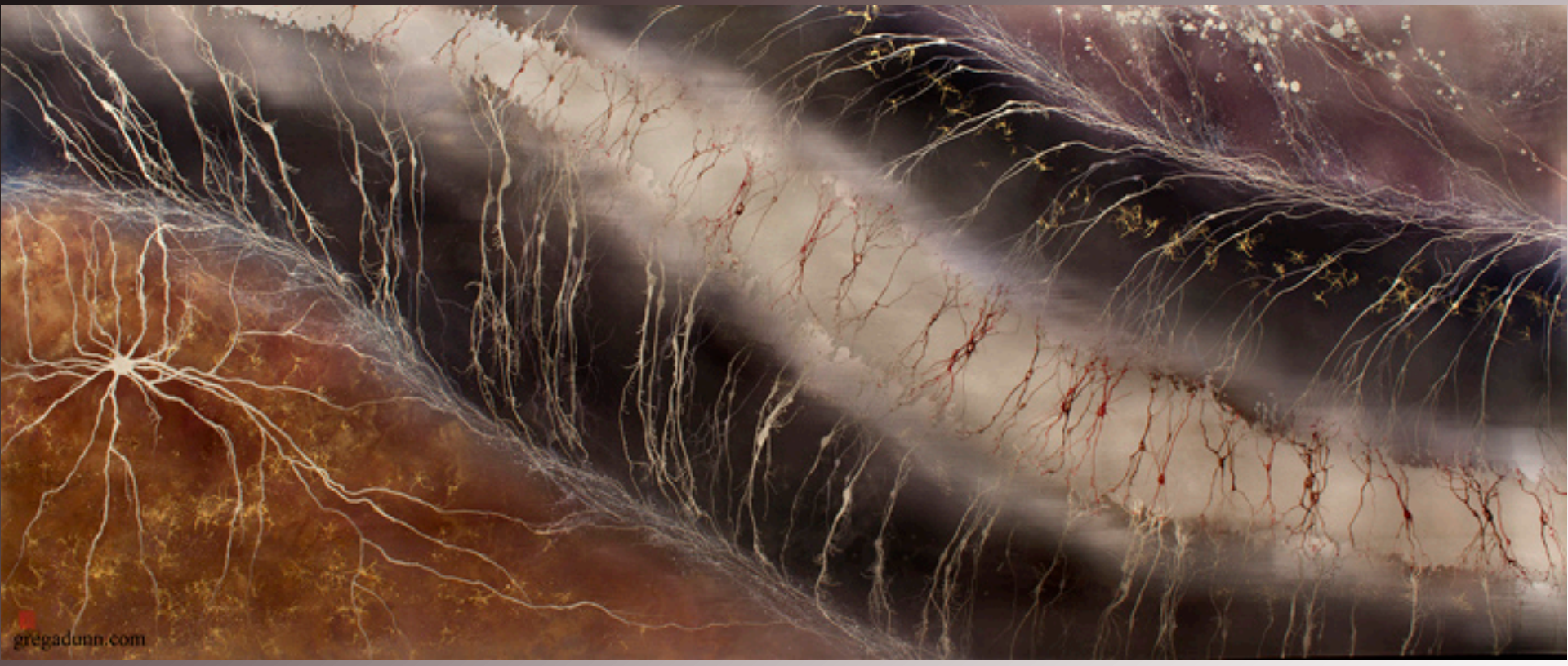
The Del Monte Institute for Neuroscience

Departments of Neuroscience and Psychiatry



From the Lab to the Clinic – Translating Research into Care

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December 14, 2018

Disclosures

Anton P. Porsteinsson, MD:

Research: AstraZeneca, Avanir, Biogen, Eisai, Eli Lilly, Genentech/Roche, Janssen, Merck, Novartis, NIA, NIMH, DOD.

Consultant: Acadia, Neurim Pharmaceuticals.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a brain disease.
It is the most common cause of dementia.

"Dementia" describes the progressive loss of thinking, memory, and other cognitive abilities impairing daily function.

In people over the age of 65, Alzheimer's disease accounts for over two-thirds of dementia cases.

MORE ON AD

The most common symptom of AD - related dementia is a gradual worsening of memory

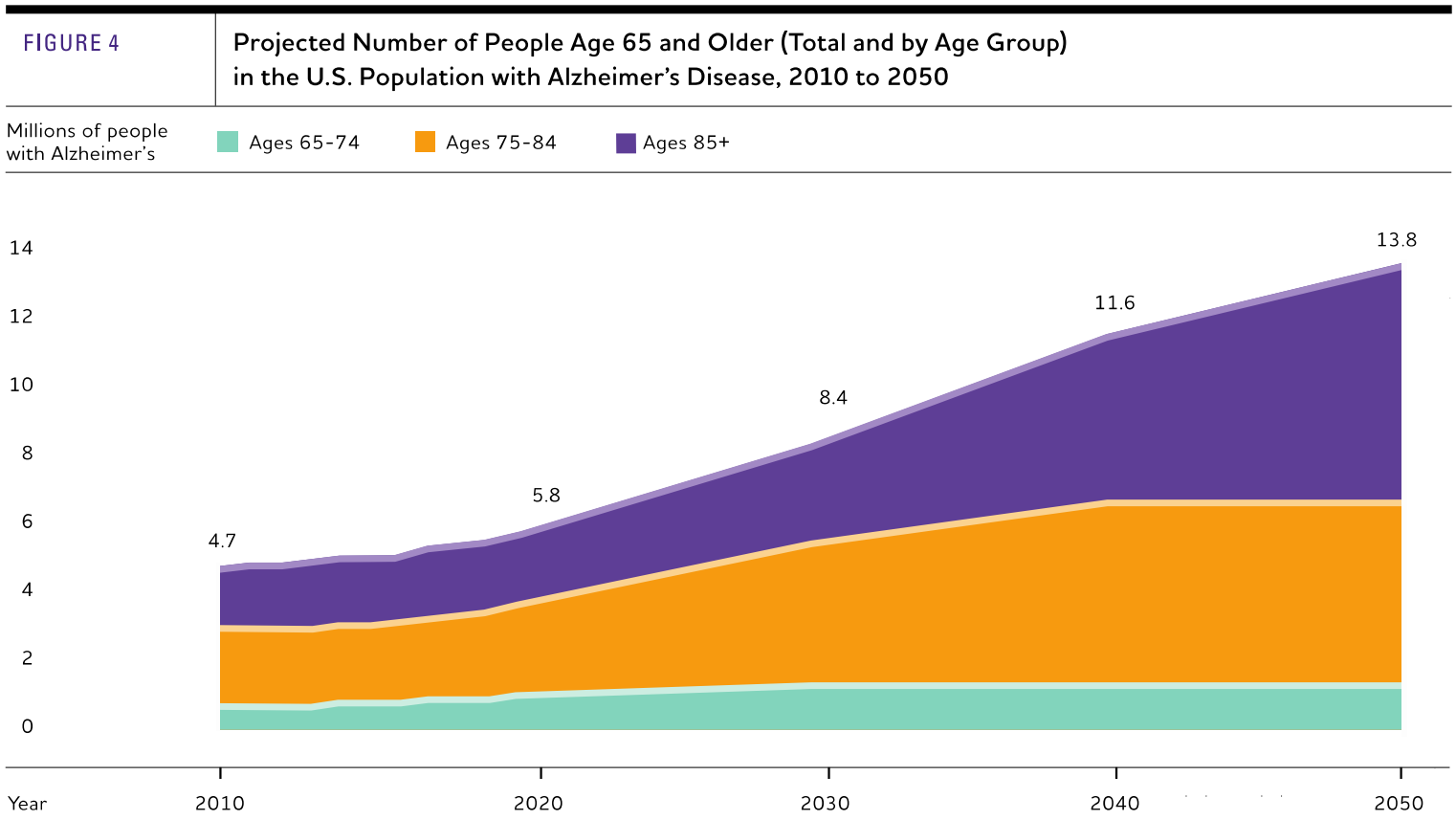
Other cognitive abilities such as logic and reasoning, geographical orientation and use of language also worsen over time.

Alzheimer's Disease

- 5.3 million Americans currently live with Alzheimer's and other related dementias
- 1 in 10 people over the age of 65
- 1 in 3 people over the age of 85
- Nearly 500,000 new cases will be diagnosed in 2018
- Lifetime risk at age 45: 10% for men and nearly 20% for women
- Health care costs exceed $250 Billion (2017)

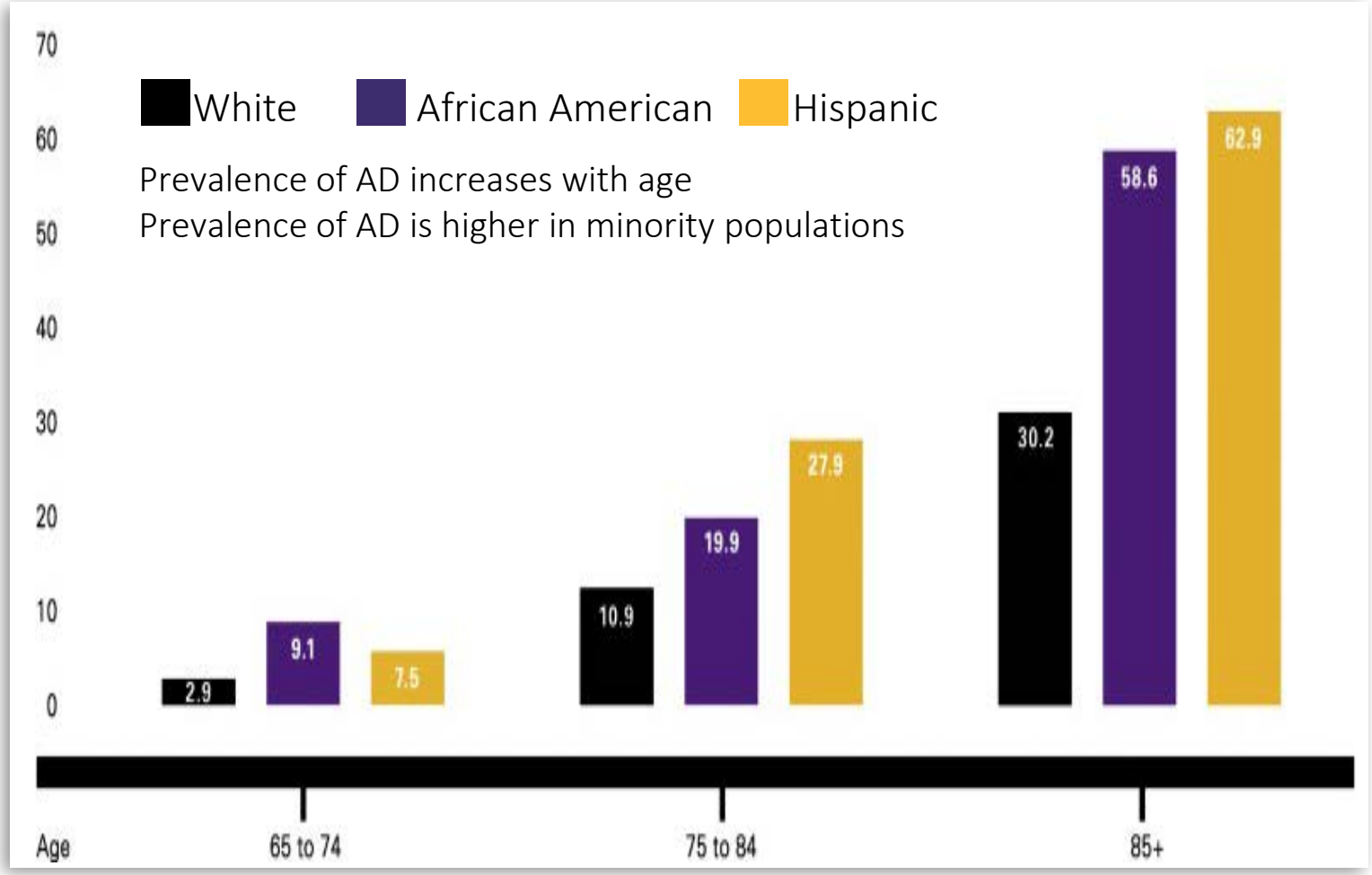
Alzheimer's Association: 2017 Alzheimer's Disease Facts and Figures

Projected Prevalence in our Aging Society



Alzheimer's Association: 2017 Alzheimer's Disease Facts and Figures

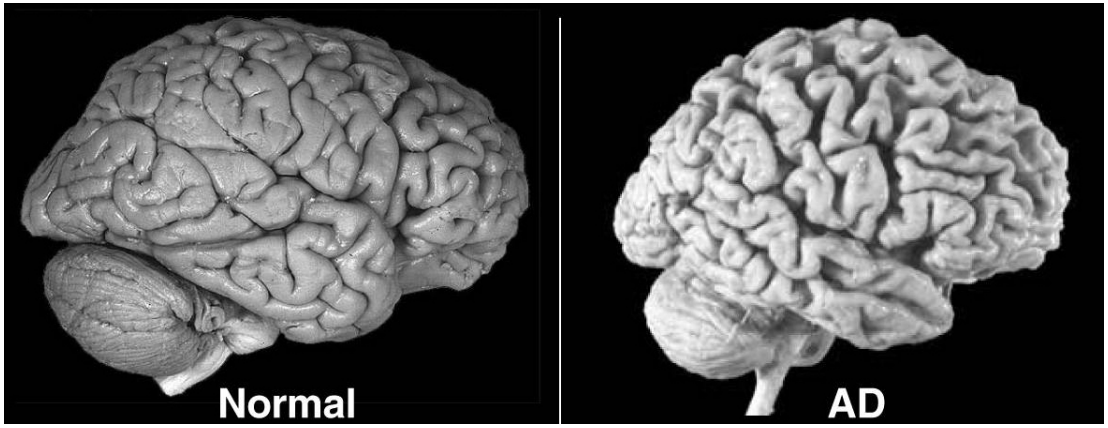
AD Prevalence



2017 Alzheimer's Disease Facts and Figures.

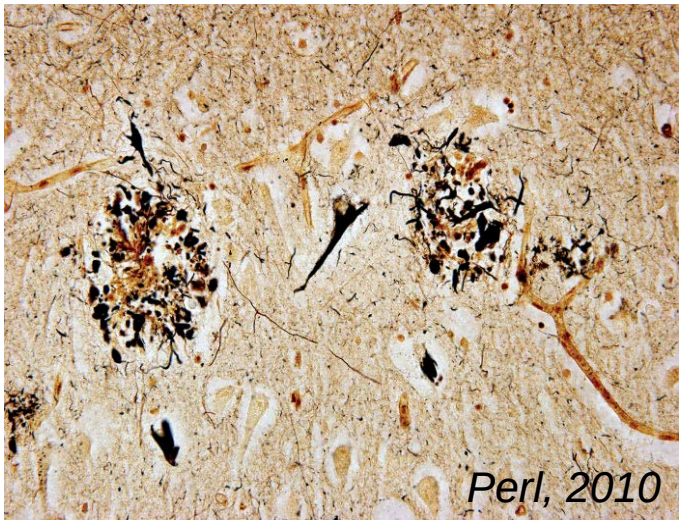
Alzheimer's Disease

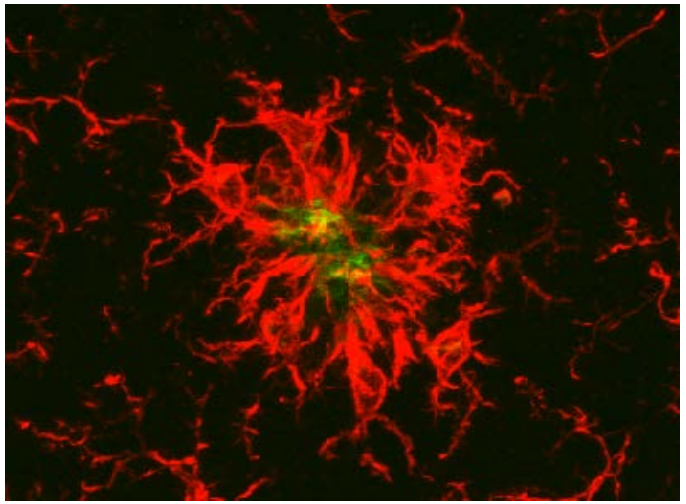
- Initially presents with memory impairment followed by progressive cognitive decline over 5 to 10 years
- Pathologically, there is a shrinkage of brain volume, caused by regional loss of neurons and their connections



Clues from Pathology

- Neuronal loss
- Amyloid plaques
- Neurofibrillary tangles
- Neuroinflammation
- Vascular changes



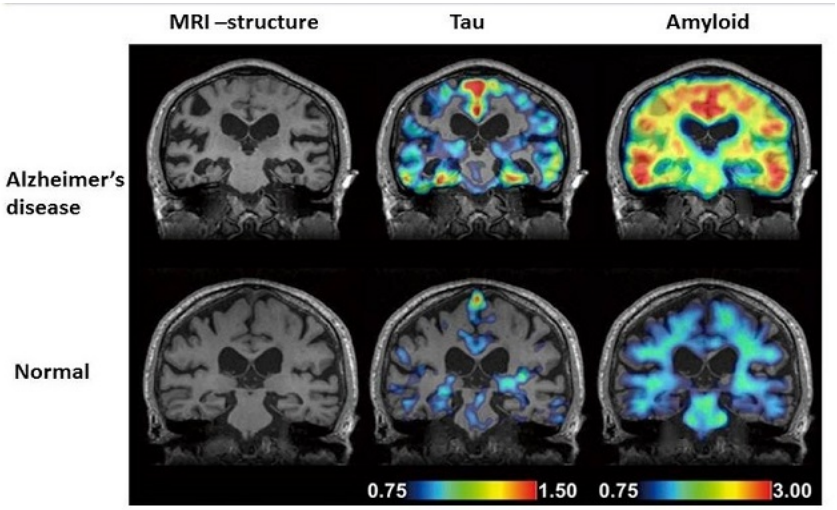


Clues from Genetics

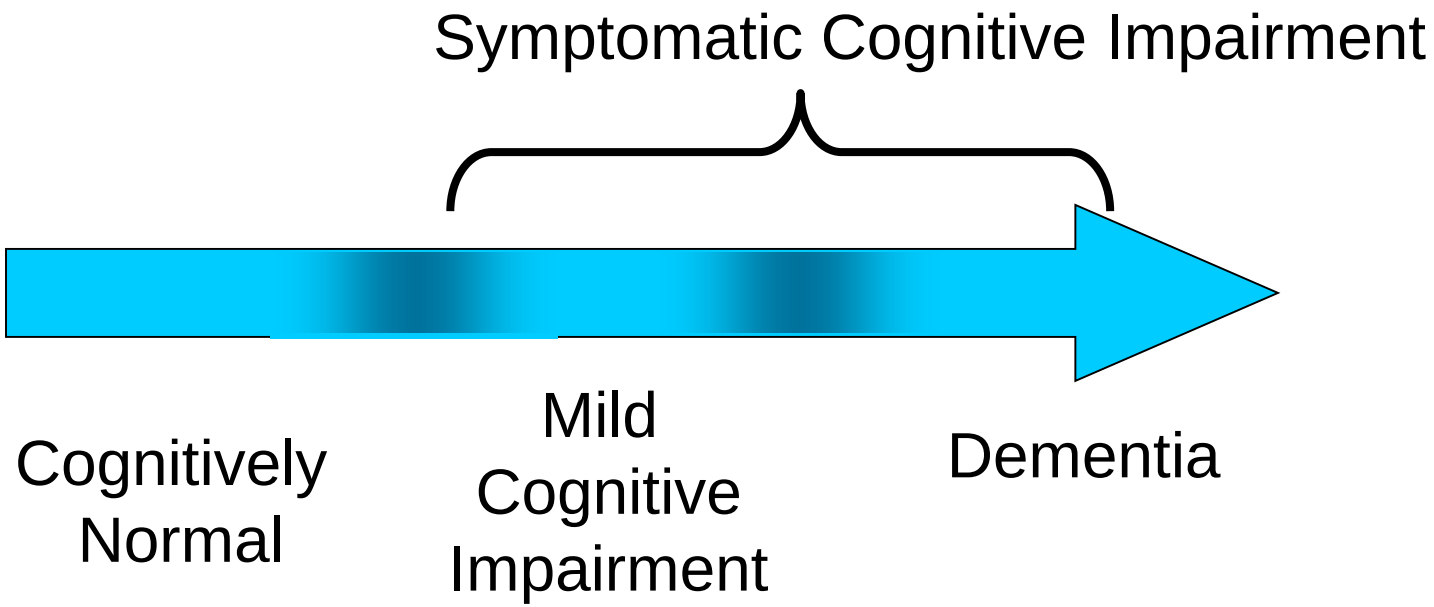
- Familial Alzheimer's disease (FAD) occurs before the age of 65 and accounts for 1% of all cases
- Genes mutated in FAD are associated with increased production of the amyloid-β peptide, which is the primary constituent of amyloid plaques
- The "Amyloid Hypothesis" has largely dominated the field for over 20 years

We haven't cured Alzheimer's, but….

- Despite 15 years of clinical trials aimed at amyloid-β, the clearest "cause" of Alzheimer's, we have not identified a cure
- We know much more about genes and pathological processes in the disease: *There are many more targets to go after*
- With neuroimaging and new biomarkers we can now track AD progression: *Provides early diagnosis and therapeutic efficacy*



Categories in Cognitive Disorders Spectrum



- Distinctions are based on history and exam

Push Back Diagnosis so Intervention Starts as Early as Possible

Cognitive continuum of aging

Normal	Presymptomatic	MCI	AD
• Thinking effectively but more slowly • Forgetting a name or appointment but remembering later • Occasionally misplacing things	• APOE-e4 risk gene • Multiple protein or gene "barcodes" • Family history • Tau or amyloid in CSF or blood • MRI, PET	• Subjective problem in memory or another domain, informant corroborated and measurable on tests • Normal overall cognition and ADLs	• Clear deficits in 2 or more core cognitive domains (memory, language, problem solving, visual interpretation) • ADLs affected

ADLs, activities of daily living; APOE, apolipoprotein E; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography

What Should Evaluation Include?

- Competent history and neurological exam
- Bedside cognitive assessment versus neuropsychological testing
  - What is added value of neuropsychological testing?
- Standard laboratory testing as in dementia
- Standard imaging (MR, no contrast) as in dementia

Diagnostic Criteria of Dementia

A. Dementia

- Interferes with ability to function at work or at usual activities
- A decline from a previous level of functioning
- Not delirium or psychiatric disorder
- Diagnosed by history, examination
- Involves at least 2 cognitive domains:
  - Memory
  - Reasoning and judgment
  - Visuospatial
  - Language
  - Personality, behavior, comportment

McKhann GM et al. *Alzheimers Dement*. 2011;7:263-269.

Diagnostic Criteria of MCI

Clinical and Cognitive Criteria

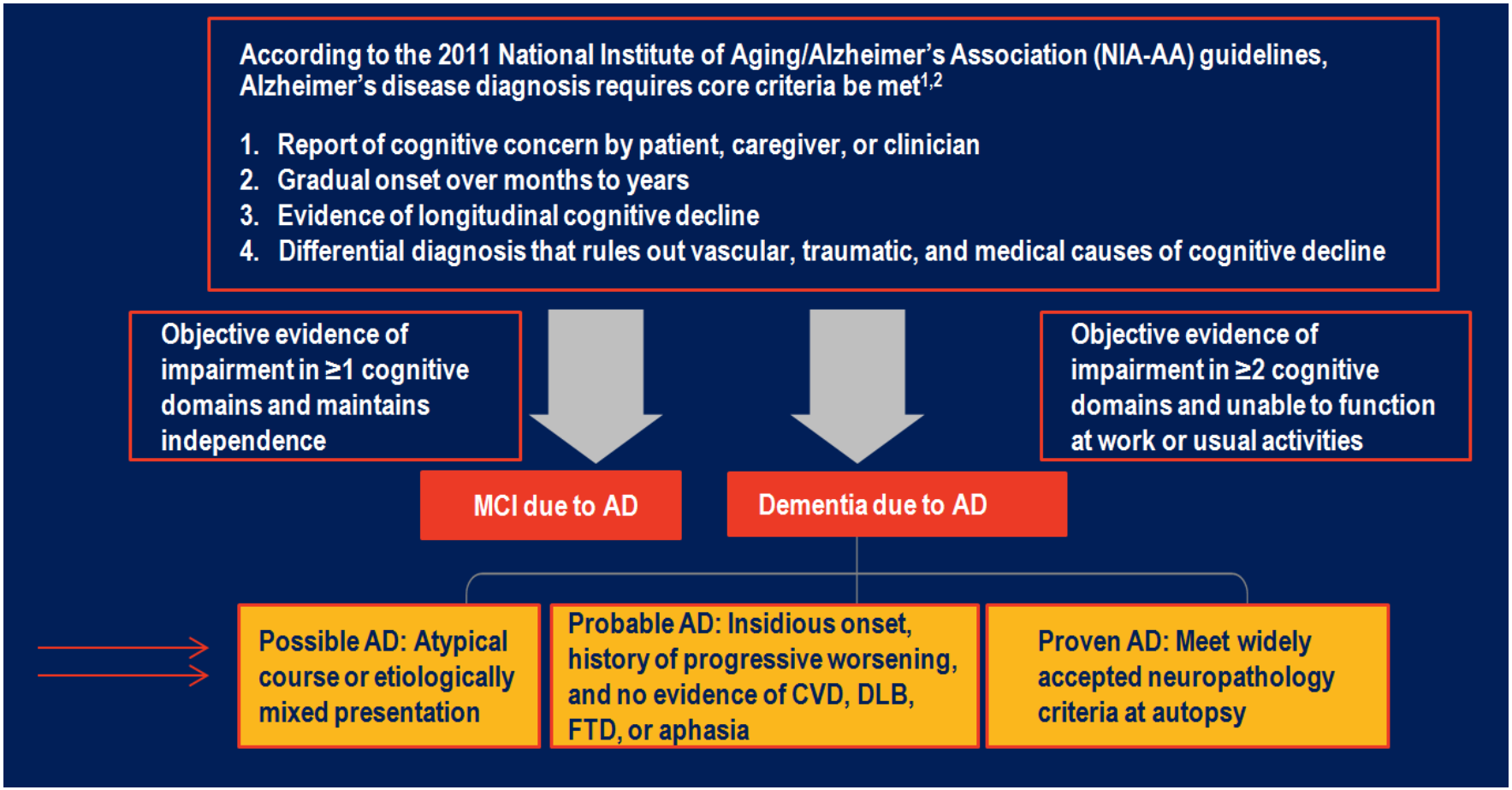
- Concern about a change in cognition reported by patient or informant or clinician (historical or observed evidence of decline)
- Objective evidence of impairment in one or more cognitive domains, typically including memory (formal or bedside testing)
- Preservation of independence in functional abilities
- Not demented

Assess etiology of MCI consistent with AD pathophysiology

- Rule out vascular, traumatic, medical causes of cognitive decline
- Provide evidence of longitudinal decline in cognition
- Report history consistent with AD genetic factors

Albert MS et al, *Alzheimers Dement*. 2011;7:270-279.

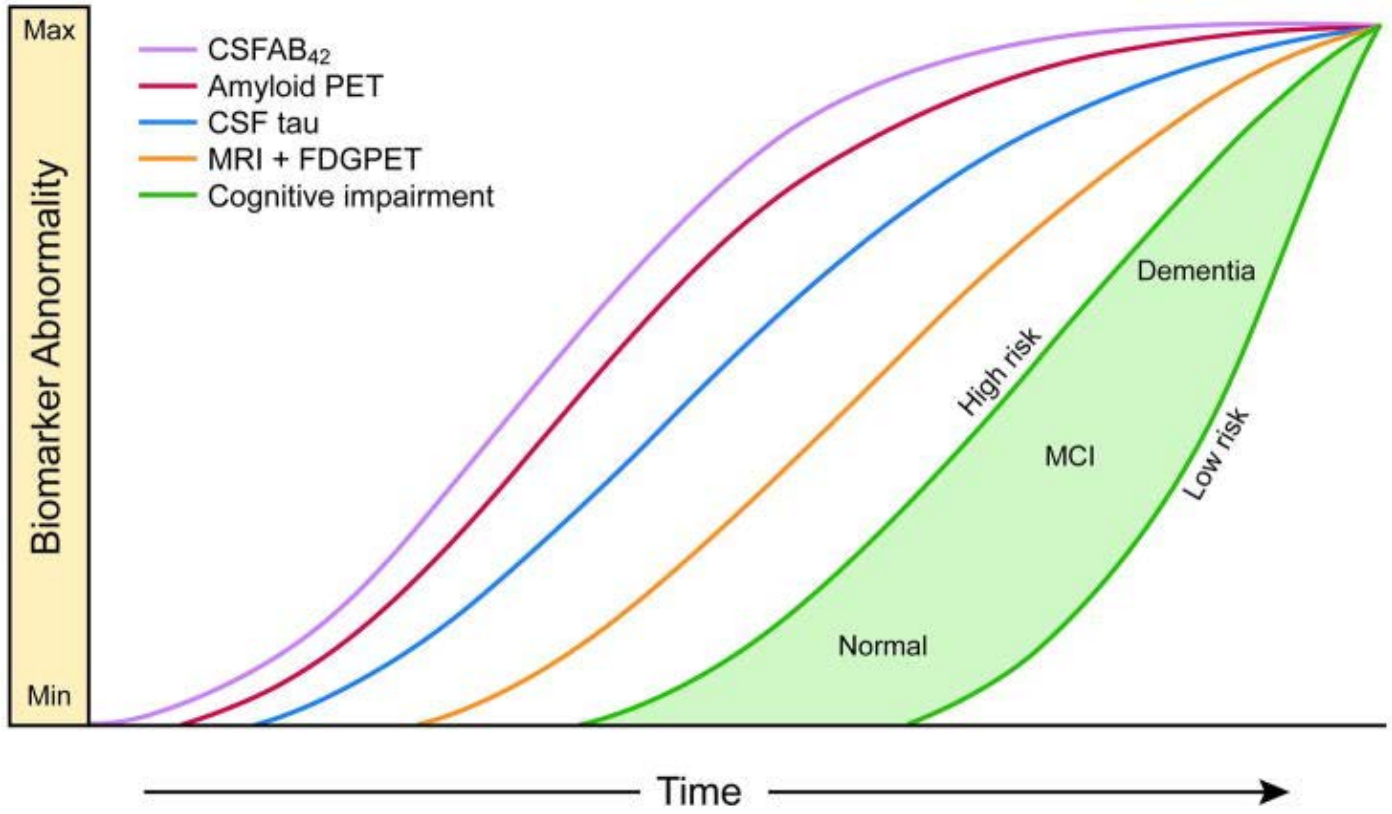
NIA-AA Core Clinical Criteria of AD Diagnosis



NIA-AA Alzheimer's disease diagnosis criteria can also be accessed at http://www.alz.org/research/diagnostic_criteria/.[3]
AD = Alzheimer's disease; CVD = cardiovascular disease; DLB = dementia with Lewy bodies; FTD = frontotemporal dementia; MCI=mild cognitive impairment.

1. Albert MS et al. *Alzheimers Dement.* 2011;7:270-279. 2. McKhann GM et al. *Alzheimers Dement.* 2011;7:263-269.

Biomarkers and Imaging



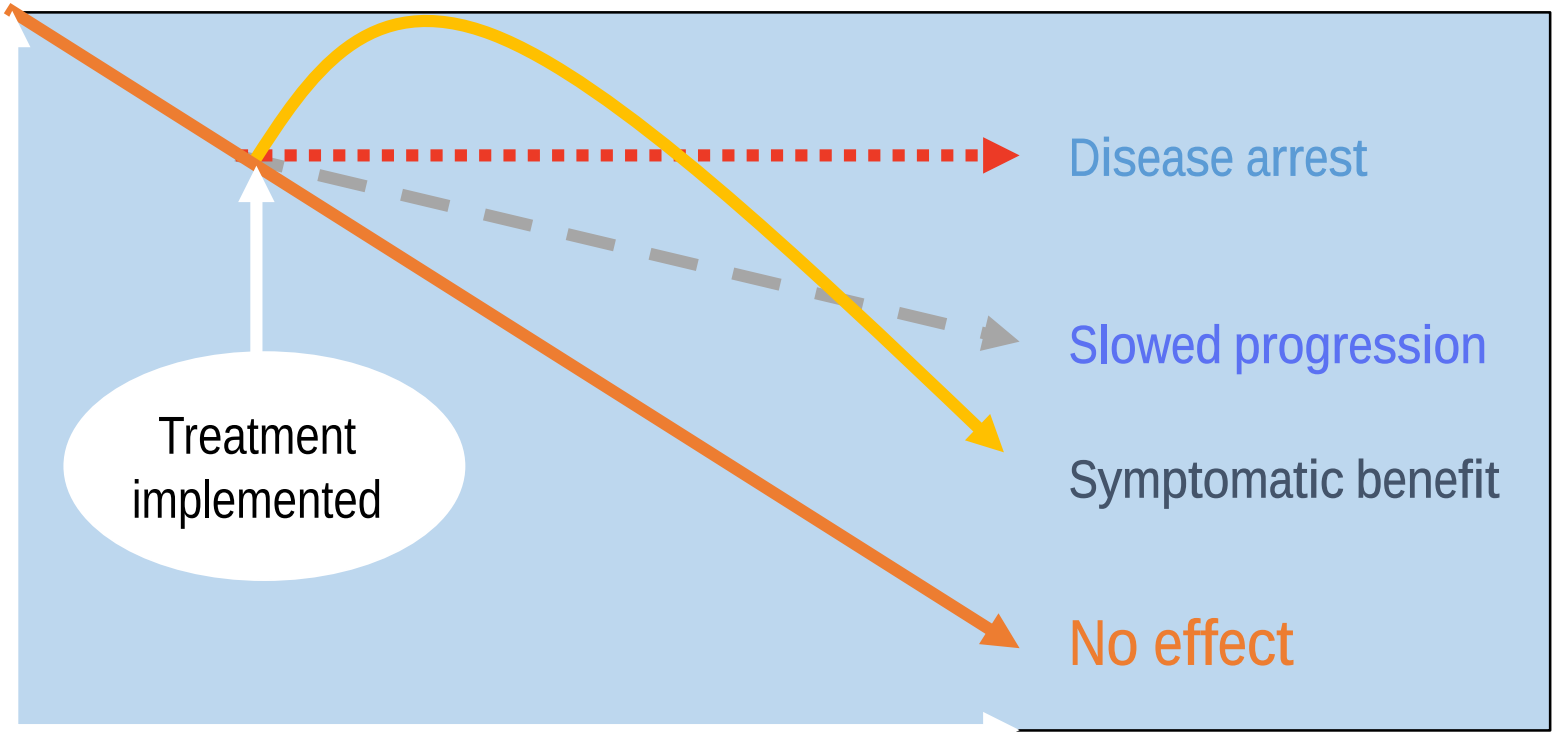
Jack et al. *Lancet Neurology* 2013

Biomarkers for AD: Blood

A blood-based biomarker represents the best avenue for preclinical AD

- Inexpensive
- Specialized equipment not required
- Readily obtained
- Minimal risk involved
- Suitable for large scale screening

What Are the Main Goals of Treatment?



Treatment Domains

Symptom improvement

- FDA-approved
  - Acetylcholinesterase inhibitors
  - NMDA-receptor antagonist
- Experimental
  - Multiple clinical trials underway

Disease modification

- No FDA-approved medications, but clinical trials are in progress on a variety of mechanisms
  - Neuronal protection
  - Protein synthesis or aggregation inhibition
  - Immunologic priming with antibodies
  - Vaccines
  - Secretase inhibition

NMDA = N-methyl-D-aspartate.

Approved Drugs Only Address the Symptoms of AD

Drug	Mechanism of Action	FDA Approved Indications
Donepezil	Cholinesterase inhibitor	• Mild-to-severe Alzheimer's dementia
Rivastigmine	Cholinesterase inhibitor	• Mild-to-severe Alzheimer's dementia • Mild-to-moderate Parkinson's dementia
Galantamine	Cholinesterase inhibitor	• Mild-to-moderate Alzheimer's dementia
Tacrine	Cholinesterase inhibitor	• Mild-to-moderate Alzheimer's dementia
Memantine	NMDA antagonist	• Mild-to-severe Alzheimer's dementia
Memantine and donepezil	Fixed-dose combination: NMDA antagonist and cholinesterase inhibitor	• Mild-to-severe Alzheimer's dementia

Source: Medtrack. http://medtrack.com.

Common Side Effects Associated with Available Therapies for AD

Cholinesterase Inhibitors	Memantine
Nausea/vomiting	Confusion
Diarrhea	Sedation
Loss of appetite	Dizziness
Dizziness	Constipation
Syncope	
Leg cramps	
Ulcers	
Cardiac arrhythmias	

Emre M et al. *J Alzheimers Dis.* 2008;14:193-199.

Homma A et al. *Dement Geriatr Cogn Disord.* 2008;25:399-407

Alzheimer's Disease: The Treatment Horizon

- Disease-modifying therapy
- Combination disease-modifying and symptomatic therapy
- Earlier recognition of AD
- Integration of biomarkers into clinical practice
  - Spinal fluid
  - Blood
  - Imaging
  - Genetics as well
- A host of unanswered questions

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