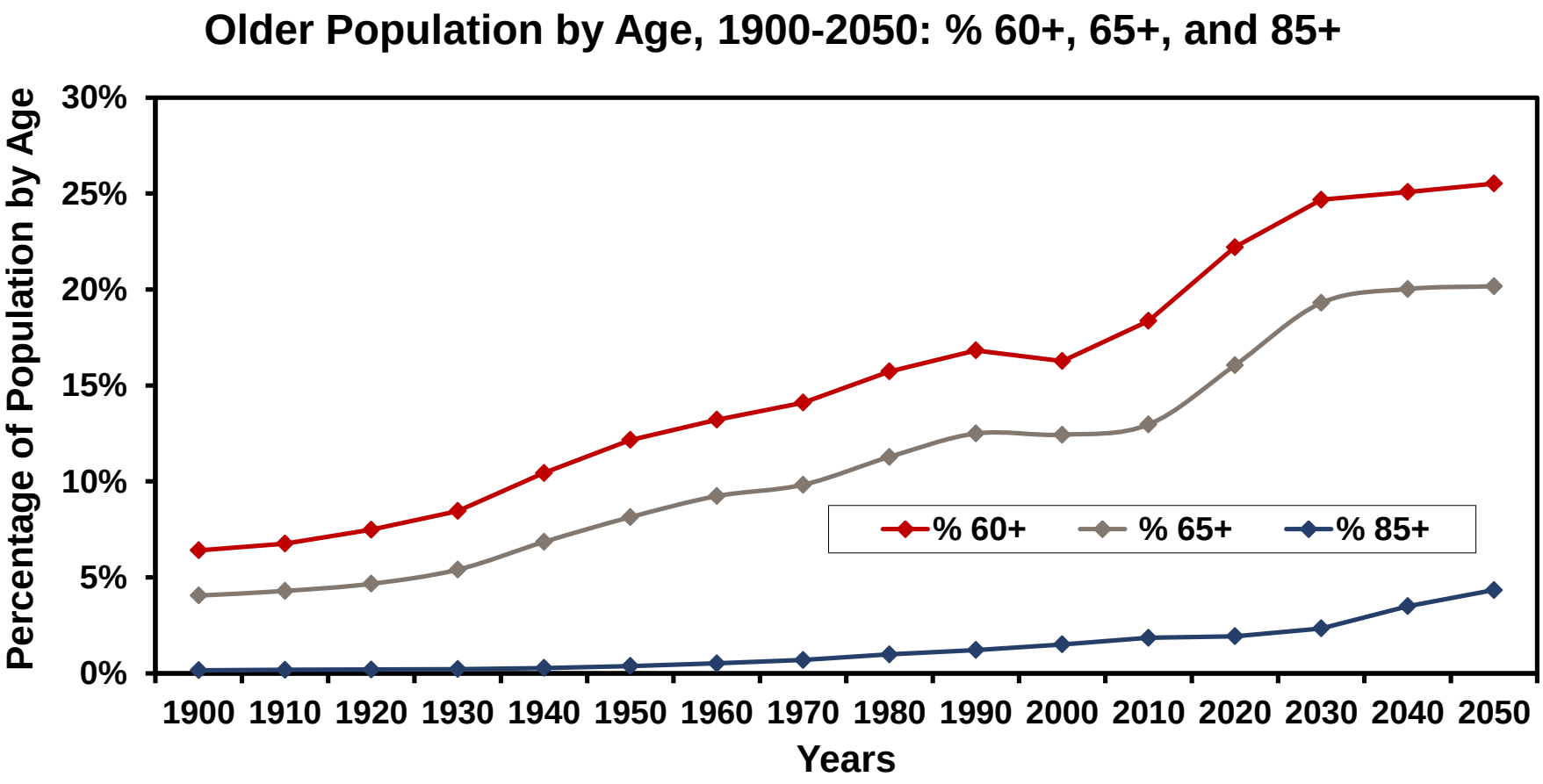
From Research to Market: The Journey of Drug Development In Alzheimer’s Disease

US Demographics for Older Persons: 1900-2050



US Department of Health and Human Services. Administration on Aging. Projected future growth of the older population

Types of Brain Aging

Delayed Aging[1-4]

"Super Agers"[5]

Natural Cognitive Aging[6,7]

Dementia[8]

1. Scarmeas N, Stern Y. *J Clin Exp Neuropsychol* 2003;25:625-33
2. Hall CB et al. *Neurology* 2009;73:356-61
3. Hedden T, Gabrieli JD. *Nat Rev Neurosci* 2004;5:87-96
4. Barnes LL et al. *Neurology* 2004;63:2322-6
5. Sanders AE et al. *JAMA* 2010;303:150-8
6. Burke SN, Barnes CA. *Nat Rev Neurosci* 2006;7:30-40
7. Hof PR, Morrison JH. *Trends Neurosci* 2004;27:607-13
8. Scharre DW, Trzepacz PT. *FOCUS* 2013;11:482-500

Types of Brain Aging and Key Associated Features

Delayed Aging

- Exercise[1]
- Intellectually challenging activities[2]
- High education[1]
- Healthy diet[3]
- Social network[4]

"Super Agers"

- *CETP* gene (valine homozygotic) found in adults ≥70 years without cognitive impairment[5]

Natural Cognitive Aging

- Word recall and information processing speed decline[6,7]
- Neuronal plasticity decreases[6,7]
- Neuronal loss does not play a significant role[6,7]

Dementia

- Cognitive and functional decline
- Neuron loss, toxic protein aggregates, and/or blood vessel changes[8]

1. Scarmeas N, Stern Y. *J Clin Exp Neuropsychol* 2003;25:625-33
2. Hall CB et al. *Neurology* 2009;73:356-61
3. Hedden T, Gabrieli JD. *Nat Rev Neurosci* 2004;5:87-96
4. Barnes LL et al. *Neurology* 2004;63:2322-6
5. Sanders AE et al. *JAMA* 2010;303:150-8
6. Burke SN, Barnes CA. *Nat Rev Neurosci* 2006;7:30-40
7. Hof PR, Morrison JH. *Trends Neurosci* 2004;27:607-13
8. Scharre DW, Trzepacz PT. *FOCUS* 2013;11:482-500

Natural Cognitive Aging

- Brain aging is characterized by considerable heterogeneity across individuals, and involves many physiological changes similar to the rest of the body[1]
- Aging accompanied by cognitive decline is common and a primary risk factor for AD[2]
- Dysfunction of medial temporal lobe memory system and frontostriatal executive system[1]
  - These same systems are affected by neurodegenerative diseases[1]
- Higher cognitive reserve delays cognitive decline[3]

1. Jagust W. *Neuron* 2013;77:219-34
2. Yankner BA et al. *Annu Rev Pathol* 2008;3:41-66
3. Scarmeas N, Stern Y. *J Clin Exp Neuropsychol* 2003;25:625-33

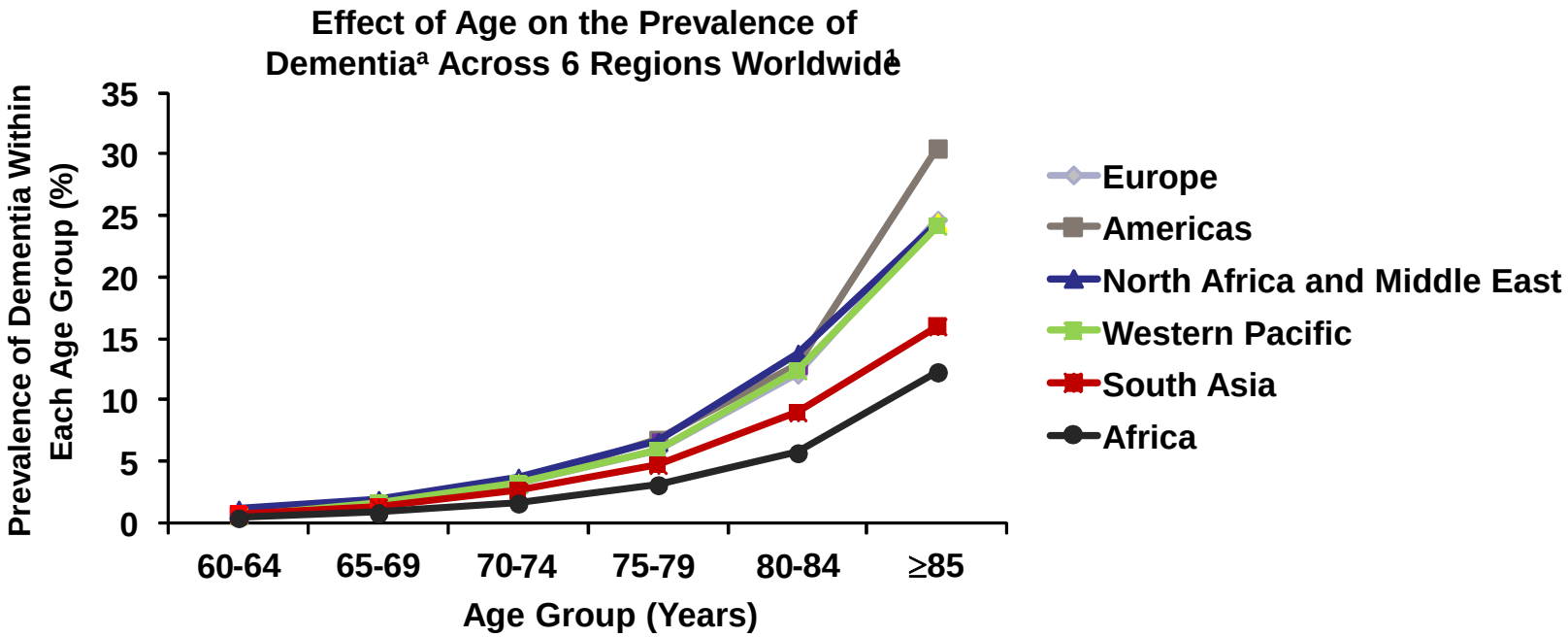
Worldwide Epidemiology of Dementia

- 35.6 million people worldwide estimated to have dementia
- Cases estimated to double every 20 years
  - 65.7 million people by 2030
  - 115.4 million people by 2050
- 7.7 million new cases of dementia each year worldwide
- Alzheimer's disease is the most common form of dementia
- Dementia is a disease and is not normal aging

World Health Organization and Alzheimer's Disease International. Dementia: a public health priority

Prevalence and Incidence Rates of Dementia

- Prevalence doubles with approximately every 5 years of age after age 60[1]
- Incidence rises with age[2,3]



[a] Dementia includes patients with dementia due to AD

1. Hsiung GRH. In: Atlas of Alzheimer's Disease, 2007
2. Fitzpatrick AL et al. *J Am Geriatr Soc* 2004;52:195-204
3. Letenneur L et al. *Int J Epidemiol* 1994;23:1256-61

Major Types of Dementias

- Alzheimer's disease is the most common cause of dementia, accounting for 50% to 60% of all cases[1,2]
- The 4 most common non-AD types of dementia[2-4]
  - Vascular dementia (VaD)
  - Dementia with Lewy bodies (DLB)
  - Parkinson's disease dementia (PDD)
  - Frontotemporal dementia (FTD); also called frontotemporal lobar degeneration (FTLD)
- Cases of mixed dementia also occur (eg, AD comorbid with VaD or DLB)[5]
- Other medical conditions should be ruled out before diagnosis of dementia, including[3,6]
  - Delirium, depression, vitamin B_{12} deficiency, hypothyroidism, and AEs due to medication

1. Querfurth HW, LaFerla FM. *N Engl J Med* 2010;362:329-44 (updated 364:588)
2. Galvin JE et al. *J Am Board Fam Med* 2012;25:367-82
3. Knopman DS et al. *Neurology* 2001;56:1143-53
4. McKeith I et al. *Lancet Neurol* 2004;3:19-28
5. National Collaborating Centre for Mental Health. Dementia: NICE-SCIE Guideline, 2007
6. Scharre DW, Trzepacz PT. *FOCUS* 2013;11:482-500

Dementia: Impairment of Multiple Higher Cortical Functions[1,2]

- Dementia (major neurocognitive disorder) describes a significant decline from previous baseline cognition and functioning
- Can involve impairments in memory, language, visuospatial ability, and executive function
- Noncognitive symptoms include personality, mood, sleep, appetite, and behavior changes
- Presentation of dementia differs on the basis of brain region(s) affected, underlying neuropathology, and stage of disease progression
- Considered sufficiently severe to interfere with independence in performing activities of daily living (ADLs)

1. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders: DSM-5; 2013
2. Alzheimer's Association. What is dementia?

Alzheimer's Disease Is the Most Common Type of Dementia Worldwide[1,2]

Dementia Subtype	Early, Characteristic Symptoms	Neuropathology	Proportion of Cases
Alzheimer's disease (AD)[a]	• Impaired memory, apathy, depression • Gradual onset	• Cortical amyloid plaques and neurofibrillary tangles	50-80%[b]
Vascular dementia (VaD)[a]	• Similar to AD, but memory less affected, and mood fluctuations more prominent • Physical frailty • Stepwise onset	• Cerebrovascular disease • Single infarcts in critical regions, or more diffuse multi-infarct disease	20-30%
Dementia with Lewy bodies (DLB)	• Marked fluctuation in cognitive ability • Visual hallucinations • Parkinsonism (tremor and rigidity)	• Cortical Lewy bodies (alpha-synuclein)	<5%
Frontotemporal dementia (FTD)	• Personality changes • Mood changes • Disinhibition • Language difficulties	• No single pathology • Damage limited to frontal and temporal lobes	5-10%

[a]Postmortem studies suggest many people with dementia have mixed AD and VaD pathology and that "mixed dementia" is underdiagnosed
[b]Alzheimer's Association 2013 report lists this estimated range as 60-80%

1. Alzheimer's Disease International. World Alzheimer Report 2009
2. Thies W et al. *Alzheimers Dement* 2013;9:208-45

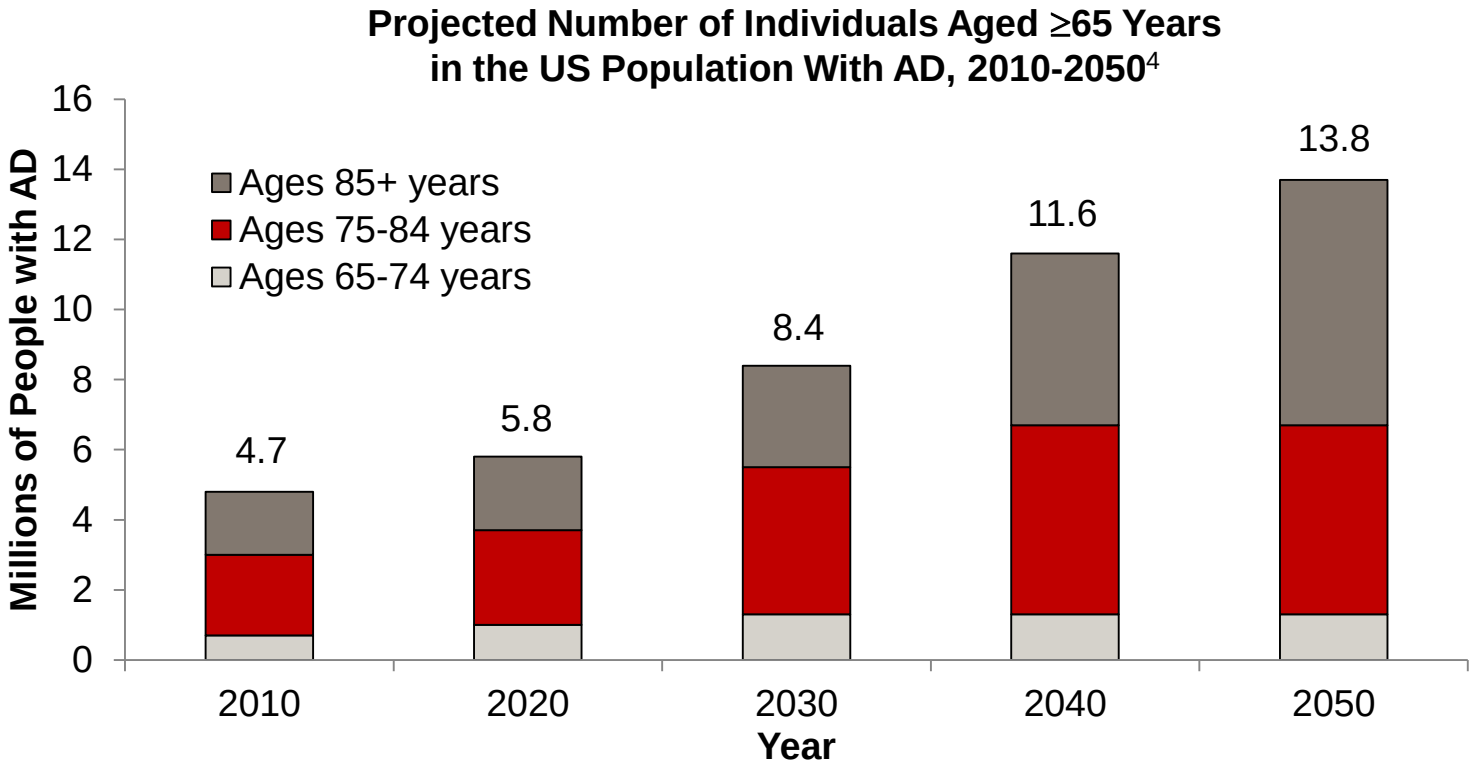
Natural History of Alzheimer's Disease

- AD shortens life expectancy[1,3]
- Survival time from the onset of AD symptoms varies in studies by age[1-3]
  - Ranges of 8 to 10 years for those diagnosed before age 70 to 75
  - 4 to 5 years in those diagnosed after age 80
- Duration usually longer for women than for men[1]
- 6th leading cause of death in the US; 5th leading cause of death for individuals ≥65 years of age[3]

1. Xie J et al. *BMJ* 2008;336:258-62
2. Ganguli M et al. *Arch Neurol* 2005;62:779-84
3. Alzheimer's Association. 2013 Alzheimer's Disease Facts and Figures

Epidemiology of Alzheimer's Disease

- Currently, 24 to 35 million estimated AD cases worldwide[1,2]; 81 million[a] cases projected by 2040[3]



[a] Based on projected 115 million dementia patients, if 70% due to AD[3]

1. Ridge PG et al. *Biomed Res Int* 2013;2013:254954
2. Ferri CP et al. *Lancet* 2005;366:2112-7
3. World Health Organization and Alzheimer's Disease International. Dementia: a public health priority
4. Hebert LE et al. *Neurology* 2013;80:1778-83

Risk Factors for Sporadic Alzheimer's Disease

- Advancing age is the greatest risk factor for AD[1]
- Other risk factors can be categorized as
  - Nonmodifiable (genetic: APOE-ε4 carrier)[2]
  - Modifiable (eg, midlife obesity, diabetes, hypertension, smoking, dyslipidemia)[3,4]
- Possible protective factors reducing risk of AD include
  - Education[4,5]
  - Social and cognitive engagement[4-6]
  - Exercise[4-6]
  - Diet[4,6]
  - Genetics (eg, APOE-ε2 carrier)[4]

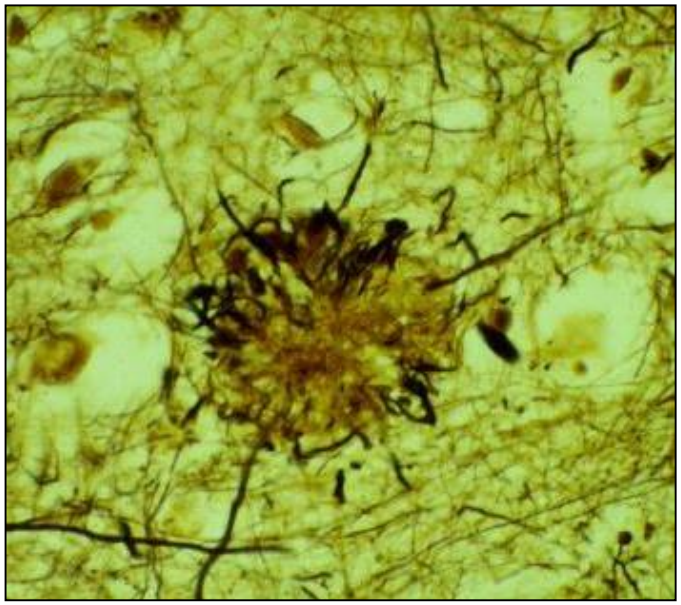
1. Hsiung GRH. In: Atlas of Alzheimer's Disease, 2007
2. Hsiung GY, Sadovnick AD. *Alzheimers Dement* 2007;3:418-27
3. Barnes DE, Yaffe K. *Lancet Neurol* 2011;10:819-28
4. Patterson C et al. *CMAJ* 2008;178:548-56
5. Stern Y. *Lancet Neurol* 2012;11:1006-12
6. Hedden T, Gabrieli JD. *Nat Rev Neurosci* 2004;5:87-96

Features of Alzheimer's Disease

- Symptoms of AD appear gradually and eventually lead to irreversible impairment of a person's ability to remember, reason, and learn[1]
- Symptoms of cognitive decline include[1,2]
  - Memory loss; inability to learn new things
  - Impaired executive functioning, such as abstract thinking and loss of judgment
  - Language impairment, affecting word-finding and meaningful communication
  - Disorientation
  - Visuospatial impairment
  - Difficulty performing familiar tasks
- Noncognitive neuropsychiatric symptoms (NPS; also called behavioral and psychological symptoms)[1,3]
  - Anxiety, depression, irritability, and apathy
  - Agitation and aggression
  - Sleep disturbance

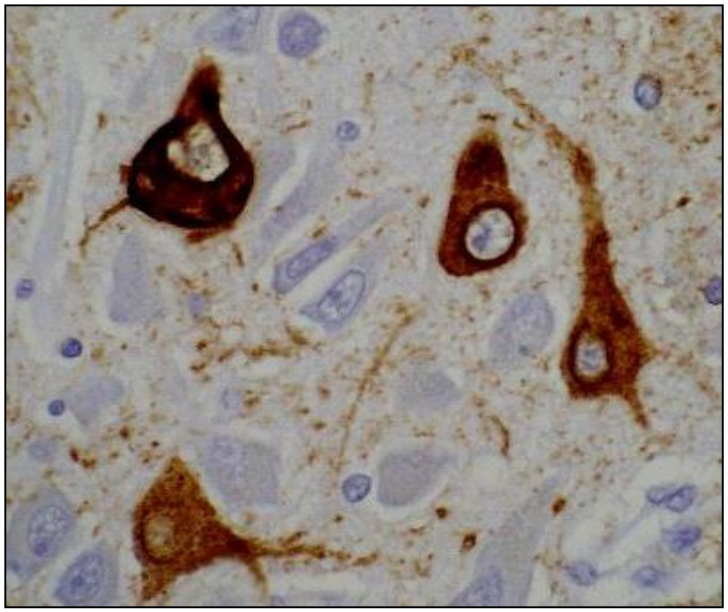
1. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders: DSM-5; 2013
2. Mayo Clinic. Diagnosing Alzheimer's
3. Lyketsos CG et al. *Alzheimers Dement* 2011;7:532-9

Defining Features of Alzheimer's Disease in the Brain



Amyloid plaques[1,2]

- Composed of insoluble amyloid-β protein (Aβ)
- Local neurodegenerative and inflammatory changes



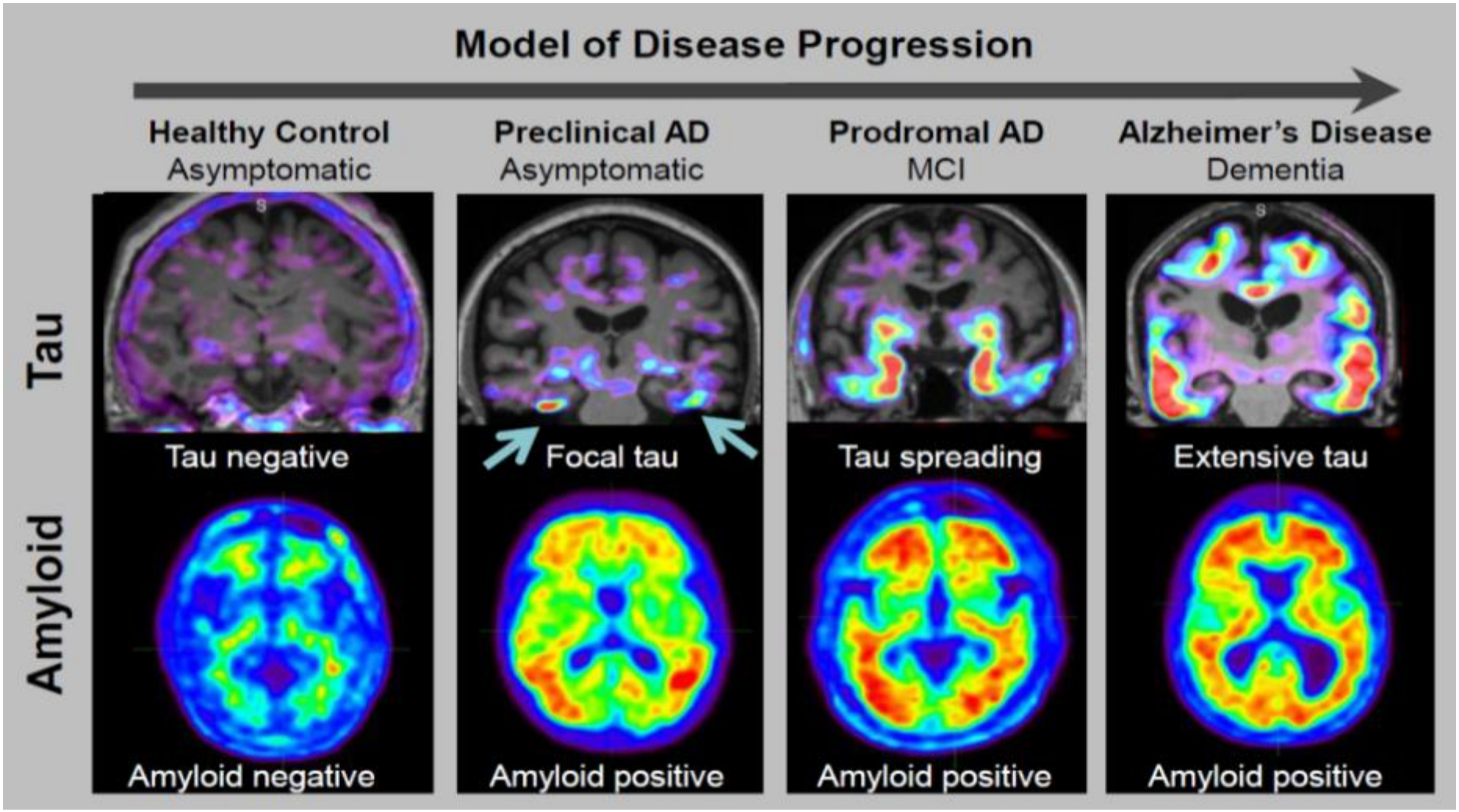
Neurofibrillary tangles[1,2]

- Filamentous inclusions within nerve cells
- Composed of tau protein

Plaques and tangles images reproduced with permission of Dr. Dennis Dickson, Mayo Clinic, Jacksonville, FL

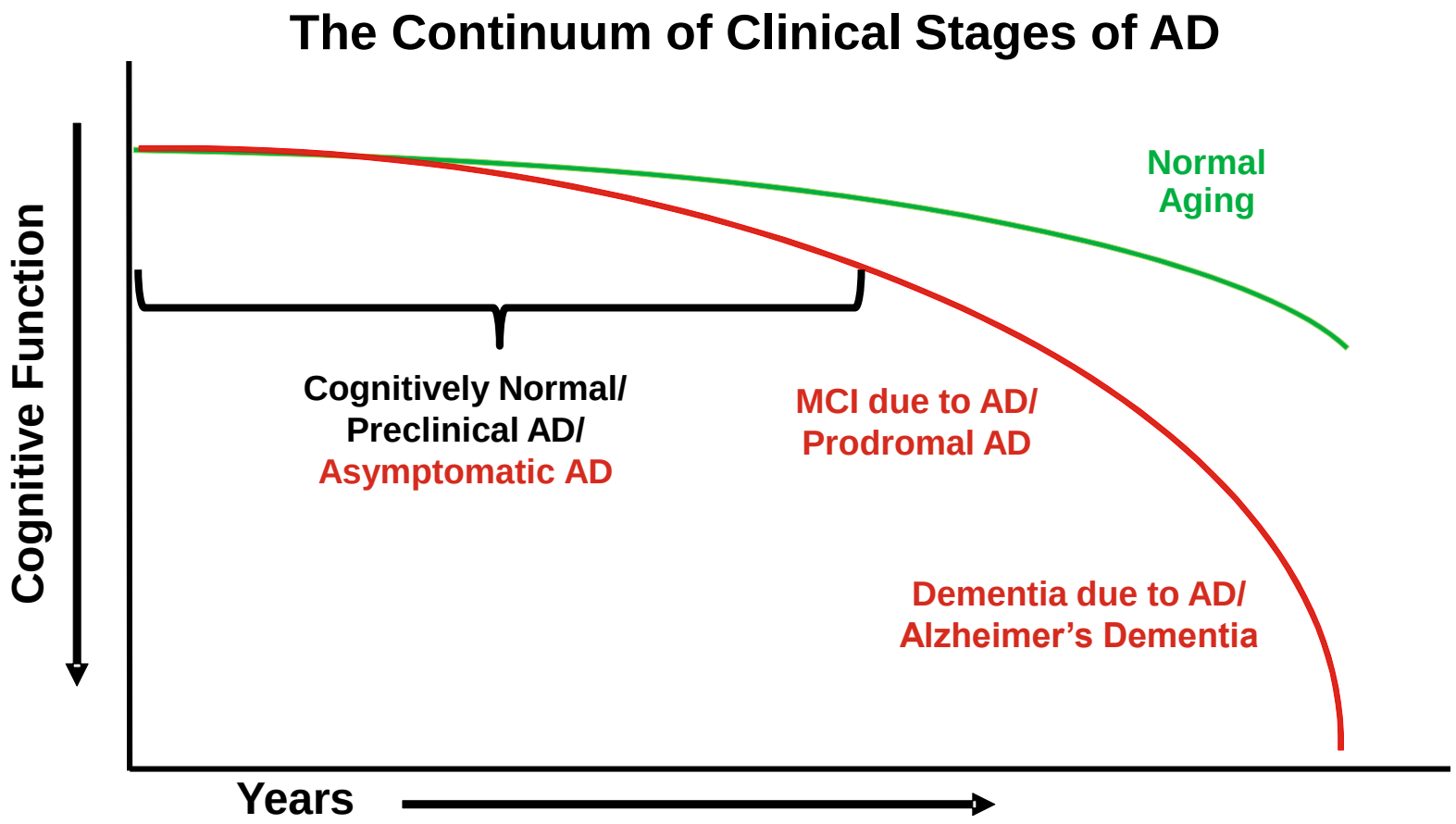
1. Jack CR, Jr. *Radiology* 2012;263(2):344-61.
2. Querfurth HW, LaFerla FM. *N Engl J Med* 2010;362(4):329-44 (updated 364:588).

Novel PET Tracers: Imaging Amyloid Plaques And Tau Tangles In People



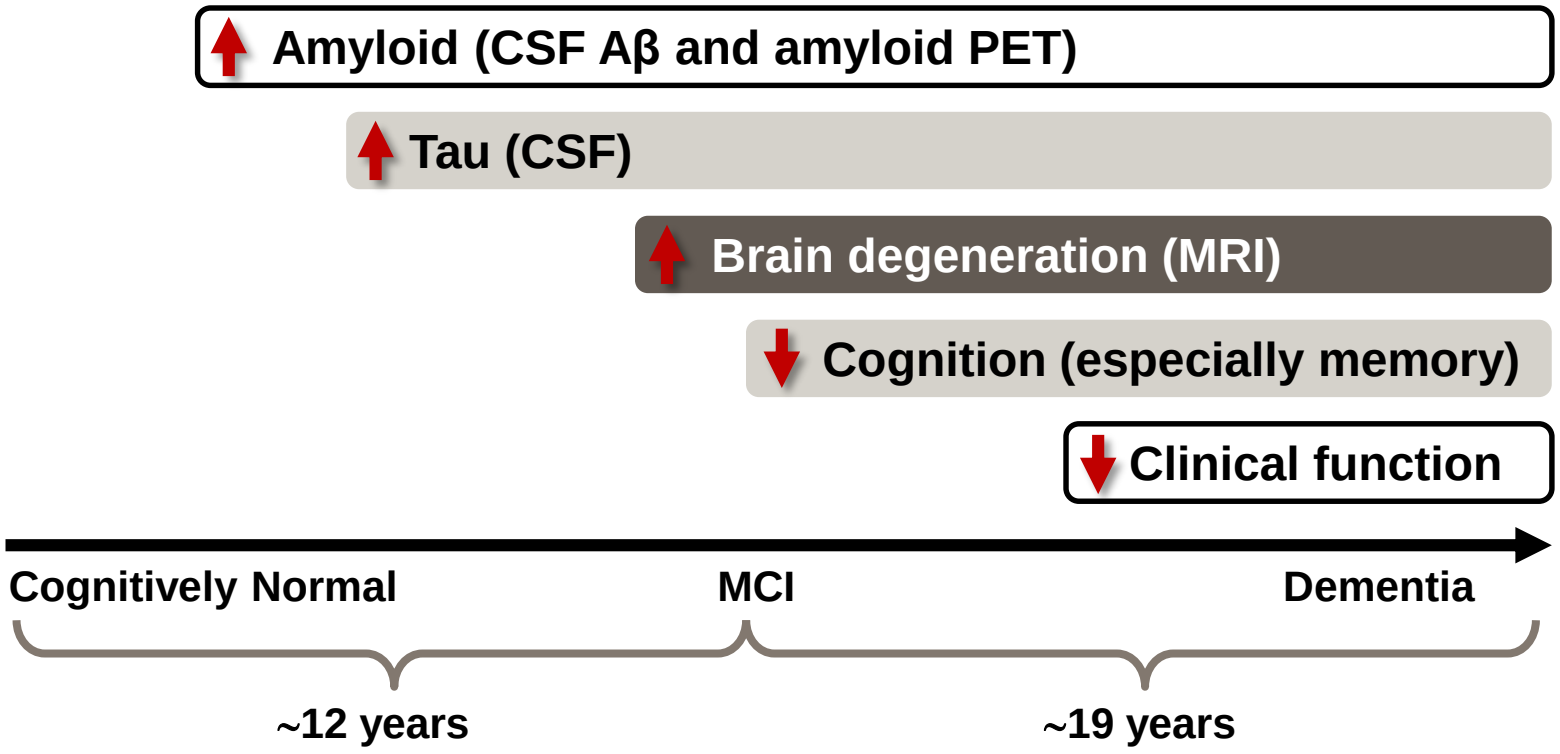
Mark Mintun, Mike Devous and Mike Pontecorvo (Avid)

Course of Illness of Alzheimer's Disease[1,2]



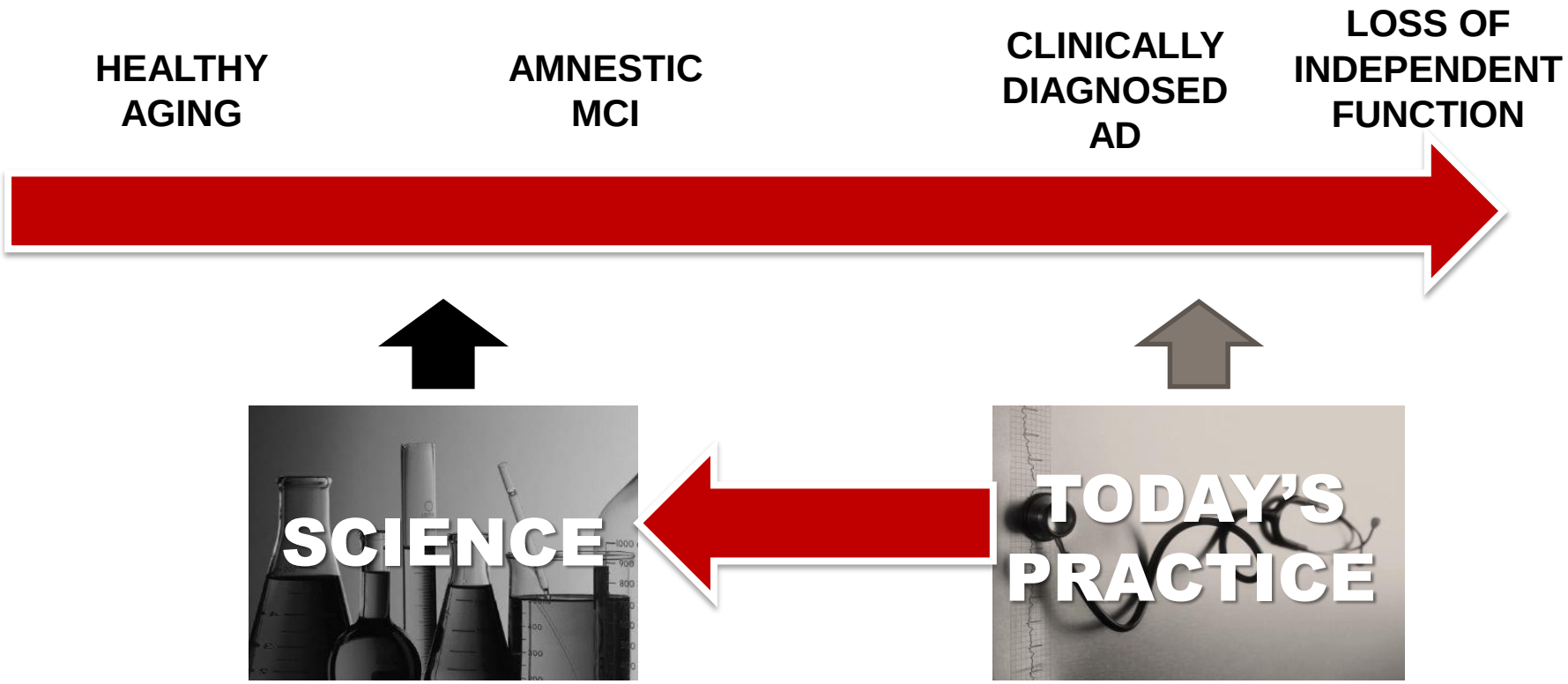
1. Sperling RA et al. *Alzheimers Dement* 2011;7:280-92
2. DuBois B et al. *Lancet Neurol* 2010;9:1118-27

The AD Disease Process May Begin >20 Years Before Dementia Symptoms[1,2]



1. Jack CR Jr et al. *Lancet Neurol* 2010;9:119-28
2. Villemagne VL et al. *Lancet Neurol* 2013;12:357-67

Today's Practice Is Shifting to Meet the Science



Importance of Timely Alzheimer's Disease Diagnosis

- AD diagnosis is often made late in the disease continuum[1,2]
- A more timely and accurate dementia diagnosis[1,2]
  - May reduce the impact of misdiagnosis
  - Provides access to a pathway of care and enables patients and their families to plan for the future
- Targeted management can improve quality of life[1,2]
- Promulgated by national dementia plans, guidelines, and advocacy documents around the world[3-8]
- Proper diagnosis offers hope[2]
  - Addresses patients' and caregivers' needs more fully
  - Appropriate information given
  - Effective intervention initiated at an early stage

1. Jones RW et al. *J Nutr Health Aging* 2010;14:525-30
2. De Lepeleire J et al. *Aging Ment Health* 2008;12:568-76
3. Alzheimer's Society. Unlocking diagnosis: all-party parliamentary group report 2012
4. Alzheimer's Disease International. World Alzheimer Report 2011
5. Department of Health (UK). Living Well With Dementia
6. European Parliament. Resolution 2010/2084(INI)
7. US Department of Health and Human Services. National Plan to Address Alzheimer's Disease: 2013 Update
8. Alzheimer Cooperative Valuation in Europe (ALCOVE). The European Joint Action on Dementia Synthesis Report 2013

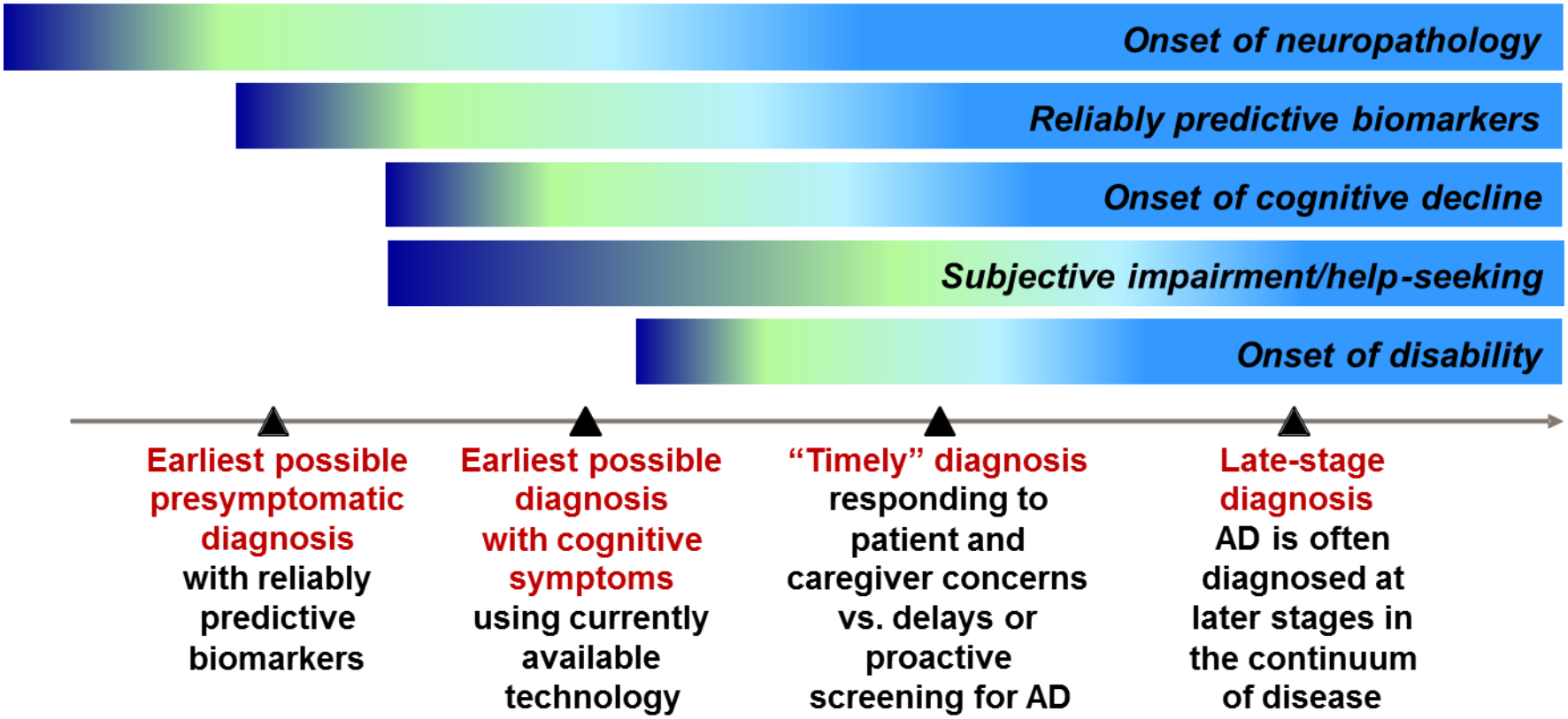
Value of Knowing: Accurate and Timely Alzheimer's Diagnosis

- A majority of people polled in multinational surveys want accurate and specific information regarding diagnosis of dementia if there is a clinical suspicion[1,2]
- Delays in diagnosis are common[3]
- Timely diagnosis may provide benefits to both patients and family members, such as
  - Reduced patient anxiety[4-6]
  - Improved quality of life of caregivers[4]
  - More realistic expectations by caregivers of dependent's abilities[4]
  - Improvement in caregiver's sense of competence and confidence as a caregiver[5]
- Most caregivers (96%) find brain scans helpful to see physical signs of the patient's condition and to better accept the diagnosis[5]

1. Blendon RJ et al. *Int J Alzheimers Dis* 2012;2012:903645
2. http://www.alzheimer-europe.org/Publications/Alzheimer-Europe-Reports
3. Jones RW et al. *J Nutr Health Aging* 2010;14:525-30
4. De Lepeleire J et al. *Aging Ment Health* 2008;12:568-76
5. Smith A et al. *J Mental Health* 1998;7:309-21
6. Carpenter BD et al. *J Am Geriatr Soc* 2008;56:405-12

AD Diagnosis Is Often Not Timely and Made Late in the Disease Continuum

Schematic Timeline of AD Progression and Potential Diagnosis Time Points Along the Disease Continuum



Created by Lilly based on information from Alzheimer's Disease International World Alzheimer Report 2011: http://www.alz.co.uk/research/WorldAlzheimerReport2011.pdf

Patients With Milder Symptoms of Dementia Are Less Likely to Receive a Clinical Diagnosis

- 60%-100% of patients with severe dementia were diagnosed in primary care vs. only 9%-41% with mild symptoms of dementia[1]
- 75% of surveyed physicians believe underdiagnosis of AD could be a result of clinicians failing to make a diagnosis at the earliest stages of disease because of their uncertainty[2]

1. Bradford A et al. *Alzheimer Dis Assoc Disord* 2009;23:306-14
2. Martinez-Lage P et al. *J Nutr Health Aging* 2010;14:537-44

Communicating a Diagnosis Is Complex[1,2]

- Doctors often shift from direct conversation with the patient to talking about or ignoring him/her regarding treatment decisions
  - May feel awkward, confusing, or overwhelming to the companion, now a caregiver
  - Can be embarrassing, even humiliating, to the patient
- Establishing and maintaining an orderly and productive encounter among patients, companions, and physicians is a complex task and requires
  - Understanding and special skills of the physician, who assumes the additional role of facilitator of triadic discourse
  - A family companion who is expected to take on the critical and continuing role of caregiver in dementia care
- A need exists for expert training for physicians in multiparticipant conversation facilitator skills

1. Karnieli-Miller O et al. *Patient Educ Couns* 2012;88:381-90
2. Klein E and Karlawish J. *Handb Clin Neurol* 2013;118:233-42

Improved Clinician Confidence May Result in More Timely Diagnosis[1-3]

- Clinicians' concerns about dementia misdiagnosis
  - Widely variable clinical features (often develops slowly, overlaps with other comorbidities, or has blurred boundaries with "normal aging")
  - Lack of a single accurate test and deficiencies with existing diagnostic tools
- Consequently, clinicians may delay diagnosis until they are more certain
- Greater confidence in the diagnostic process could reduce delays currently associated with "watchful waiting" and further testing

1. Koch T et al. *BMC Fam Pract* 2010;11:52
2. Bradford A et al. *Alzheimer Dis Assoc Disor* 2009;23:306-14
3. http://alzheimers.org.uk/site/scripts/download_info.php?fileID=1457

In Summary

- AD diagnosis is often made late in the disease continuum
- Timely and accurate diagnosis may reduce consequences of misdiagnosis and allow access to care pathways that enable patients and their families to plan for the future
- Early diagnosis and treatment of patients with AD can improve quality of life and may reduce costs
- Proper diagnosis offers hope to address patients' needs fully and those of their care partners, with appropriate information given and effective intervention initiated at an early stage
- Amyloid PET for appropriate clinical use represents a major advance in the evaluation of patients with cognitive impairment when AD is suspected
- Amyloid PET should be utilized by experienced imaging and treating physicians in appropriately selected patients and only in the context of a comprehensive clinical evaluation with adequate explanations before and after the scan

Current Alzheimer's Disease Management

- Current drug therapies temporarily treat symptoms of AD but may not be appropriate in other types of dementia such as FTD[1-3]
- Cholinesterase inhibitors[4]
  - Donepezil
  - Galantamine
  - Rivastigmine
- NMDA-receptor antagonist[4]
  - Memantine
- Treatment of neuropsychiatric and behavioral symptoms such as apathy, restlessness, anxiety, depression, and aggression is often necessary[5]
- Nonpharmacologic management includes[5]
  - Cognitive training, behavioral interventions, exercise, and sleep hygiene
- Caregiver and family support[1]

1. Alzheimer's Association. 2013 Alzheimer's Disease Facts and Figures
2. Boise L et al. *J Gerontol A Biol Sci Med Sci* 2004;59:M621-6
3. Mendez MF et al. *Am J Geriatr Psychiatry* 2007;15:84-7
4. US Department of Health and Human Services. National Institute on Aging. Alzheimer's Disease Medications Fact Sheet
5. Zec RF, Burkett NR. *NeuroRehabilitation* 2008;23:425-38

Biopharmaceutical Companies Use Today's Revenues To Invest In Tomorrow's Treatments And Cures

Invested about

$75 Billion

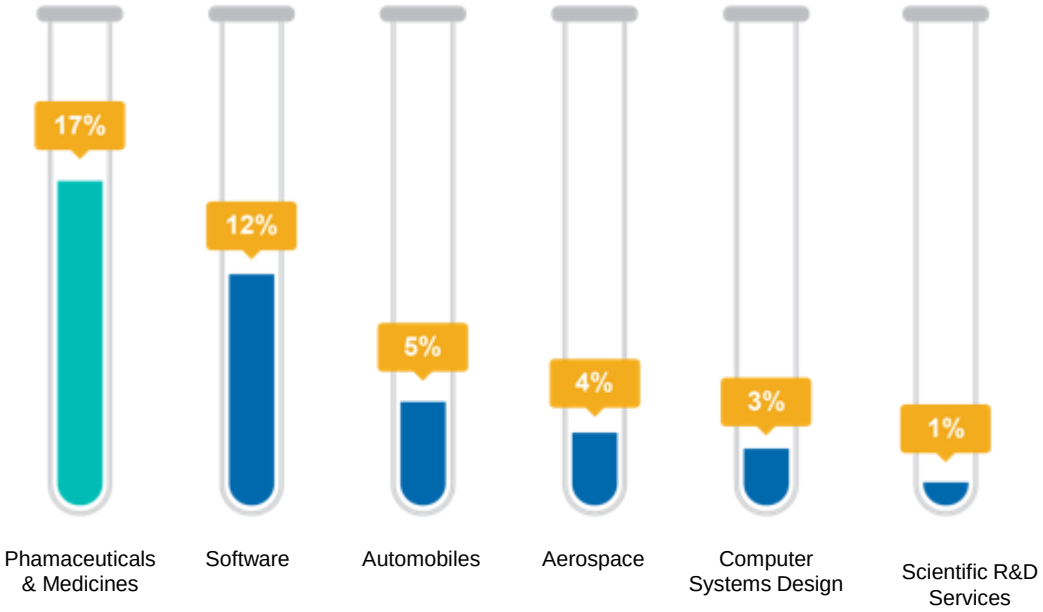
in R&D in 2015

And

20%

of revenues are reinvested into R&D

Industry invests **17%** of all domestic research and development funded by U.S. businesses



Note: The remaining 57% share of business R&D spending is conducted by other industries, including subsectors of the machinery sector, the electrical equipment sector, and the professional, scientific, and technical services sector.
Source: Research!America report and PhRMA analysis of National Science Foundation data.

It Takes More Than 10 Years and $2.6B To Research & Develop A New Medicine

BETWEEN 1998 AND 2014

Unsuccessful Attempts

123
Alzheimer's Disease

96
Melanoma

167
Lung Cancer

Just
12%
of drug candidates that enter clinical testing are approved for use by patients

Successful Attempts

4
Alzheimer's Disease

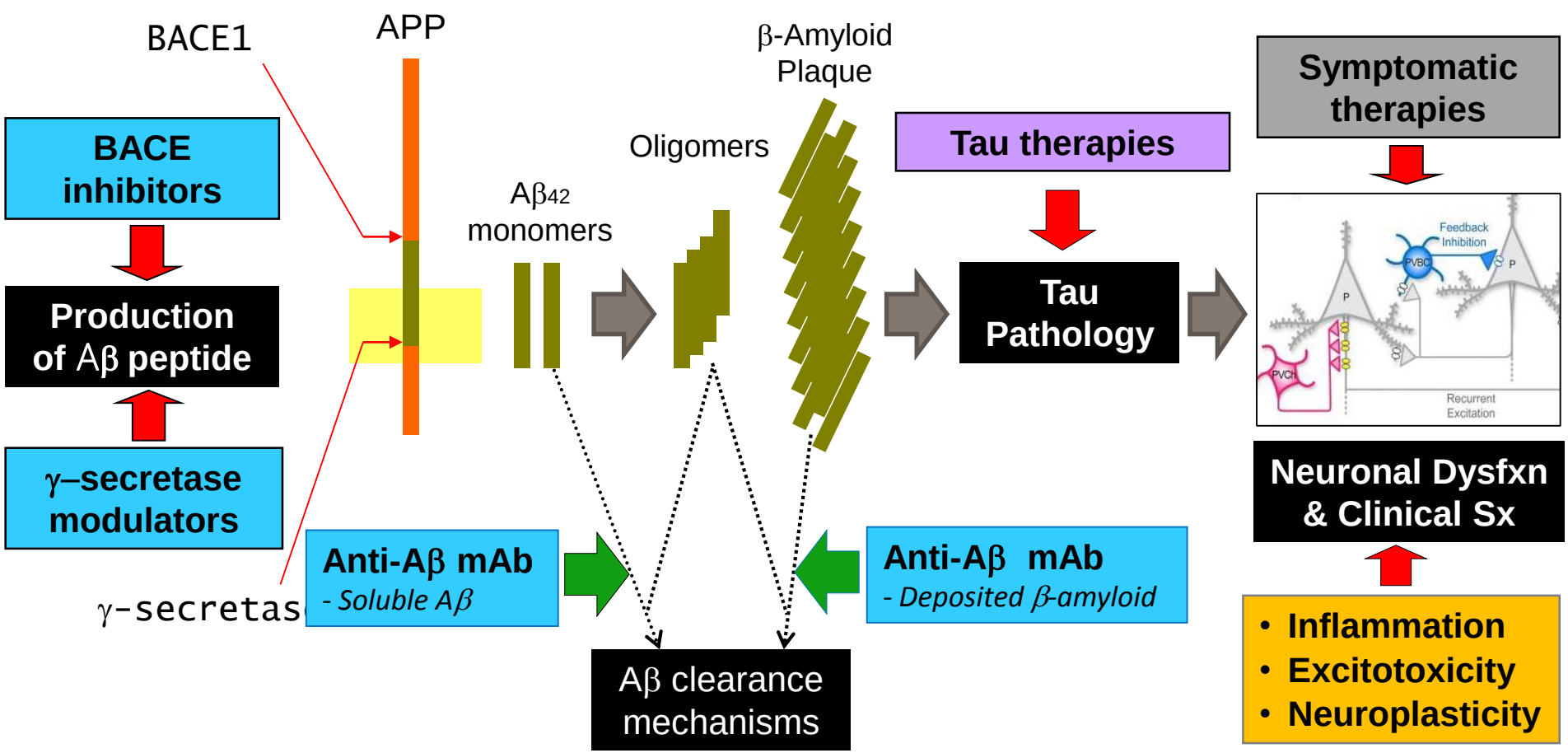
7
Melanoma

10
Lung Cancer

Prescription Medicines: Costs in Context www.phrma.org/cost

Source: Tufts Center for the Study of Drug Development (CSDD).
Source: Pharmaceutical Research and Manufacturers of America (PhRMA), "Researching Alzheimer's Medicines: Setbacks and Stepping Stones," 2015.
Source: Pharmaceutical Research and Manufacturers of America (PhRMA), "Researching Cancer Medicines: Setbacks and Stepping Stones," 2014.

Examples of Potential AD Drug Targets



Future combination of investigational therapies that target multiple points in the cascade may potentially enhance efficacy versus individual monotherapies

Citron M. *Nature* 2010;9:387-98.

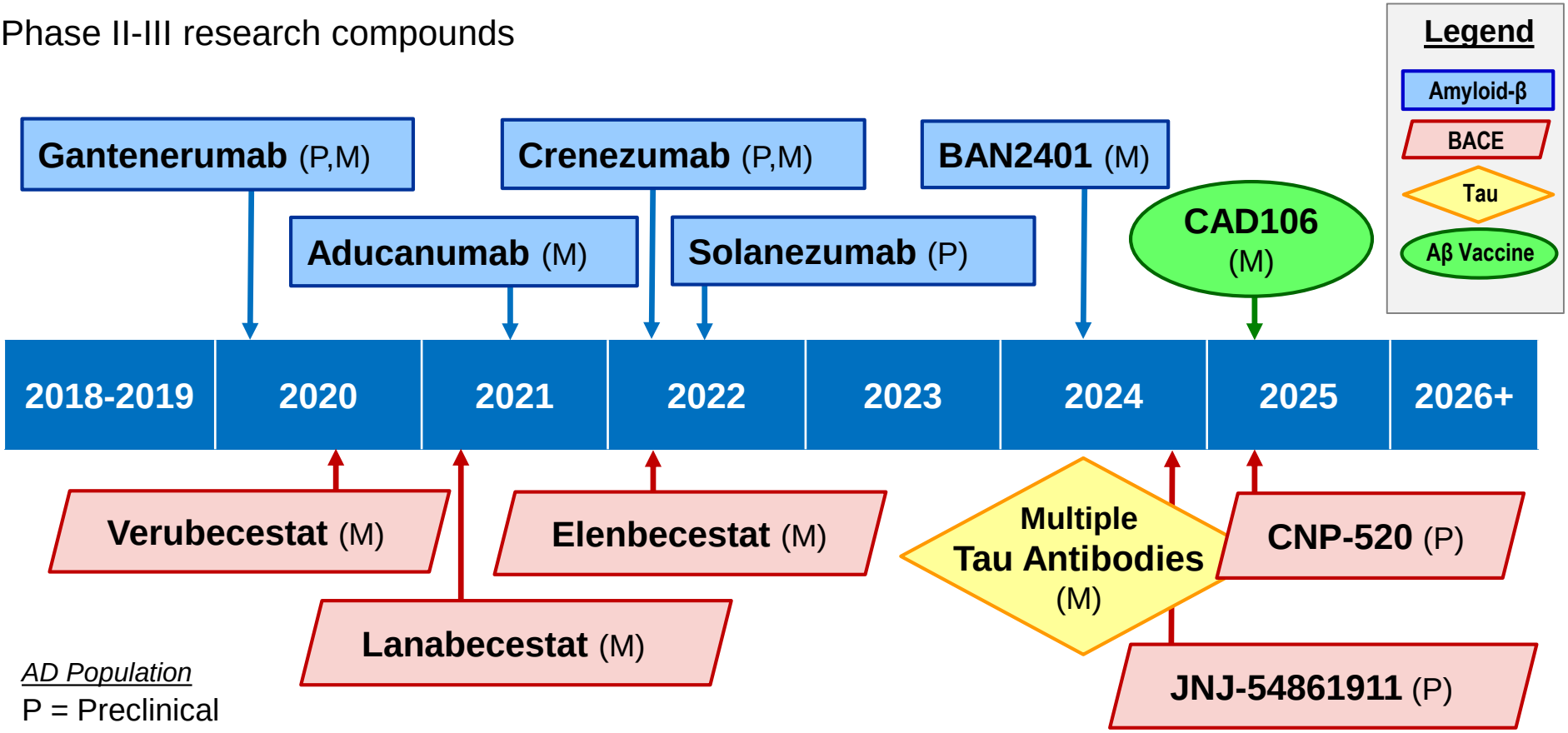
Investigational Treatments in Development for Alzheimer's Disease

- Classes of compounds in late-stage development from multiple sponsors, estimated to be available between 2016-2022
  - Amyloid related
    - Cerebral Aβ clearing agents
    - BACE inhibitors
    - Amyloid aggregation inhibitor
    - Peptide-based Aβ vaccine
    - Gamma-secretase modulator
  - Tau related
    - Tau-aggregation inhibitor
  - Anti-inflammatory
  - Cholinergic agents

Data on file, Eli Lilly and Company

Potential AD Disease Modifying Compounds: Estimation of Approval Dates

Phase II-III research compounds



AD Population
P = Preclinical
M = MCI ± Mild dementia

Safety & efficacy of agents not established – no guarantee of regulatory approval for the uses being studied.

Earliest approval dates estimated using the equation by Scott, et al

1. https://clinicaltrials.gov/. Accessed March 20,2017. 2. Scott TJ, et al. Econ Analysis of Opportunities to Accelerate Alzheimer's R&D. NY Academy of Science, Research Triangle Institute, 2013.

Lilly Alzheimer's Disease Purpose and Goal

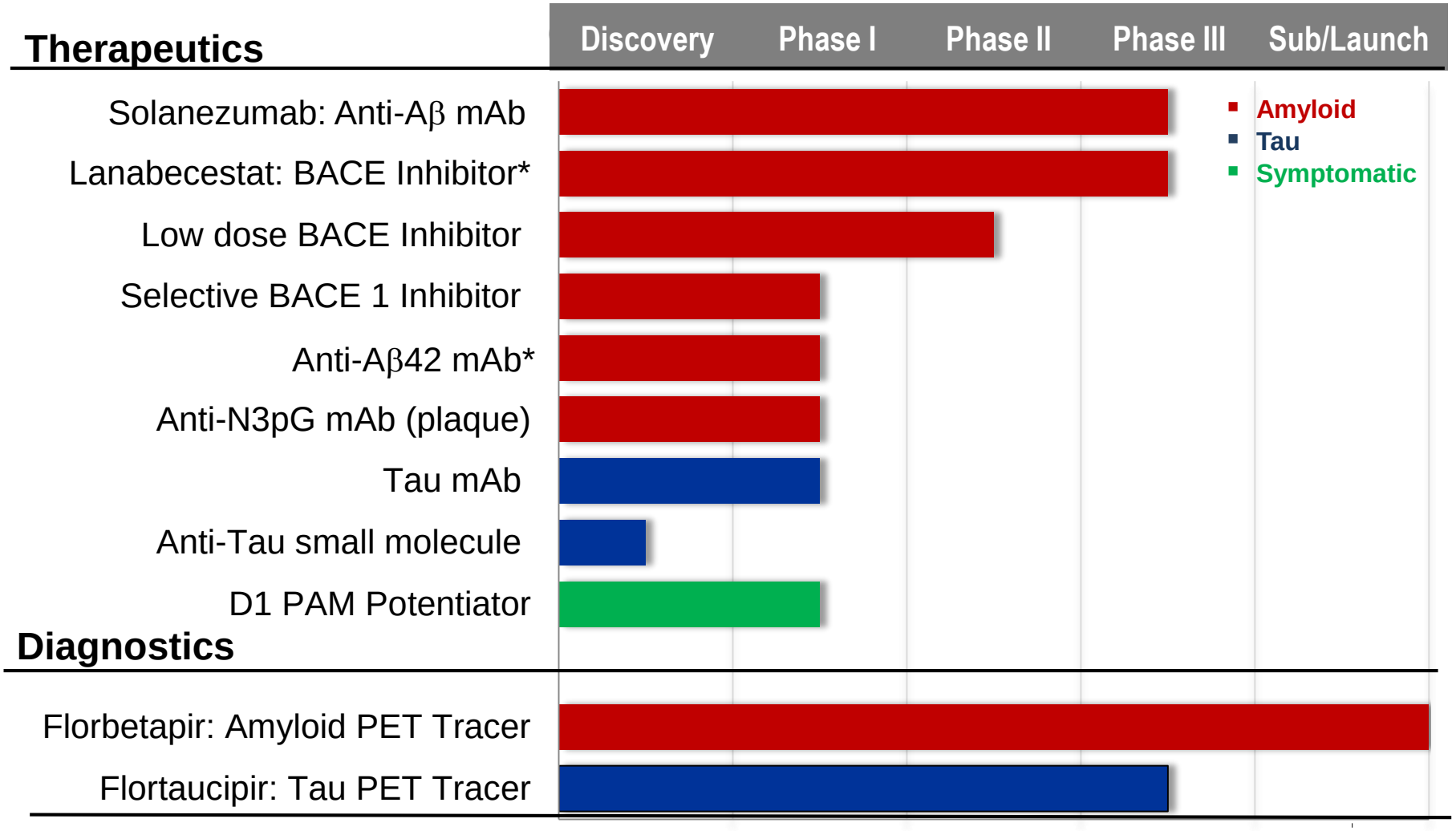
Why are we here?

To Make AD a Distant Memory

And together we will…….

Make AD Dementia Preventable by 2025

Alzheimer's Disease Portfolio
Therapeutics and Diagnostics – April 2017



*Partnership with AstraZeneca

In Conclusion…

- Worldwide dementia prevalence will increase as demographics shift toward more older persons
- AD is an age-related, progressive, neurodegenerative disorder with genetic and environmental etiologies and is the most common form of dementia
- ε4 allele of apolipoprotein E has been genetically linked to late onset of sporadic AD
- Some biomarkers become abnormal before the onset of clinical symptoms
- Early diagnosis and intervention can impact biopsychosocial issues for patients and caregivers
- Informal caregiving is common and carries high personal costs and burdens
- Ongoing research on disease mechanisms may lead to treatment innovations in the foreseeable future