DIAGNOSTIC APPROACH

Medical Perspective, and Use of Biomarkers

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Updates on Dementia
Foster City, CA – May 22, 2013

CASE

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

Biomarkers for Alzheimer's Disease

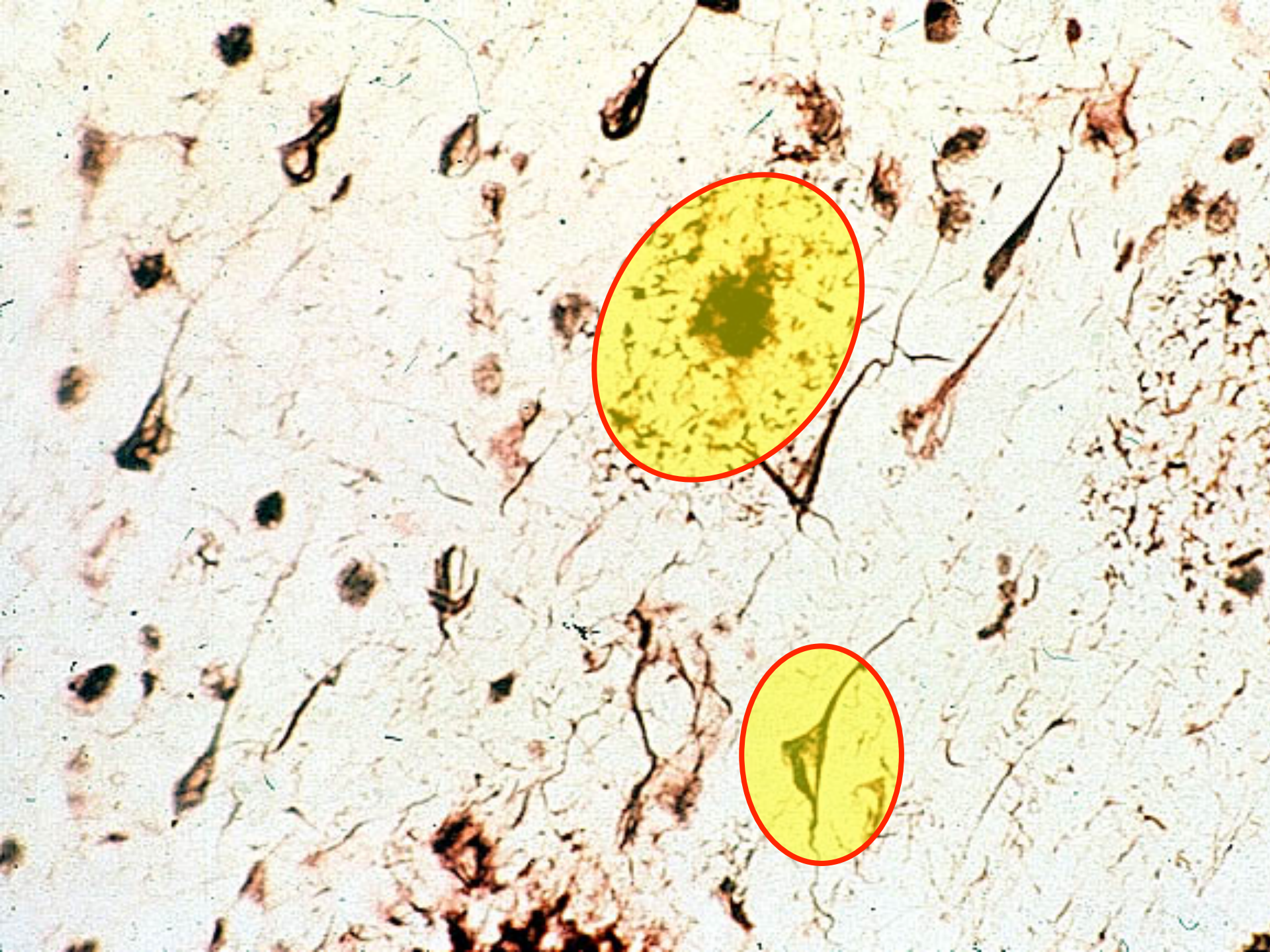
WHY BOTHER?

- 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.

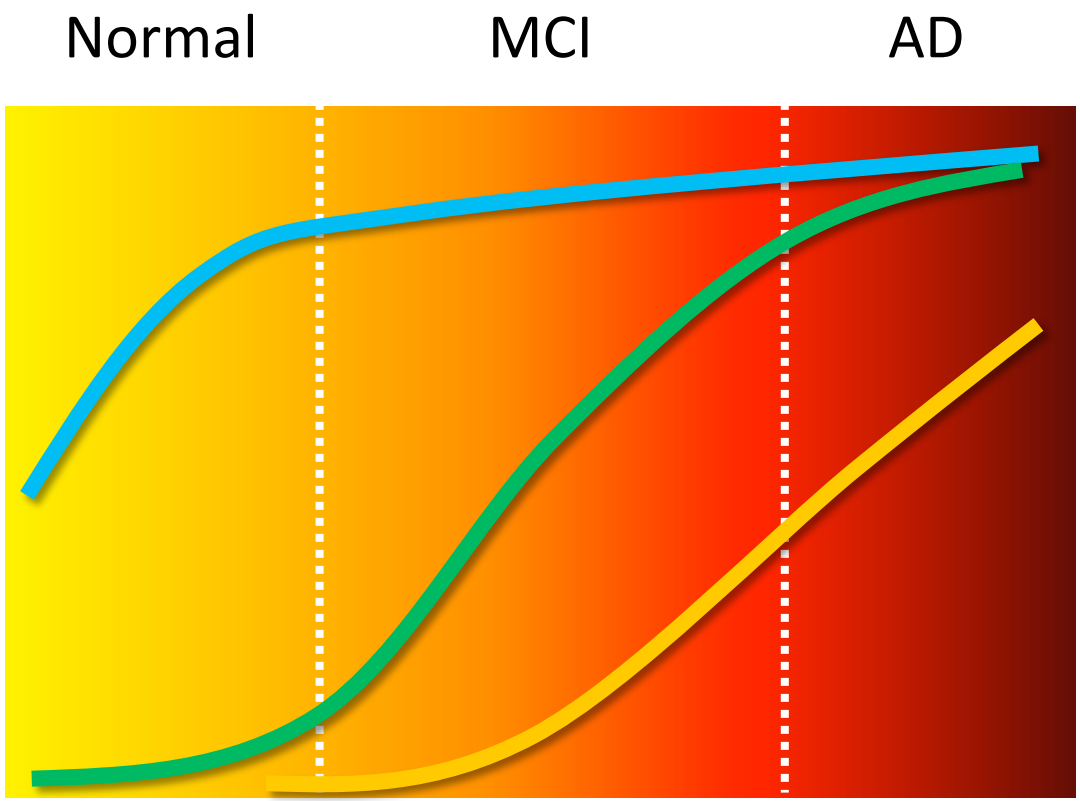
Biomarkers for Alzheimer's Disease

TWO CATEGORIES:

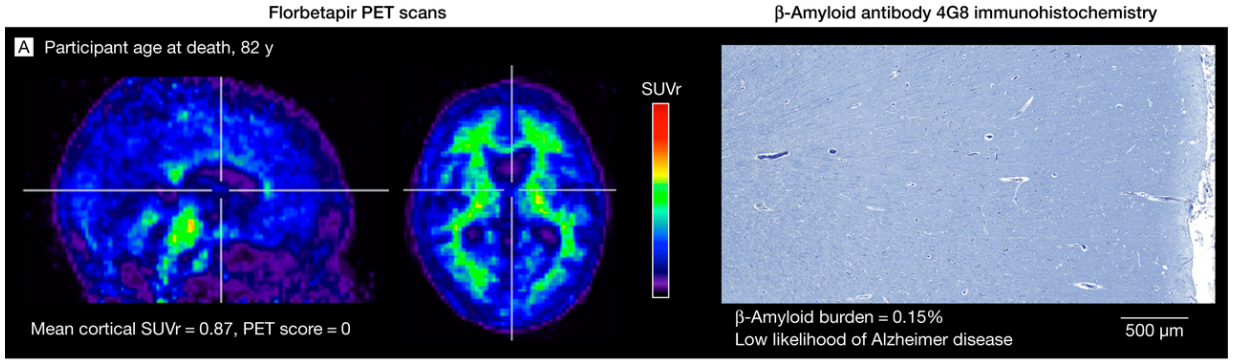
- Biomarkers of *amyloidosis*
  - CSF amyloid-beta
  - Amyloid PET imaging
- Biomarkers of *neuronal injury*
  - CSF tau
  - FDG-PET
  - Structural MRI



Hypothetical Timeline



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

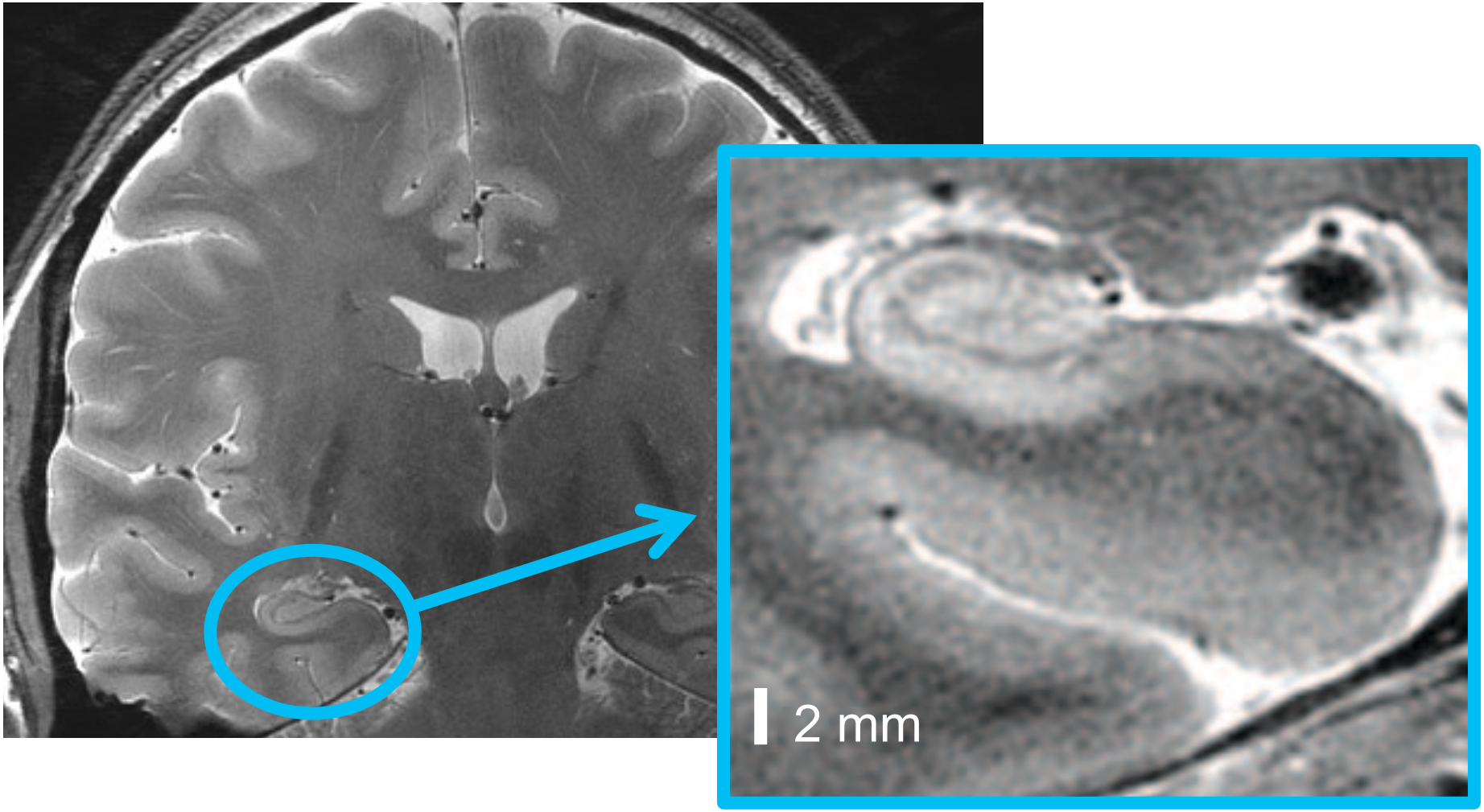
Metabolic or Perfusion Imaging
(Neuronal injury)

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

DIAGNOSTIC STAGE	Cognitive Decline	Functional Decline	Amyloidosis	Neuronal Injury
Preclinical – Stage 1	-	-	+	-
Preclinical – Stage 2	-	-	+	+
Preclinical – Stage 3	~	-	+	+

Adapted from Sperling et al., 2011; Albert et al., 2011; McKhann et al., 2011

Research Criteria

DIAGNOSTIC STAGE	Cognitive Decline	Functional Decline	Amyloidosis	Neuronal Injury
Preclinical – Stage 1	-	-	+	-
Preclinical – Stage 2	-	-	+	+
Preclinical – Stage 3	~	-	+	+
MCI – clinical only	+	-	uninformative	uninformative
MCI – unlikely due to AD	+	-	-	-
MCI – intermediate likelihood of AD	+	-	One is positive, not the other	
MCI – high likelihood of AD	+	-	+	+

Adapted from Sperling et al., 2011; Albert et al., 2011; McKhann et al., 2011

Research Criteria

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MCI – unlikely due to AD	+	-	-	-
MCI – intermediate likelihood of AD	+	-	One is positive, not the other	
MCI – high likelihood of AD	+	-	+	+
Possible/Probable AD – clinical only	+	+	Uninformative	Uninformative
Prob AD – intermediate likelihood	+	+	One is positive, not the other	
Poss/Prob AD – high likelihood	+	+	+	+

Adapted from Sperling et al., 2011; Albert et al., 2011; McKhann et al., 2011

Research Criteria

DIAGNOSTIC STAGE	Cognitive Decline	Functional Decline	Amyloidosis	Neuronal Injury
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Preclinical – Stage 2	-	-	+	+
Possible/Probable AD – clinical only	+	+	Uninformative	uninformative
Poss/Prob AD – intermediate likelihood	+	+	One is positive, not the other	
Poss/Prob AD – high likelihood	+	+	+	+

http://www.alz.orglresearch/diagnostic criteria/#access

Adapted from Sperling et al., 2011; Albert et al., 2011; McKhann et al., 2011

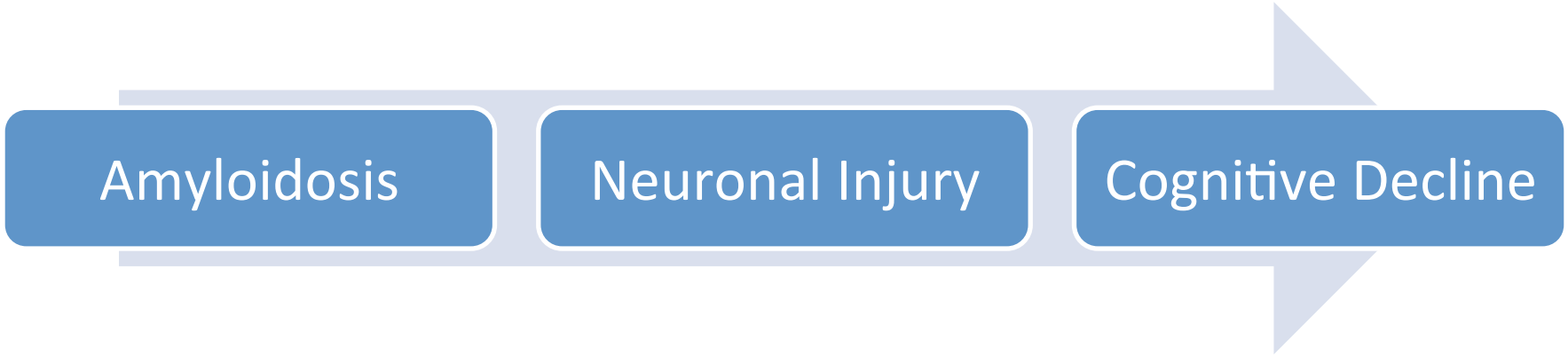
CAUTION

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

CAUTION

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