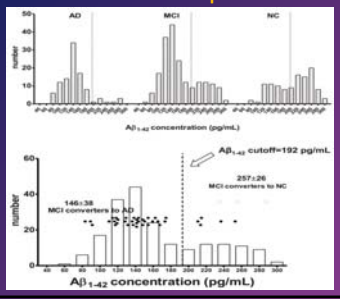
## Cerebrospinal Fluid Biomarkers



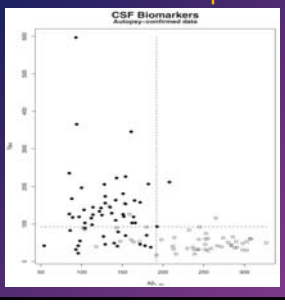

Aβ(1-42) is very sensitive at distinguishing AD from control cases in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohorts.

Note:

Absolute levels vary depending upon the exact technique used to make the determination and are not well-harmonized from lab to lab. When you obtain these levels commercially, use that lab's cut-offs.

Shaw et al., 2009

## Cerebrospinal Fluid Biomarkers



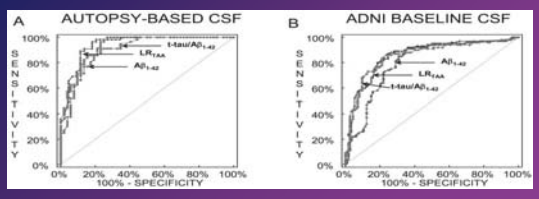

Elevated tau adds some specificity, strengthening the suspicion of AD.

LIMITATIONS OF TAU

Any injury causing neuronal lysis could conceivably elevate tau. Prion disease is a notable example; other neurodegenerative diseases are less-studied.

Shaw et al., 2009

## Cerebrospinal Fluid Biomarkers




Shaw et al., 2009

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## Use of Biomarkers in Dementia

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- CSF amyloid-beta and tau
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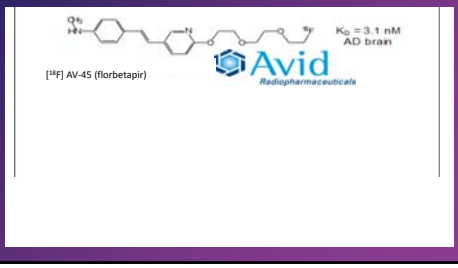
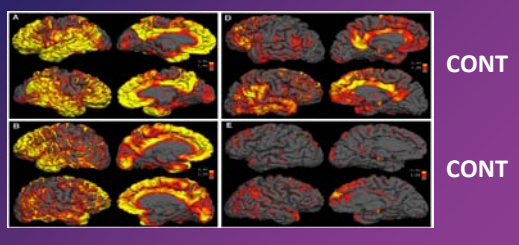
- Structural MRI

POSSIBLE FUTURE BIOMARKERS
- High resolution structural MRI
- Functional MRI
- Others

## Amyloid Imaging: Coming to a PET scanner near you…




## Amyloid Imaging

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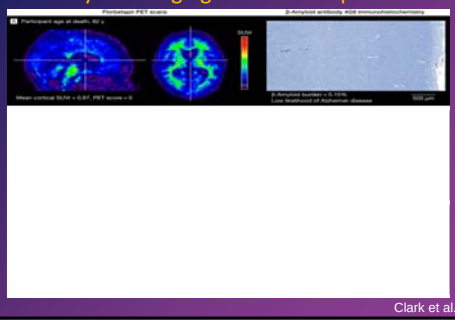
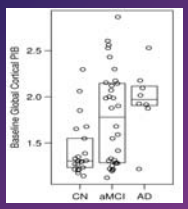
## Amyloid Imaging with $^{18}$F Compounds



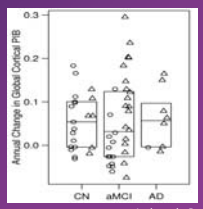
Clark et al., *JAMA*, 2011

## Amyloid Imaging: What does it tell us?

Although absolute PIB uptake differs according to diagnosis…

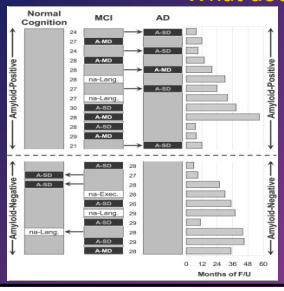



…the annual rate of change in PIB burden does not differ.




Jack et al., *Brain* 2009

## Amyloid Imaging: What does it tell us?




**MILD COGNITIVE IMPAIRMENT**

- The significance of plaques is still not completely worked out.
- While it may always be preferable to have a *negative* PIB scan, it may not always be a bad thing to have a positive one.

Wolk et al., *Annals of Neurology* 2009

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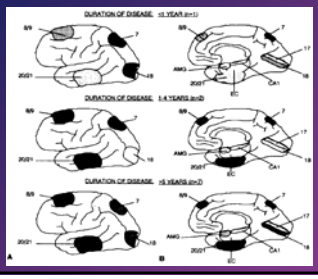
## Amyloid Imaging: What does it tell us?



Amyloid plaques appear densely in the neocortex, but rarely occur in the entorhinal cortex or CA1.

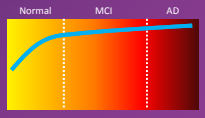
Arriagada et al., *Neurology* 1992

## Limitations to Amyloid Biomarkers

Amyloid positivity ≠ AD

- Plaques may occur in normal elders in the absence of tangles, atrophy, or cognitive loss
- Does not exclude a comorbid pathogenic process that may be driving cognitive decline

Amyloid biomarkers do not track disease progression over time




## Use of Biomarkers in Dementia

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POSSIBLE FUTURE BIOMARKERS

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## Metabolic Imaging

Modalities:
- Fluorodeoxyglucose (FDG) PET
- Arterial spin labeling (ASL) MRI

What it tells us:
- The *anatomy* of which brain areas are hypofunctional
- However, a well-trained neuropsychologist or cognitive neurologist can make the same observations from a detailed clinical exam

What it doesn't tell us:
- Underlying neuropathology
- Especially in atypical cases, there is a poor correlation between the anatomical pattern of neurodegeneration and the underlying molecular diagnosis

## Metabolic Imaging

Utility:
- Limited use in differential diagnosis
- Limited use in predictions about future cognitive decline
- Possible use in tracking disease progression or response to therapeutic intervention

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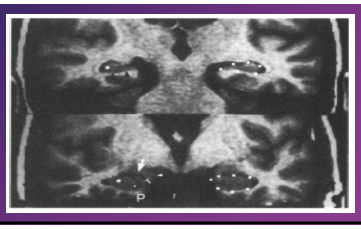
## MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease

Clifford R. Jack, Jr., MD; Ronald C. Petersen, PhD, MD; Peter C. O'Brien, PhD; and Eric G. Tangalos, MD

NEUROLOGY 1992;42:183-188

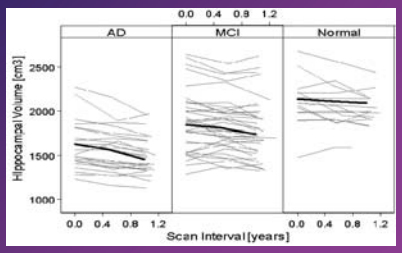


## Hippocampal Volume

**ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE**

96 AD
226 MCI
112 Normal

Scanned 3 times over the course of a year




Schuff et al., *Brain* 2009

## Structural Neuroimaging

Hippocampal atrophy is the key metric of interest

- Neither sensitive nor specific for AD
- May be helpful longitudinally (e.g., to demonstrate atrophy over 1-2 years), but the information yield may not be enough to justify subjecting a patient to multiple sequential scans
- Newer techniques (like 7T) may improve sensitivity and specificity

Every older patient with a memory complaint should have a standard clinical MRI scan

- The purpose is to evaluate for cerebrovascular disease and other differential considerations; this remains a standard of care.
- At this time, however, it is of uncertain value at providing positive evidence in favor of AD.

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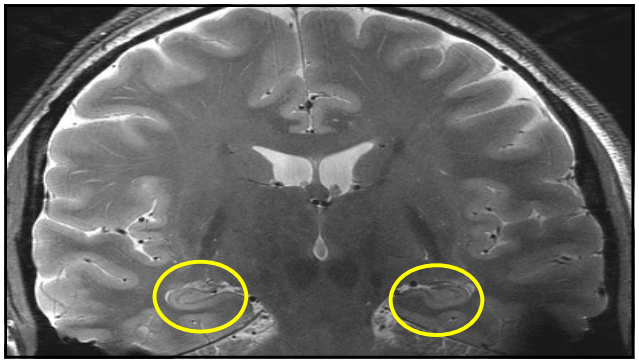
## 7.0 Tesla MRI

- Compare to 3.0 Tesla, the current standard at many state-of-the-art medical facilities
- ~140,000x stronger than Earth's field
- Extra signal-to-noise
  - Higher resolution
  - Shorter scan times
- Some problems
  - Exaggeration of artifacts
  - Exaggeration of side effects



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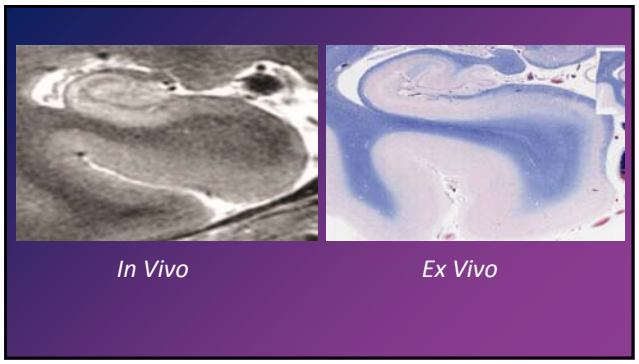


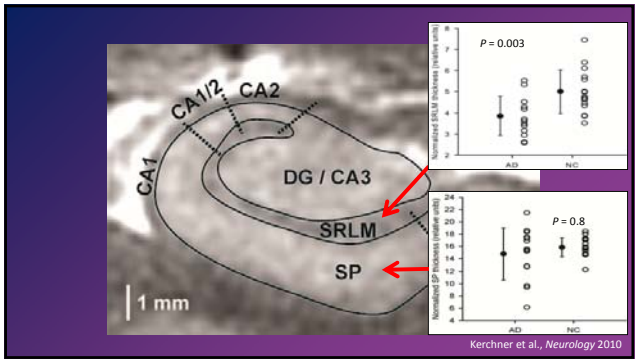


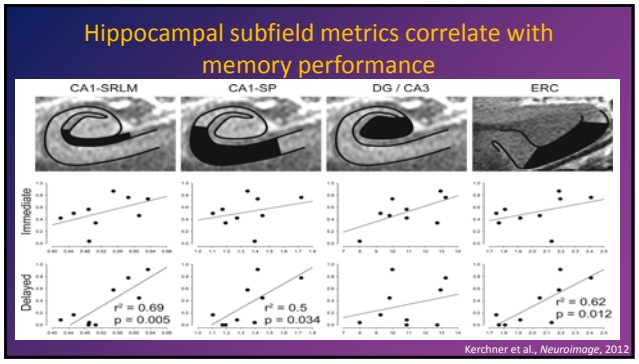


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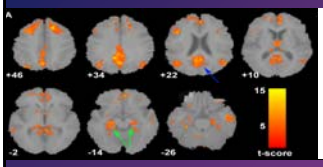
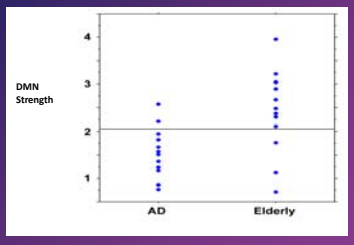
## Default-Mode Network in AD




Healthy Older Controls Alzheimer's Disease

Greicius et al., *PNAS*, 2004

## Single-Subject Default Mode Network Measure




85% sensitivity
77% specificity

Greicius et al., *PNAS*, 2004

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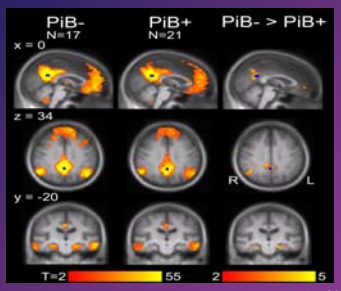
## Reduced DMN Connectivity in PIB+ Controls




Hedden et al., *J Neurosci*, 2009
Sheline et al., *Biol Psych* 2010

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## CASE HISTORY

A 57 year-old man presents to clinic complaining of short term memory loss…

- Neuropsychological testing is indeterminate
- Structural neuroimaging shows "mild global cerebral volume loss that may be excessive for age"
- CSF Aβ is low, and CSF tau is elevated
- You counsel the patient that based on his lumbar puncture, there is evidence in support of Alzheimer's disease being the cause of his symptoms

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## CASE HISTORY

An 87-year-old woman has been depressed since her husband died a year ago. She no longer leaves home, and her family have taken over bill payments and scheduling appointments. Her children want to know if she is demented.

- Neuropsychological testing is limited by poor concentration
- Structural neuroimaging shows "mild global cerebral volume loss that may be excessive for age"
- CSF Aβ and tau are normal
- You counsel the family that there is no sign of Alzheimer's disease, and that depression may be a primary cause of her symptoms.

## CASE HISTORY

A 61-year-old man has severe word-finding problems. His personality is mostly normal, although he has become obsessive and has developed some odd habits. You want to distinguish between frontotemporal dementia (language variant) and Alzheimer's disease

- Amyloid PET imaging is positive
- FDG-PET reveals left more than right temporal/parietal hypometabolism
- You conclude that Alzheimer's disease is the more likely cause of his symptoms

**Thank You!**

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## Q & A

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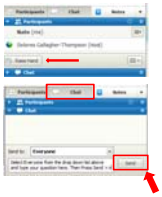

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Final Question
Thank You for Participating!

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