

Alzheimer's and Related Dementias Research Update

Advisory Committee to the Director

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Director, National Institute on Aging



National Institute
on Aging

December 13, 2024

Advancing the AD/ADRD Research Enterprise

National Plan to Address Alzheimer's Disease



National Plan
to Address
Alzheimer's Disease

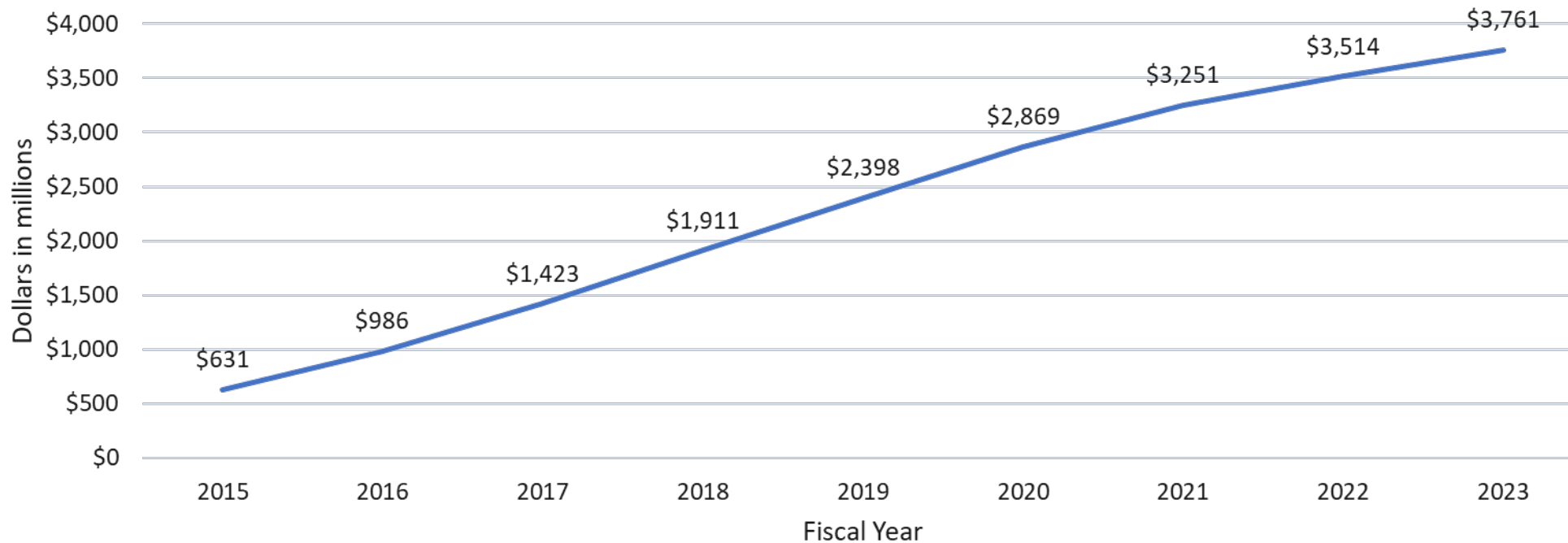


- The National Plan to Address Alzheimer's Disease, originally released in 2012 and updated annually, calls for **action to accelerate research and improve care and services** for people living with dementia and their families
- Required by the **National Alzheimer's Project Act (NAPA)**, first passed in 2011 & reauthorized in 2024
- Led by HHS ASPE, with NIH and other agencies contributing
- Includes six key goals covering risk reduction, treatment, care/support, and public awareness

Growth in Funding Leads to AD/ADRD Advances

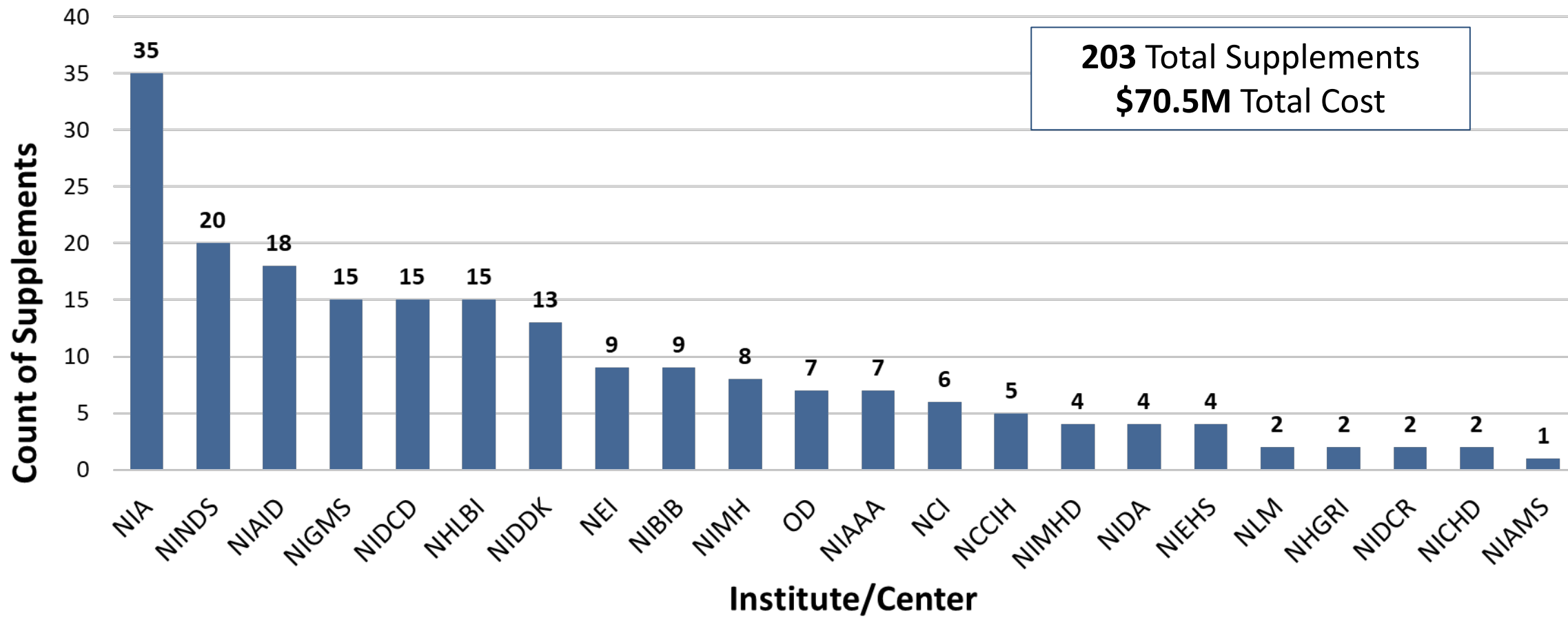
- Over the past decade, increases in Congressional appropriations allowed NIH to significantly expand its investments in AD/ADRD research.
- Through sustained NIH investment, scientists have made significant strides in understanding AD/ADRD, and progress toward how to effectively diagnose, treat, and prevent them.

AD/ADRD Spending at NIH

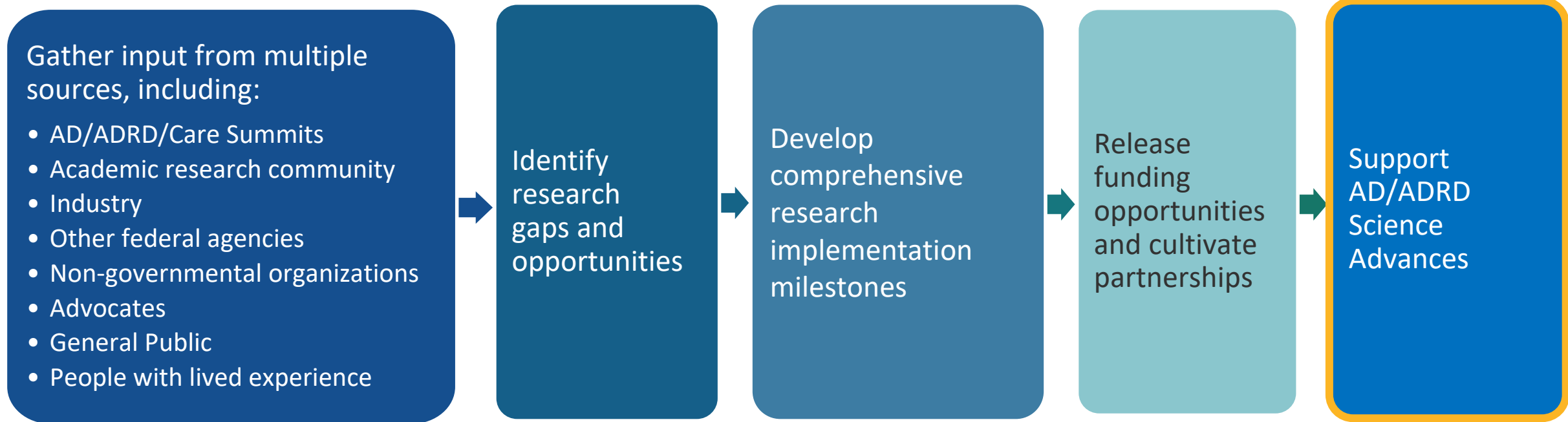


**Six-fold
increase from
2015-2023**

FY 2023 AD/ADRD Supplements to Non-AD/ADRD Awards by Institute/Center



AD/ADRD Research Strategy Incorporates External and Internal Input



AD/ADRD Research Implementation Milestones

- NIH research implementation milestones are generated with input from hundreds of members of a **community of leading experts working on AD/ADRD and other chronic diseases and public advocates.**
- These milestones represent a **research framework detailing specific steps and success criteria** towards achieving National Plan goals.
- This research framework **directly informs the development of the NIH AD/ADRD Professional Judgment Budget and NIH Funding Opportunities.**

Research Implementation Milestones

Epidemiology/Population Studies

Disease Mechanisms

Diagnosis, Assessment, & Disease Monitoring

Translational Research and Clinical Interventions

Dementia Care and Impact of Disease

Research Resources

AD Related Dementias Focus

Fiscal Year 2026 AD/ADRD Professional Judgment Budget & 2024 AD/ADRD Progress Report



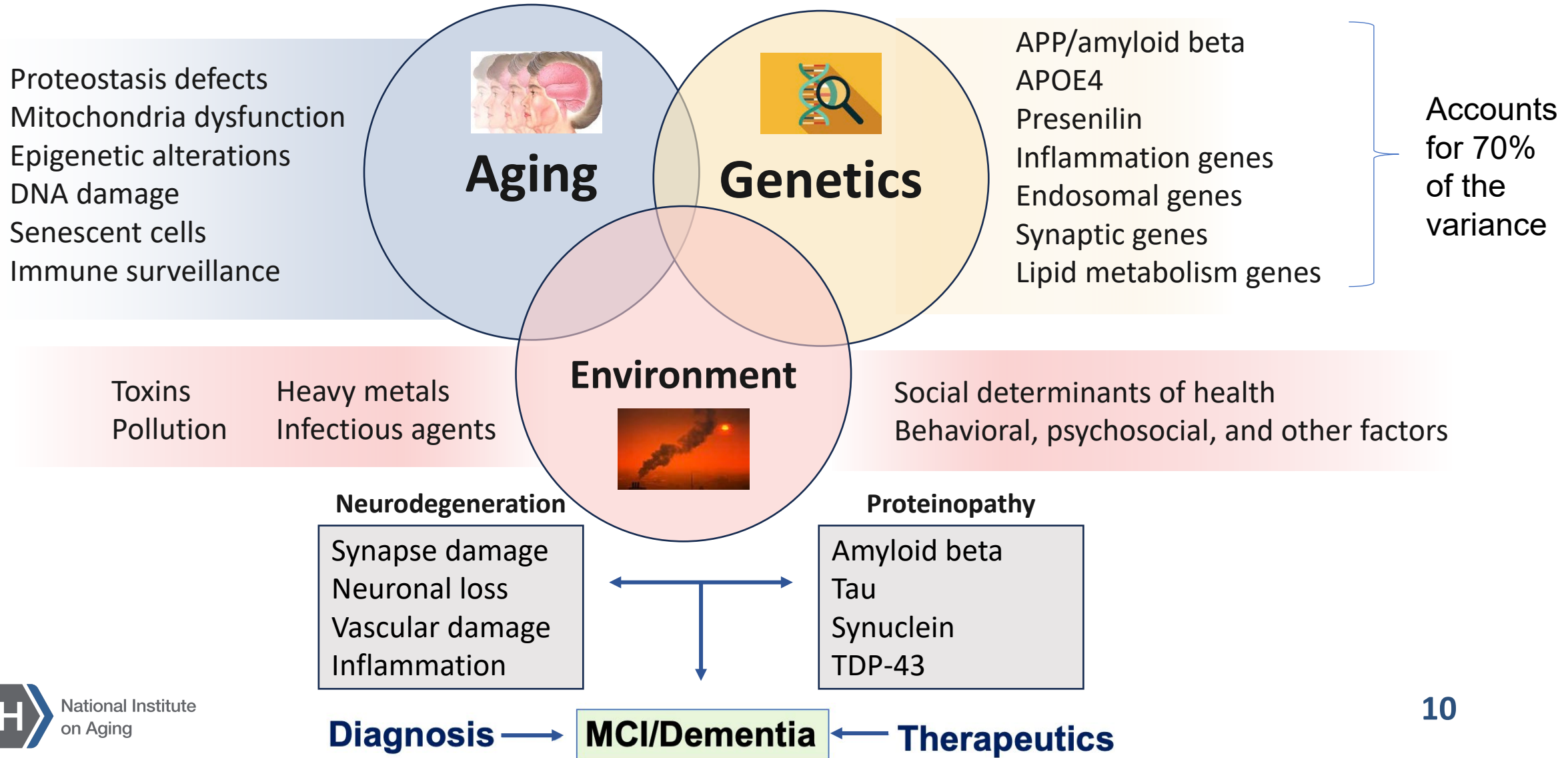
Estimates the additional future funding needed to most effectively leverage promising scientific opportunities in dementia research



Summarizes significant NIH-funded dementia research advances from the last year

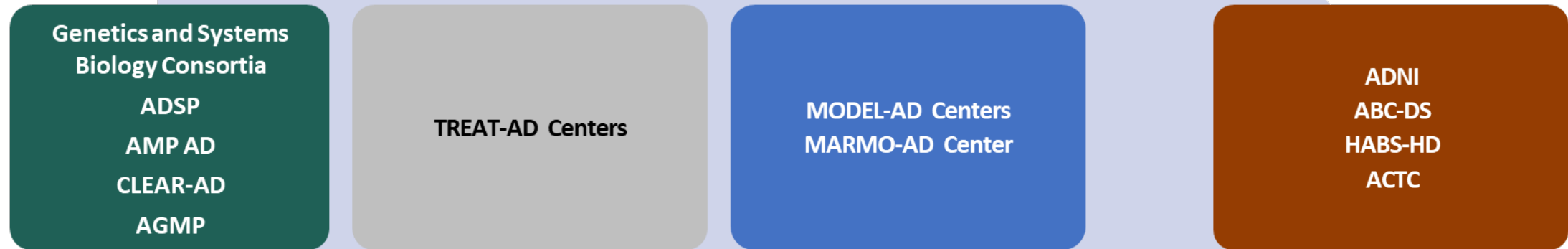
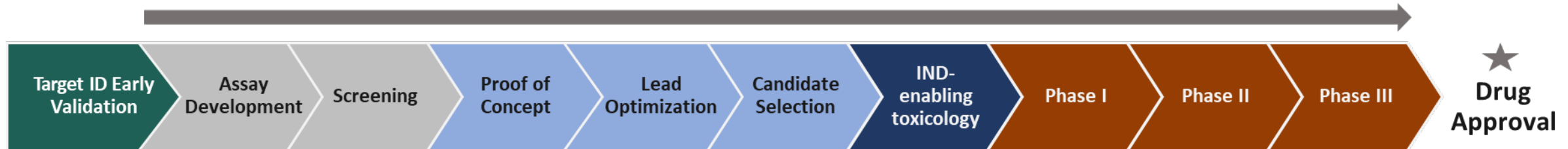
NIH Research Infrastructure

NIA Approach to AD/ADRD Research



Diversifying the Therapeutic Pipeline and Enabling a Precision Medicine Approach to Drug Development

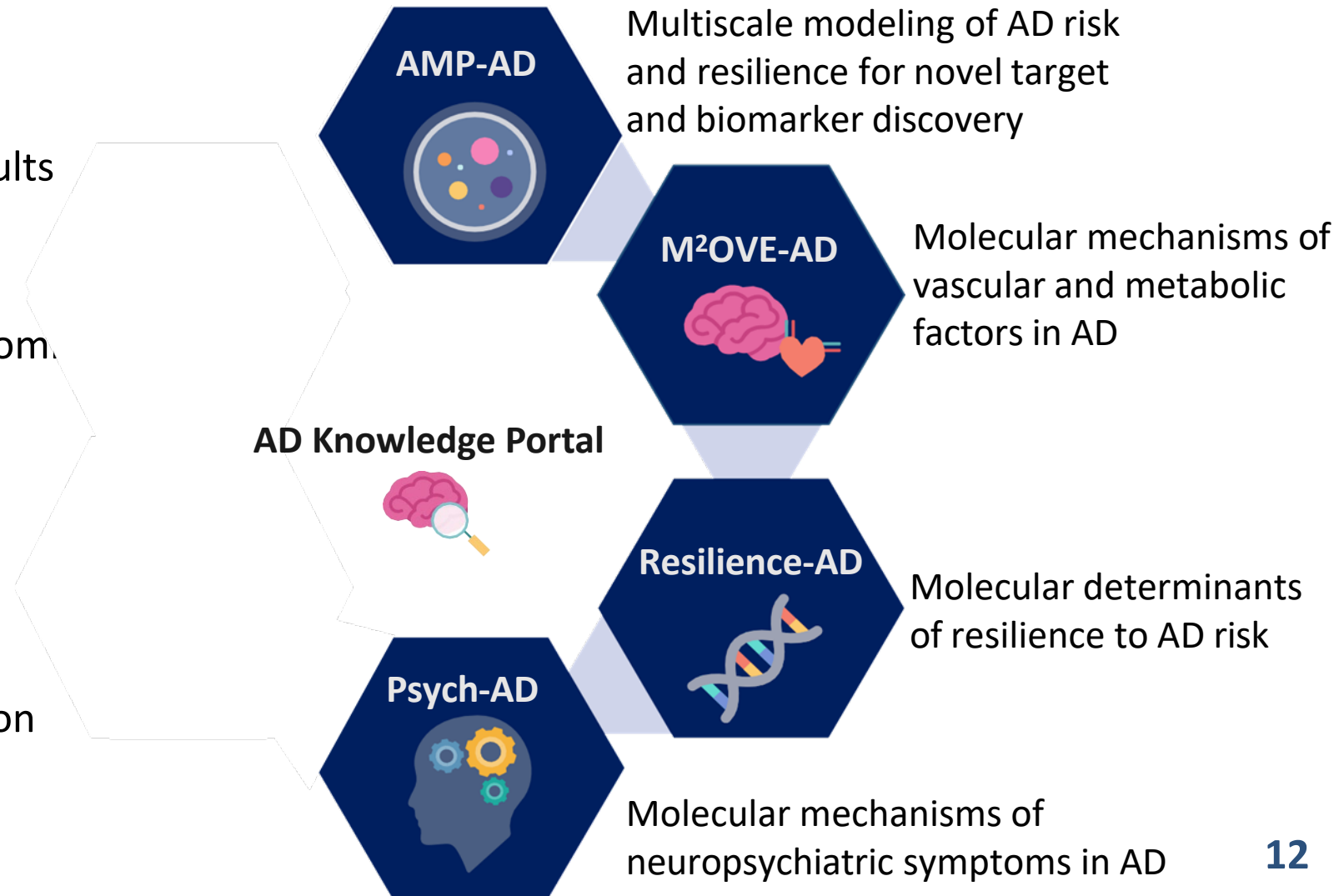
A Pipeline of Translational Research Funding Opportunities (R21/R01, U01, SBIR/STTR)



Enabling Discovery Programs and Infrastructure for
Data Driven and Predictive Drug Development

Systems-Based Approach to Deconstructing Disease Complexity for Novel Targets and Biomarkers Discovery

- Large scale team science
- Sharing of data, methods and results through centralized data infrastructure
- Integration of epidemiologic, genomic, and mechanistic research
- Integration of data generation, computational analyses, and experimental validation
- Cross-species analyses
- CNS–Peripheral systems integration



Accelerating Medicines Partnership® for Alzheimer's Disease (AMP-AD) Program

- **A public-private partnership among government, the pharmaceutical industry, and non-profit foundations** (*Launched in 2014*)
 - Uses big data approaches to better understand AD to identify new targets for treatment.
- **AMP-AD Program Accomplishments**
 - **Centralized data resources** for sharing data, analytical results, and target nominations
 - Rich, **high-quality data** and network models of disease pathways and targets
 - **Over 1000 novel candidate targets identified** through the AMP AD program and related target discovery projects
- **AMP-AD 2.0: Enabling a Precision Medicine Approach to Target and Biomarker Discovery** (*Launched in 2021*)

AMP AD 2.0 Partners



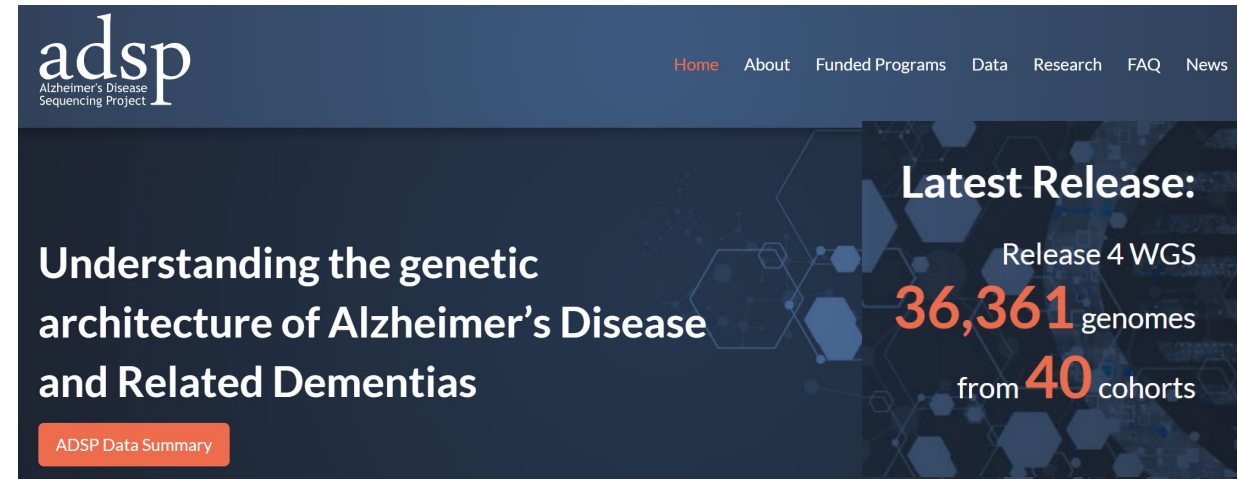
AMP AD 2.0 brings together **8 research teams** from over **20 academic institutions** and **9 public-private partner organizations**.

Alzheimer's Disease Sequencing Project (ADSP)

- Studies the genetic basis of Alzheimer's in major populations including Asians/Asian Americans, Africans/African Americans, Hispanics, and Non-Hispanic Whites, with global outreach
- Processes, stores, and **shares biospecimens** for multi-omics analyses

Deliverables:

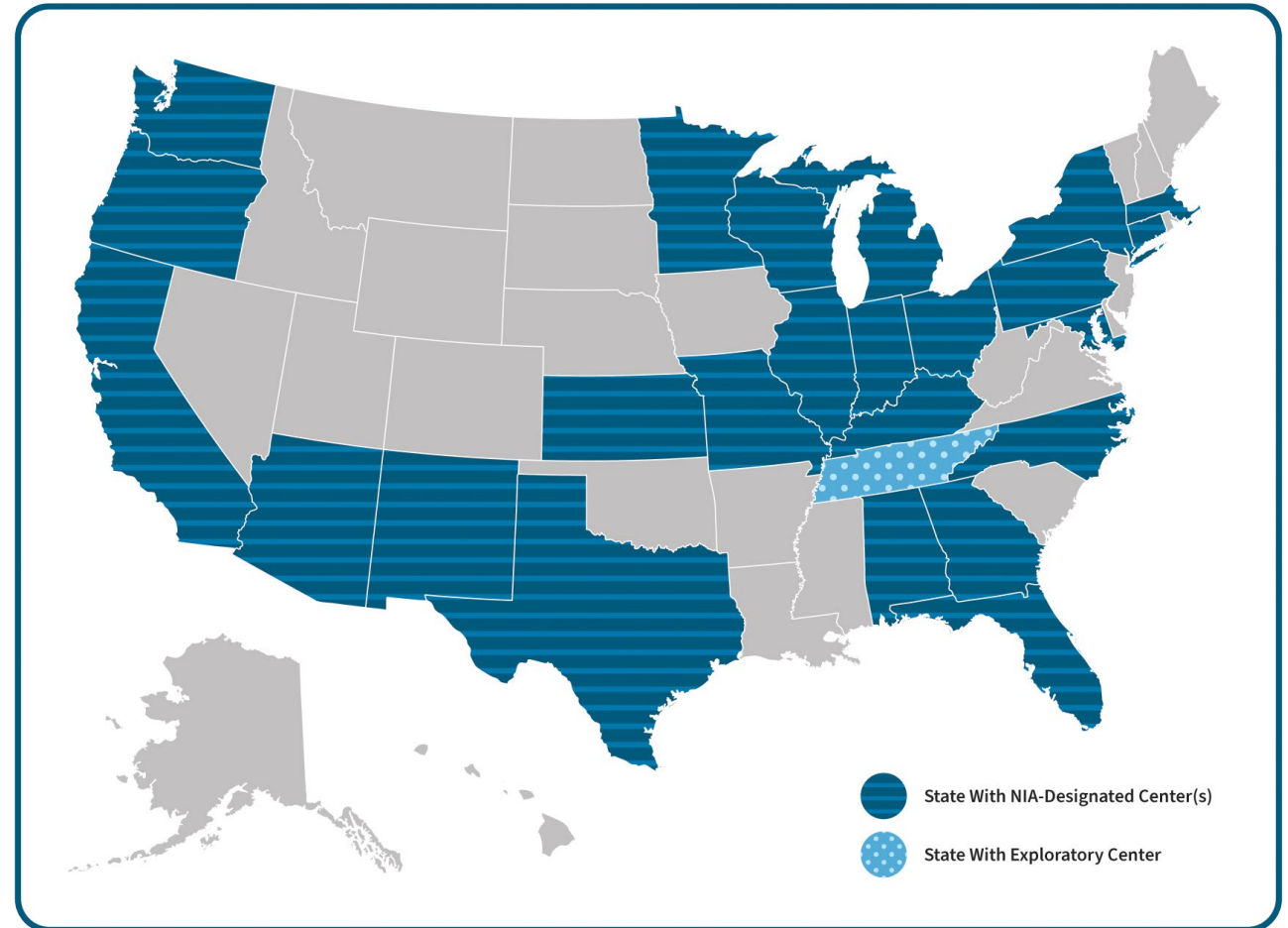
- Define **disease subtypes** & risk factors that may vary across populations
- Identify **genetically-driven therapeutic targets** that may vary across populations
- Inform genetically-driven clinical trials that target different genetic variants in different populations: **precision medicine**



The screenshot shows the ADSP website homepage. The header includes the ADSP logo and navigation links: Home, About, Funded Programs, Data, Research, FAQ, News. The main content area features a large heading: "Understanding the genetic architecture of Alzheimer's Disease and Related Dementias" with a button for "ADSP Data Summary". To the right, a "Latest Release:" section highlights "Release 4 WGS 36,361 genomes from 40 cohorts".

Alzheimer's Disease Research Centers Network

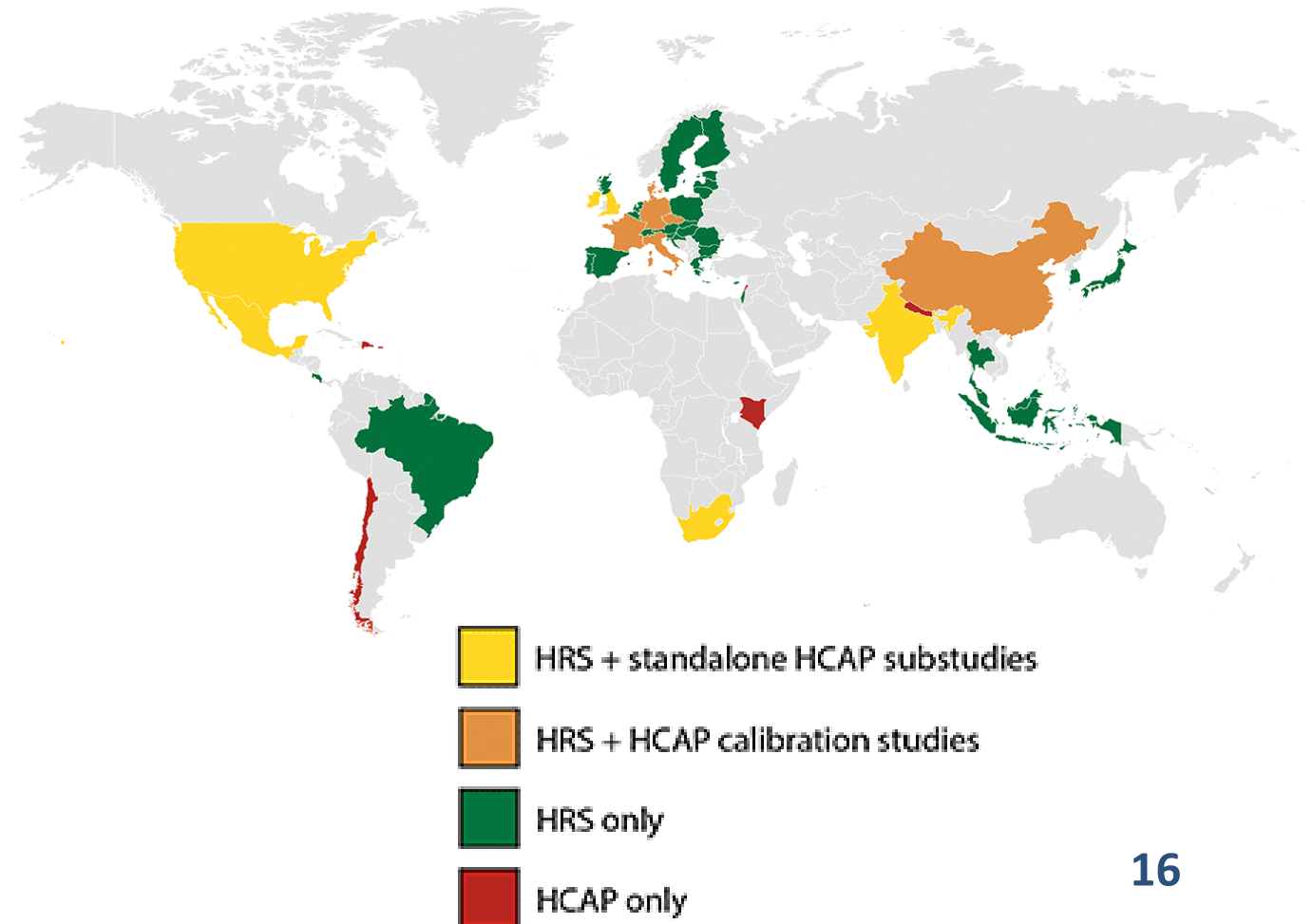
- 35 ADRCs + 1 exploratory center
- Conduct clinical, neuropathology, imaging, biomarkers, genetics, pathogenesis, and therapeutics research
- Perform state of the art Alzheimer's and related dementias diagnosis and provide related information to diverse participants and their families



The Health & Retirement Study (HRS)

- The nation's largest and most comprehensive **population-representative longitudinal study** of adults ages 50 and older.
- HRS maintains **linkages** with Social Security Administration earnings and benefit data, Medicare files, data from the National Death Index, and more.
- **Harmonized Cognitive Assessment Protocol (HCAP):** HRS substudy to measure and understand dementia risk within ongoing **longitudinal studies of aging around the world.**

Countries with HRS or HCAP studies



Gateway Exposome Coordinating Center for AD/ADRD Research

- In July 2024, NIA established the Gateway Exposome Coordinating Center for AD/ADRD Research to serve as a **centralized hub for accessing, harmonizing, linking, and sharing environmental contextual data and individual exposure data** relevant to dementia.
- The goal is **to foster collaboration and accelerate life course research** on the social, behavioral, economic, and environmental exposures that shape AD/ADRD outcomes and inequities.



**GATEWAY
EXPOSOME
COORDINATING
CENTER**



Climate



Physical
Environment



Social
Environment



Policy
Environment



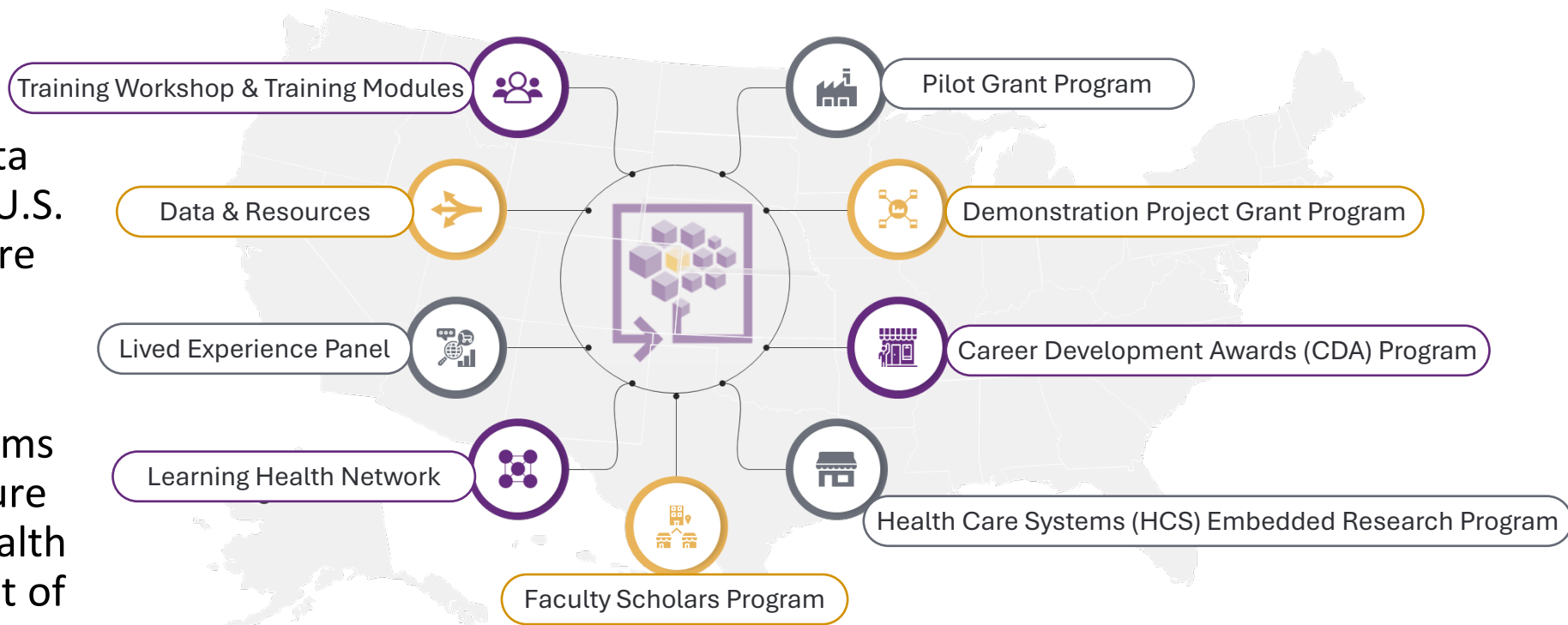
Community
Services
Environment



Life
Experiences

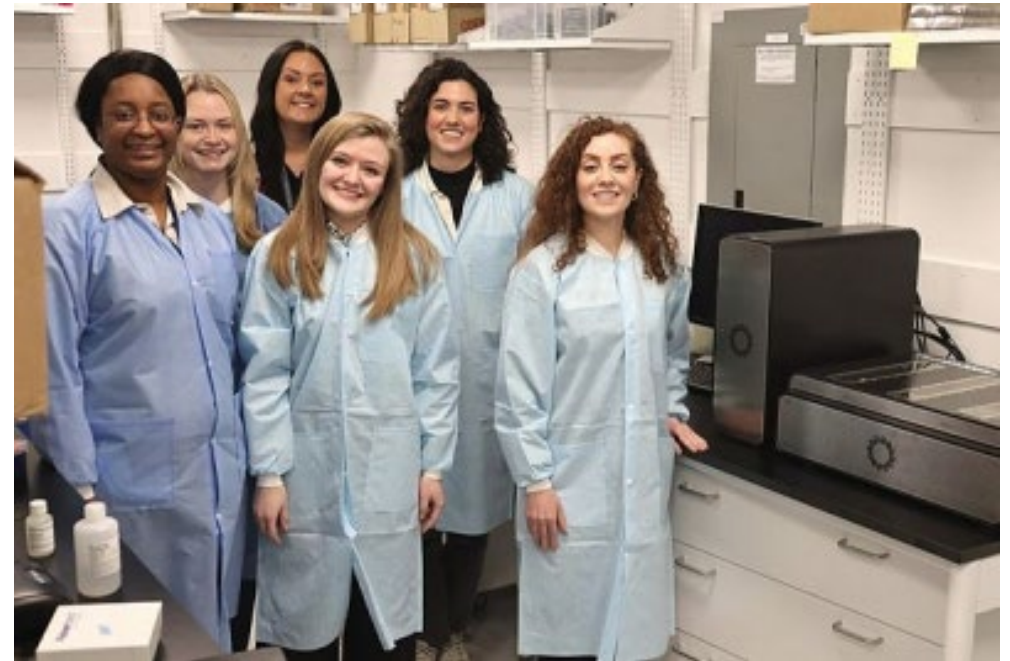
IMPACT Collaboratory: A National Resource

- The Collaboratory is a national resource for embedded pragmatic clinical trials to **improve the care and health outcomes of persons living with dementia** and their care partners.
- **The Long-Term Care Data Cooperative** is the largest integrated database of electronic health record data from nursing homes in the U.S. More than 2,000 facilities are enrolled, representing 500,000+ residents.
- Linkages with Medicare claims establish a data infrastructure to monitor future public health emergencies and the impact of treatment and policy changes.



NIH Center for Alzheimer's and Related Dementias (CARD)

- The NIH CARD facility works to accelerate dementia research and collaboration.
- In addition to **performing cutting-edge research**, CARD makes a broad range of resources available to the global research community:
 - **Creating a map of different brain cell types** based on gene activity.
 - **Establishing a stem cell (iPSC) repository**, with cells from both healthy individuals and those diagnosed with dementia.
 - **Developing advanced tools** for genetic sequencing and data analysis.



CARD experts on sequencing long sections of DNA associated with dementia.

Building construction progress



May 2021



July 2021



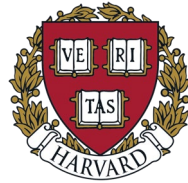
August 2021



September 2022

Collaboration and Cooperation

-  National Institute on Aging
-  National Institute of Neurological Disorders and Stroke
-  National Human Genome Research Institute
-  National Center for Advancing Translational Sciences
-  National Institute of Diabetes and Digestive and Kidney Diseases
-  NATIONAL CANCER INSTITUTE
-  National Heart, Lung, and Blood Institute
-  National Institute of Mental Health
-  National Institute on Deafness and Other Communication Disorders
-  National Institute of Environmental Health Sciences



NIH Research Progress

Drug Interventions to Slow Cognitive Decline and Treat Early-Stage Alzheimer's

- Increased federal investment in AD/ADRD research has contributed to the development of new treatments for early-stage Alzheimer's, including **those which harness anti-amyloid antibodies to target the underlying disease process of Alzheimer's**, instead of only treating symptoms of the disease:
 - **Lecanemab (Leqembi)**: Granted FDA full approval in July 2023
 - **Donanemab (Kisunla)**: Granted FDA full approval in July 2024
- Although NIH did not fund these specific trials, NIH supported basic science research that was integral to these developments:
 - Advanced understanding the role of amyloid in dementia
 - Led foundational efforts with immunotherapies
 - Enhanced brain imaging techniques, including PET
 - Developed more accurate cognitive assessment tools

Genetic Advancements in AD/ADRD

Advancing Understanding of AD/ADRD Genetics-

- In 2010, we knew of just 10 genes associated with Alzheimer's disease.
- Today, thanks in large part to the work of researchers supported by the NIH, we know of more than 80 genetic areas associated with Alzheimer's, leading to new approaches in developing potential dementia therapeutics.

10

80+

For example:

Lipid metabolism Inflammation Protein trafficking
Amyloid production/processing

2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024

Identification of Alzheimer's Protective Variants Suggests Novel Treatment Strategies

- Scientists are uncovering **rare gene variants that may help protect against AD.**
- An *APOE* variant (*APOE3ch*) and a variant of the *RELN* gene (*RELN-COLBOS*) were found to be protective against a variant that causes early onset AD (*PSEN1-E280A*). The individuals carrying these protective variants are members of a well-studied extended family from Colombia.
- Both individuals remained cognitively unimpaired more than 20 years later than expected.
- Understanding how these rare variants promote dementia resilience opens **new avenues for developing treatments.**

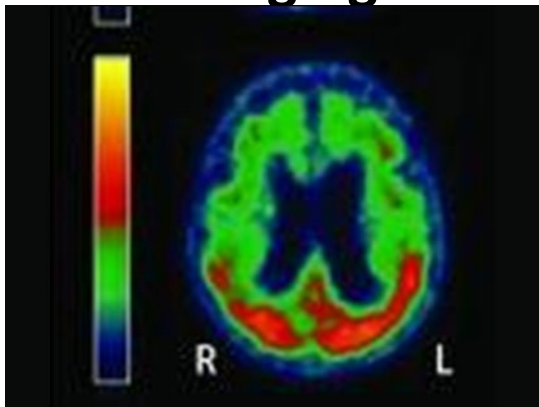


Photo courtesy of Dr. Yakeel Quiroz

Detecting & Diagnosing AD/ADRD at Earlier Stages

- Recent advances are enabling identification of AD/ADRD at early stages, when interventions are most likely to be effective. This requires reliable and accessible biomarkers and diagnostic tools.
- In addition to investing in ongoing research in this area, NIA is leading a challenge prize competition to **discover the best data, methods, and strategies** for the early prediction of Alzheimer's and related dementias.

Imaging



^{18}F -dopamine PET scanning

Blood biomarkers



PrecivityAD2

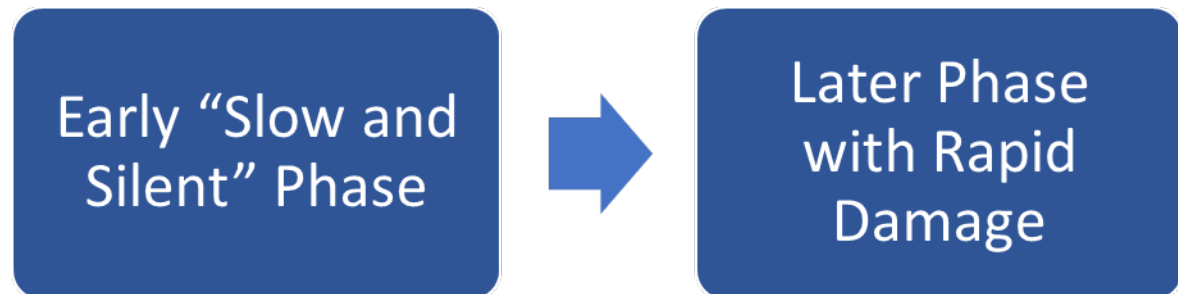
Data tools



eRADAR

A New Timeline of Alzheimer's Disease Progression

- Researchers analyzed brains from the [Seattle Alzheimer's Disease Brain Cell Atlas](#) (SEA-AD) program, which aims to create a highly detailed **map of the brain damage that occurs during Alzheimer's**.
- Findings from SEA-AD indicate that **Alzheimer's may damage the brain in two distinct phases**, a slow a silent phases and a later rapid phase.
- This **enhanced understanding** of the disease can help researchers develop **new therapeutic approaches** to prevent and treat Alzheimer's.
- SEA-AD has made these findings and other important resources openly available to the scientific community.
 - Size of amyloid plaques increase but low detected number
 - Rapid increase in number of amyloid plaques and tau tangles
 - Symptoms of cognitive decline appear



Hearing Aids May Slow Cognitive Decline in Older Adults With Hearing Loss

- The Aging and Cognitive Health Evaluation in Elders (ACHIEVE) Study found that a **hearing intervention may reduce cognitive change over 3 years in older adults who are at increased risk for cognitive decline** (e.g., older age, lower cognitive scores, worse cardiovascular health) but had no detectable effect in those at lower risk for cognitive decline.
- Findings suggest that **older adults at increased risk for cognitive decline who also have hearing loss may benefit the most from hearing interventions.**
- Longer follow-up of the low risk, healthier cohort will be needed to determine whether hearing treatment might reduce the risk of developing dementia in the long term.



22 Drug Candidates Supported by the NIA Have Advanced to Clinical Development

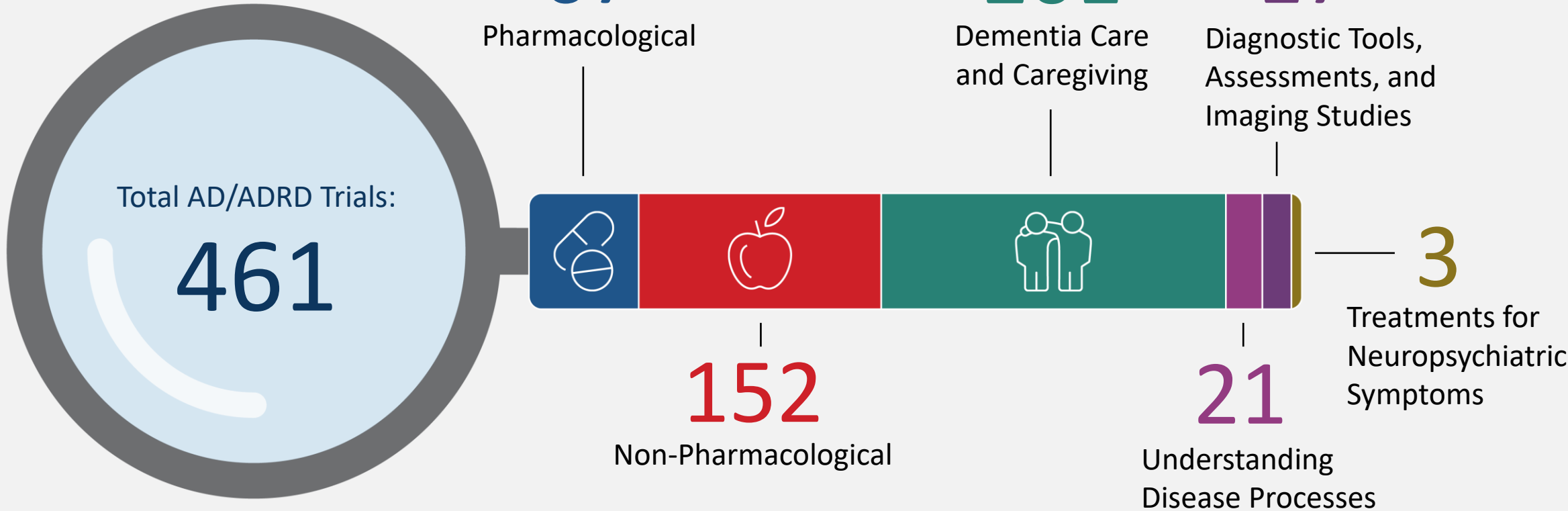
NIA has supported/is supporting the **clinical development of several drug candidates**, including:

- 7 small molecule drug candidates are now in Phase 1/Phase 2 or Phase 2 Clinical Trials
- 15 drug candidates now in Phase 1 Clinical Trials
 - 9 small molecule therapy
 - 6 biologic therapy (DNA-based or recombinant protein vaccine, gene therapy, monoclonal antibody, or peptide)

Candidates are **targeting diverse mechanisms/processes**:

- Amyloid beta
- ApoE, lipids, and lipoprotein receptors
- Inflammation
- Metabolism/Bioenergetics
- Neurogenesis
- Neuroprotective/resilience factors
- Tau
- Vasculature
- Multi-target

Total Active NIA AD/ADRD Clinical Trials



Active NIA AD/ADRD Clinical Trials, part 1



Pharmacological

67
TRIALS

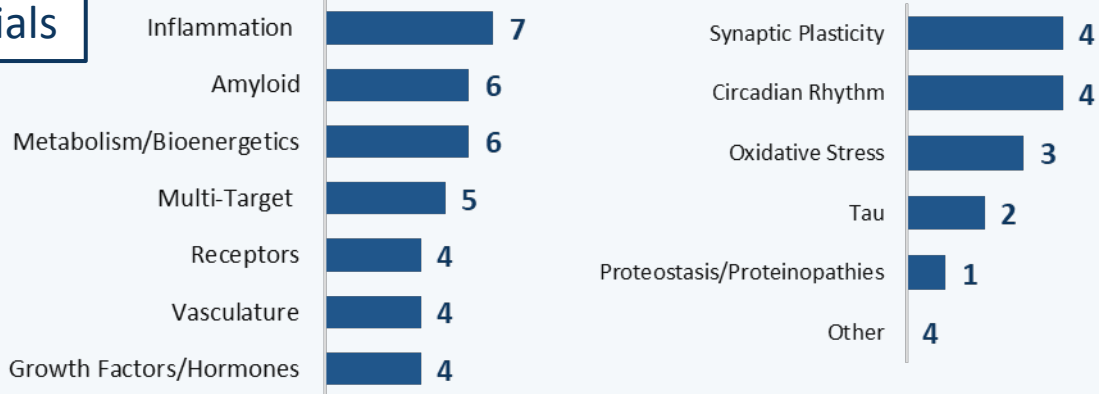


Non-Pharmacological

152
TRIALS

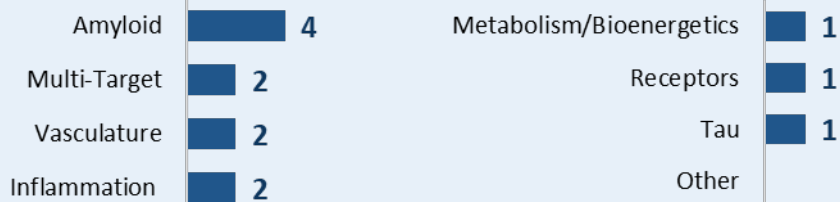
54
trials

Phase I & Phase II Targeted Disease Process



13
trials

Phase II/III, III, and IV Targeted Disease Process



Modality



For more information please visit
www.nia.nih.gov/research/ongoing-AD-trials



Data last updated: June 2024

Active NIA AD/ADRD Clinical Trials, part 2

Dementia Care and Caregiving

201
TRIALS

Understanding Disease
Processes

21
TRIALS

Type



Diagnostic Tools, Assessments,
& Imaging Studies

17
TRIALS

Treatments for
Neuropsychiatric Symptoms

3
TRIALS

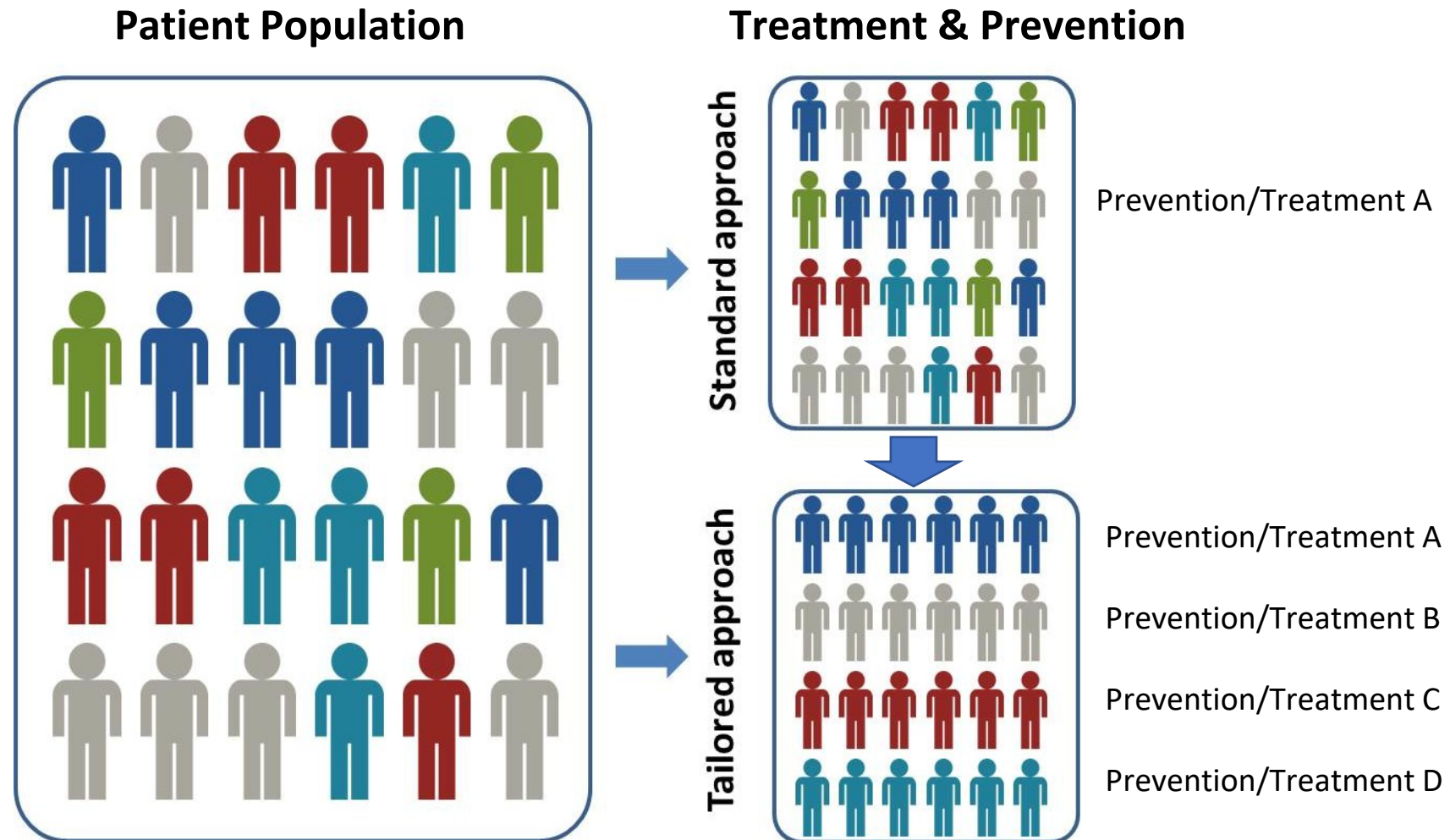
Total Number of Trials

461

For more information, please visit
www.nia.nih.gov/research/ongoing-AD-trials



Aiming to Develop a Precision Treatment & Prevention Approach



Summary of Recent Progress in AD, part 1

	2016	2024
Diagnostics	<ul style="list-style-type: none">• Amyloid PET agents	<ul style="list-style-type: none">• Amyloid PET agents• Tau PET agents• Blood biomarkers for amyloid and tau (e.g., PrecivityAD2)• Data-based tools (e.g., eRADAR)• Electronic/digital assessments
Symptom Management	<ul style="list-style-type: none">• Cholinesterase inhibitors (e.g., donepezil)• Glutamate regulators (e.g., memantine)	<p>Pharmacological options:</p> <ul style="list-style-type: none">• Brexpiprazole for agitation related to AD (approved 2023)• Cholinesterase inhibitors (e.g., donepezil)• Glutamate regulators (e.g., memantine) <p>Non-drug options:</p> <ul style="list-style-type: none">• Interventions for care and caregivers

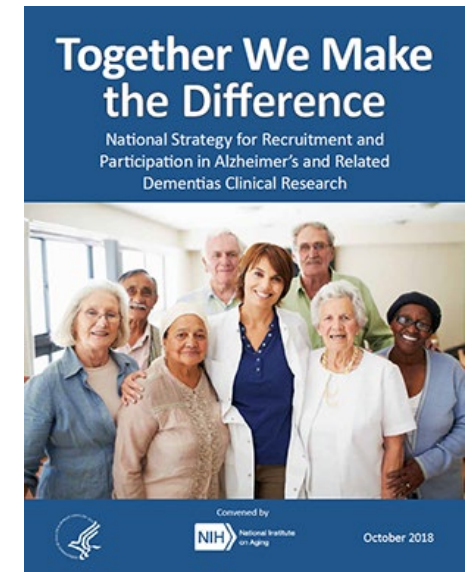
Summary of Recent Progress in AD, part 2

	2016	2024
Disease-modifying therapies	None	<ul style="list-style-type: none"> • Lecanemab (FDA traditional approval in 2023) • Donanemab (FDA traditional approval in 2024) • Several additional therapies in the pipeline, with more diverse targets than ever before
Risk reduction	None	<ul style="list-style-type: none"> • Intensive blood pressure control • Hearing interventions • Personalized lifestyle interventions • Multivitamin use
Dementia care & caregiving	Foundational work to develop and test specific care models for efficacy & effectiveness	<ul style="list-style-type: none"> • Two intervention types for care and/or caregiver support identified as ready for broader implementation with continued evaluation • Multiple lines of study on adaptations and broader implementation of promising models

Resources and Opportunities

NIA Resources for Recruitment of Diverse Participants in Clinical Trials

- **National Strategy for Recruitment and Participation in Alzheimer's and Related Dementias Clinical Research:** Focuses on the pressing need for increased participation in research studies, with a specific emphasis on inclusion of individuals from diverse backgrounds.
- **Alzheimer's and Dementia Outreach, Recruitment, and Engagement (ADORE):** Online, searchable database of resources for engagement, recruitment, and retention of study participants into clinical trials and studies on AD/ADRD.
- **OutreachPro:** Recently launched tool to enable health care professionals to more easily produce and brand tailored clinical trial recruitment materials and strategies.
- **NIA's Clinical Research Operations & Management System (CROMS):** New system that provides NIA staff and grantees access to real-time clinical research enrollment and inclusion data.



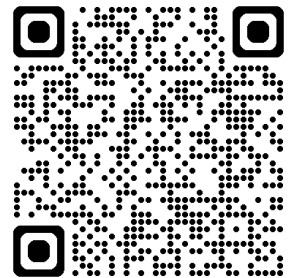
OUTREACHPRO

National Institute on Aging
Clinical Research Operations & Management System (CROMS)

NIH Alzheimer's Disease-Related Dementias Summit 2025



- **SAVE THE DATE: March 25-26, 2025**
- The ADRD Summit 2025 will address research priorities for **Alzheimer's disease-related dementias**, including frontotemporal degeneration, Lewy body, multiple etiology dementias, and vascular contributions to cognitive impairment and dementia, along with broader cross-cutting areas, including health equity.
- <https://www.ninds.nih.gov/news-events/events/adrd-summit-2025>



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