

# Translating Scientific Discovery into Better Care: Groundbreaking Research at the National Institute on Aging

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Friends of the NIA Briefing

**Richard J. Hodes, M.D., Director**  
**Marie A. Bernard, M.D., Deputy Director**  
**National Institute on Aging**

May 9, 2018



National Institutes of Health  
*Turning Discovery Into Health*

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# **APPROPRIATIONS & FUNDING**

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# FY18 Budget Status – Funding Increases Across the Board

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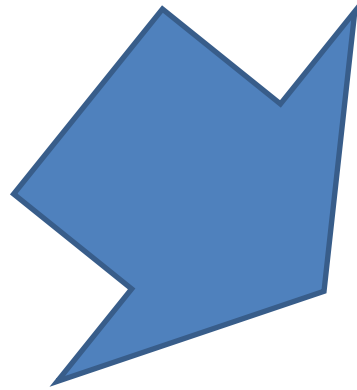
**\$37 Billion  
for the NIH**

→ **\$500M for Opioids**

→ **\$140M for BRAIN**

→ **\$60M for All of US**

→ **\$414M for AD**



- **\$2.6B for the NIA**
- **\$111M increase for non-targeted NIA research; percent increase comparable to other ICs**
- **All divisions will benefit**
  - DBSR
  - DGCG
  - DAB
  - DN

# Appropriations

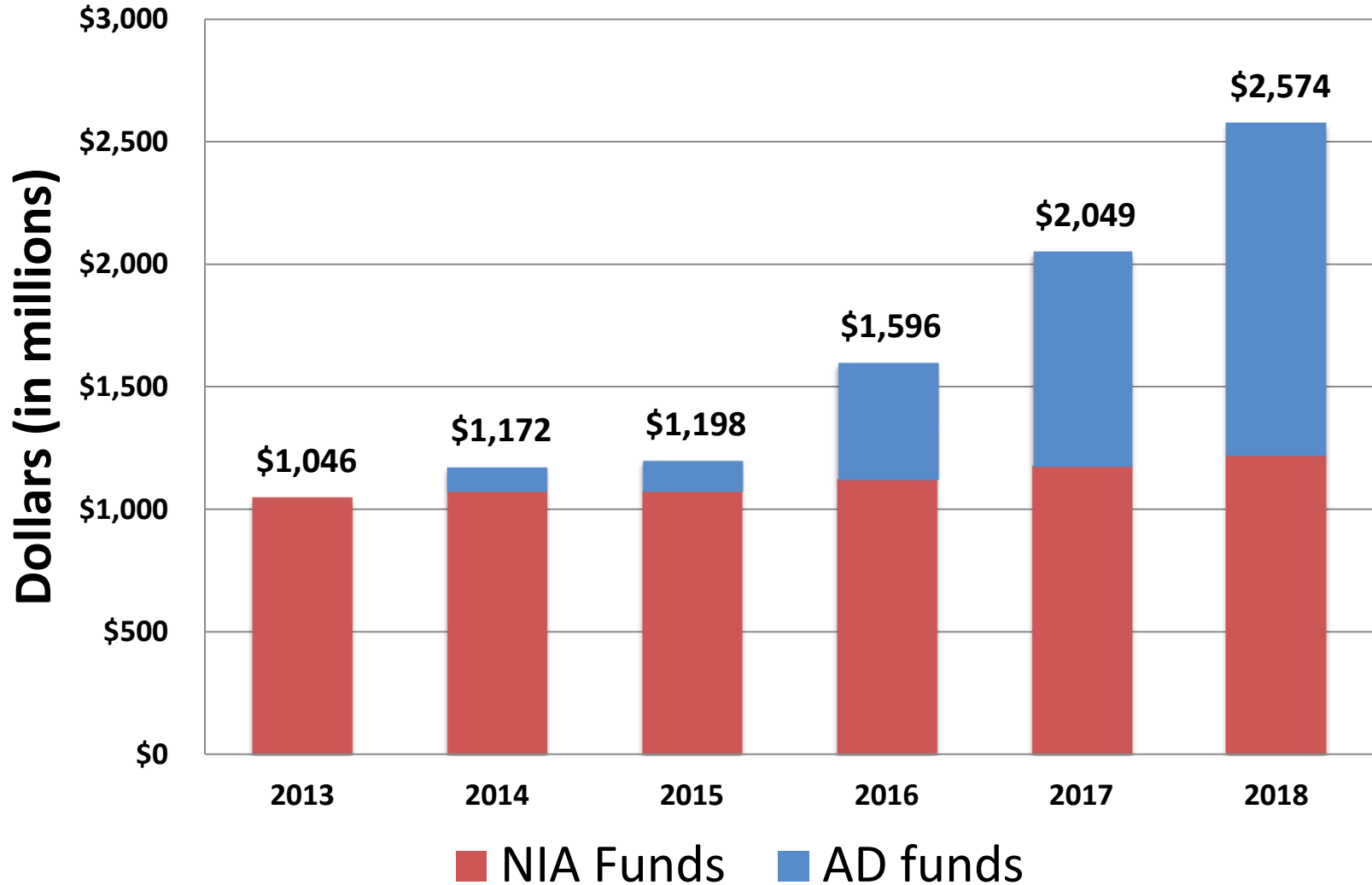
2011	2012	2013	2014	2015	2016	2017	2018
National Alzheimer's Project Act (NAPA)	<b>\$50 M*</b> redirected within NIH budget	<b>\$40 M*</b> redirected within NIH budget	<b>\$100 M</b> additional approp	<b>\$25 M</b> additional approp	<b>\$350 M</b> additional approp	<b>\$400 M</b> additional approp	<b>\$414 M in additional appropriations as of 3/23/18</b>

\*one-year money

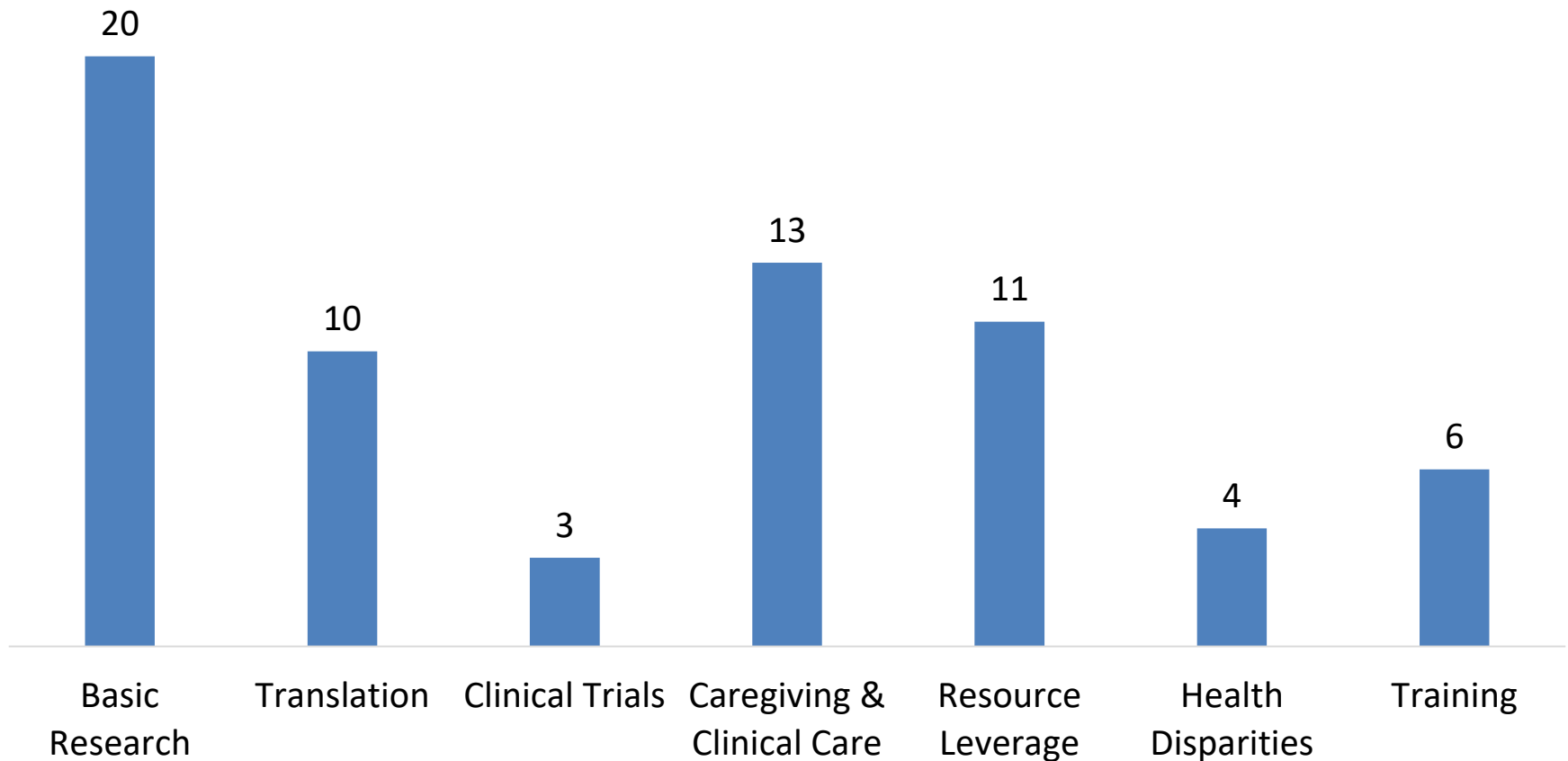
Years displayed are Fiscal Years

# NIA Appropriations

*Fiscal Years 2013-2018*

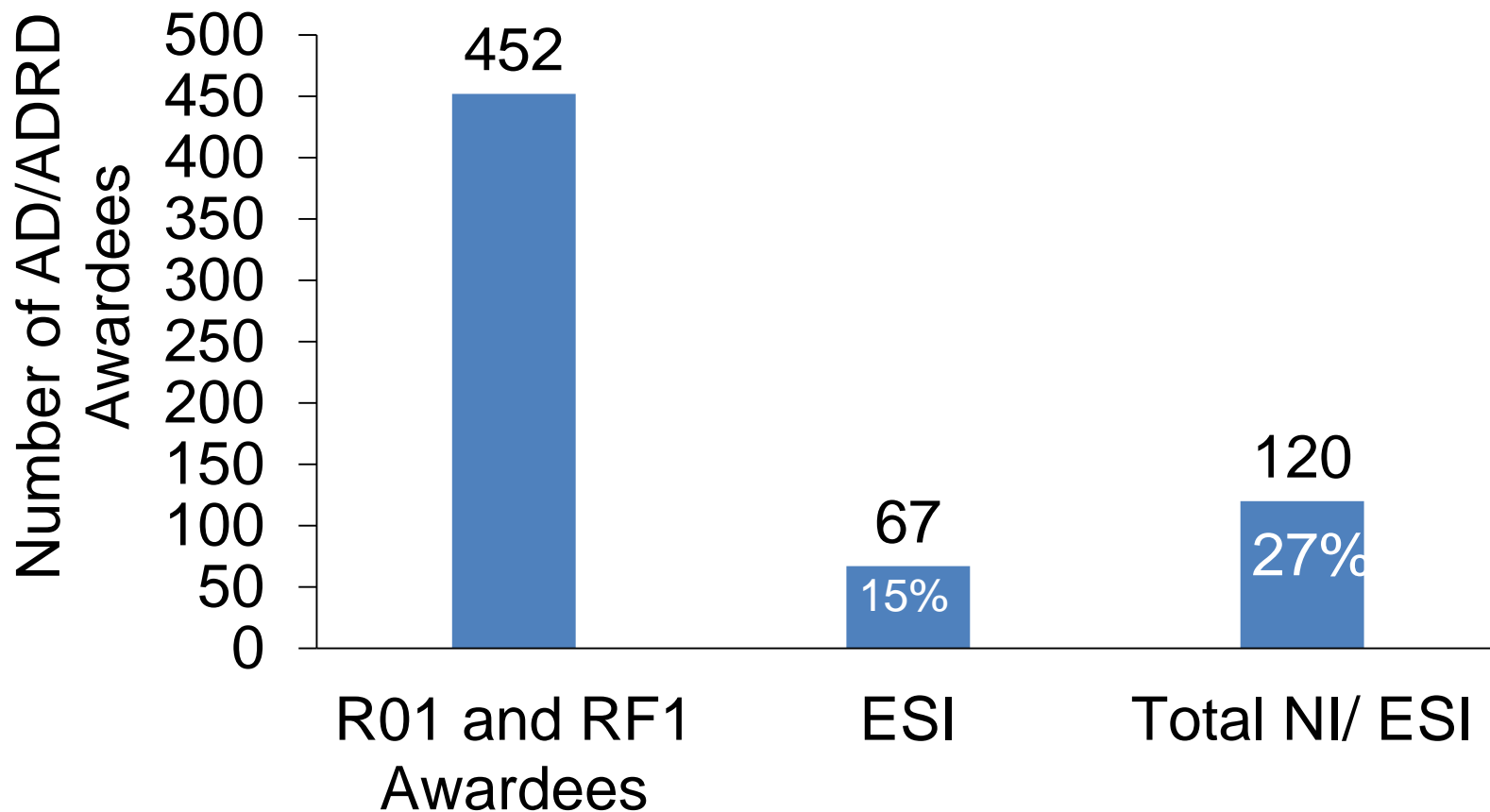


# Total Active AD/ADRD FOAs



# New Investigator (NI) and Early Stage Investigator (ESI) AD/ADRD Awardees FY2015-2017

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**ESI:** Early Stage Investigator  
**NI:** New Investigator

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# **ADVANCING AGING RESEARCH**

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# Intramural Research Program

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- 10 Intramural Laboratories
- Core facilities
- Home of the BLSA and HANDLS

# NIA Laboratory of Neurogenetics

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- Found >90% of the genes and risk factors for Parkinson's disease
- Identified the first rare risk variant for Alzheimer's disease (*TREM2*)
- Identified multiple genes for Amyotrophic Lateral Sclerosis and frontotemporal dementia, including the most common cause (*c9orf72*)

**Identified:**

- >90% of genes and risk factors for PD
- The first rare risk variant for AD
- The most common disease-causing mutations in ALS and FTD

Created foundational data to link these gene products together, to provide insights regarding biology, mechanisms, and potential druggable targets

*Identify the locus*

*Find the gene*

*Understand the pathobiology*

*Target Identification*

*dissect the disease*

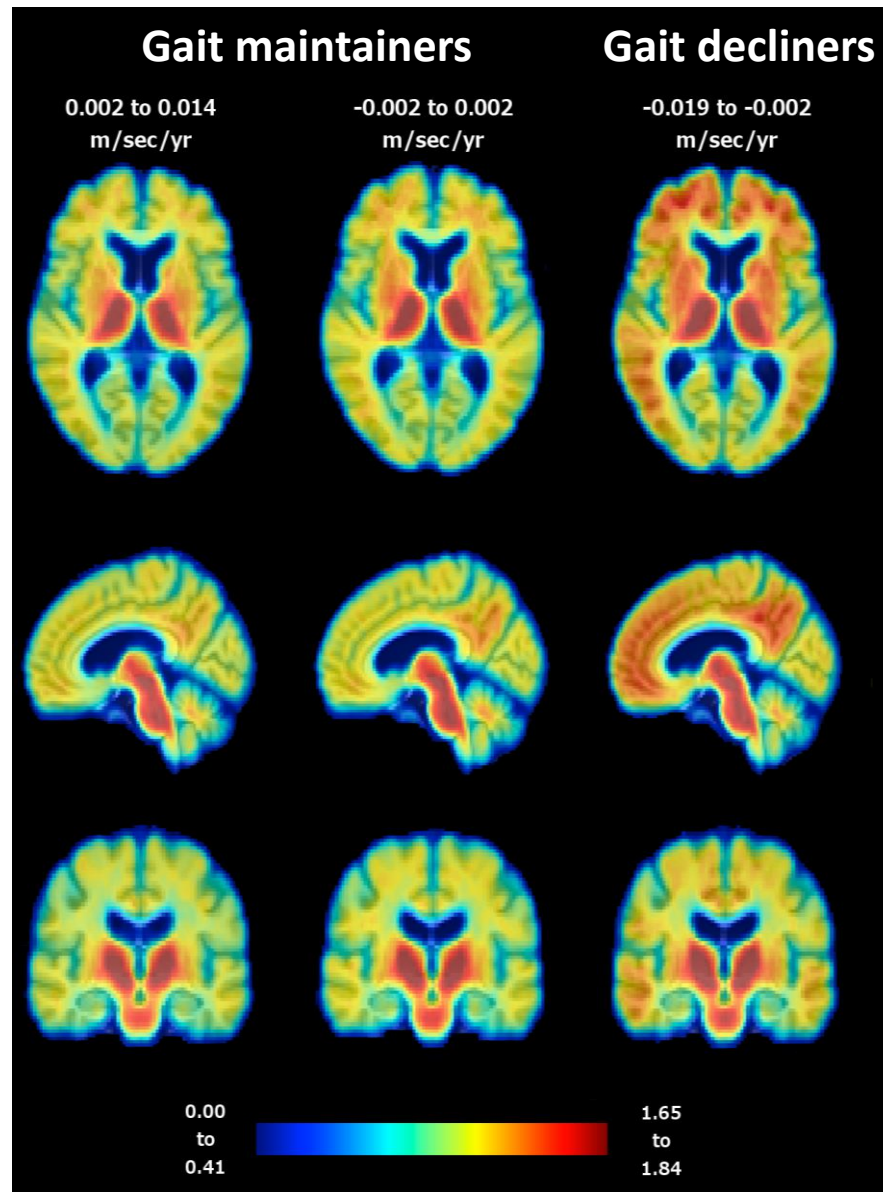
*Treatment*

**Identified:**

- A classifier of PD case status that works with 98.7% accuracy at first presentation
- A classifier that detects apparent PD cases that aren't really PD

Both *SNCA* level, and *LRRK2* kinase activity are in development as targets for PD

# Amyloid Deposition is Associated with Motor Impairment Before Cognitive Decline



# Division of Aging Biology

- **Nathan Shock Centers of Excellence**

- **Genetics and Cell Biology**

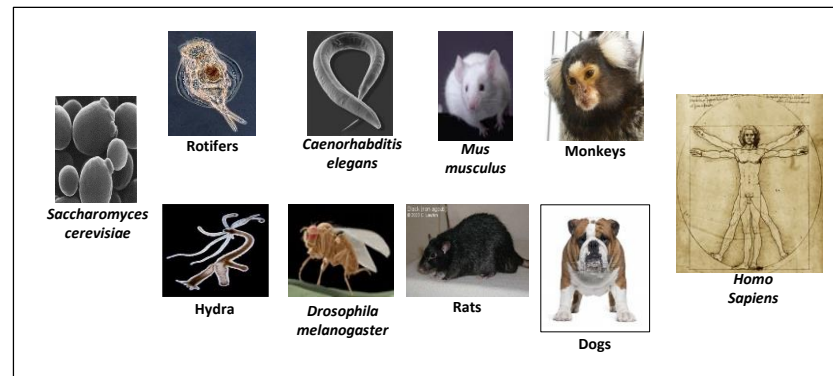
- Genetics
- Cell Biology
- Metabolic Regulation

- **Aging Physiology**

- Stem cells & Regenerative Biology
- Immunology
- Endocrinology
- Musculoskeletal Biology
- Tissue Physiology

- **Biological Resources**

- Animal Models
- Biological Resources



**Director: Felipe Sierra, Ph.D.**

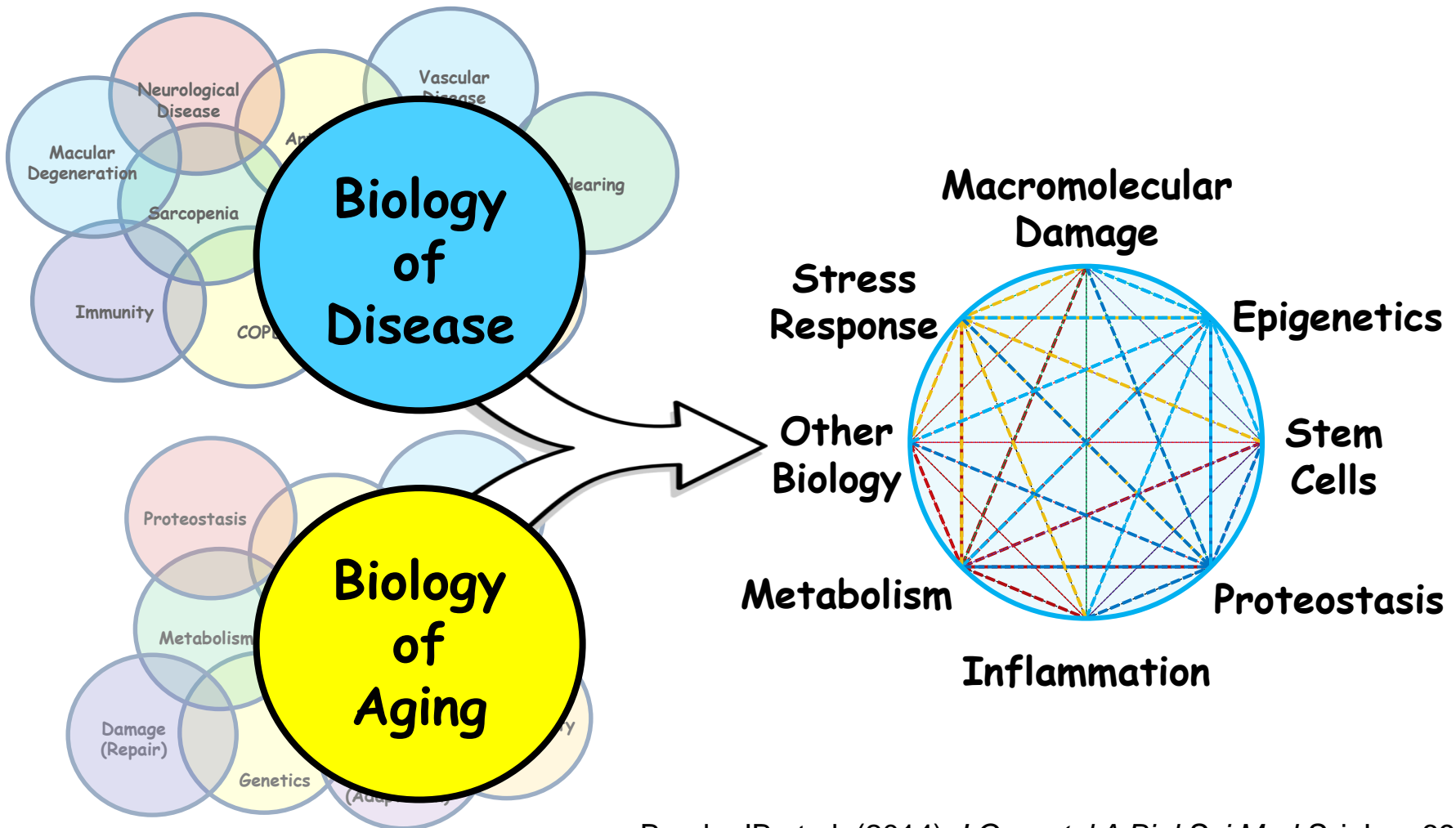
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# “Geroscience” is the Convergence of Two Fields of Study

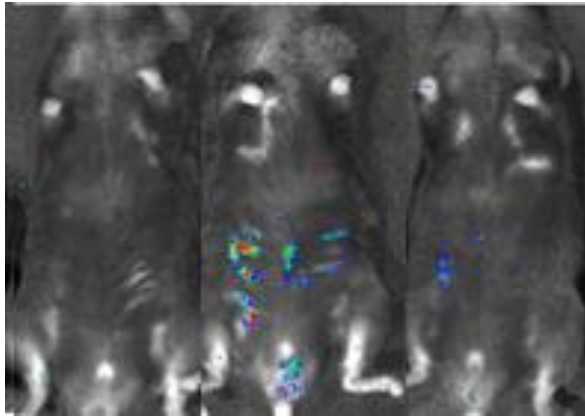
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# Chemotherapy-induced fatigue is diminished by removing senescent cells

*In humans, chemotherapy-induced fatigue correlates positively with senescent cell burden*

*In mice, elimination of senescent cells diminishes side effects of chemotherapy*

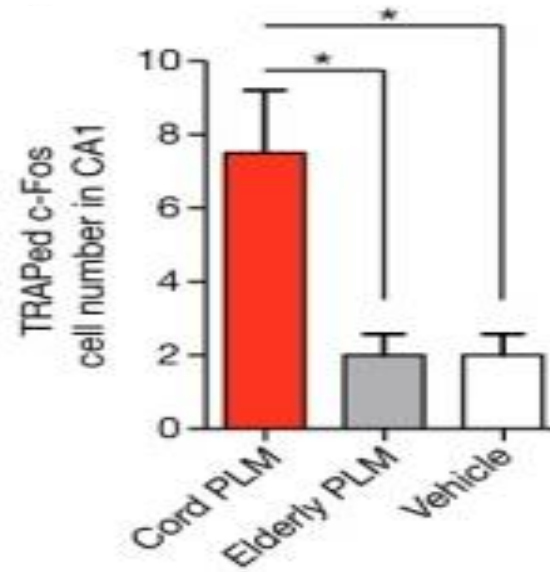


-	+	+	Doxo
-	-	+	Gancyclovir

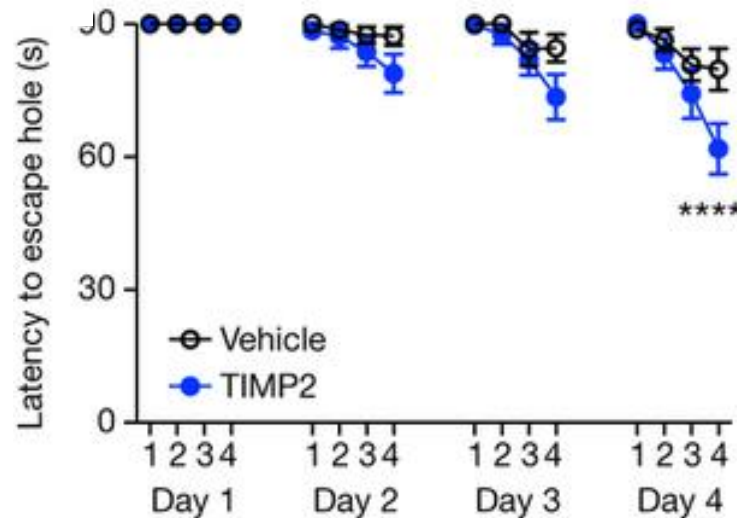
Toxicity	Chemotherapy	Chemotherapy + Senolytic
Inflammation	+++	+
Fatigue	+++	-
Cardiac dysfunction	++	-
Myelosuppression	++	-
Cancer relapse	+++	+

# TIMP2 from Human Umbilical Cord Plasma Revitalizes Hippocampal Function in Aged Mice

Synaptic  
Plasticity



Cognitive  
Effect





# Division of Neuroscience

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- Basic Neurobiology
- Alzheimer's Disease
- Sensory Processes
- Learning and Memory
- Sleep
- Cognitive Health

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**Acting Deputy Director: Brad Wise, Ph.D.**

**[wiseb@nia.nih.gov](mailto:wiseb@nia.nih.gov)**

# What Counts as AD/ADRD Research?

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- The AD/ADRD payline applies to applications/awards that are coded as AD or Alzheimer's disease-related dementias (ADRD)
- The ADRD RCDC categories that report related dementias specifically named in the National Plan to Address Alzheimer's Disease are:
  - Lewy Body dementia (LBD)
  - Frontotemporal dementia (FTD)
  - Vascular Cognitive Impairment/Dementia (VCI/D)

# Diversity of AD/ADRD Research

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Aging  
metabolic  
changes in AD

Comparative  
biology of  
neurodegeneration

Basic Biological  
Processes of AD

Geroscience

Biomarkers

Research on  
Disease  
Mechanisms

Research on  
Care and  
Caregiver  
Support

Cognitive  
outcomes in  
Population  
Studies

Disparities, Sex  
differences,  
and AD risk

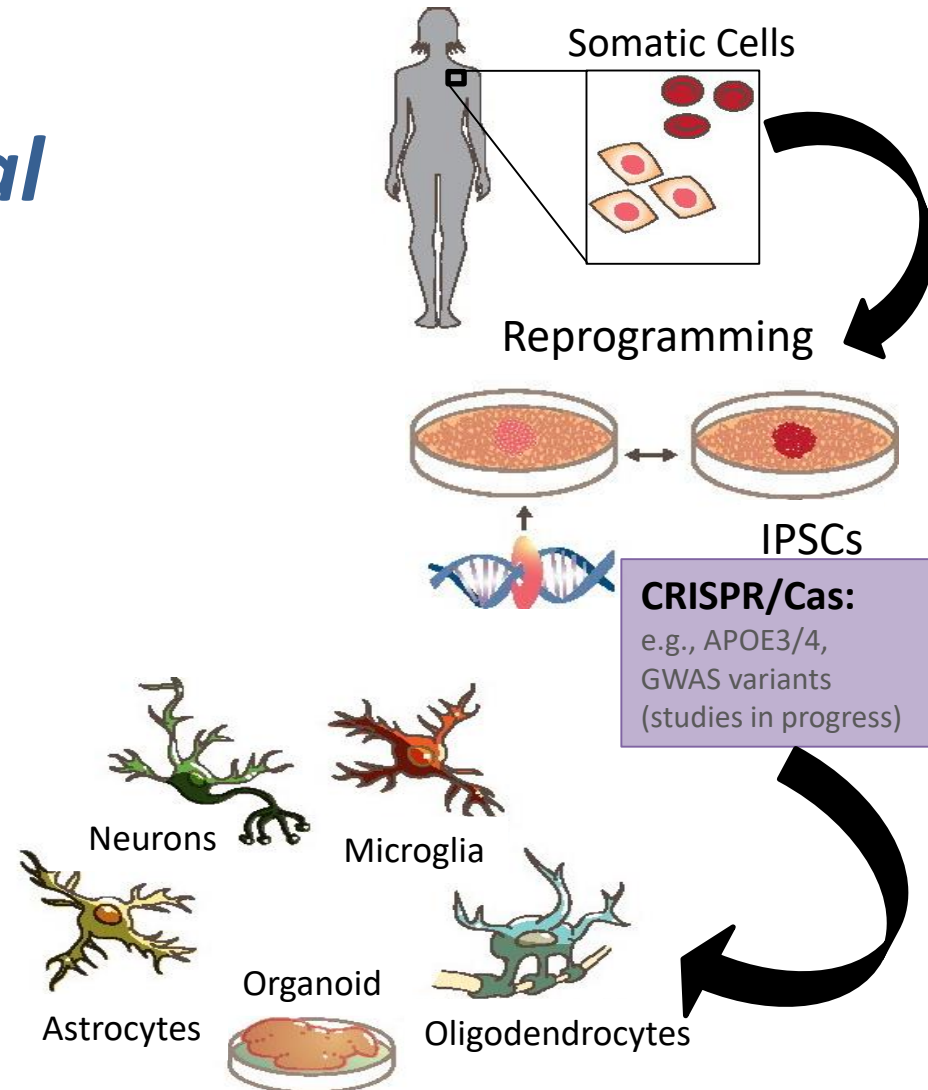
**Alzheimer's  
Research**

```
graph TD; A[Aging metabolic changes in AD] --> C((Alzheimer's Research)); B[Comparative biology of neurodegeneration] --> C; D[Basic Biological Processes of AD] --> C; E[Geroscience] --> C; F[Biomarkers] --> C; G[Research on Disease Mechanisms] --> C; H[Research on Care and Caregiver Support] --> C; I[Cognitive outcomes in Population Studies] --> C; J[Disparities, Sex differences, and AD risk] --> C;
```

# What is CRISPR & How are we using it?

## Studying human genes in human brain cells

*It's part of a bacterial defense system that allows us to "edit" a genome*

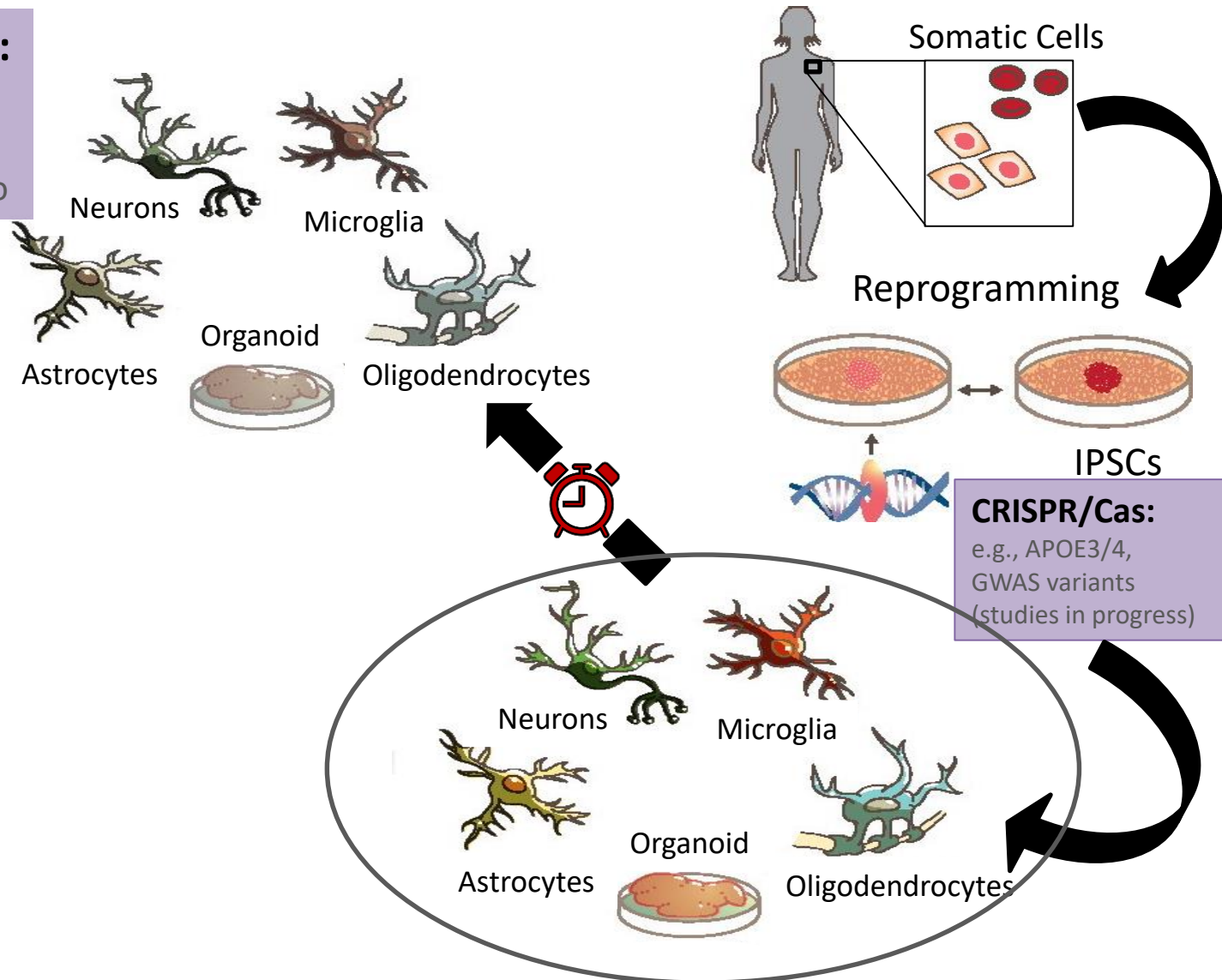


# Studying human genes in human brain cells

## Accelerating Aging:

RFA-AG17-009

e.g., Progerin, ERCC;  
CRISPR/Cas TERT, Klotho



# Studying human genes in human brain cells

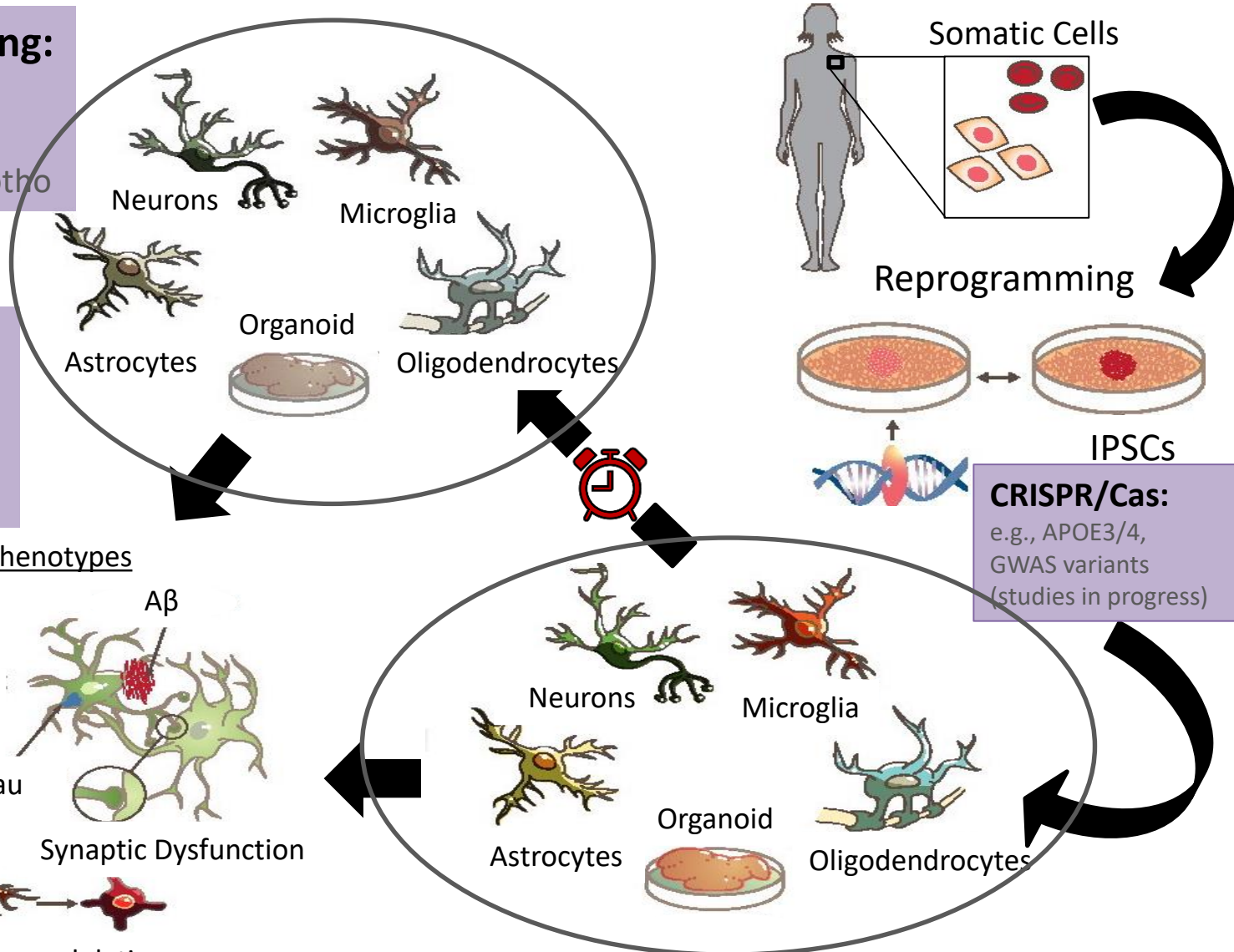
## Accelerating Aging:

*RFA-AG17-009*

e.g., Progerin, ERCC;  
CRISPR/Cas TERT, Klotho

## Functional Genetics of AD:

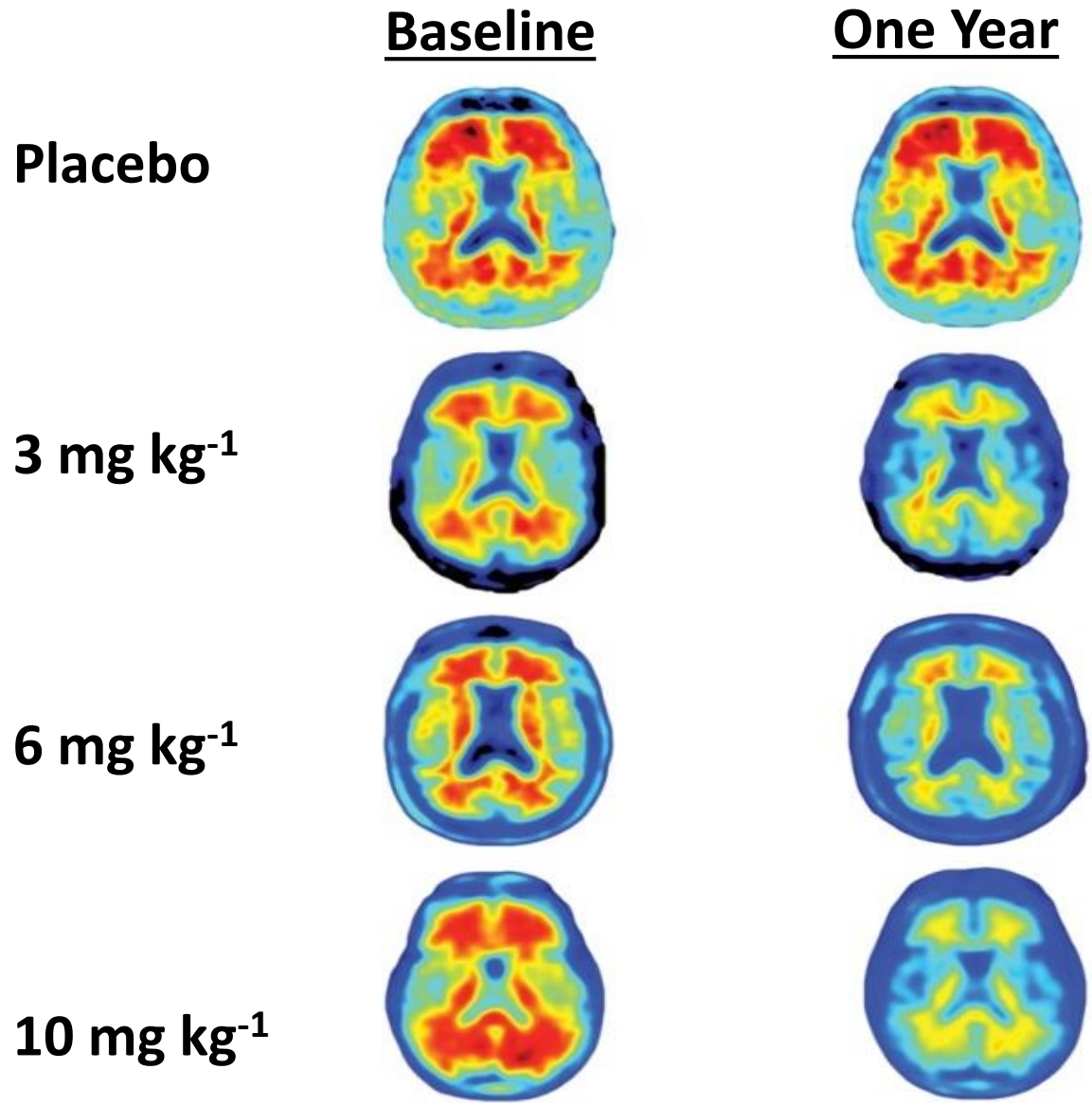
*RFA-AG14-012,*  
*RFA-AG17-053*





# Aducanumab Reduces Amyloid $\beta$ plaques in AD

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Sevigny J. et al. (2016).  
*Nature*. 537(7618):50-6.

# Accelerating Medicines Partnership *Alzheimer's Disease Program*

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Managing Partner →

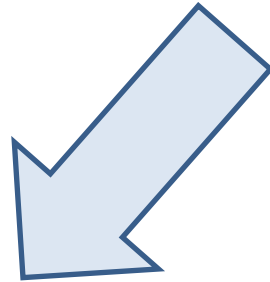


<https://www.nia.nih.gov/alzheimers/amp-ad>



# Accelerating Medicines Partnership – AD Knowledge Portal

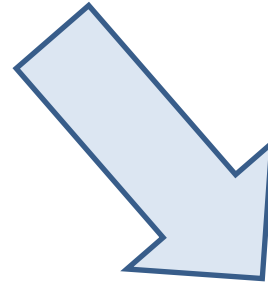
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**Target Discovery  
and Preclinical  
Validation**



**AMP-AD Knowledge  
Portal (SAGE)**



**Predictive  
Biomarkers in  
Secondary  
Prevention Trials**



# Accelerating Medicines Partnership – AD Knowledge Portal

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***A hub for data, analysis results, analytical methodology and research tools***

**Researchers can use it for:**

**Data Integration** (*learning from large pools of data*)

**Predictive Modeling** (*using what we know to better match compounds to targets*)

**Molecular Profiling** (*understanding new targets better*)

**Experimental Validation** (testing interventions in models)

+

**Rapid and Broad Sharing** (*of what we are learning*)

# AMP-AD Mount Sinai Team

## Candidate Targets: Preliminary list

**“Wall” of  
Targets - Over  
100 novel  
targets  
discovered**

Rank	Driver
1	RGS4
2	SCN2A
3	OLFM3
4	SLC22A10
5	ENAH
6	WWTR1
7	LRP10
8	SYP
9	PCSK1
10	KMO
11	PTTG1IP
12	MLIP
13	PLXNB1
14	DLGAP1
15	MOAP1
16	PRKCB
17	VGF
18	YAP1
19	GNA13
20	TRIM56
21	KCNV1
22	STXBP5L
23	DOCK2
24	GABRG2
25	STAT3

Rank	Driver
26	SV2B
27	RBFOX1
28	STAT4
29	PAK1
30	RASAL2
31	SYT1
32	NCKAP1L
33	PARD3B
34	TLN1
35	NRXN1
36	TNFRSF1B
37	ARHGEF9
38	DUSP4
39	DTX3L
40	SNAP25
41	PLCB1
42	WDR49
43	NFIA
44	XK
45	NAPB
46	MVP
47	GABRA1
48	CD68
49	LAPTM5
50	ANGPT1

# Ongoing NIA AD/ADRD and Related Intervention and Prevention Trials (140+)

40 Early-stage Clinical Drug Development (Phase I and Phase II Clinical Trials)

8 Late-stage Clinical Drug Development (Phase II/III and Phase III Clinical Trials)

62 Non-Pharmacological Interventions

7 Clinical Therapy Development for the Neuropsychiatric Symptoms of AD/ADRD

37 Care and Caregiver Interventions

Amyloid (9)  
Neurotransmitter Receptors (3)  
Metabolism and Bioenergetics (4)  
Vasculature (3)  
Growth Factors and Hormones (1)  
Multi-target (6)  
Oxidative Stress (1)

Amyloid (6)  
Vasculature (2)

Exercise (16)  
Diet (2)  
Cognitive Training (20)  
Combination Therapy (11)

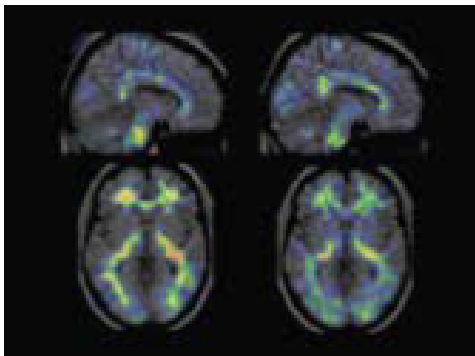
Pharmacological (5)  
Non-Pharmacological (2)

# Early Intervention May Be Possible – Thanks to Trial Volunteers from a Colombian Family

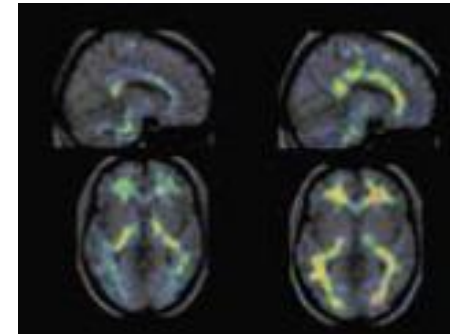


**Caption:** One of many Colombian families who have a genetic mutation that leads them to develop Alzheimer's disease.  
**Credit:** Forget Me Not Initiative/Grupo de Neurociencias de Antioquia

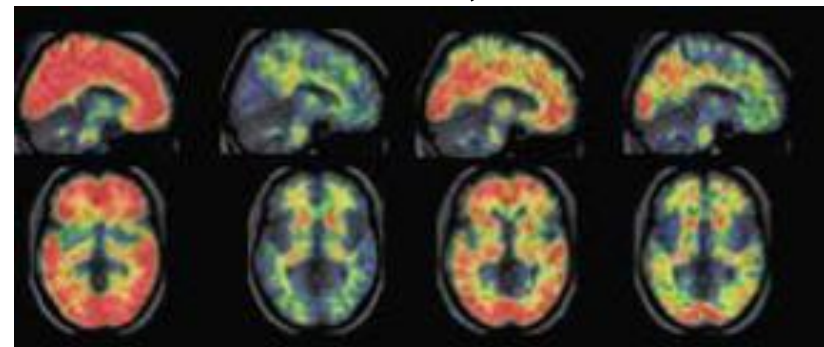
**Beta-amyloid, late 20's**



**Non-Carriers, late 30's**



**Gene Carriers, late 30's**



**Dementia onset is in late 40's**

# Challenges for AD/ADRD Studies

- Lack of eligibility
- Lack of capacity, awareness and resources among primary care providers
- Study partner requirements
- Invasive procedures
- Need for pre-symptomatic volunteers
- Barriers for underrepresented communities
- National Recruitment Strategy in development – for release in the summer of 2018

**ALZHEIMER'S RESEARCH NEEDS YOU!**

The number of older Americans 65+ with Alzheimer's disease is rapidly growing'

Year	Number of Older Americans 65+ with Alzheimer's Disease
2014	6.0 MILLION
2030	13.8 MILLION

**GOOD NEWS** IMPORTANT ALZHEIMER'S RESEARCH IS MOVING FORWARD

**BUT WE NEED YOUR HELP**

More than **150** Alzheimer's and related clinical trials in the U.S. are looking for volunteers

At least **70,000** people with Alzheimer's, healthy volunteers, and caregivers are urgently needed

**1** volunteer at a time is what it takes

**YOU** COULD BE THAT VOLUNTEER

**YOU CAN MAKE A DIFFERENCE**

**Join Us!** TAKE THE FIRST STEP TODAY

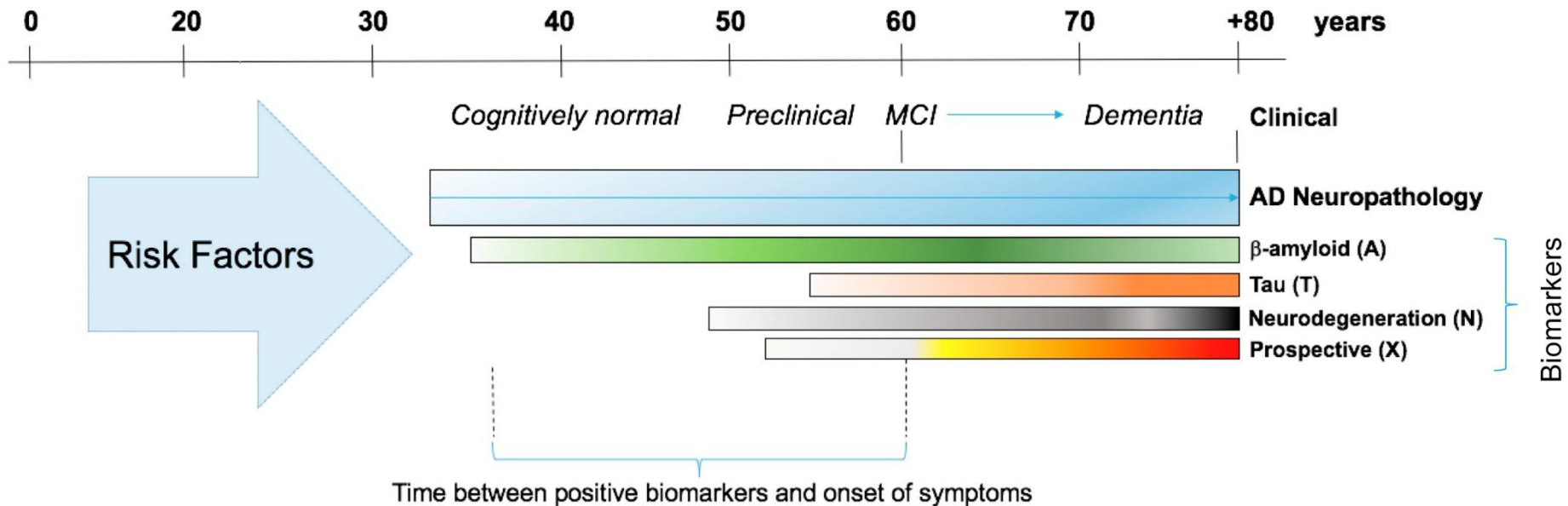
Call 1-800-438-4380  
Go to [www.nia.nih.gov/alzheimers/volunteer](http://www.nia.nih.gov/alzheimers/volunteer)

Alzheimer's Disease Education & Referral Center  
NIH National Institute on Aging  
Follow us on Twitter: @Alzheimers\_NIH

\*David L.E. Wesson, J. Lynette BA, Evelyn DA. Alzheimer disease in the United States (2000-2050) estimated using the 2010 census. Neurology 2015;85(16):1779-1783.

# NIA-Alzheimer's Association Research Framework

The framework will hopefully aid researchers in identifying individuals at risk for disease sufficiently early to test new prevention strategies as they emerge





# Division of Behavioral and Social Research

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- Elucidating causal links between behavioral and social factors and aging trajectories
- Explaining and reducing disparities in health at older ages
- Reversing or mitigating effects of early-life risk factors
- Improving dementia care and health of caregivers
- Behavioral interventions and preventing disability



c/o Gerontology Society of Iowa

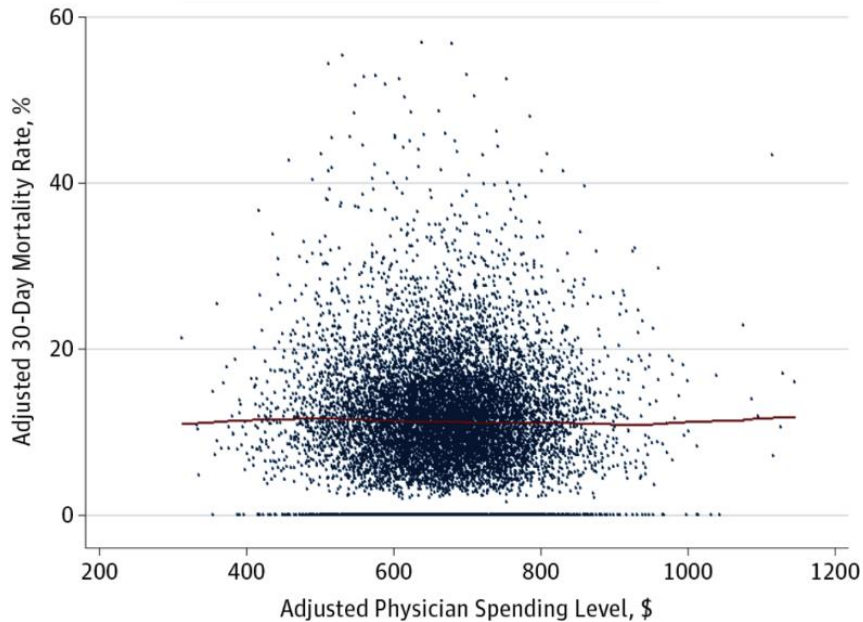
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**Deputy Director: Dana Plude, Ph.D.**  
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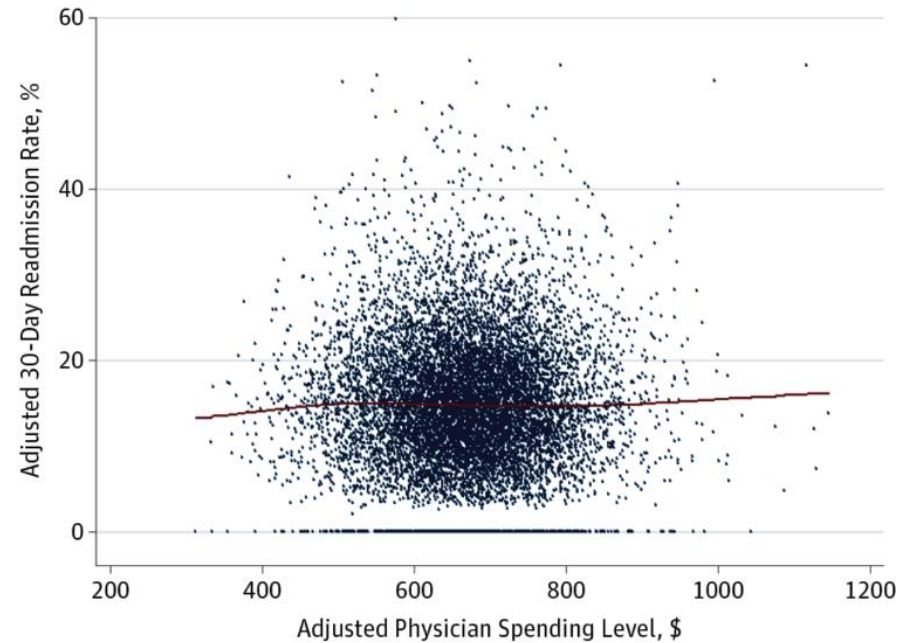


# Higher Physician Spending is Not Associated with Lower Mortality or Hospital Readmission

## 30-Day Mortality Rate

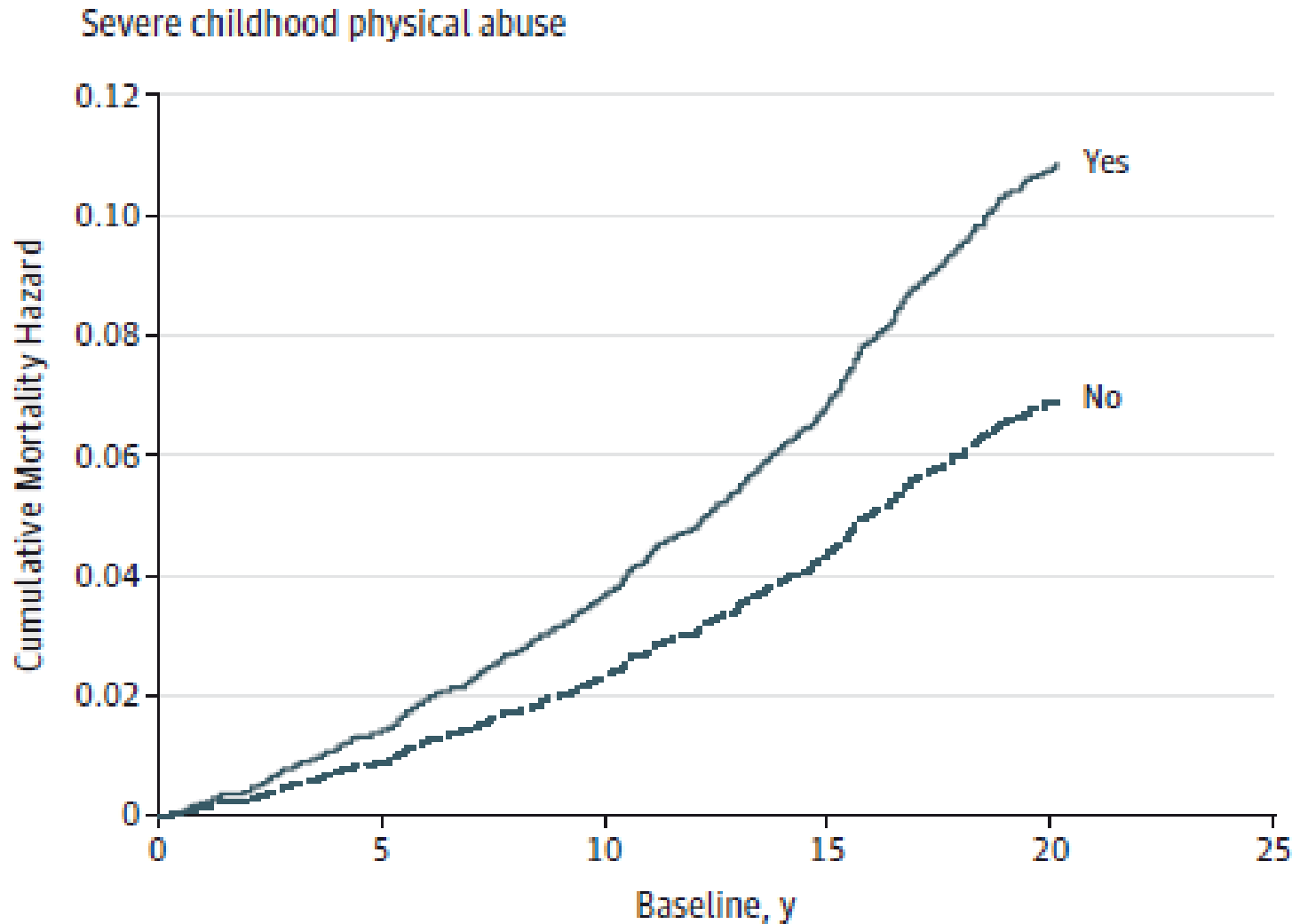


## 30-Day Readmission Rate

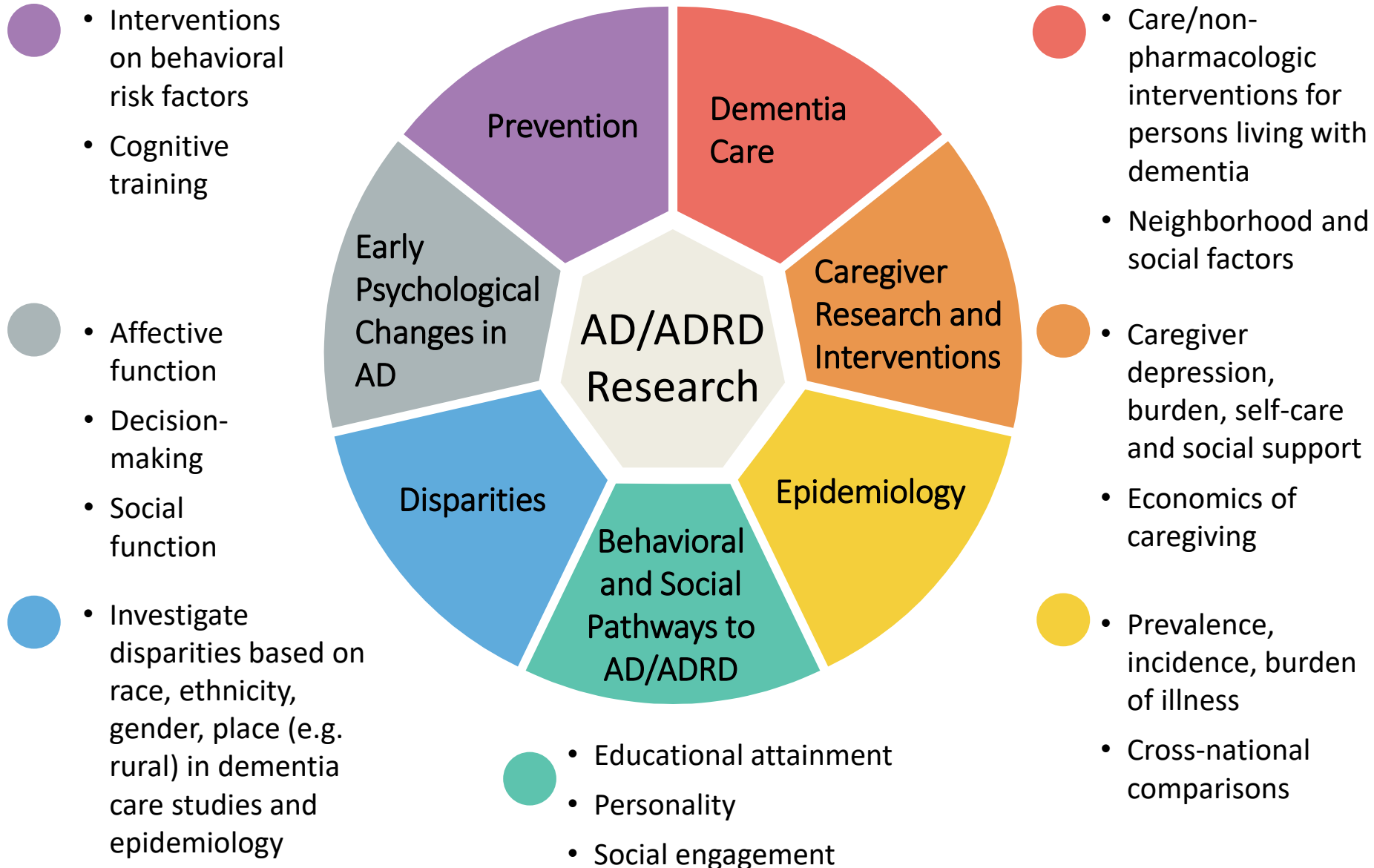


- Life expectancy in US is 78.8 years, falling short of OECD average of 80.5 years.
- There is substantial variation in health care spending across US – is spending associated with outcomes?
- Spending varies more across individual physicians rather than hospitals, and higher physician spending is not associated with better outcomes for patients.

# Childhood Abuse Increases Mortality Rates in Women

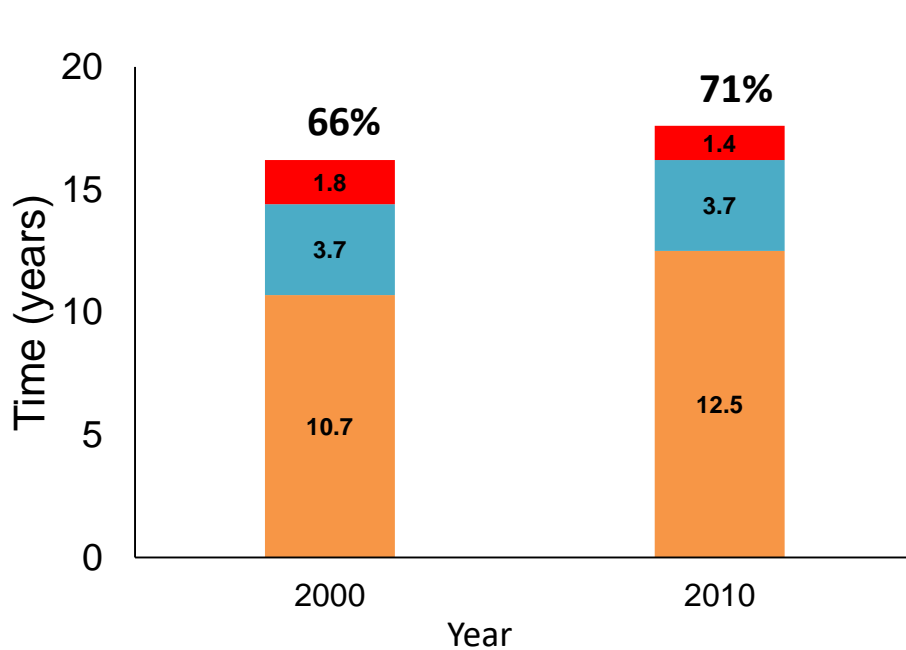


# Some Approaches used in Behavioral and Social AD/ADRD Research

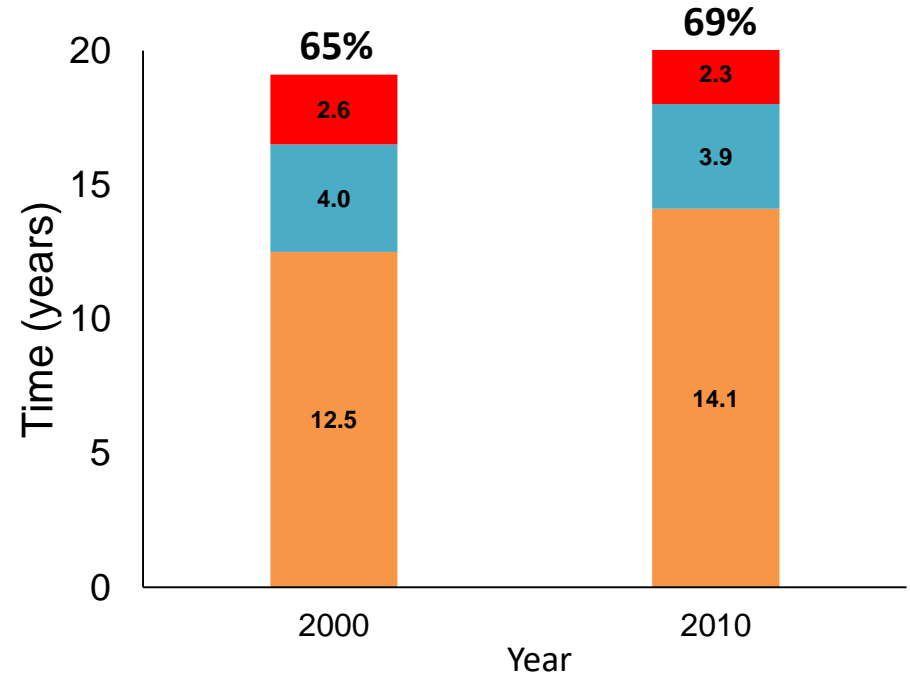


# Cognitively healthy life span has increased as much as life span

## Male Life Expectancy at Age 65



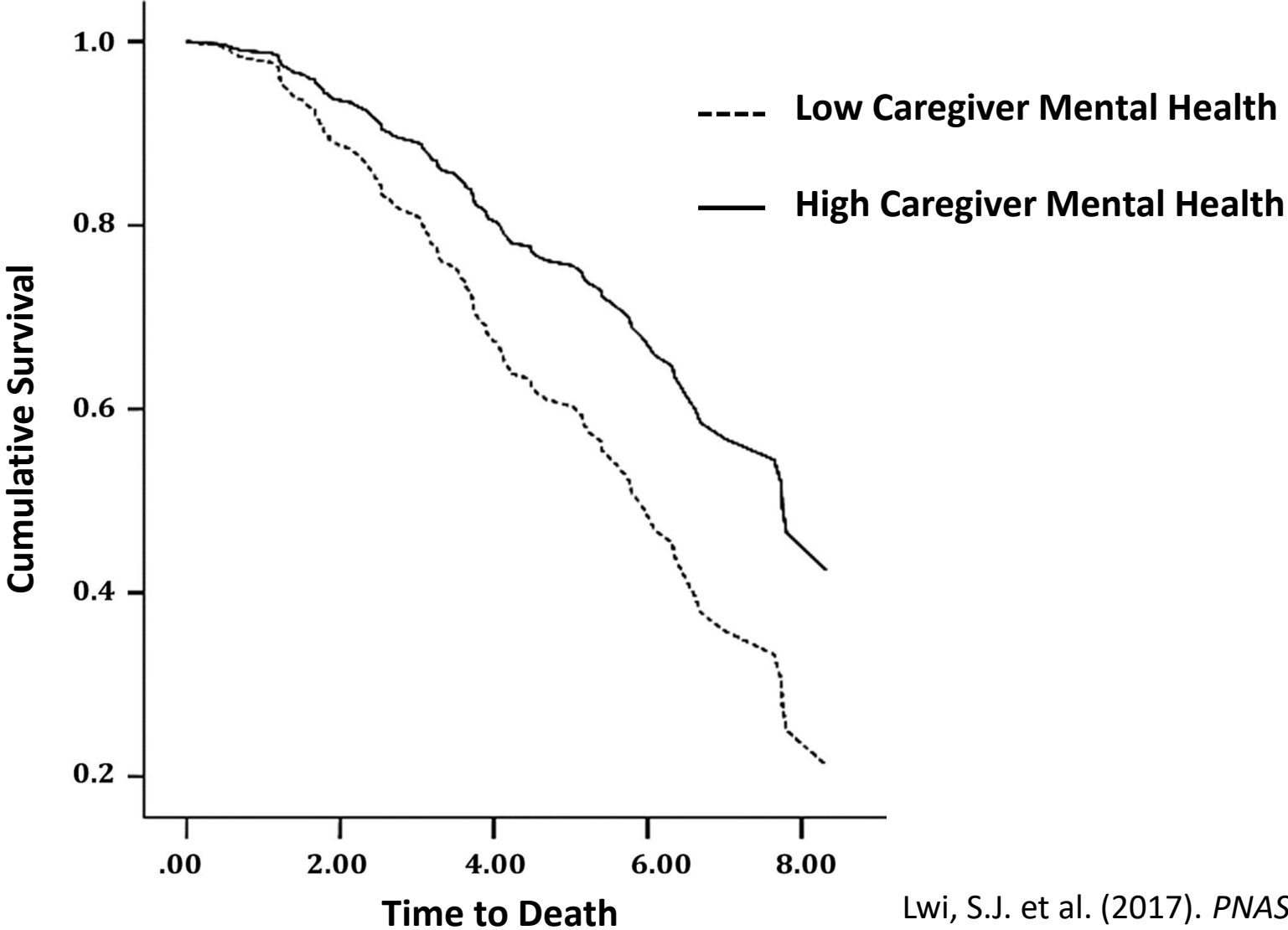
## Female Life Expectancy at Age 65



## Predicted Cognitively Intact Years (%)

- Cognitively Intact
- Cognitive Impairment without Dementia
- Dementia

# Poor Caregiver Mental Health Predicts Mortality of Patients with Neurodegenerative Disease



Lwi, S.J. et al. (2017). *PNAS*. Early Edition: 1-6.

# Caregiving Research: More Active than Ever

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- Integration of recommendations from the 2017 Care/Services Summit into FY2020 AD/ADRD Bypass Budget Planning:

<https://aspe.hhs.gov/national-research-summit-care-services-and-supports-persons-dementia-and-their-caregivers-final-report#FinalRpt>

- Funding opportunity announcements already released
- Next Care/Services Summit dates: March 24-25, 2020
- Planned systematic review of care/caregiving interventions – what's ready for prime time?

# Division of Geriatrics and Clinical Gerontology

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- Maintaining health and independence in old age
- Improving functional abilities in old age
- Coexisting conditions
- Aging across the life span; exceptionally healthy aging
- Aging mechanisms influencing health span and longevity
- Clinical trials: Prevention and treatment



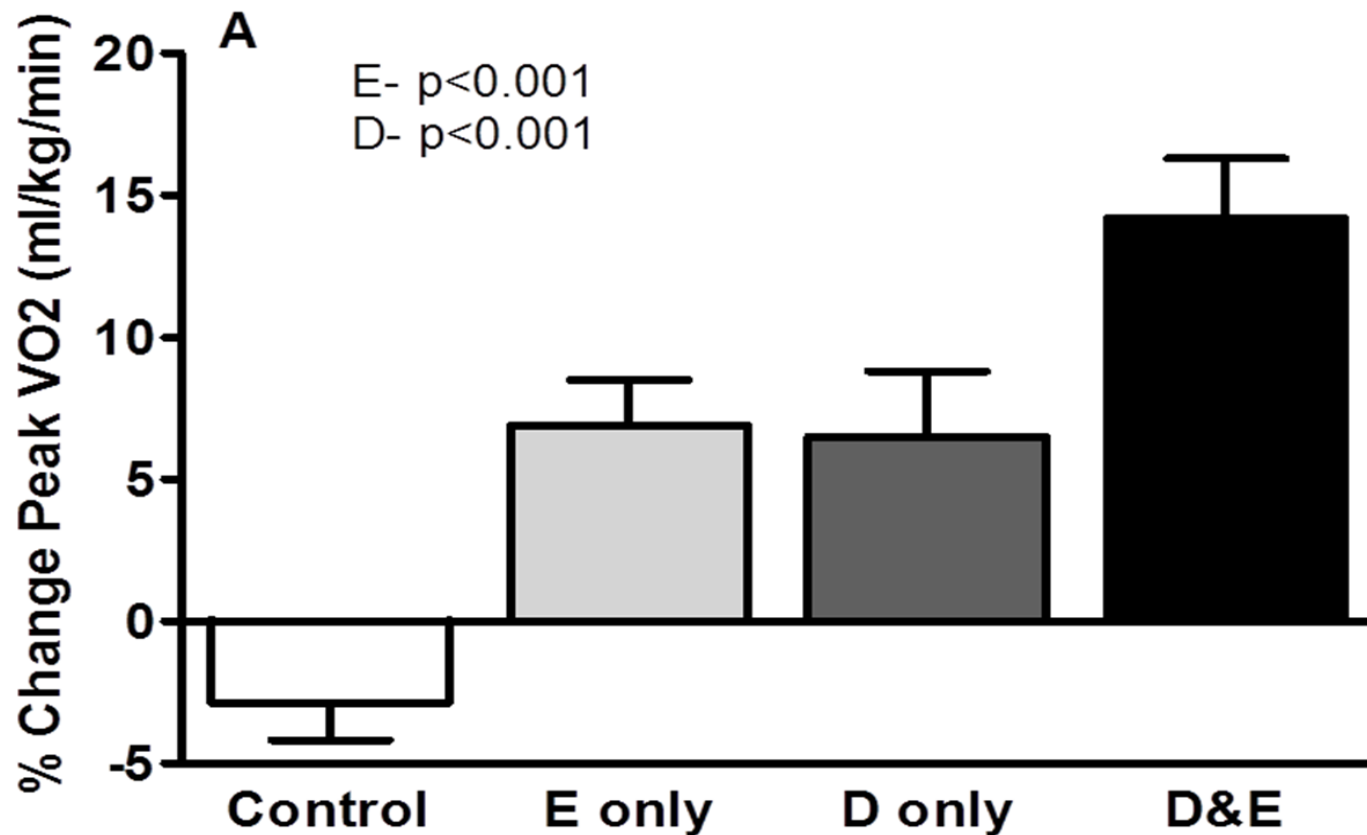
**Director: Evan Hadley, M.D.**

**[ehadley@nih.gov](mailto:ehadley@nih.gov)**

**Deputy Director: Winifred Rossi, M.A.**

**[rossiw@nia.nih.gov](mailto:rossiw@nia.nih.gov)**

# Diet and/or Exercise to Treat Heart Failure with Preserved Ejection Fraction

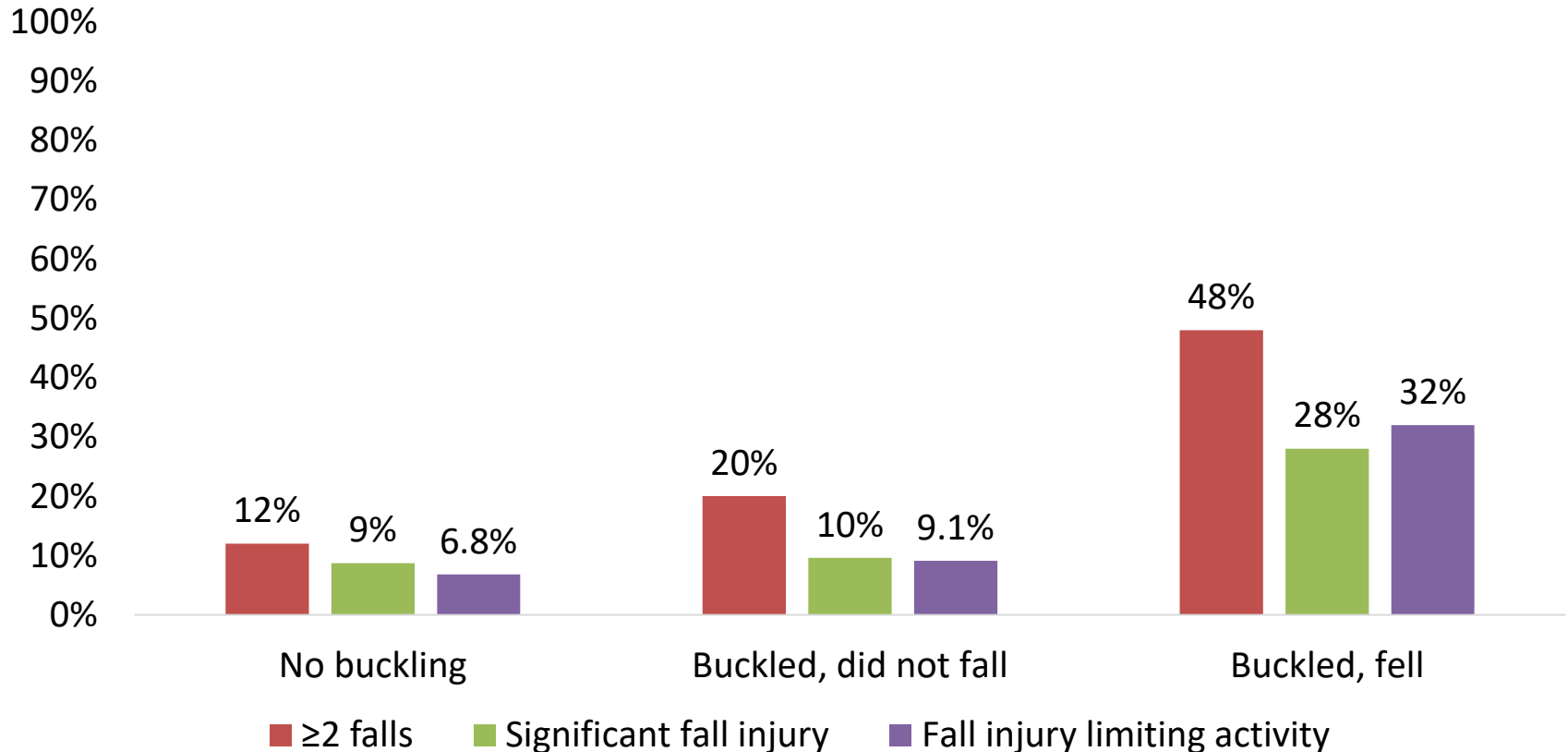


Kitzman, D et al. (2016) *JAMA* 315(1):36-46.



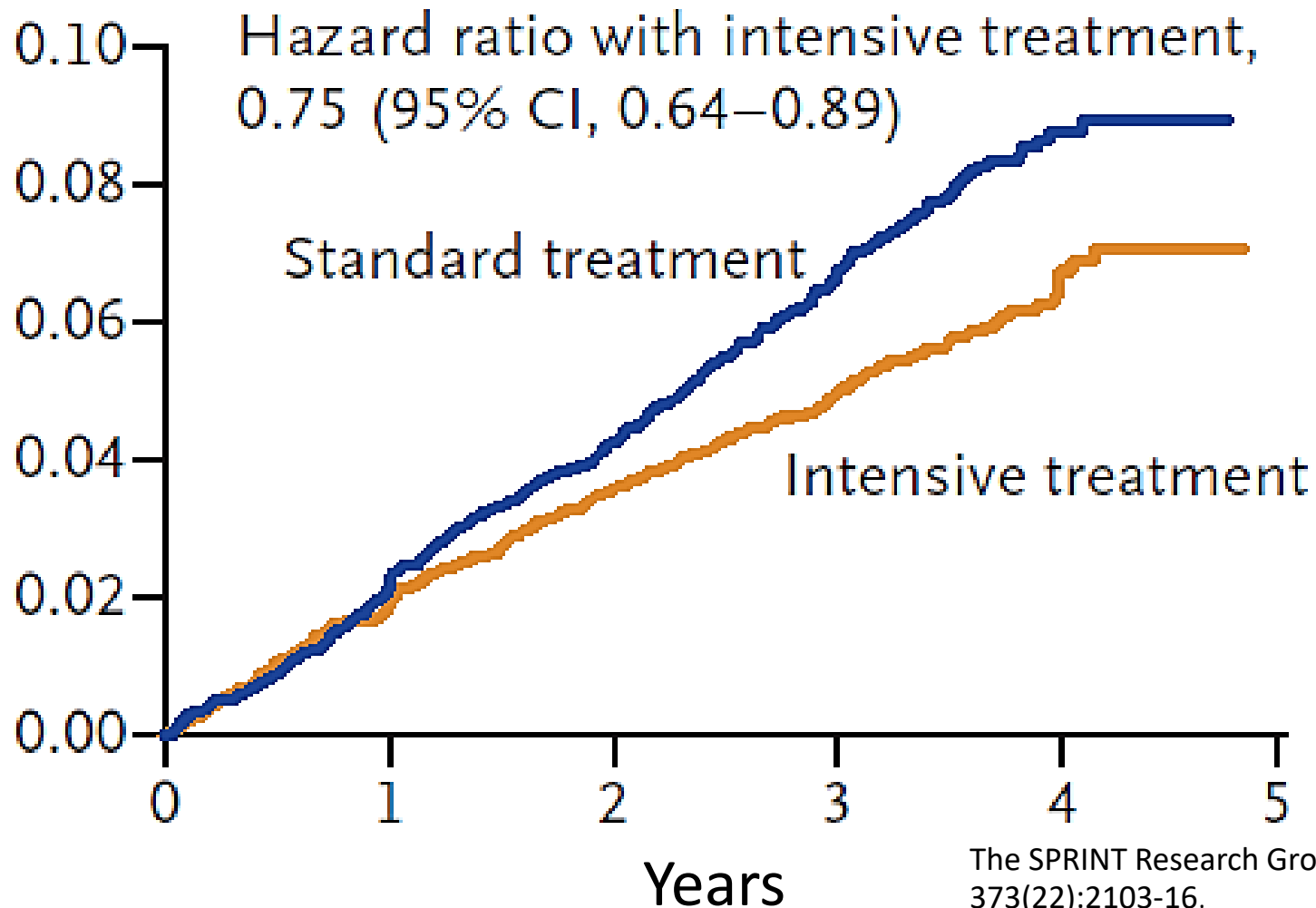
# Falling when a knee buckled at baseline

Association of knee buckling without a fall and buckling with a fall at baseline with falls and fall injuries at 84 months



Nevitt MC et al. (2016) *Arthritis Care Res* 68(8): 1089-97.

# SPRINT Study



The SPRINT Research Group (2015) *NEJM* 373(22):2103-16.

# Revised ACC/AHA BP Management Guidelines

## 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

GUIDELINES MADE SIMPLE  
A Selection of Tables and Figures



### 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

GUIDELINES MADE SIMPLE

Selected Table or Figure	Page
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Corresponding Values of Systolic BP/Diastolic BP for Clinic, Home (HBPM), Daytime, Nighttime, and 24-Hour Ambulatory (ABPM) Measurement .....	4
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# Inclusion Across the Lifespan Policy Update

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# Timeline of NIH Inclusion Policies and Participant Data Collection

1986

- NIH establishes policy encouraging researchers to include women in studies

1993

- [PL103-43](#) requires inclusion of women and minorities in NIH clinical research

1998

- NIH issues [policy](#) requiring inclusion of children in NIH clinical research

2002

- NIH issues [notice](#) changing definition of child from individuals under 21 to under 18

2015

- 21<sup>st</sup> Century Cures Act includes new requirements on age of participants in NIH Clinical Research

2016



# Summary of Key Findings in Older Adult Inclusion

- For diseases highly prevalent among older people, clinical trials often excluded subjects based on age
  - 27% of studies had arbitrary upper age caps
- Indirect exclusion factors may apply
  - Co-morbid conditions (hypertension, diabetes, cancer, etc.)
  - Polypharmacy
- Participants in trials may not represent real-world populations with the disease



# H.R.34 - 21st Century Cures Act

114th Congress (2015-2016) | [Get alerts](#)

## Requires NIH to:

1. Convene a workshop on age groupings and age exclusions in clinical research within 180 days of enactment
  - Post workshop findings on NIH website
2. Publish data on age of participants in NIH clinical research, including pediatric subgroups
3. NIH Director must determine whether the inclusion guidelines on age need revision within 180 days of the workshop



# Inclusion Across the Lifespan Workshop

## June 1-2, 2017 Bethesda, MD

**Purpose:** To discuss the challenges and barriers to including children and older adults in clinical research and to identify strategies that would produce more age-inclusive clinical studies.





# Inclusion Across the Lifespan Working Groups

- Videocast available at <https://videocast.nih.gov/launch.asp?23334>
- Workshop summary available at [https://report.nih.gov/UploadDocs/NIH%20Inclusion%20Across%20the%20Lifespan%20Workshop%20Summary%20Report%20 FINAL 508.pdf](https://report.nih.gov/UploadDocs/NIH%20Inclusion%20Across%20the%20Lifespan%20Workshop%20Summary%20Report%20FINAL%20508.pdf)

# www.report.nih.gov



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# Inclusion Policy Developments Continued

- **NOT-OD-18-116: Revision: NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects (12/19/17)**

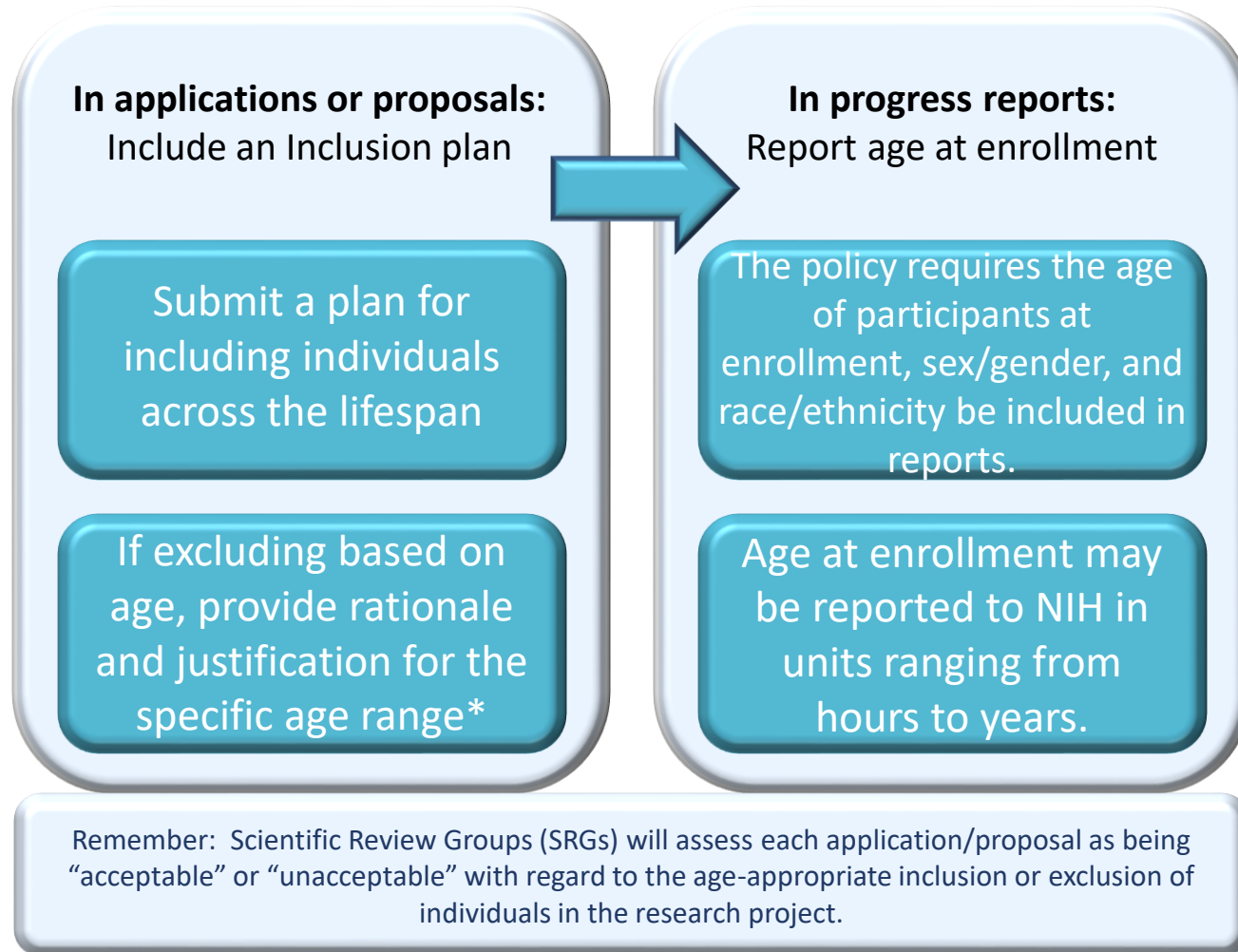
<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-116.html>



## **Changes to the policy include:**

- (1) the applicability of the policy to individuals of all ages, including children and older adults
- (2) clarification of potentially acceptable reasons for excluding participants based on age
- (3) a requirement to provide data on participant age at enrollment in progress reports.

# Inclusion Across the Lifespan: Guidance for Applying the Policy





from the National Institute on Aging at NIH

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