

# The Brain: Alzheimer's Disease

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ASU Retirees Association Seminar

February 12, 2015

# Disclosure

- Site investigator for clinical trials sponsored by Genentech and Avid
- Member of the Clinical Core of the Arizona Alzheimer's Consortium
- Personally impacted by Alzheimer's disease – multiple affected relatives

# Red Flags or Not?

“I can’t find my car keys (glasses, etc...).”

“Why did I come in here again?”

“Where did I park my car?”

“What was the name of that actor?”

# Memory is not perfect.

Memory lapses are a part of life, but there is a difference between “normal” memory lapses and more serious memory problems.

# “Real” Red Flags

- Frequent repetition. (Not just for emphasis)
- Lack of awareness of memory difficulties.
- Medication errors.
- Disorientation in familiar areas.
- Trouble doing cognitively demanding tasks that were previously done without difficulty.

# In short...

Any loss of a previous skill is concerning.

- An accountant who now is having trouble balancing the checkbook.
- Someone who has never balanced a checkbook shouldn't be expected to be proficient at it.

# What is Dementia?

- A progressive neurological disorder characterized by:
  - Deficits in two or more areas of cognition
  - Impaired memory and/or other cognitive functions
  - Absence of delirium
  - Absence of other brain disease or systemic disease that could account for the clinical observations

# Cognitive Spectrum

- Optimal cognitive functioning - “sharp as a tack”
- Age-associated cognitive changes
- Individual aptitudes & relative weaknesses
- Mild cognitive impairment (MCI)
- Dementia



# MCI versus Dementia

## Mild Cognitive Impairment (amnestic)

- Memory complaint
- Confirmed by reliable informant
- No impairment in functional status
- Isolated memory impairment on formal assessment

## Dementia

- Cognitive complaint (memory and often other complaints)
- Confirmed by reliable informant
- Impairment in functional status
- Objective evidence of impairment in memory and other cognitive domains

# Dementia Subtypes

- **Alzheimer's Disease**
- Lewy Body Dementia, Parkinson's Disease with Dementia
- Vascular Dementia
- Frontotemporal Dementia
- Progressive Supranuclear Palsy, Corticobasal Ganglionic Degeneration
- Prion Disease (Creutzfeldt-Jakob Disease, "Mad Cow" Disease)
- Other Dementias (Huntington's Disease, Normal Pressure Hydrocephalus, mitochondrial disorders, etc.)

# Alzheimer's Disease: Facts and Figures

- More than 5 million Americans living with the disease
- Someone in the US develops AD every 67 seconds
- 5<sup>th</sup> leading cause of death in the US for those 65 & older
- 1 in 3 seniors dies with AD or other form of dementia
- In 2013, 15.5 million caregivers provided 17.7 billion hours of unpaid care valued at \$220 billion
- AD will cost an estimated \$1.2 trillion (in today's dollars) in 2050

# Clinical History

- **Reliable informant**
- Cognitive symptoms
- Functional status
- Behavioral symptoms
- Safety concerns
- Contributing medical factors
- Risk factors

# Clinical History - Cognitive Symptoms

- Memory
- Language
- Visuospatial
- Executive

# Clinical History - Functional Status

- Employment (errors, liability)
- Personal care (hygiene, nutrition)
- Finances (errors, delinquent or double payment, excessive donation)
- Medication management
- *Informant history is key*

# Clinical History - Behavioral Symptoms

- Impaired insight and judgement
- Agitation and irritability
- Depression and apathy
- Anxiety
- “Sundowning”
- “Shadowing”
- Psychosis (hallucinations, delusions)
- Disinhibition and mental inflexibility

# Clinical History - Safety

- Medication errors
- Financial errors/victimization
- Driving
- Firearms and power tools
- Wandering
- Scalding
- Fall risk
- *All incorporate the need for increasing supervision of the patient*



# Clinical History - Contributing Medical Factors

- Psychiatric illness
- Sleep disturbance
- Medical conditions (hormone, lung, liver, kidney, etc.)
- Medication adverse effects
- Substance abuse

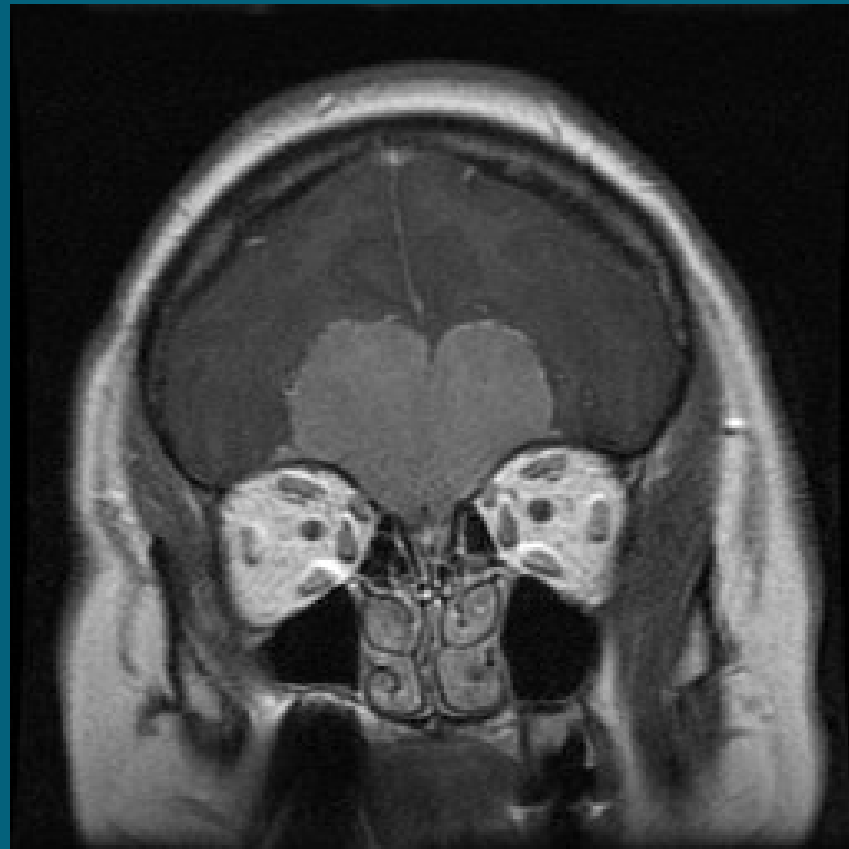
# Neurological Examination

- Mental Status Exam
  - Orientation
  - Learning and Recall
  - Attention
  - Visuospatial
  - Abstract thinking
  - Language
  - Calculation
- Physical Exam
  - Gait
  - Speech
  - Strength
  - Reflexes
  - Sensation
  - Coordination
  - Abnormal movements

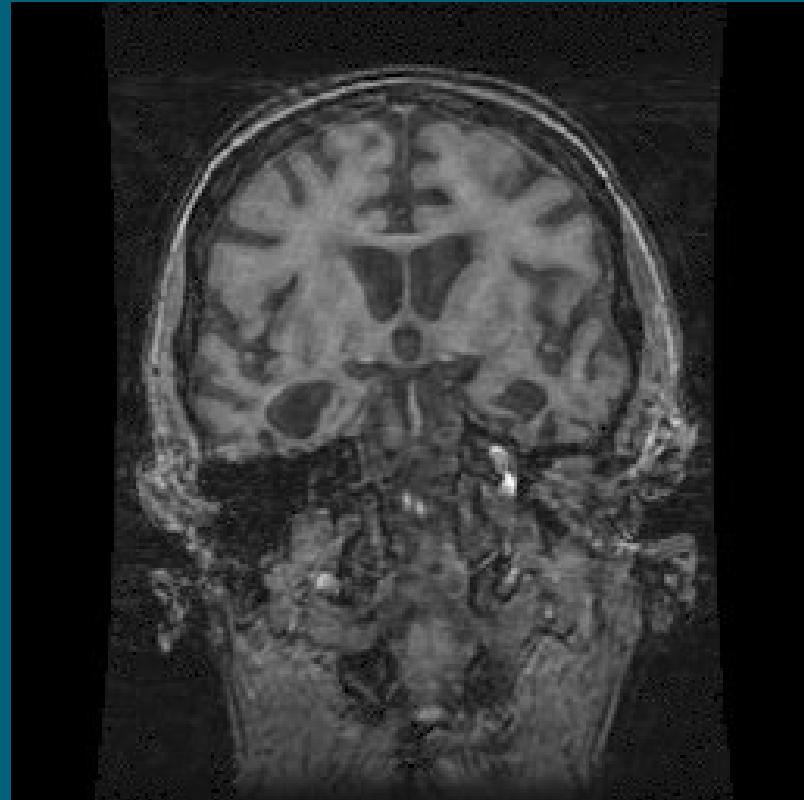
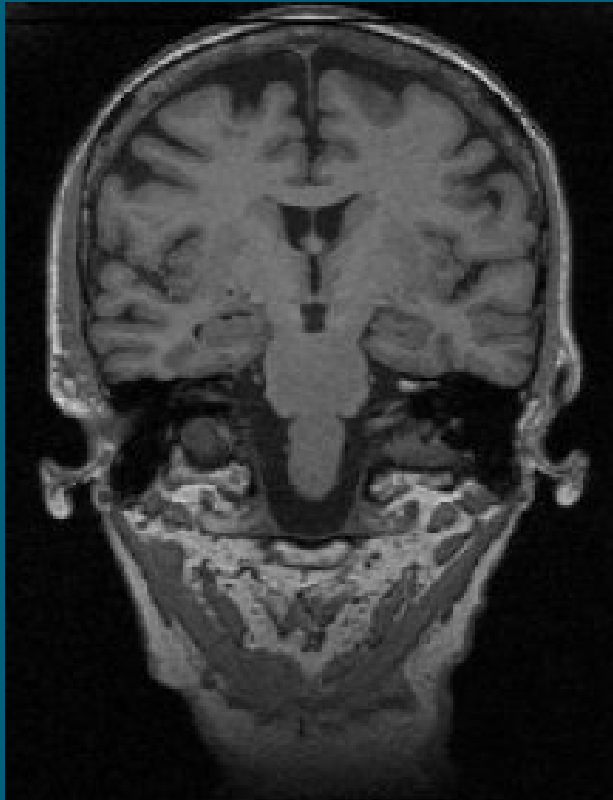
# Diagnostic Studies

- Routine Laboratory – Thyroid, B<sub>12</sub>, basic chemistries to exclude metabolic derangements
- Brain imaging – CT or MRI (structural); less commonly SPECT, FDG-PET (metabolic), or amyloid PET (biomarker)
- Neuropsychological Assessment
- Psychiatry referral or sleep evaluation if indicated
- Infrequently, EEG or spinal fluid analysis
- Rarely, genetic testing

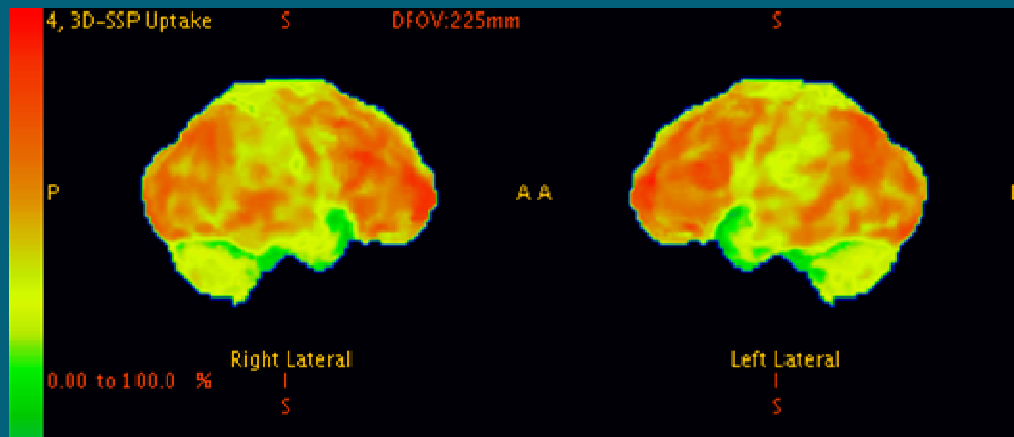
One of the reasons to get a scan:



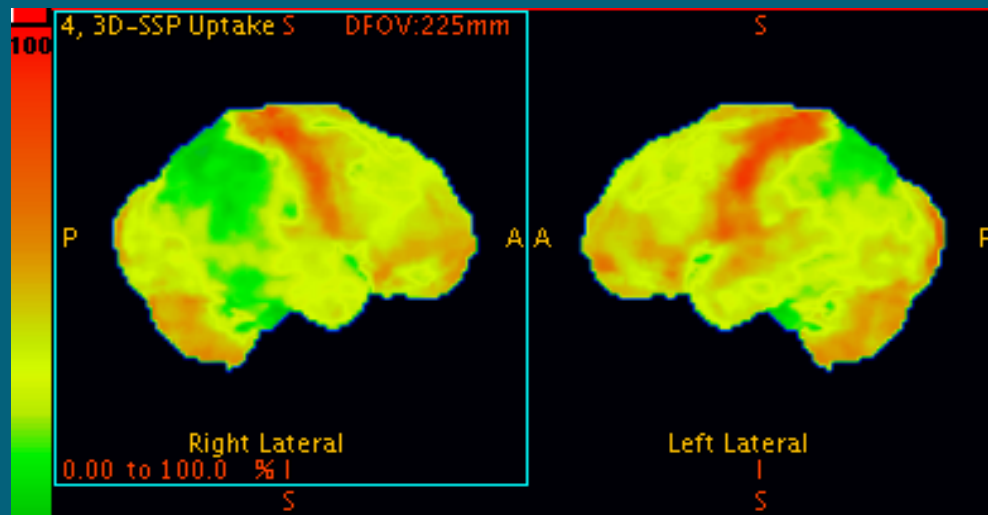
# Imaging: Normal and AD



# FDG- PET



Normal

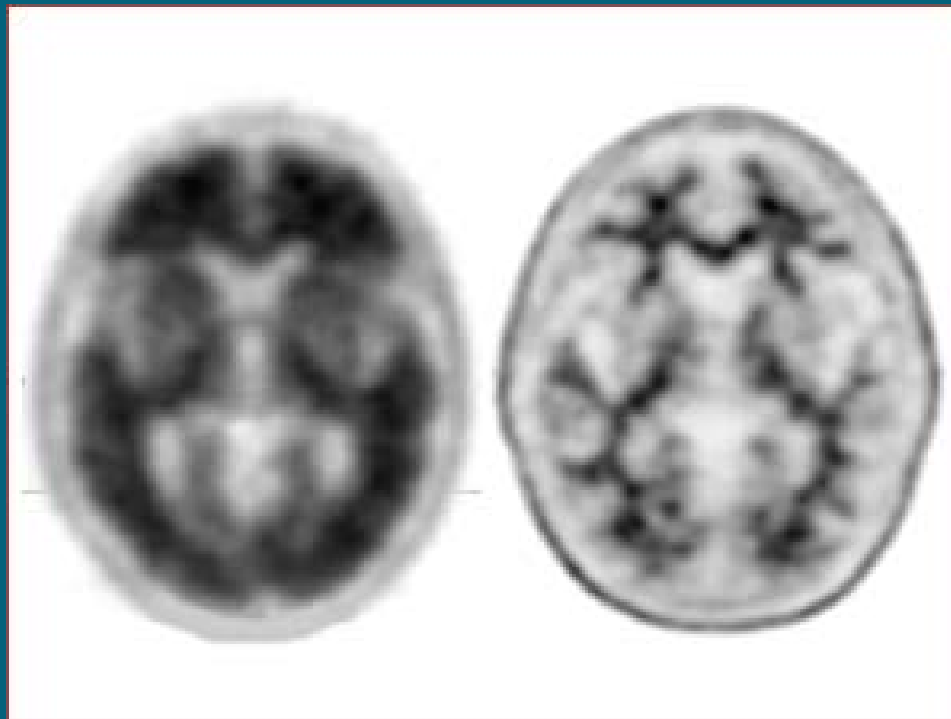


AD

# Amyloid PET Imaging: FDA-approved 2012

AD

Normal



<http://www.medscape.com/viewarticle/762347>

# Treatment

- Cognitive
  - Acetylcholinesterase Inhibitors (Aricept - donepezil, Exelon - rivastigmine, Razadyne - galantamine)
  - Glutamate Antagonist (Namenda - memantine)
- Behavioral
  - Antidepressants
  - Anxiolytics
  - Antipsychotics



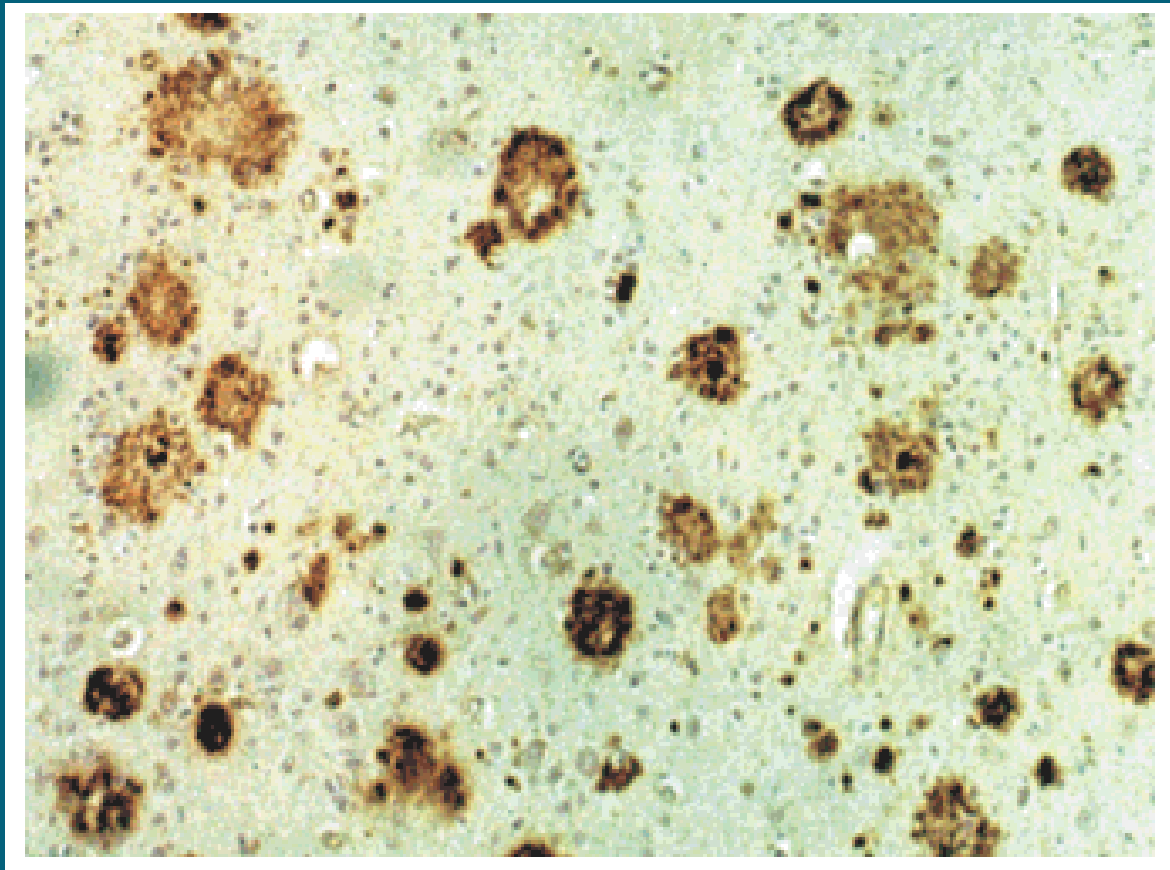
# So how well do they work?

- Specific mechanism of action
- Complex mechanism of disease
- Adverse effects

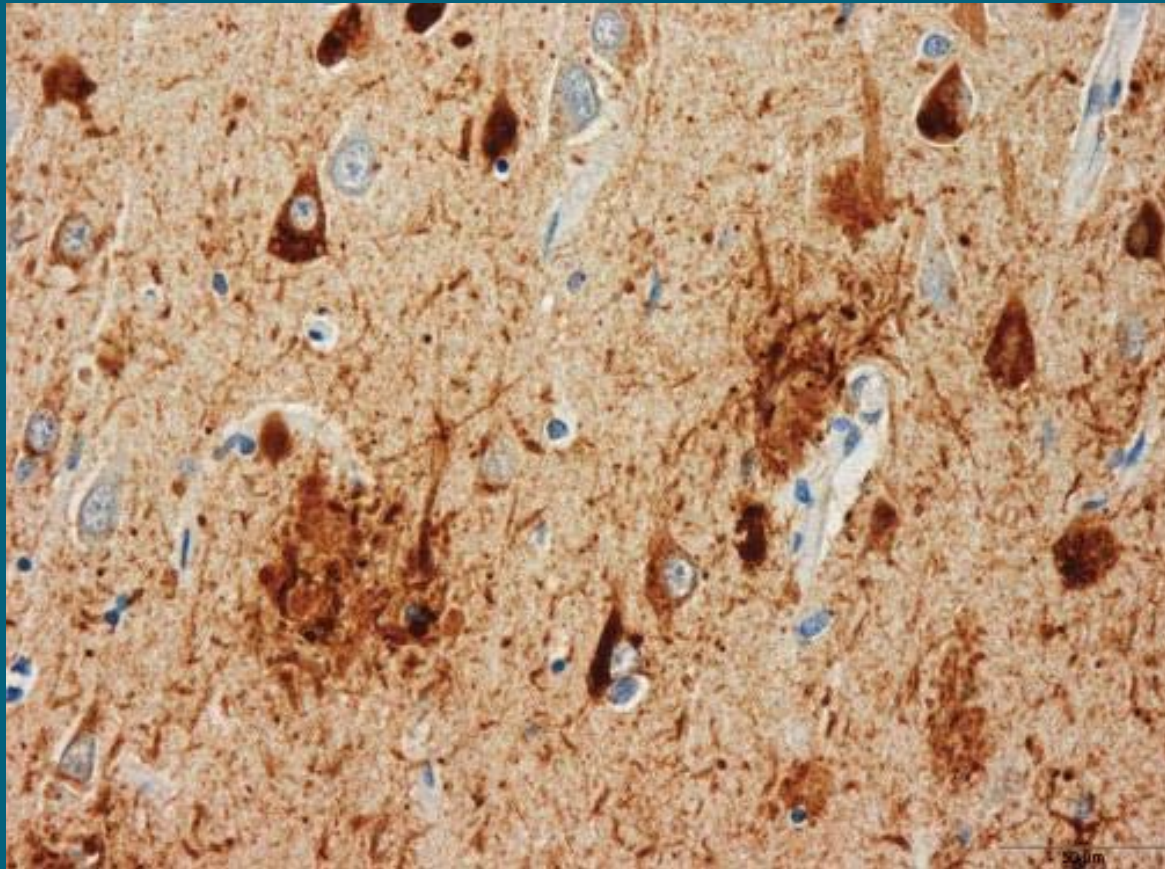
# Alzheimer's pathophysiology

- Accumulation of abnormal proteins
  - Amyloid plaques (amyloid beta protein)
  - Neurofibrillary tangles (tau protein)
- Gliosis
- Impaired synaptic transmission
- Neuronal loss
- Abnormal brain metabolism

# Amyloid plaques



# Neurofibrillary tangles



# Alzheimer's Disease Genetics

- Risk Factor Genes
  - *APOE* (common)
  - Probable multiple others with weak effects
- Causative Genes (rare)
  - Presenilin 1
  - Presenilin 2
  - APP (Down's syndrome)

# Treatment Trials

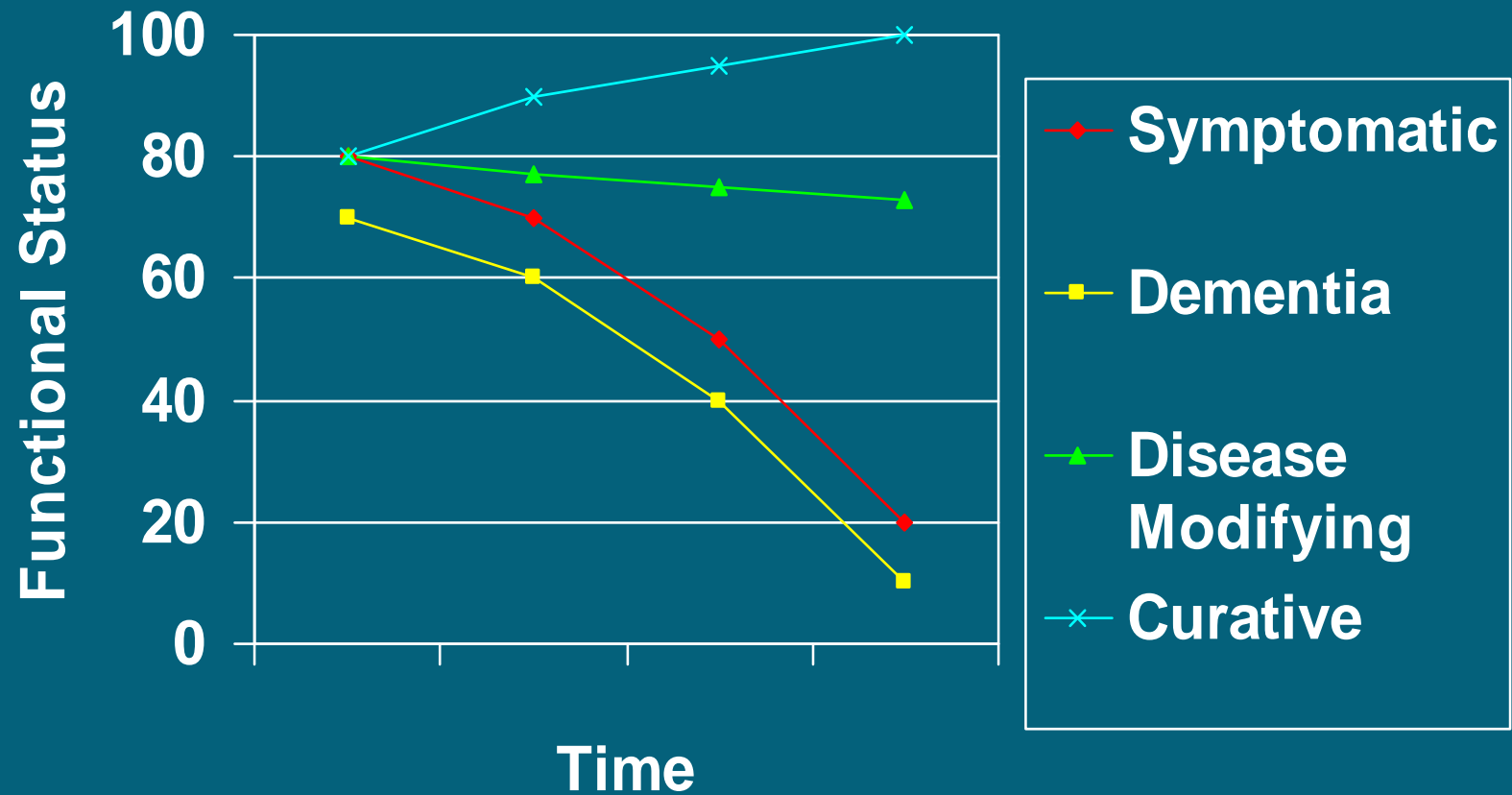
## Targets

- Anti-amyloid (plaques)
- Anti-tau (tangles)
- Metabolic (glucose utilization)
- Anti-inflammatory (gliosis)
- Immune therapy
- Deep brain stimulation
- Stem cell therapeutics (neuronal loss)

## Caveats

- Promising early phase studies often fail in later phase trials
- Timing of intervention may be critical; “too little, too late”
- Mice are not people

# Dementia Therapy



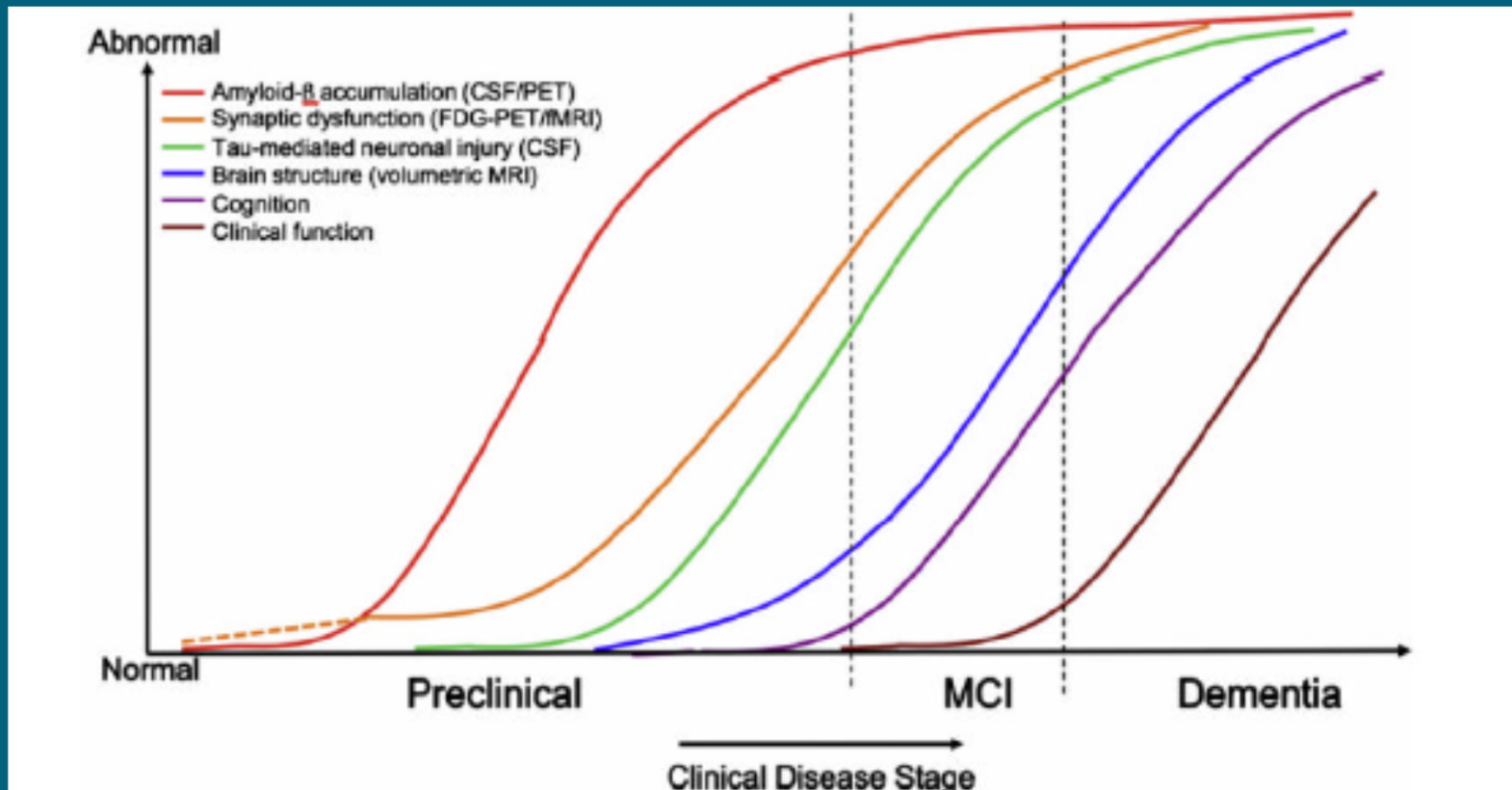
# Earlier detection?

- Initiating treatment at an early dementia or MCI stage may be too late.
- Already significant neuropathology
- Push for more reliable biomarkers of disease prior to advent of clinical symptoms
- Impetus for Alzheimer's Primary Prevention Trial



# AD Prevention Initiative

- Collaborative project between researchers here and Colombia
- Goal of proving that primary prevention is feasible in a large extended family with a rare early-onset genetic form of AD
- Success there could pave the way for similar trials in more common forms of AD



Sperling, RA 2011

# Additional Prevention Strategies

- Health management
  - Diet
  - High blood pressure
  - Diabetes
  - Cholesterol
- Activity level
  - Physical
  - Mental
  - Social

# Questions?

