Alzheimer's and Dementia: Research Priorities

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Loss of Self

Agenda

- The scope of the problem
- The state of the science
- What can you do?

The Scope of the Problem

Prevalence of Alzheimer's Disease

5.8 million

Americans living with Alzheimer's

1 in 10

age 65+ has Alzheimer's

Nearly **2/3**

with Alzheimer's are women

Every **65 seconds**

a new case develops

African Americans are

2x more likely

to have Alzheimer's than older whites

Hispanics are

1.5x more likely

To have Alzheimer's than older whites

2019 Alzheimer's Association Facts and Figures.

UCI MIND

Impact of Alzheimer's on **California**

11%
of California seniors have Alzheimer's disease

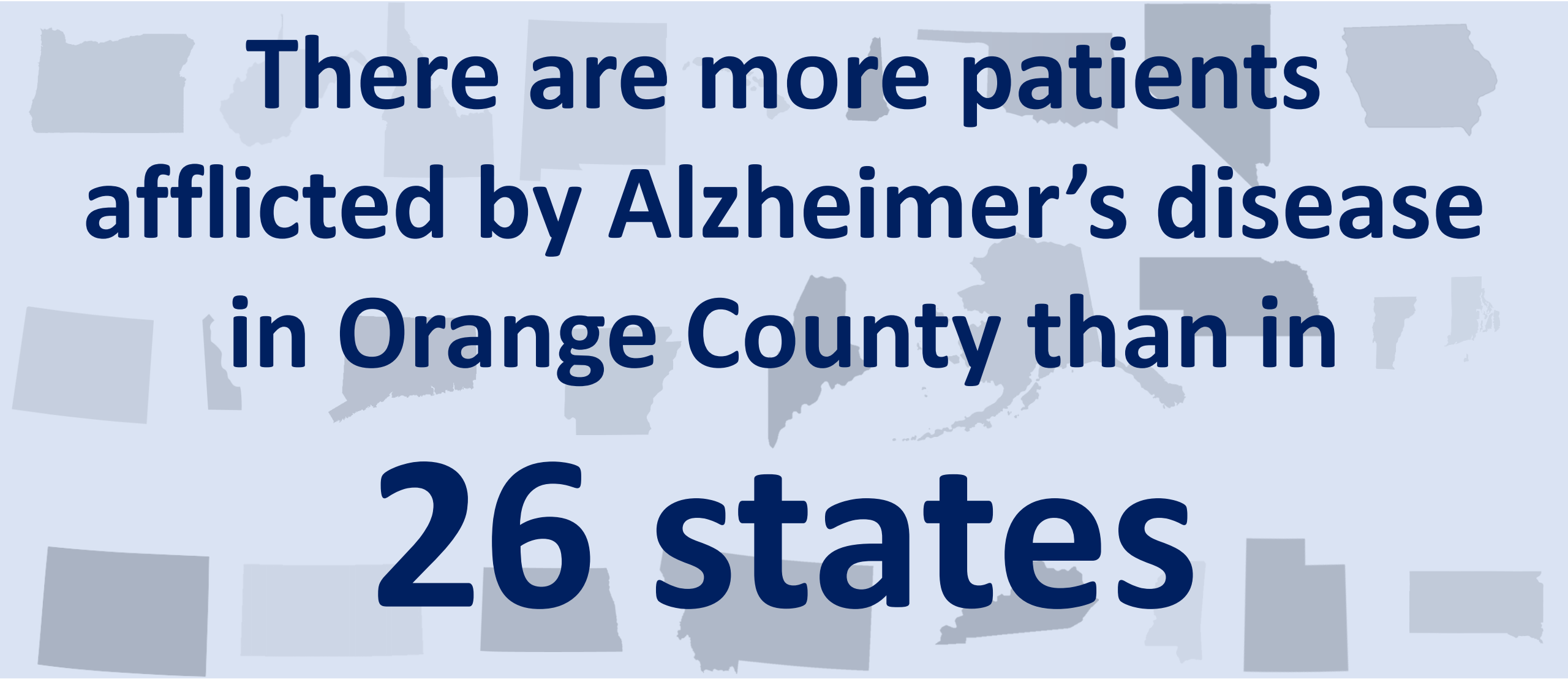
5th
leading cause of death

By 2025, the number of people with Alzheimer's disease will increase by
29.2%

650K
California seniors have Alzheimer's disease

Among baby boomers age 55 years and older,
1 in 8
will develop Alzheimer's disease

Alzheimer's Association, Facts & Figures, 2016, 2018


There are more patients
afflicted by Alzheimer's disease
in Orange County than in
26 states

Cost of Alzheimer's Disease

In 2019,

Alzheimer's costs the U.S.

$290 billion

By 2050,

Alzheimer's will cost the U.S.

$1.1 trillion

18.5 billion

Hours of unpaid care

$234 billion

Value of unpaid care

$350,174

Approximate lifetime cost of care for an individual living with dementia (in 2018 dollars)

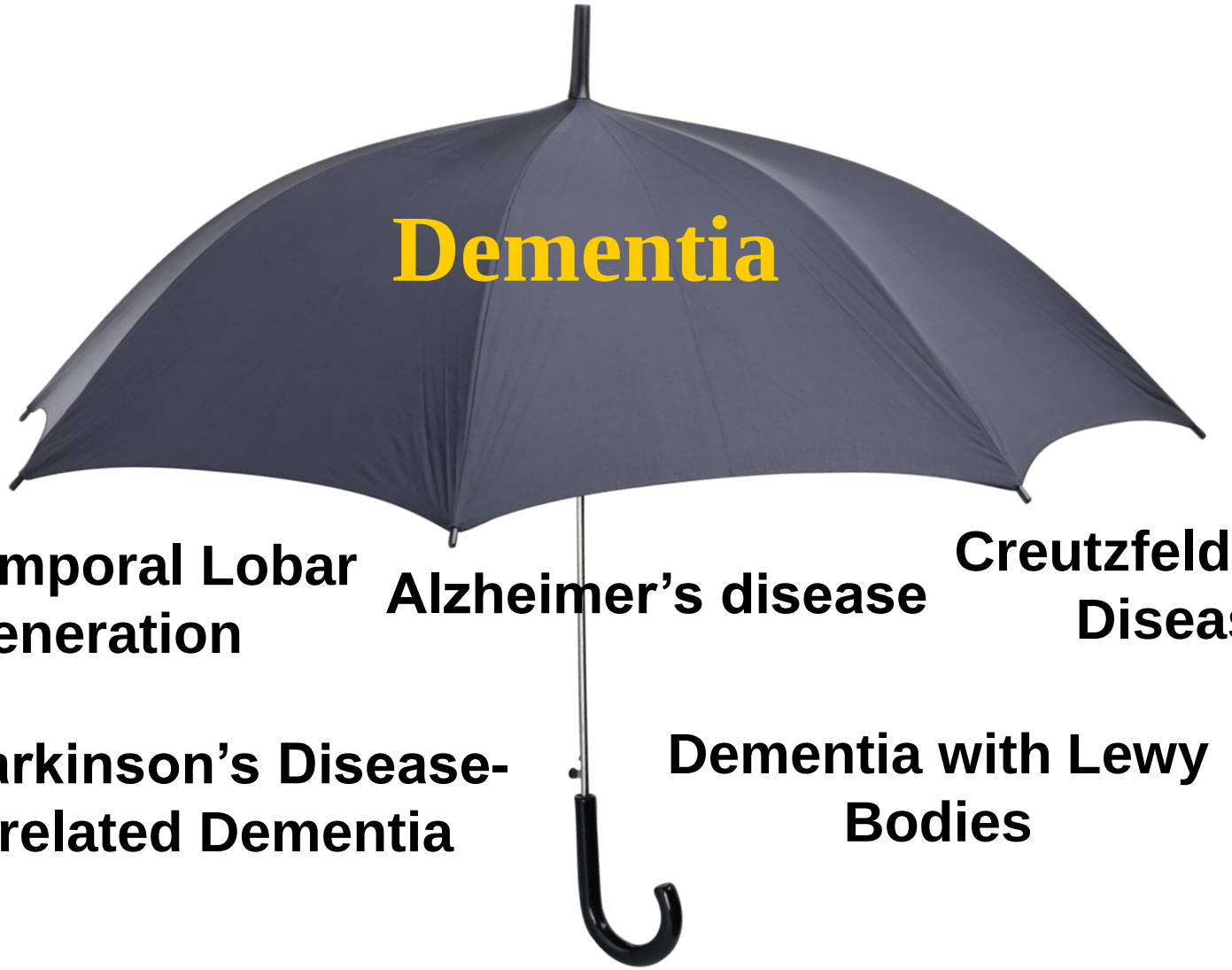
2019 Alzheimer's Association Facts and Figures.

UCI MIND

What is Dementia?

- Cognitive impairment (memory, decision making, language, orientation) that interrupts activities of daily living
- Instrumental activities of daily living
  - Working
  - Volunteering
  - Cooking
- Basic activities of daily living
  - Feeding
  - Bathing
  - Toileting

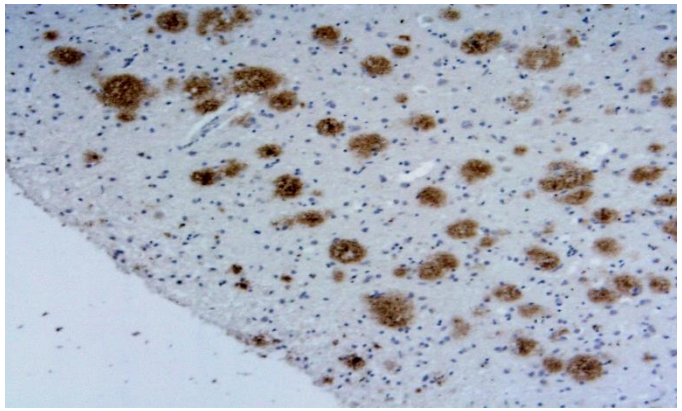
What is Dementia?



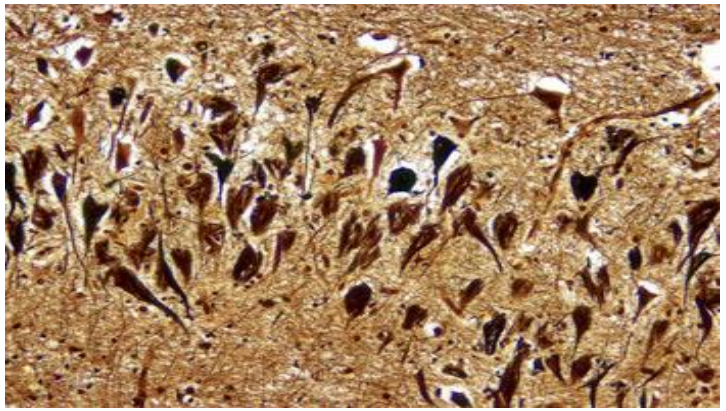
Distinguishing Features of Neurodegenerative Diseases that Cause Dementia

- Symptoms
- Age of onset
- Genetic underpinnings
- Response to therapies
- Disease pathology

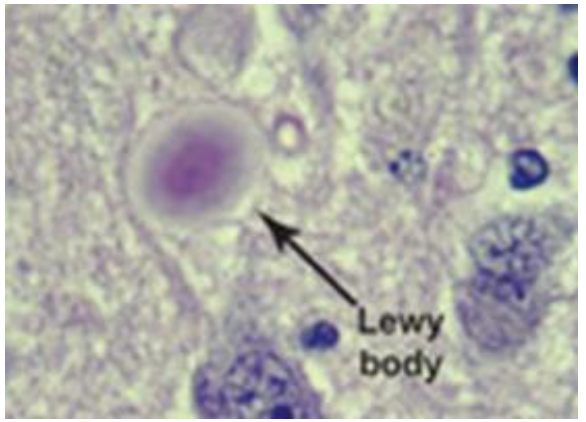
Brain Pathologies that Contribute to Dementia



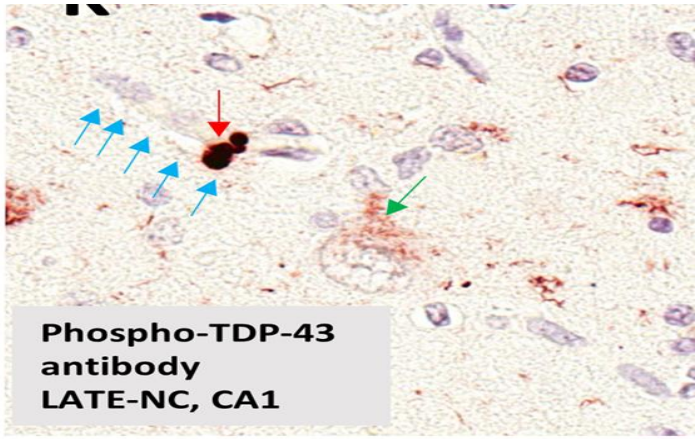
Amyloid (Aβ) plaques



Neurofibrillary (3R and 4R tau) Tangles

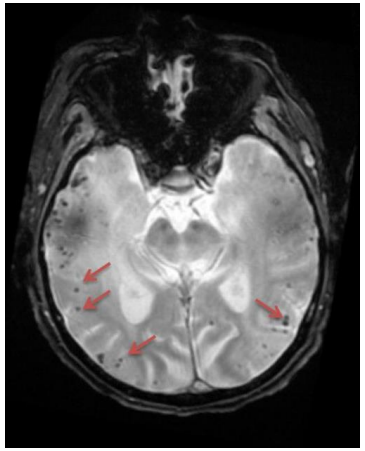


Lewy Bodies (alpha synuclein)



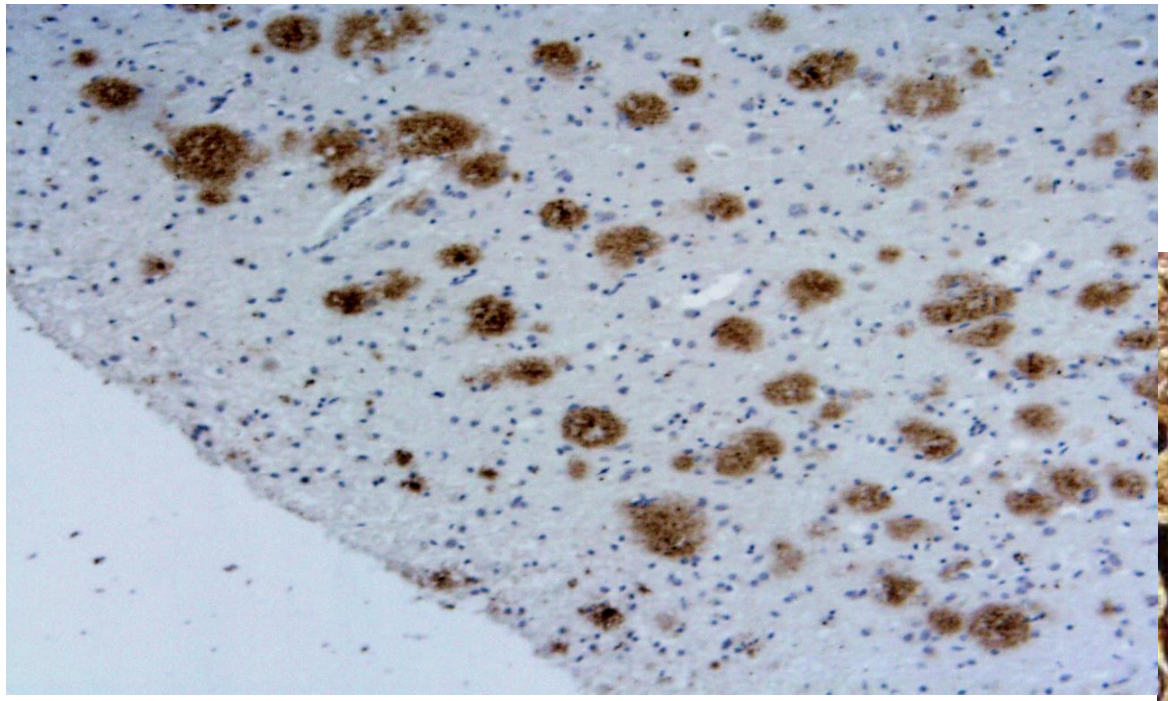
TDP-43

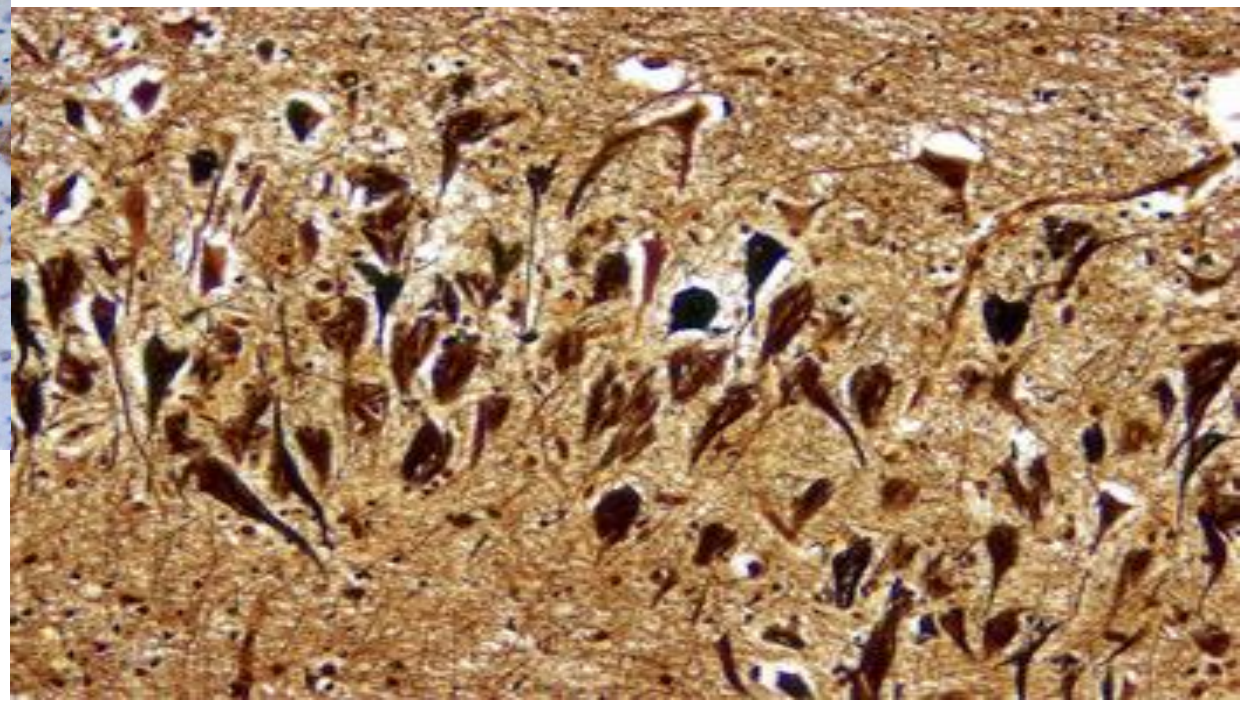
Hippocampal Sclerosis



microbleeds

Amyloid Plaques and Neurofibrillary Tangles





Diagnostic Criteria

- Diagnostic and Statistics Manual (several iterations)
- NINCDS-ADRDA (1984)
- International Work Group (2000’s)
- NIA-AA (2011)
- A/T/N (2018)

NIA-AA Core Features

MCI due to AD

- Concern regarding cognition
- Impairment in one or more domains
- Preserved function
- Not demented

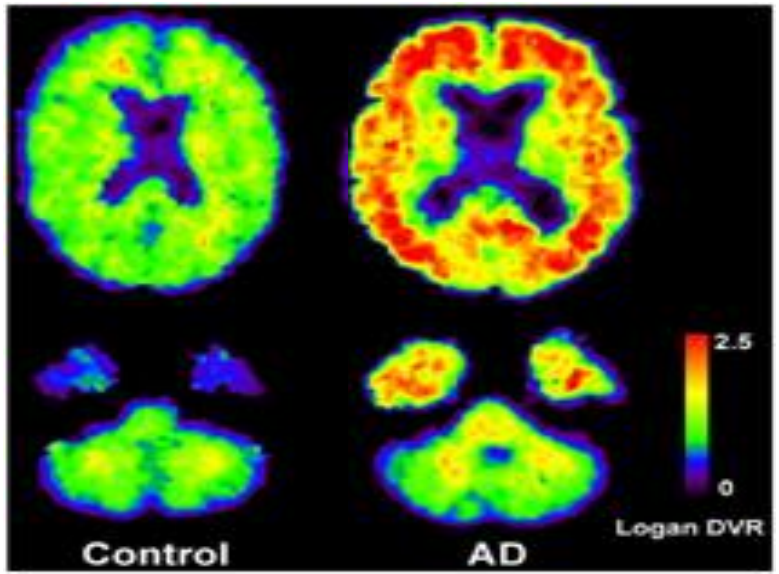
Dementia due to AD

- Insidious onset
- History of worsening
  - Amnestic presentation
  - Nonamnestic presentations
    - Language
    - Visuospatial
    - Executive dysfunction

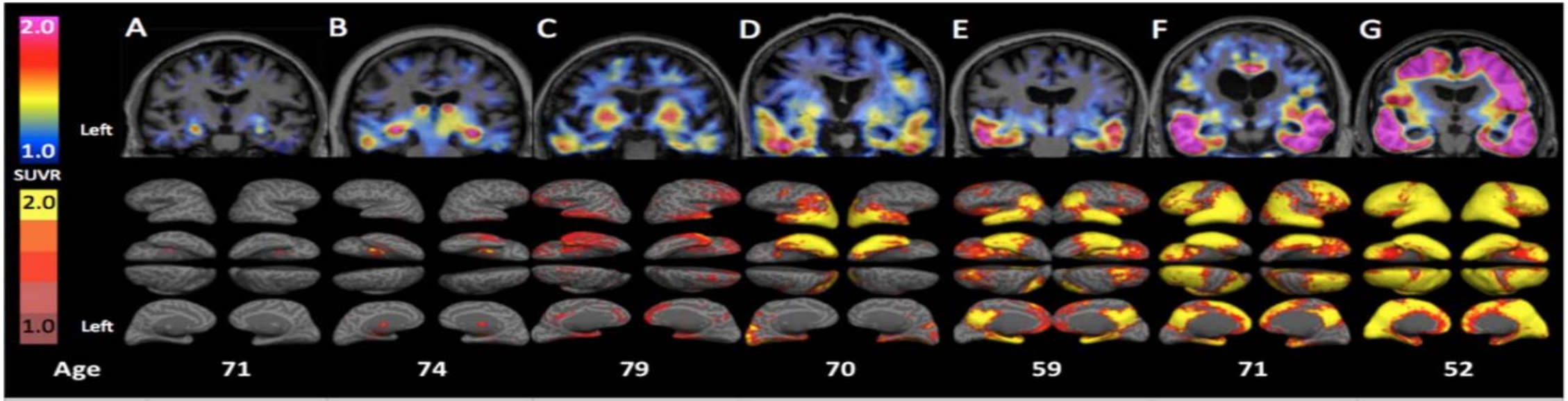
Albert et al., Alz Demen 2011. McKhann et al., Alz Dement 2011.

Amyloid Imaging

- Positron Emission Tomography (PET) imaging tool to assess the presence or absence of brain β-amyloid neuritic plaques
- Approved in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive decline
- Does not equate to diagnosis
- Three approved agents
  - Amyvid, Vizamyl, Neuraceq



Tau PET



MMSE	30	30	29	27	26	23	11
PiB (DVR)	Low (1.0)	High (1.2)	High (1.8)	High (1.5)	High (1.7)	High (1.5)	High (1.5)
Dx	CN	CN	CN	MCI	MCI	AD	AD
PET Braak	0, I-II	III-IV	III-IV	III-IV	III-IV	V-VI	V-VI

Johnson et al., Ann Neurol 2016.

VIEWPOINT

The Rise of Pseudomedicine for Dementia and Brain Health

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The US population is aging, and with it is an increasing prevalence of Alzheimer disease, which lacks effective approaches for prevention or a cure.[1] Many individuals are concerned about developing cognitive changes and dementia. With increasing amounts of readily accessible information, people independently seek and find material about brain health interventions, although not all sources contain quality medical information.

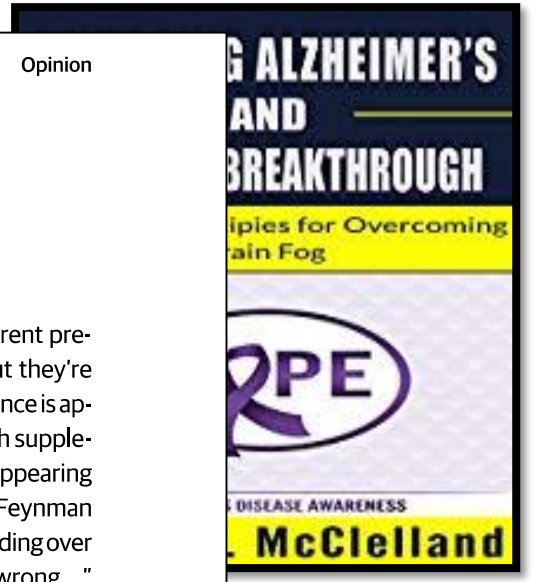
This landscape of limited treatments for dementia, concern about Alzheimer disease, and wide access to information have brought a troubling increase in "pseudomedicine." Pseudomedicine refers to supplements and medical interventions that exist within the law and are often promoted as scientifically supported treatments, but lack credible efficacy data. Practitioners of pseudomedicine often appeal to health concerns, promote individual testimony as established fact, advocate for unproven therapies, and achieve financial gains.

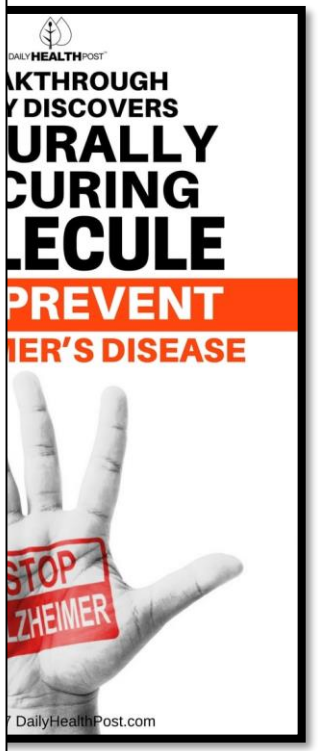
With neurodegenerative disease, the most common example of pseudomedicine is the promotion of dietary supplements to improve cognition and brain health. This $3.2-billion industry promoting brain health to describe endeavors that follow "...the apparent precepts and forms of scientific investigation, but they're missing something essential...."[6] Cargo cult science is apparent in material promoting some brain health supplements; "evidence" is presented in a scientific-appearing format that lacks actual substance and rigor. Feynman suggested 1 feature of scientific integrity is "bending over backwards to show how [the study] may be wrong...," which is a feature that is often lacking when interventions are promoted for financial gain.[6]

A similarly concerning category of pseudomedicine involves interventions promoted by licensed medical professionals that target unsubstantiated etiologies of neurodegenerative disease (eg, metal toxicity; mold exposure; infectious causes, such as Lyme disease). Some of these practitioners may stand to gain financially by promoting interventions that are not covered by insurance, such as intravenous nutrition, personalized detoxification, chelation therapy, antibiotics, or stem cell therapy. These interventions lack a known mechanism for treating dementia and are costly, unregulated, and potentially harmful.

Recently, detailed protocols to reverse cognitive changes have been promoted, but these protocols merely repackage known dementia interventions (eg, cognitive training, exercise, a heart-healthy diet) and add supplements and other lifestyle changes. Such protocols are promoted by medical professionals with legitimate credentials, offer a unique

> Patients and caregivers encounter sophisticated techniques that supply false "scientific" backing for brain health interventions.





In 2019

- We cannot slow dementia progression
- We cannot stop dementia progression
- We cannot reverse dementia progression
- We cannot prevent dementia

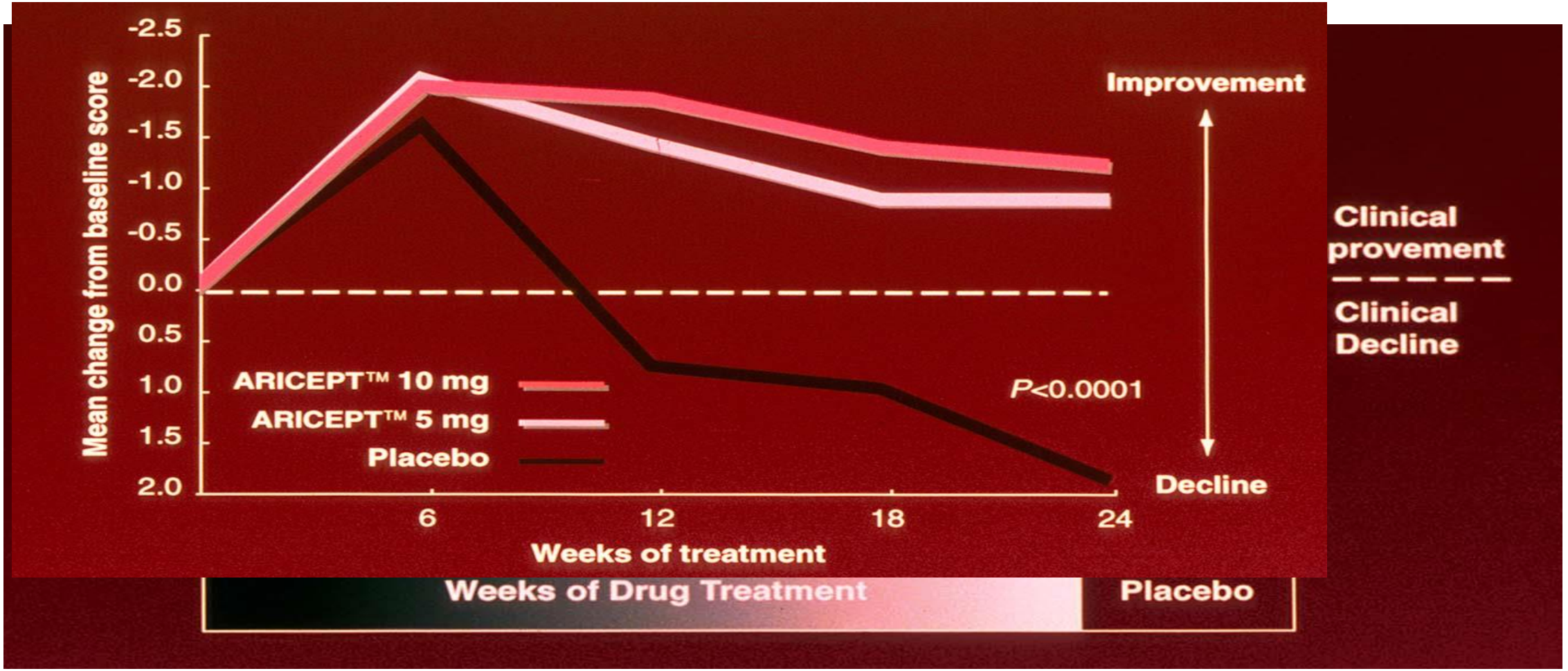
- NOT YET

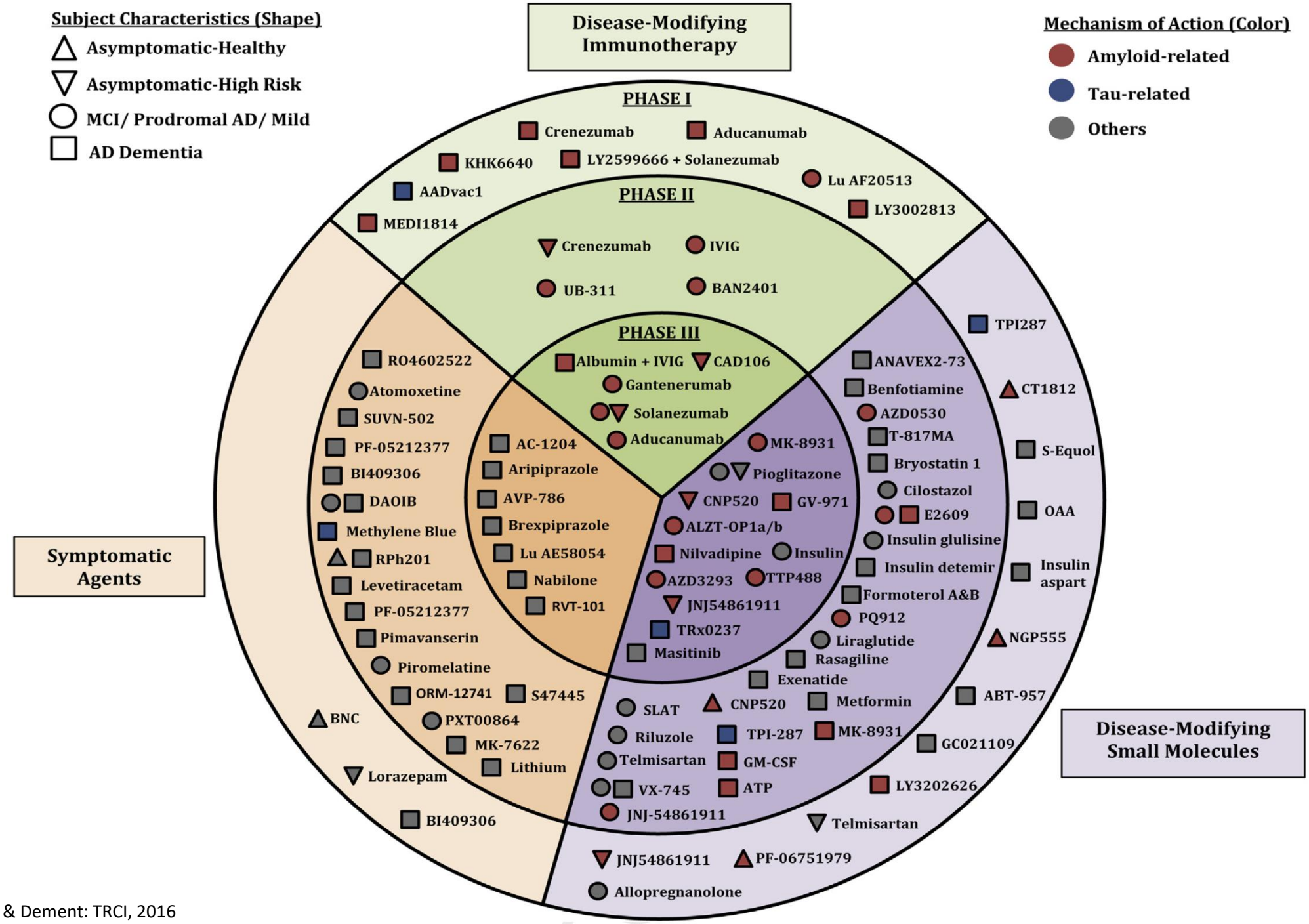
FDA Approved AD Treatments

- Aricept® (donepezil)—all stages
- Razadyne® (galantamine)—mild to moderate
- Exelon® (rivastigmine)—all stages
- Namenda® (memantine)—moderate to severe
- Namzaric® (memantine/donepezil) —moderate to severe

- None are approved in people with mild cognitive impairment or normal memories
- None have been shown to slow the course of Alzheimer’s disease

Symptomatic AD Treatments





Cummings et al., Alz & Dement: TRCI, 2016

Forbes Billionaires Innovation Leadership Money Consumer Industry Lifesty

How Will The Failure Of Biogen's Alzheimer's Drug, Aducanumab, Impact R&D?

John LaMattina Contributor ⓘ
Healthcare
I cover news on drugs and R&D in the pharma industry

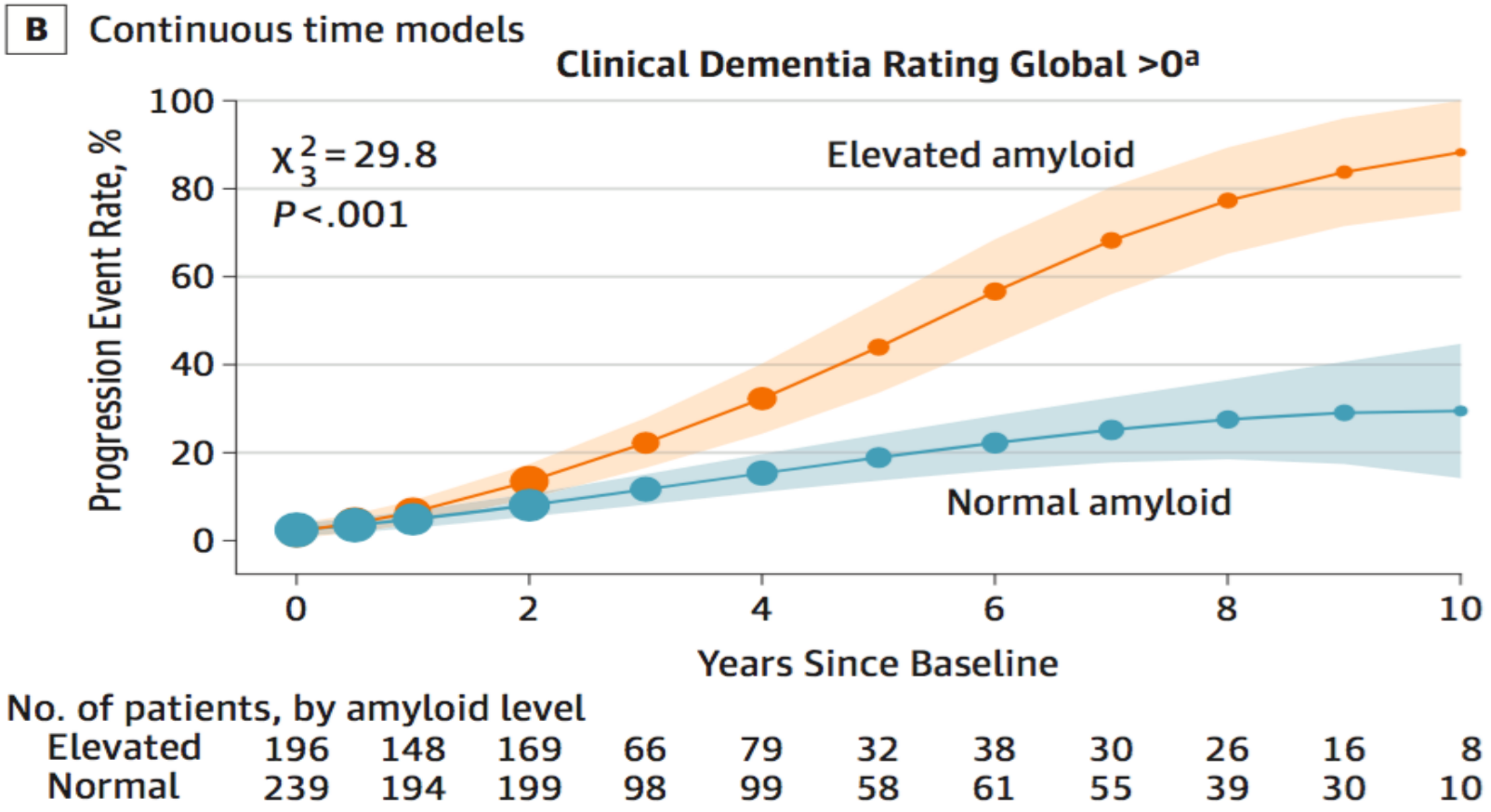
The landscape of experimental Alzheimer's disease (AD) drugs is strewn with failures, so much so that it has been referred to as "an unrelenting disaster zone". Recognizing the greatly increasing number of patients with this disease, many biopharma companies have invested a lot of resources in attacking this problem, only to be turned away in late stage studies as happened to Merck with its BACE inhibitor, verubecestat, and Lilly with its beta-amyloid antibody, solanezumab.

The New York Times

An Alzheimer's Drug Trial Gave Me Hope, and Then It Ended

I was a small piece in the search to find a cure. Now I feel as if I'm getting erased, and medical science doesn't have any answers.

Preclinical AD Increases Risk for Dementia



"…clearly indicates that amyloid pathology in cognitively normal older persons is not a benign phenomenon of normal aging but part of a progressive neurodegenerative disease."

Visser and Tijms, JAMA 2017

Donohue et al. JAMA 2017.

Anti-Amyloid in Asymptomatic Alzheimer's disease (A4) Trial

- 1300 older adults with normal cognition who have preclinical AD (elevated amyloid PET)
- Treating with potential disease-slowing drug - Solanezumab
- Follow for 4.5 years
- Measure if drug slows cognitive decline (composite outcome measure)

ORANGE COUNTY REGISTER

Paula Hunter is giving something very precious to help Alzheimer's fight - her brain

July 13, 2015 | Updated 9:52 p.m.

VIEW SLIDESHOW

Nurse Diane Capobianco, left, waits while Paula Hunter receives a monthly infusion at UC Irvine as part of the A4 study

Family fun!
FREE outdoor con
Symphony in the
July 18 - Mission Vi
July 19 - Irvine

MOST POPULAR

Disneyland employee a
admission tickets in ex

'Hoax' no more: Man ar
Huntington Beach kidn
sh

Lakers' young players s

What Can You Do?

Life Style Risk Factors

- Family history
- Head trauma
- Midlife Obesity
- Midlife Hypertension
- High Cholesterol
- Poor sleep

- Higher education
- Healthy diet
- Physical exercise
- Cognitive activity
- Social activity

Can This Work?

Selected Recent Studies of the Dementia Epidemic.

Study	Outcome	Data Source	Key Findings	Factors
Manton et al. (United States)[1]	Prevalence of severe cognitive impairment	National long-term care survey interviews, 1982–1999	Decline in dementia prevalence among people ≥65 yr of age (5.7% to 2.9%)	Higher educational level, decline in stroke incidence
Langa et al. (United States)[2]	Prevalence of cognitive impairment	Ongoing population-based survey of people ≥51 yr of age	Prevalence of cognitive impairment among people ≥70 yr of age (12.2% in 1993 vs. 8.7% in 2002)	Higher educational level; combination of medical, lifestyle, demographic, and social factors
Schrijvers et al. (Rotterdam)[3]	Incidence of dementia	Population-based cohort ≥55 yr of age in 1990, extended in 2000	Incidence rate ratios (6.56 per 1000 person-yr in 1990 vs. 4.92 per 1000 person-yr in 2000)	Higher educational level, reduction in vascular risk, decline in stroke incidence
Qiu et al. (Stockholm)[4]	Prevalence of DSM-III-R dementia*	Cross-sectional survey of people ≥75 yr of age, 1987–1989 and 2001–2004	Age- and sex-standardized dementia prevalence (17.5% in 1987–1989 vs. 17.9% in 2001–2004); lower hazard ratio for death in later cohort suggests decreased dementia incidence	Favorable changes in risk factors, especially vascular risk; healthier lifestyles
Matthews et al. (England)[5]†	Prevalence of dementia in 3 regions	Survey interviews of people ≥65 yr of age, 1989–1994 (in CFAS I) and 2008–2011 (in CFAS II)	Dementia prevalence (8.3% in CFAS I vs. 6.5% in CFAS II)	Higher educational level, better prevention of vascular disease

Larson et al. NEJM, 2013.

What Can YOU do?

- **<u>Everyone</u>** can contribute
- Consider the three –**ates**

advoc**ate**

don**ate**

particip**ate**

Advocate

“No longer Orange County’s best kept secret”

Donate

Participate

UCI Consent-to-Contact (C2C) Registry

- New online tool to match people in OC with research studies at UCI
- Enrollment goal: 10,000 adults

c2c.uci.edu

THE ORANGE COUNTY REGISTER

PRICE: $1 ▪ TUESDAY, DEC. 27, 2016 ▪ OCREGISTER.COM

LOCAL NEWS

Tuesday, Dec. 27, 2016 » MORE AT FACEBOOK.COM/OCREGISTER AND TWITTER.COM/OCREGISTER

PAUL RODRIGUEZ, STAFF PHOTOGRAPHER

Steve O'Leary, whose wife has Alzheimer's, has signed up for a registry that matches volunteers with research opportunities.

LOOKING FOR 'RESEARCH HEROES'

New UC Irvine registry matches research volunteers with those studying an array of diseases.

By COURTNEY PERKES
STAFF WRITER

Steve O'Leary, 69, has too often felt helpless as Alzheimer's disease takes over his wife's mind.

But recently he took the empowering step of participating in medical research, after joining a new UC Irvine registry called Consent 2 Contact, or C2C. It was created to match willing Orange County volunteers with doctors and scientists studying an array of diseases.

A few weeks ago, for example, O'Leary underwent a test for tinnitus that looked at how his brain responded to sound. While the condition is not related to Alzheimer's, he's hopeful that others will volunteer for the Alzheimer's study and help eliminate the disease for future generations.

"You get to a point where you're trying to find out ways of contributing to finding a solution to this disease," said O'Leary, who lives in Dana Point. "Not only is it affecting her in a terrible way, but I worry about our kids. If there's a way for me to do something and make a difference, I'm more than on board."

"The single greatest deterrent to improving treatment and care is low levels of participation in research."

JOSHUA GRILL
UCI ALZHEIMER'S RESEARCHER

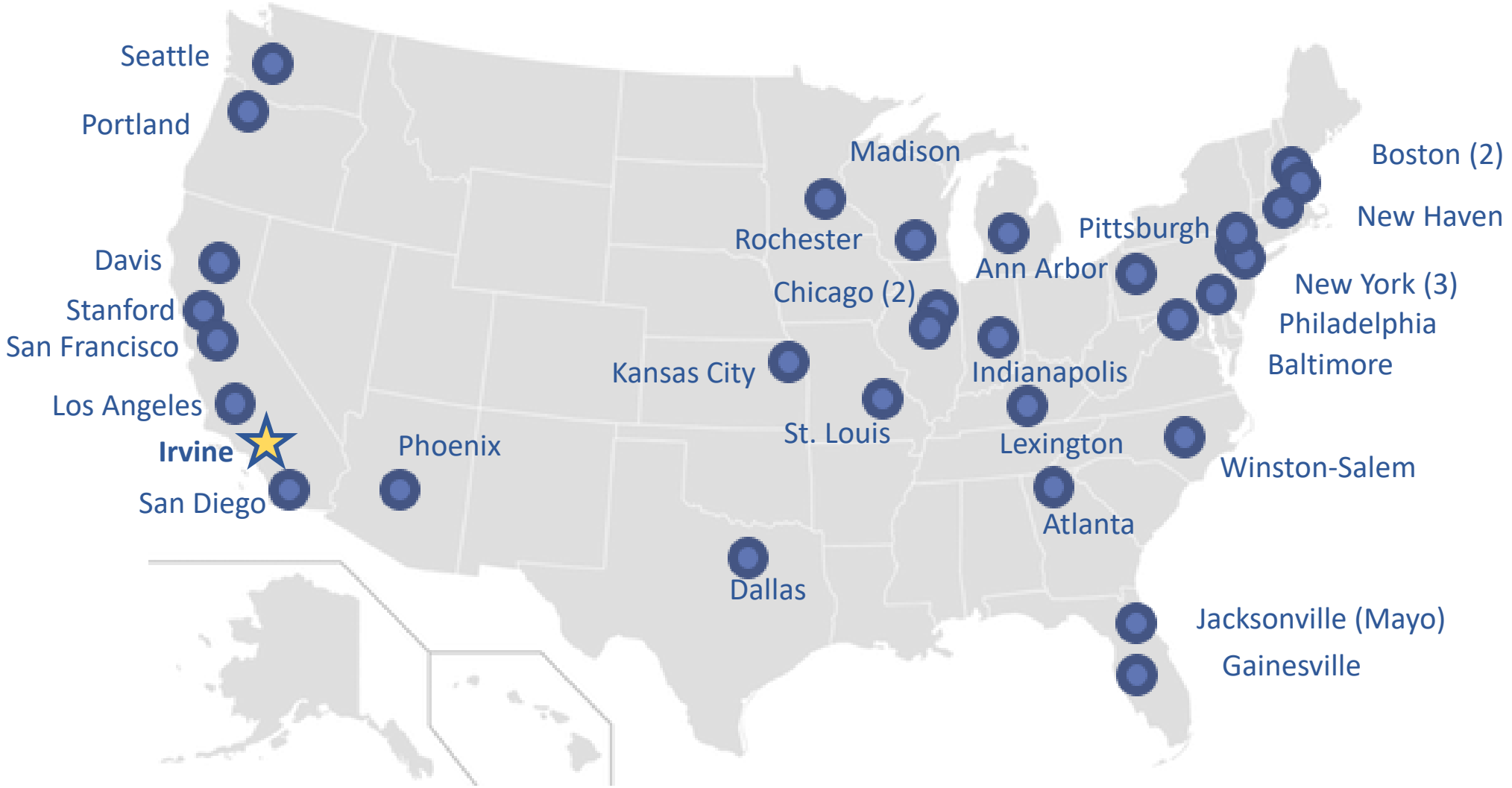
Joshua Grill, a UCI Alzheimer's researcher, said clinical trials and other kinds of medical research are often hindered by a shortage of volunteers who can be recruited quickly.

"Simply put, across all areas of medicine, the single greatest deterrent to improving treatment and care is low levels of participation in research," Grill said. "Studies have shown the single most common reason clinical trials fail is they fail to accrue an appropriate number of patient participants."

He noted that conducting a clinical trial

SEE REGISTRY • PAGE 6

Alzheimer's Disease Research Center (ADRC)



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Faculty Impact

Our >50 faculty rank highly in the National Research Council faculty productivity ratings and have the honor of being the most highly cited among all campus colleagues.

Acknowledgements

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The participants in our studies and all AD trials