DIAGNOSTIC APPROACH
Medical Perspective, and Use of Biomarkers

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Updates on Dementia
Foster City, CA – May 22, 2013
A 68-year-old right-handed man presents to clinic with a cognitive change reported by his wife...
Biomarkers for Alzheimer’s Disease

**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
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.
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
Hypothetical Timeline

- **Normal**
- **MCI**
- **AD**

**Age / Severity**

- Plaque deposition
- Tangle accumulation and neurodegeneration
- Cognitive decline
Amyloid PET Imaging (Amyloidosis)

Clark et al., *JAMA*, 2011
Cerebrospinal Fluid Biomarkers
(Amyloidosis and neuronal injury)

WHAT ARE WE MEASURING?

- Aβ(1-42) peptide
- Total tau protein
- Phospho-tau (Y181)

- CSF Aβ *declines* in AD
  - Equivalent (?) to a positive amyloid PET scan

- CSF tau *rises* in AD
  - Probably reflects neuronal death
  - ...But it also rises in other neurodegenerative diseases
Metabolic or Perfusion Imaging
(*Neuronal injury*)

Modalities:
- Fluorodeoxyglucose (FDG) PET
- Single photon emission computed tomography (SPECT)
- Arterial spin labeling (ASL) MRI

What it tells us:
- The presence and anatomical pattern of any hypofunctional brain area

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
Structural MRI

(Neuronal injury)

Kerchner et al., 2010, 2011, 2012
Core Clinical Criteria

Mild Cognitive Impairment (MCI)
- Concern regarding a change in cognition
- Impairment in one or more cognitive domains
- Preservation of independent function
- Not demented

Alzheimer’s Disease
- Dementia
  - Loss of functional independence, interfering with work or usual activities, representing a decline
  - Not delirium or psychiatric disease
  - Impairment in at least two cognitive domains
- Insidious onset
- Worsening by report or observation
- Cognitive deficits should fit either:
  - Amnestic presentation
  - Non-amnestic presentation
- No competing neurological process that could cause cognitive decline

“Probable” AD fits all the above

“Possible” AD is atypical in course or presentation
## Research Criteria

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Adapted from Sperling et al., 2011; Albert et al., 2011; McKhann et al., 2011
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For more information, visit [http://www.alz.org/research/diagnostic-criteria/#access](http://www.alz.org/research/diagnostic-criteria/#access)
Clinical diagnosis is different from research diagnosis

- We do not perform biomarker testing on asymptomatic patients, and so the “preclinical” diagnostic categories do not exist in the clinical world

- Biomarker tests are often not offered to symptomatic patients; they are useful only when they will meaningfully inform clinical management

- In research, participants are homogeneous, whereas in the real world, they are heterogeneous
  - Clinicians must consider a broader context when making a diagnosis
  - Sensitivity and specificity of available biomarkers are not well-defined for routine clinical practice
The “march” of biomarkers may not be so simple:

- Tau-based (neuronal injury) changes may occur before amyloid accumulation.

- Amyloidosis may not be uniformly bad
  - Up to 30% of healthy elders have evidence of amyloid accumulation, and it is not clear if or when they will experience symptoms
  - Some may be able to “tolerate” pathology better than others
Examples of Biomarker Use

A 56-year-old woman presents with progressive aphasia

- AD vs. FTD?
  - Structural MRI shows no evidence of focal frontal or temporal atrophy
  - CSF Aβ is low, and tau is high

An 87-year-old woman is morose, withdrawn, and inattentive to her basic care needs

- Depression vs. AD?
  - Neuropsychological assessment is limited by poor attention and low effort
  - Amyloid PET scan is negative

A 62-year-old man has become subtly forgetful and feels he has to work harder to maintain constant performance at work

- MCI vs. typical aging?
  - Neuropsychological assessment shows borderline impairment in delayed recall, but is otherwise normal
  - CSF Aβ is low, but tau appears normal