



The Impact of Cognitive Impairment: An Overview

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Disclosure Statement (2017-2018)

- Sources of Research Support

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2. Anonymous Foundation
3. Alzheimer's Association
4. Barnes-Jewish Hospital Foundation

- Consulting Relationships

1. Lilly USA

- Industry-Sponsored Trials

1. Eli Lilly
2. Biogen
3. Janssen

- Fees > \$10,000

None

- Stock Equity

None

- Speaker's Bureaus

None

- Editorial Boards

1. *Neurology Now*

Knight ADRC Faculty and Staff



45 Faculty, 85 Staff in 20 departments/schools

And – thanks to all of our >900 dedicated volunteer participants!

Cognitive Impairment

- Only acquired impairment addressed here
- Many causes and forms
 - e.g., traumatic brain injury/chronic traumatic encephalopathy
 - Delirium
- Focus here is on **age-associated** neurodegenerative dementing disorders, by far the leading causes of cognitive impairment
 - These disorders cause incipient cognitive impairment that has several names (subjective cognitive decline; mild cognitive impairment; prodromal dementia) but inevitably result in progressive impairment (dementia)
 - Distinguishing MCI from Alzheimer dementia is inherently artificial as both are part of a continuum: process of continuous synaptic/neuronal loss
 - Strive for an etiologic diagnosis



Societal and Economic Consequences of Relentless Aging – I.

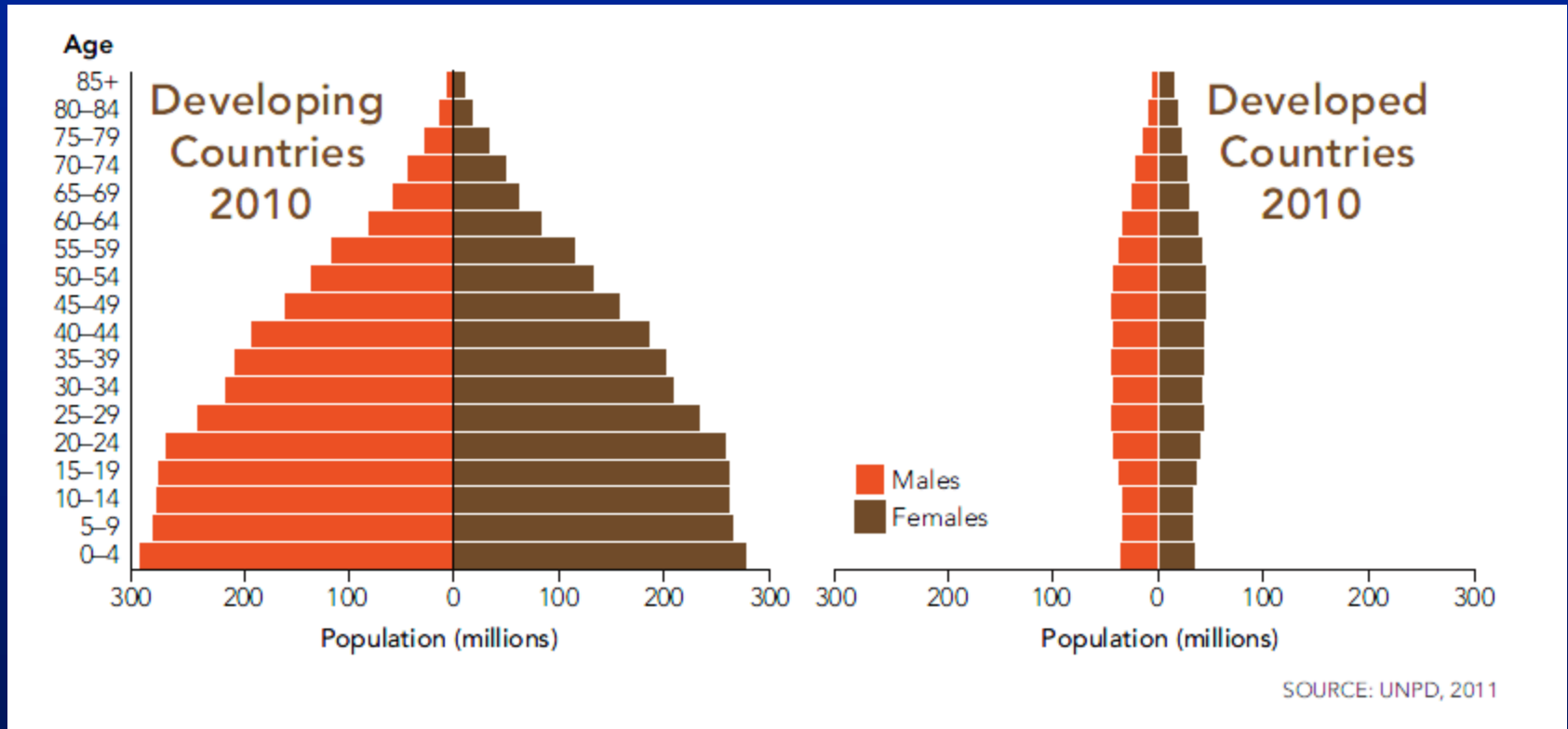
- Population aging: emblem of prosperity and progress
 - Baby boomers (b: 1946-1964) provided both workers and consumers, fueling economic growth; first baby boomers turned 65 in 2011
 - Aging is a slow-moving but inexorable process that will profoundly challenge established economic patterns
- Longer lifespans result from decreased infant mortality and progress treating diseases
 - 1 out of every 7 Americans now is 65 or older; by 2030 it will be more than 1 out of every 5 and will soon outnumber those 18 and younger
 - Lower birthrates in developed societies (e.g., China's one-child policy) shrink working age population
 - Now 4 European workers labor to support 1 retiree; by 2050, fewer than 2 workers per retiree will be available



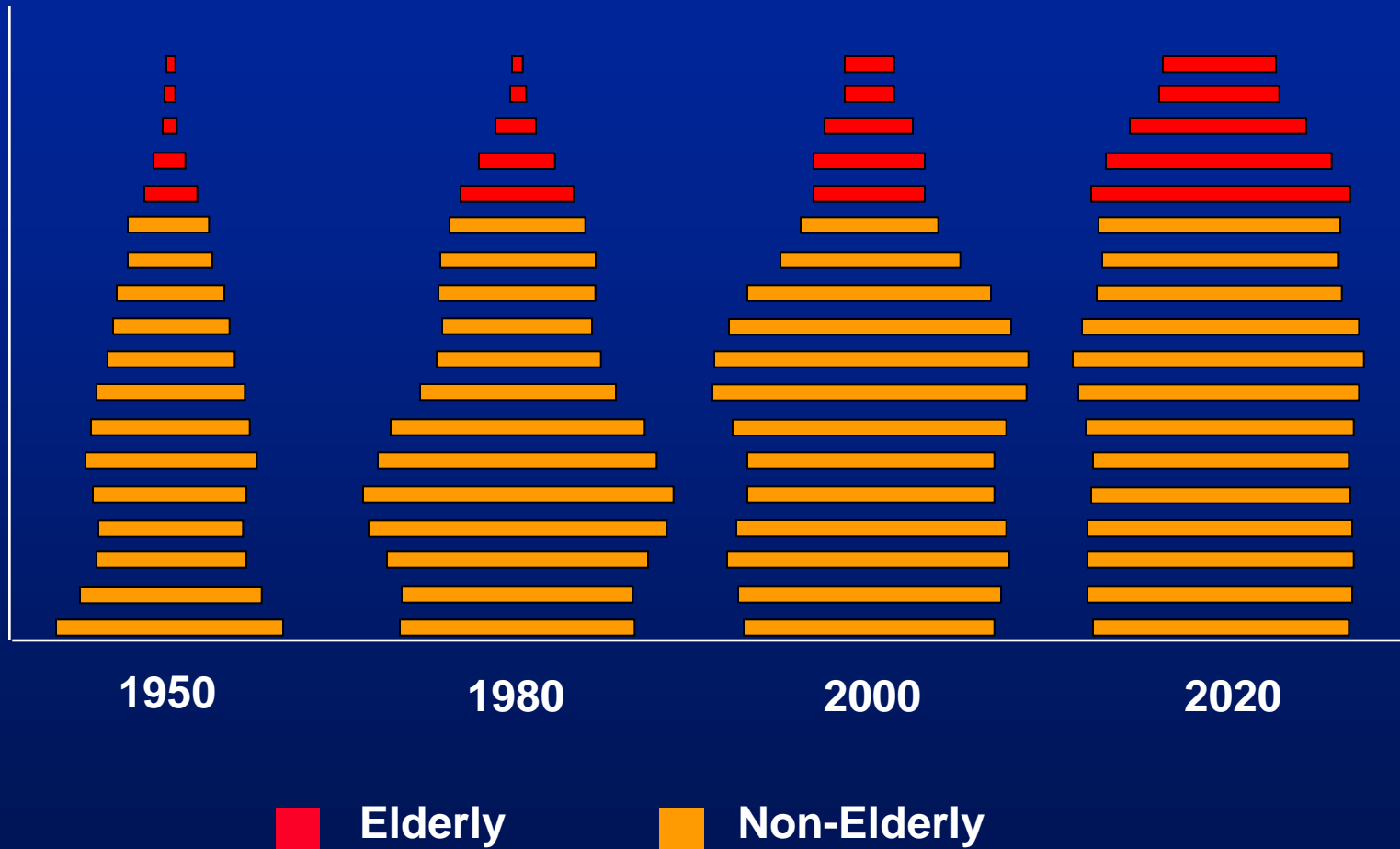
Societal and Economic Consequences of Relentless Aging – II.

- Longevity risk
 - Under current policies, entitlement programs for elderly Americans, soon will be bankrupt; proposed changes in Social Security and Medicare are stymied by partisan politics
 - Lifespan increases strain corporate and governmental pension fund obligations (many already underfunded); a cure for heart disease, cancer, or Alzheimer disease would have catastrophic consequences
- Changes will be unpopular
 - Trade leisure for work (already, 20% of persons 65+ are working)
 - Decrease consumption in favor of savings

Young and Growing Vs. Aging and Stable



National Population: Notice the increase in the elderly as baby-boomers age



Source: U.S. Census Bureau

Age Effect in Medical Scholarship

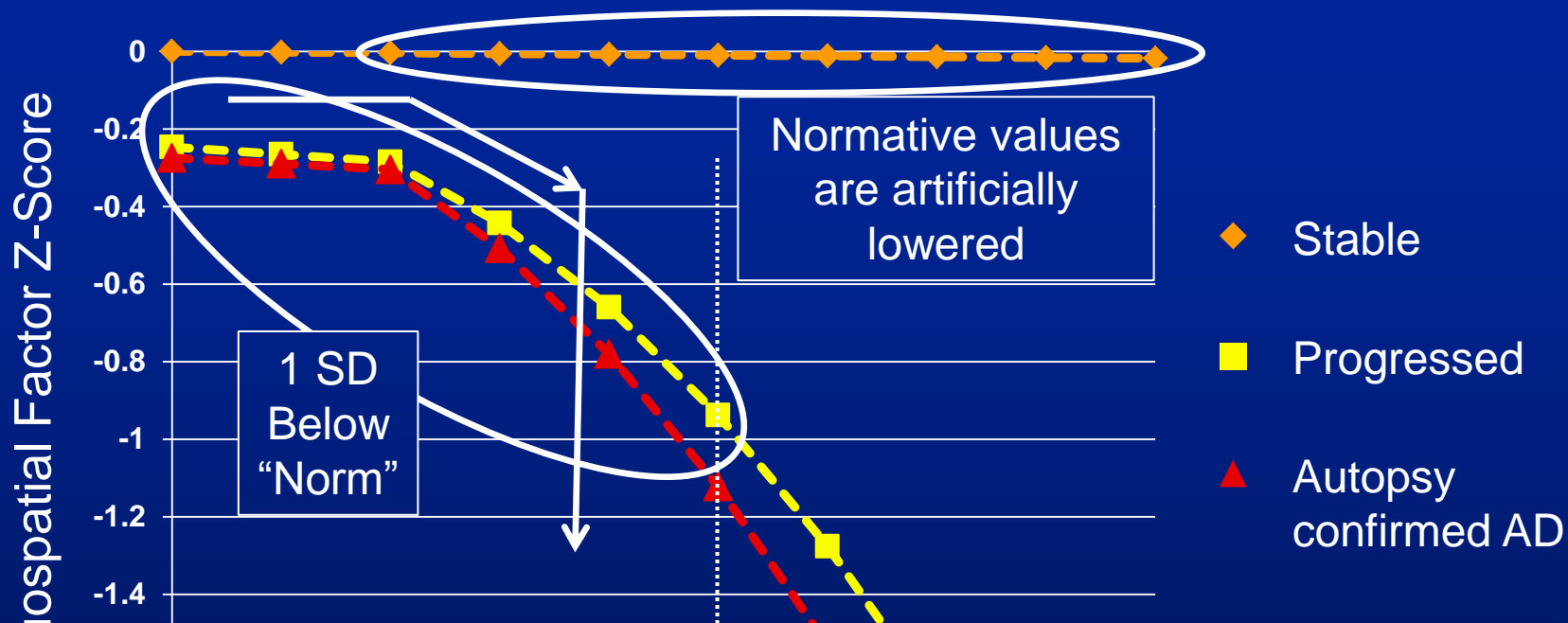
- Medical Student: Reads entire article, doesn't understand any of it
- Resident: Would like to read article, eats dinner instead
- Attending: Reads entire article to pimp students
- Chief of Service: Reads references to see if he/she was cited
- Emeritus Professor: Reads entire article, doesn't understand any of it



Cognitive Function in Truly Healthy Aging

- “Diseases commonly occurring in the elderly play a substantial role in the cognitive and functional decline often attributed solely to aging.” (Howieson DB et al, Neurology, 1993)
- Hypotheses
 - Longitudinal cognitive performance is relatively stable in unimpaired elderly
 - Cognitive decline is a marker for disease

Longitudinal Change in Global and Domain-specific Factor Scores in Older Adults Who Begin as Cognitively Normal



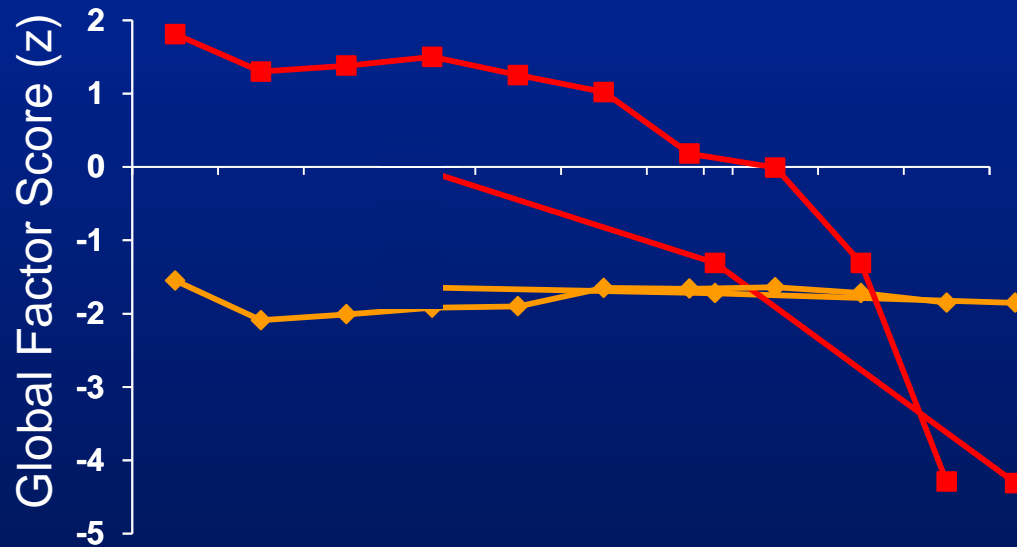
Inclusion of asymptomatic persons with preclinical AD negatively biases norms for cognitive performance in truly healthy aging

- Means and cutpoints to detect impairment are too low
- Reliance on test norms to detect the earliest stages of Alzheimer dementia is ineffective because of insensitivity

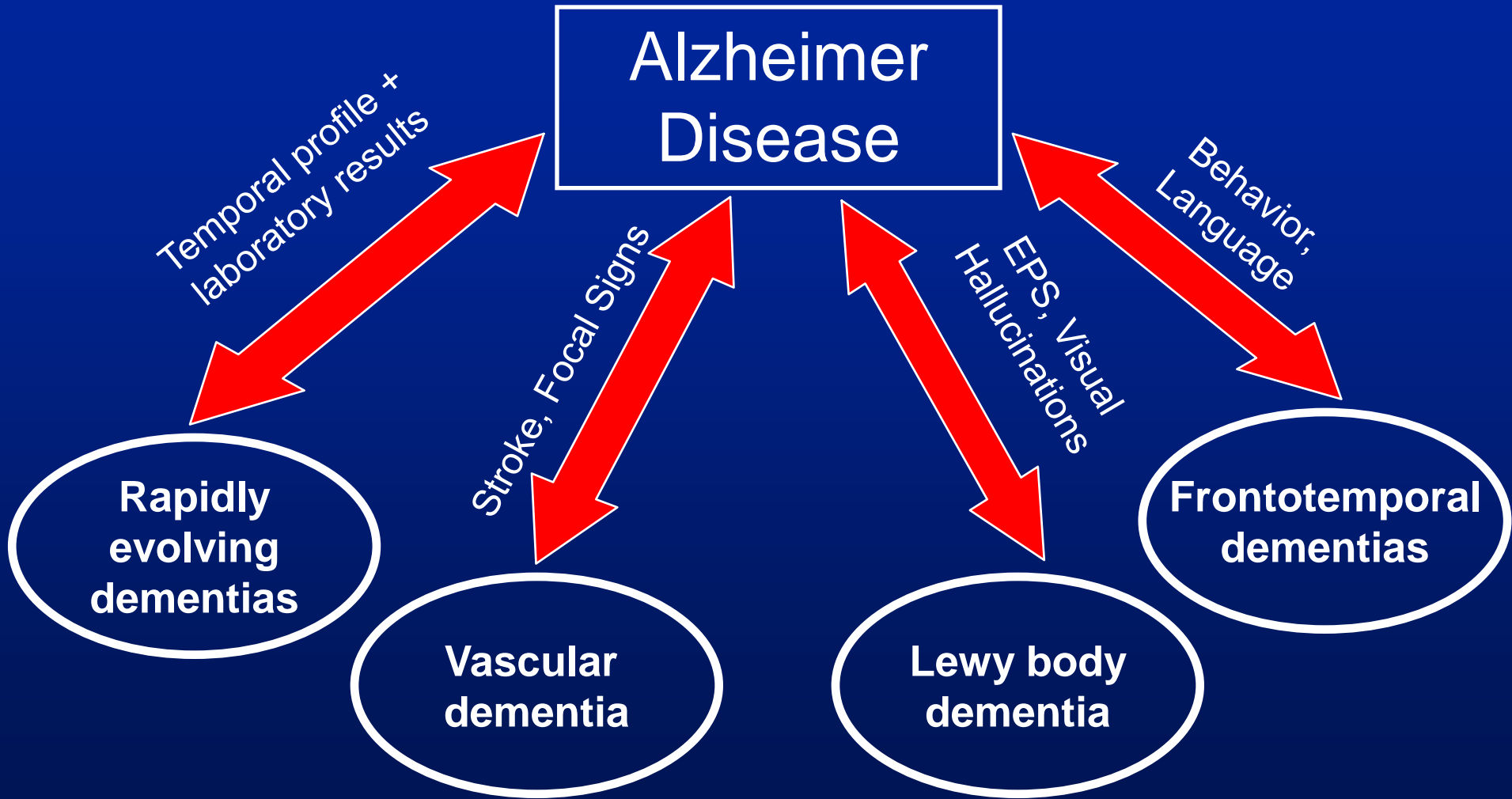
Dementia

- Definition: An acquired syndrome of decline in memory and other cognitive domains sufficient to affect daily function
- Etiology: Any disorder that damages higher-order brain regions that are responsible for cognition; etiology often is multifactorial
- Detection:
 - Intra-individual change: Informant observations about decline in previously established cognitive and functional abilities
 - Inter-individual differences: Cognitive test performance compared with age- and education-matched norms

Intraindividual Decline, Not Test Score, Marks Alzheimer Dementia

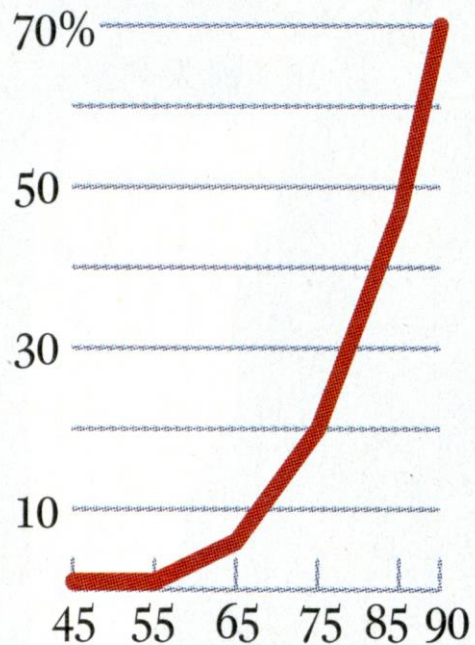


Clues to Differential Diagnosis

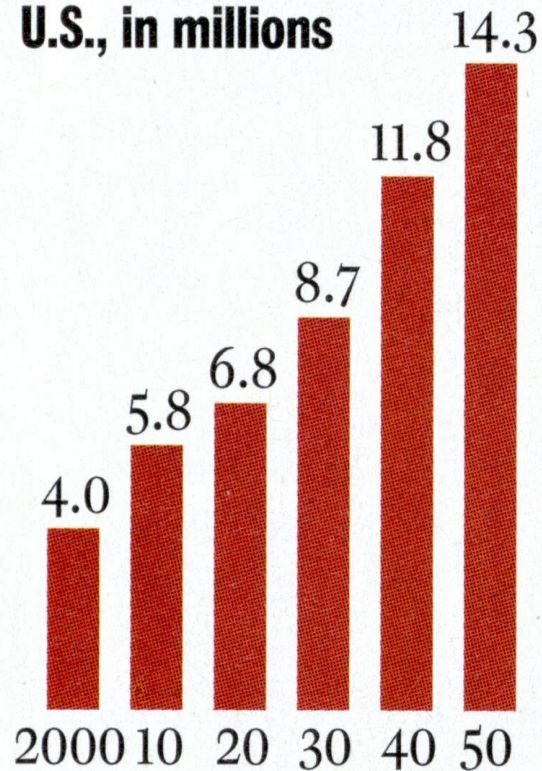


The Growth

Alzheimer's prevalence
in the U.S., by age, 1997



Projected Alzheimer's
patients in the
U.S., in millions



Knight ADRC View of AD

- “Alzheimer disease” (AD) refers to the neurodegenerative brain disorder, regardless of clinical status, representing a continuous process of synaptic and neuronal deterioration
- AD has two major stages:
 - Preclinical (presymptomatic; asymptomatic), undetectable by current clinical methods
 - Symptomatic (clinical)
- Symptomatic AD is defined by intraindividual cognitive decline, from subtle to severe, that interferes with daily function, and can be subclassified on symptom severity:
 - Incipient (prodromal; mild cognitive impairment)
 - Dementia

Alzheimer Facts

- 10% of people 65 and older have AD dementia
 - 2/3 are women
 - African Americans and Hispanics have 1.5-2 times the risk of AD
- Only major cause of death in US for which there is no prevention or effective treatment
- >80% of caregiving comes from family members
- Direct costs of caring for persons with Alzheimer dementia total \$277 billion (\$186 billion in Medicare and Medicaid payments)

Stages of Alzheimer Dementia (Clinical Dementia Rating)

CDR 0
(normal)

Insidious onset

“Forgetful”; repetitious; impaired decisional abilities; independent in self-care; looks and acts “normal”, can perform some IADLs but often impaired to some degree

Only highly learned material recalled; little or no pretense of IADLs; disruptive behaviors; supervised BADLs

Oriented only to self; requires full care for BADLs; akinetic mutism

Course of Dementia

← 7-10 yr →

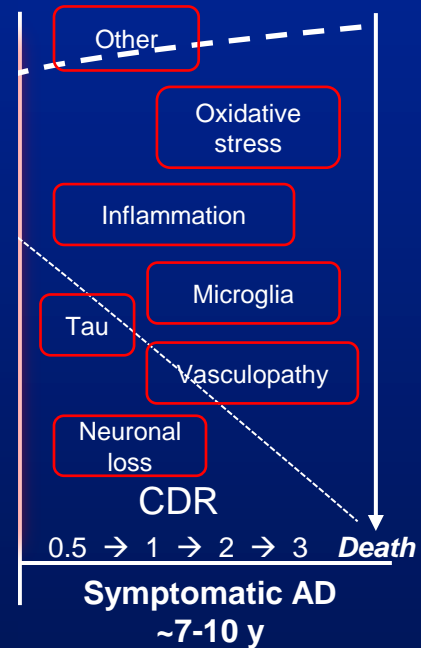
Failure of AD Candidate Therapeutics

Agent	Target/Mechanism	Outcome
Non-Aβ		
Atorvastatin; Simvastatin	Cholesterol (HMG CoA reductase inhibitor)	Negative
NSAIDs	Inflammation	Negative
Rosiglitazone	Insulin (PPAR gamma agonist)	Negative
Latrepidine	Mitochondrial function	Negative
Encenicline	$\alpha 7$ nAChR agonist	Negative (AEs)
Intepiridine	5-HT6 antagonist	Negative
Aβ		
AN1792	Amyloid immunoRx	Negative (AEs)
Tramiprosate	Amyloid aggregation	Negative
Tarenflurbil	Gamma secretase	Negative
Semagacestat; Avagacestat	Gamma secretase	Negative
Bapineuzumab	Amyloid immunoRx	Negative
Solanezumab	Amyloid immunoRx	Negative (+/-)
Crenezumab	Amyloid immunoRx	Negative
Gantenerumab	Amyloid immunoRx	Negative
IVIG	Nonselective immunoRx	Negative
LY2886721	Beta secretase	AEs
ACC-001	Amyloid immunoRx	Negative

Possible Reasons for Failed Trials

- Ineffective drug
- Wrong target
- Initiate too late
- AD rarely occurs in isolation; frequent comorbidities include vasculopathy (including infarcts), synucleinopathy, other proteinopathies (e.g., TDP-43), inflammation, oxidative stress, etc. – rather than monotherapy, likely need combination therapy that addresses multiple targets

Preclinical and Symptomatic AD



Healthy Aging and Senile Dementia

JC Morris, PI (P01 AG03991)

8-15-14 to 4-30-19 (since 1984)

Project 1: Cognitive and Functional Indicators of Transition to Symptomatic AD
Morris

Project 2: Sleep: Potential Prognostic and Theranostic Marker for Preclinical AD
Holtzman

Project 3: Identification of Genetic Variants Associated with Rate of Disease Progression
Cruchaga

Project 4: Imaging Markers of Neuronal Dysfunction in Preclinical AD
Benzinger

Antecedent Biomarkers for AD: The Adult Children Study

JC Morris, PI (P01 AG026276)

9-30-16 to 5-31-21 (since 2005)

Project 1: Preclinical Predictors of Progression from Cognitive Normality to Impairment
Morris

Project 2: CSF Biomarkers of AD Progression
Fagan

Project 4: Dynamic Ordering of Imaging Biomarkers in Preclinical AD
Benzinger

Knight ADRC and Affiliated Grants

Cores

Administration
Morris/Bateman

Clinical &
AA Outreach
Morris

Biostatistics
Xiong

Neuropathology
Perrin/Cairns

Imaging
Benzinger

Genetics
Cruchaga/Goate

Outreach, Recruitment,
Education & Rural Core
Denny

Biomarker
Fagan

Informatics
Marcus

Knight Alzheimer's Disease Research Center

JC Morris, PI (P50 AG05681)

5-1-15 to 4-30-20 (since 1985)

Project 1: Correlation of Tau PET Imaging with CSF AD Biomarkers
Fagan

Project 2: Synergy of A β Clearance Mechanisms in vivo
Cirrito

Project 3: Circadian Rhythms in Regulation of A β Pathology and Brain Oxidative Stress
Musiek

Other affiliations: NACC, NCRAD, LOAD, ADCS, ADNI, GWAS, Alzheimer's Assn, AAA Board, NIH & Industry Clinical Trials, affiliated R01 & other grants

Dominantly Inherited Alzheimer Network (DIAN)

RJ Bateman, PI (UF1 AG032438)

7-16-14 to 12-31-19 (since 2008)

USA Brigham & Women's Hospital/MGH
Butler H/Brown U Columbia U

Indiana U USC U Pittsburgh

Mayo Clinic – Jacksonville Washington U

United Kingdom ION-UC London

Australia Edith Cowan U – Perth
U New South Wales – Sydney

Germany Univ Tübingen
Ludwig-Maximilians-Universität – Munich

Argentina Inst Neurol Research – Buenos Aires

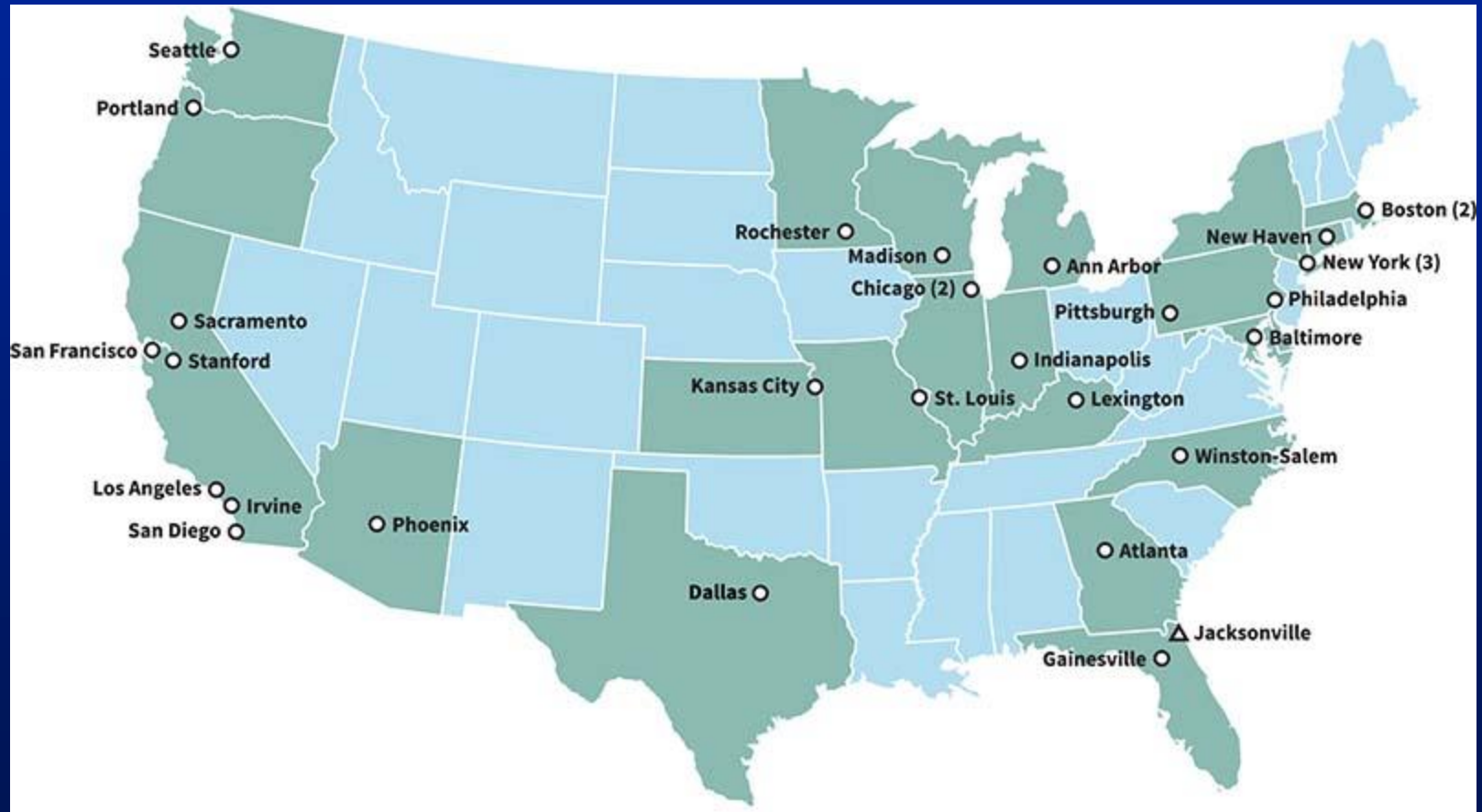
Japan Osaka City Univ Hirosaki Univ
Niigata Univ Univ Tokyo

Korea Asan Medical Center

Knight ADRC

- Cross-disciplinary to answer a broad range of scientific questions
 - Faculty from WUSM Departments/Divisions (Neurology, Neurosurgery, Psychiatry, Pathology & Immunology, Radiology, Medicine/Geriatrics, Biostatistics, Ophthalmology, Occupational Therapy, Physical Therapy, Emergency Medicine, Anesthesiology, Biochemistry & Biophysics, and Neuroscience) AND from Schools on Danforth Campus (Law, Social Work, Engineering, and Arts and Sciences: Departments of Chemistry, Political Science, and Psychology)
- Multi-institutional

NACC/ADC Network



DIAN Sites



Knight ADRC Interdisciplinary Research

■ PERIOPERATIVE MEDICINE

Anesthesiology 2009; 111:963-9

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Long-term Cognitive Decline in Older Subjects Was Not Attributable to Noncardiac Surgery or Major Illness

Michael S. Avidan, M.B.B.Ch., F.C.A.S.A., Adam C. Searleman, B.S.,† Martha Storandt, Ph.D.,‡ Kara Barnett, M.D.,§ Andrea Vannucci, M.D.,|| Leif Saager, M.D.,# Chengjie Xiong, Ph.D.,** Elizabeth A. Grant, Ph.D.,†† Dagmar Kaiser, M.D.,‡‡ John C. Morris, M.D.,§§ Alex S. Evers, M.D.||||*

- Cognitive trajectories in older adults were not affected by non-cardiac surgery

Knight ADRC Interdisciplinary Research

Four Sensitive Screening Tools to Detect Cognitive Dysfunction in Geriatric Emergency Department Patients: Brief Alzheimer's Screen, Short Blessed Test, Ottawa 3DY, and the Caregiver-completed AD8

Christopher R. Carpenter, MD, MS, Elizabeth R. Bassett, Grant M. Fischer, Jonathan Shirshekan, James E. Galvin, MD, MPH, and John C. Morris, MD

ACADEMIC EMERGENCY MEDICINE 2011; 18:374-384 © 2011 by the Society for Academic Emergency Medicine

- Dementia often unrecognized (~50% of persons with AD dementia in US are undiagnosed)
 - Needs to be identified in emergency departments to reduce recidivism and institutionalization
- Four sensitive screening tools



Current NIA Funding Opportunity Announcements in Alzheimer Disease and Related Dementias

- RFA-AG-18-028 Pragmatic Trials of Managing Multimorbidity in AD
 - “[persons] with dementia... average four additional chronic medical disorders”
 - Examples: hypertension, diabetes, heart disease, obstructive lung disease, incontinence, and hip fracture
 - Develop effective treatment for comorbid conditions that occur in dementia
- RFA-AG-18-029 Interdisciplinary Research to Understand the Complex Biology of Resilience to AD Risk
 - AD is heterogeneous with a “multifactorial etiology”
 - What are the molecular drivers of successful brain aging and cognitive resilience that can inform prevention strategies?

Current NIH FOAs (cont'd)

- PAR-17-031 Role of Age-Associated Metabolic Changes in AD
- PAR-17-029 Dynamic Interactions between Systemic or Non-Neuronal Systems and the Brain in Aging and AD
- PAR-18-587 Assistive Technology for Persons with AD and Related Dementias and Their Caregivers
- PAR-18-185 Development of Socially Assistive Robots to Engage Persons with AD and Related Disorders
- PAR-18-497 Sleep Disorders and Circadian Clock Disruption in AD and Other Dementias of Aging
- PAR-18-519 Sensory and Motor System Changes as Predictors of Preclinical AD

Conclusions

- Relentless aging will result in the public health crisis of cognitive impairment/dementia
 - \$277 billion a year spent caring for AD dementia alone
- Remarkable advances in AD, but nonetheless the full understanding of this complex disorder is far from complete
 - No effective therapies or preventions
- Inter-disciplinary approaches are needed to solve the complexities of AD and other causes of cognitive impairment