National Institutes of Health

Brief Remarks from NIH Leadership

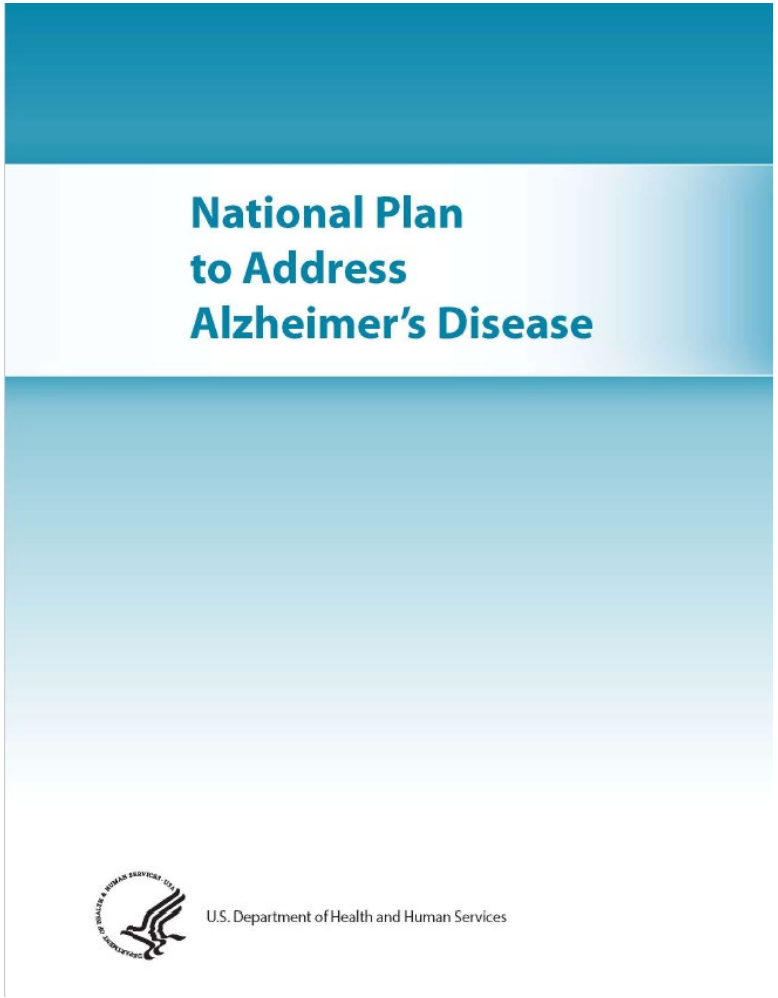
Dr. Richard Hodes &
Dr. Walter Koroshetz

National Institutes of Health

Presentation of the Charge to the Committee

Dr. Melinda Kelley

National Plan to Address Alzheimer's Disease



- Originally released in May 2012
- Updated annually, last in 2022
- Led by HHS ASPE, but NIH and other agencies contribute
- Five goals formed the foundation of the original plan:
  - ❑ *Prevent and Effectively Treat Alzheimer's Disease by 2025*
  - ❑ *Optimize Care Quality and Efficiency*
  - ❑ *Expand Supports for People with Alzheimer's Disease and Their Families*
  - ❑ *Enhance Public Awareness and Engagement*
  - ❑ *Track Progress and Drive Improvement*
- One additional goal has been recently added:
  - ❑ *Accelerate Action to Promote Healthy Aging and Reduce Risk Factors for Alzheimer's Disease and Related Dementias*

Breadth of AD/ADRD Research

- The National Plan to Address Alzheimer's Disease, originally released in 2012, calls for **action to accelerate research and improve care and services** for people living with dementia and their families
- **NIH leads research efforts** associated with the National Plan, including the first goal targeted at preventing and treating AD/ADRD
- These efforts **span basic, translational, and clinical** research in AD/ADRD

NIA AD/ADRD Appropriations

2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
National Alzheimer's Project Act (NAPA)	**$50 M*** redirected within NIH budget	**$40 M*** redirected within NIH budget	**$100 M** additional approp.	**$25 M** additional approp.	**$350 M** additional approp.	**$400 M** additional approp.	**$414 M** additional approp.	**$425 M** additional approp.	**$350 M** additional approp.

2021	2022	2023
$300 M additional approp.	**$289 M** additional approp.	**$151 M**** additional approp.

*One-year money; years displayed are fiscal years.

**This figure does not include an additional $75M in AD/ADRD funds to NINDS, giving an overall increase in AD/ADRD funds of $226M in FY 2023.

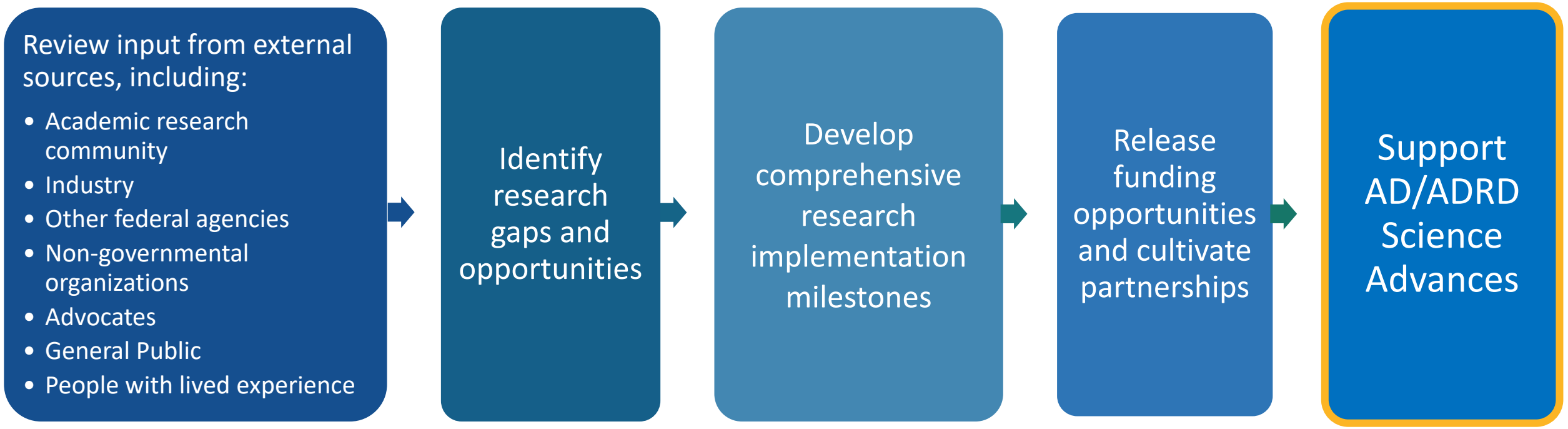
AD/ADRD Spending at NIH

Research/Disease Areas	FY 2015	FY 2016	FY 2017	FY 2018	FY 2019	FY 2020	FY 2021	FY 2022	Difference – FY 2015 to FY 2022
AD/ADRD[1]	$631	$986	$1,423	$1,911	$2,398	$2,869	$3,251	$3,514	5.6-fold increase
Alzheimer's Disease (AD)	$589	$929	$1,361	$1,789	$2,240	$2,683	$3,059	$3,314	5.6-fold increase
Alzheimer's Disease Related Dementias (ADRD)[2,3]	$120	$175	$249	$387	$515	$600	$725	$730	6.1-fold increase
Lewy Body Dementia	$15	$22	$31	$38	$66	$84	$113	$118	7.9-fold increase
Frontotemporal Dementia	$36	$65	$91	$94	$158	$166	$164	$169	4.7-fold increase
Vascular Cognitive Impairment/Dementia	$72	$89	$130	$259	$299	$362	$455	$445	6.2-fold increase

[1] The category Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD) reflects the sum of the two existing RCDC categories: Alzheimer's Disease (AD) and the above Alzheimer's Disease Related Dementias (ADRD) – where duplicates are removed.
[2] The category ADRD reflects the sum of three existing RCDC categories: Frontotemporal Dementia, Lewy Body Dementia, and Vascular Cognitive Impairment/Dementia—where duplicates are removed.
[3] These categories were established pursuant to Section 230, Division G of the Consolidated and Further Continuing Appropriations Act of 2015 as related to reporting of NIH initiatives supporting the National Alzheimer's Project Act (NAPA), https://aspe.hhs.gov/national-alzheimers-project-act.

https://report.nih.gov/categorical_spending.aspx

AD/ADRD Research Strategy Builds from External and Internal Input



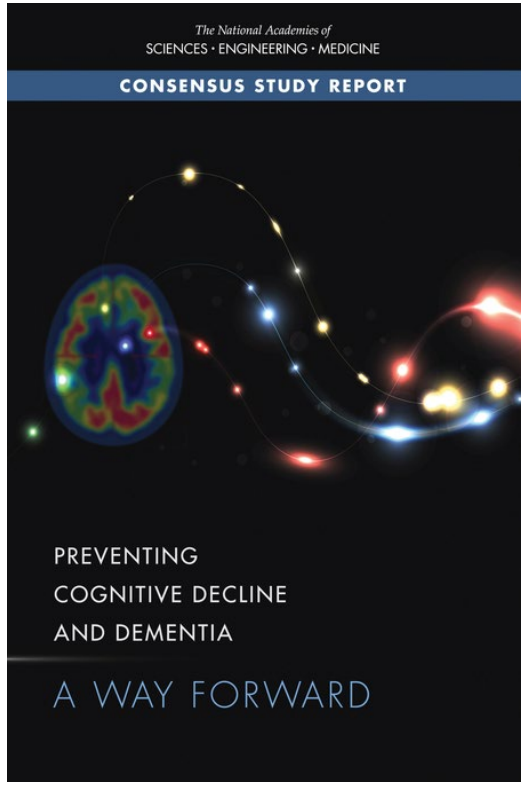
AD/ADRD Research Summits

- The NIH hosts three triannual strategic planning research summits:
  - Alzheimer's Disease Research Summit: Path to Treatment & Prevention (2012, 2015, 2018, 2021, 2024)
  - Alzheimer's Disease-Related Dementias (ADRD) Summit (2013, 2016, 2019, 2022)
  - National Research Summit on Care, Services, and Supports for Persons with Dementia and their Caregivers (2017, 2020, 2023)

- The overarching aim of these summits is to gather scientific input to formulate a blueprint for an integrated, translational research agenda.

- Although this is a major way NIH receives input from external audiences, it is not the only avenue. NIH also hosts planning activities with NASEM and other expert meetings/workshops.

Vital Input: AHRQ/NASEM Study on Preventing Cognitive Decline



Preventing Cognitive Decline and Dementia: A Way Forward (NASEM: 2017)

Encouraging but inconclusive evidence suggest further research in following areas:

- Cognitive training
- Blood pressure management in hypertensives
- Increased physical activity

Other recommendations:

- Tailor interventions to individuals at highest risk of decline and dementia
- Begin more interventions at younger ages and have longer follow-up
- Use consistent cognitive outcome measures across trials
- Include biomarkers as intermediate outcomes
- Increase participation of under-represented populations to study intervention effectiveness in these populations
- Conduct large trials designed to test the effectiveness of an intervention in broad routine clinical practices or community settings

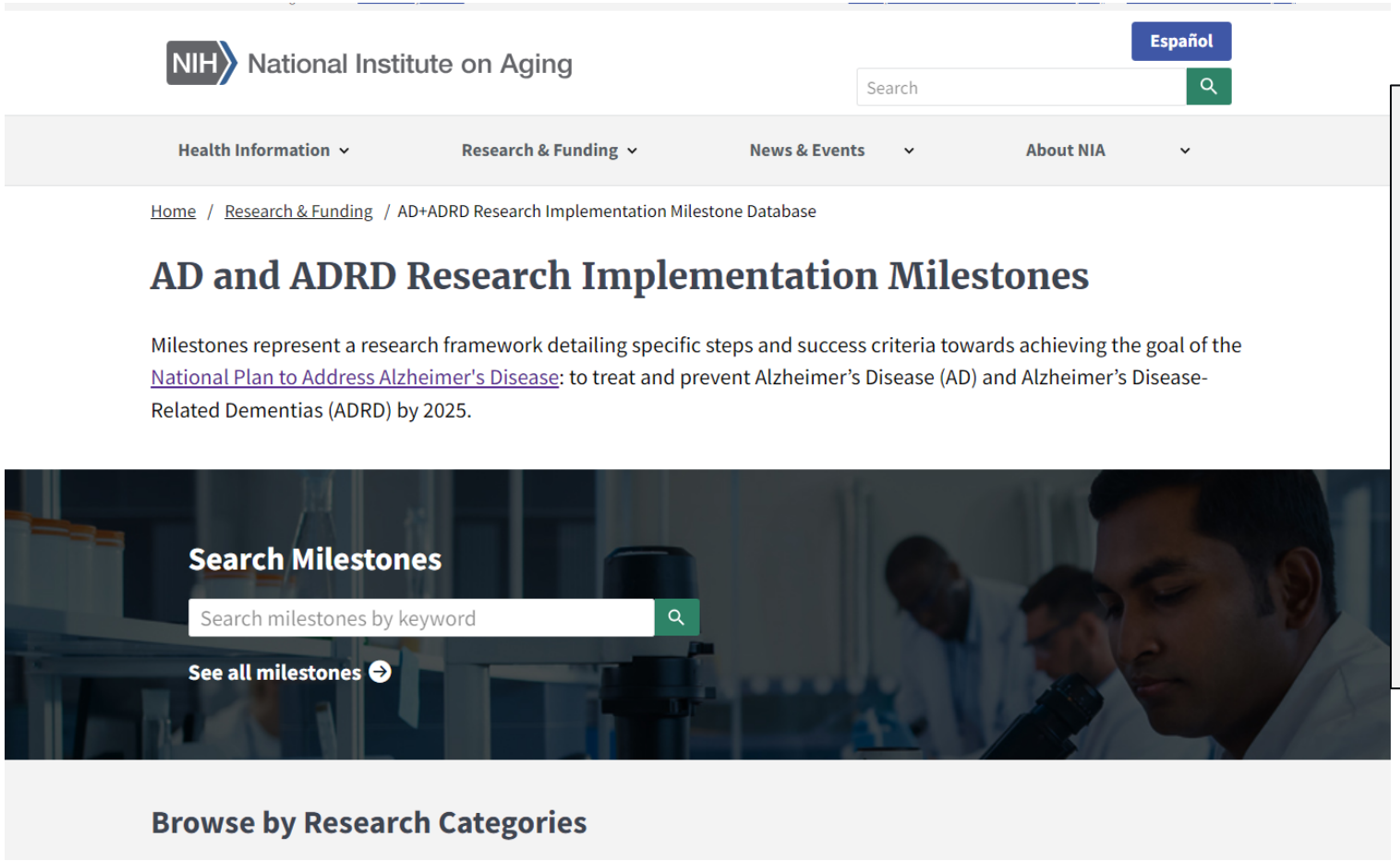
AD/ADRD Research Implementation Milestones

- NIH research implementation milestones are generated with input from hundreds of members of a **multistakeholder 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 NIH Funding Opportunities.**
  - NOTE: This framework represents all NIH-funded AD/ADRD research and extends beyond research areas immediately applicable to this committee's task.

Research Implementation Milestones
https://www.nia.nih.gov/research/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

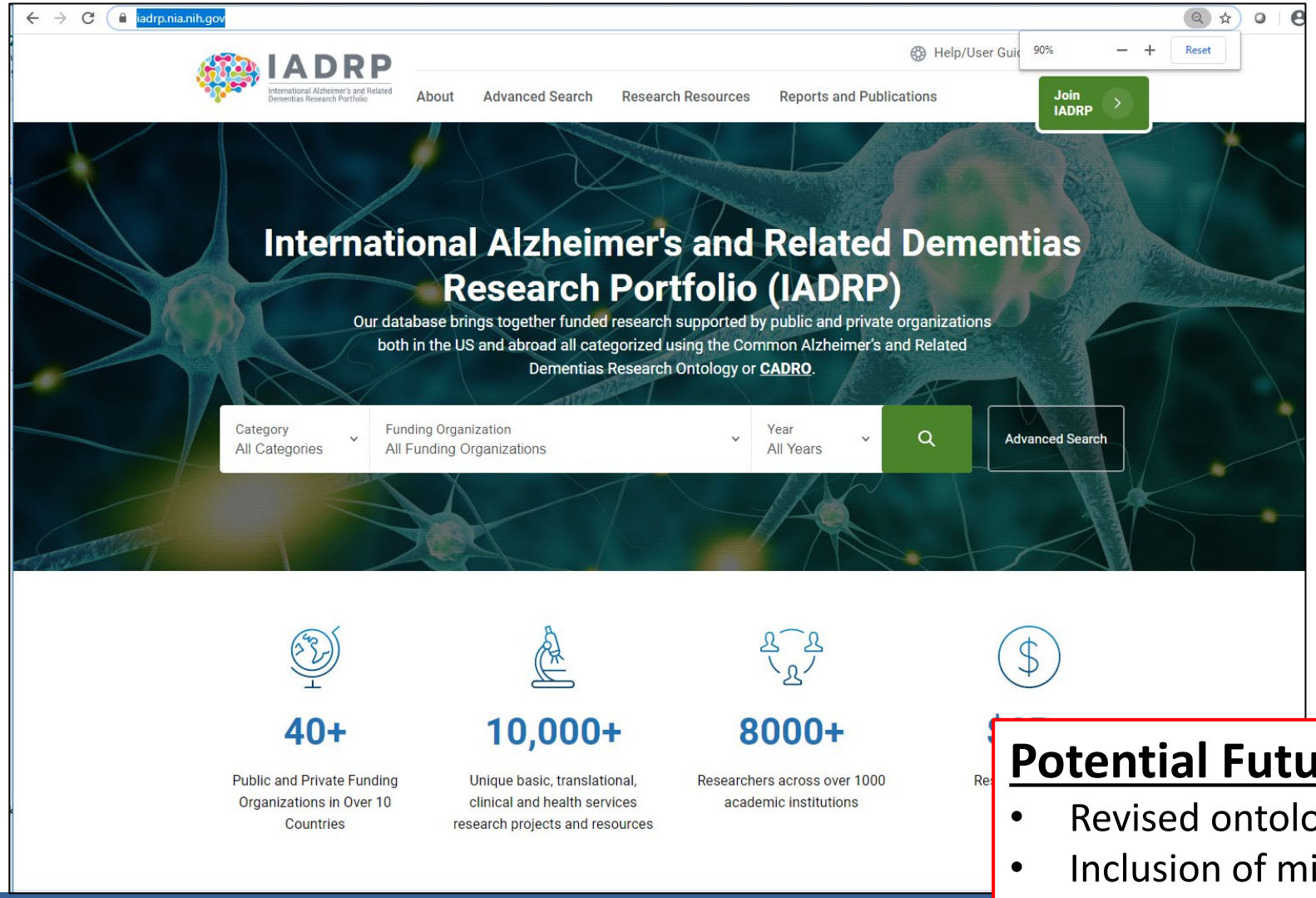
NIH AD/ADRD Milestone Database



Enables users to review the goals of individual milestones and to track progress towards meeting the success criteria for each milestone

https://www.nia.nih.gov/research/milestones

Tracking AD/ADRD Research Across Funding Organizations: International Alzheimer's Disease Research Portfolio (IADRP)



Potential Future Updates

- Revised ontology (CADRO categories)
- Inclusion of milestone coding

FY23 Congressional Report Language

- An ad hoc committee of NASEM will **conduct a study and recommend research priorities** to advance the prevention and treatment of AD/ADRD.

- In conducting its study, the committee will:
  1) Examine and assess the current state of **biomedical research aimed at preventing and effectively treating AD/ADRD**, along the R&D pipeline from **basic to translational to clinical research**;
  2) Assess the **evidence on nonpharmacological interventions** aimed at preventing and treating AD/ADRD;
  3) Identify **key barriers to advancing AD/ADRD prevention and treatment** (e.g., infrastructure challenges that impede large scale precision medicine approaches, inadequate biomarkers for assessing response to treatment, lack of diversity in biobanks and clinical trials), and **opportunities to address these key barriers** and catalyze advances across the field;
  4) Explore the **most promising areas of research** into preventing and treating AD/ADRD.

FY23 Congressional Report Language

- The committee's study will include dementia caused by **Alzheimer's disease as well as related conditions such as frontotemporal disorders, Lewy body dementia, vascular dementias, and multiple etiology dementias**.
  - Dementias with a clear etiology (e.g., incident stroke, AIDS, traumatic brain injury) will be excluded from the analysis.

- Based on its review of the literature, consultations, and other expert input, the committee will develop a report with its findings, conclusions, and specific recommendations on research priorities for preventing and treating AD/ADRD, including **identifying specific near and medium-term scientific questions (i.e., in a 3 to 10 year period) that may be addressed through NIH funding**. The report will also include strategies for addressing major barriers to progress on these scientific questions.

Scope of "Prevention" and Treatment" Research Terms

- At the NIH, **prevention research** targets biology, individual behavior, factors in the social and physical environments, and health services, and informs and evaluates health-related policies and regulations. This research encompasses both primary and secondary prevention.
  - Primary prevention includes research designed to promote health; identify risk factors for developing a new health condition (e.g., disease, disorder, injury); and prevent the onset of a new health condition.
  - Secondary prevention includes research designed to identify risk factors for the progression or recurrence of a health condition and detecting and preventing progression of an asymptomatic or early-stage condition.

- For this task, **treatment research** is focused on pharmacological or non-pharmacological treatment, including treatment of cognitive decline, and not on treatment coordination or on co-morbidities, which are major foci of dementia care research.
  - Research to treat neuropsychiatric symptoms of AD/ADRD is **not** within scope of this committee's charge.

Potential NIH Considerations for the Consensus Study

- Importance of health equity in AD/ADRD research
- Benefits of precision medicine approaches to prevention and treatment
- Recognition that a clinical diagnosis of dementia typically represents more than one disease pathology, and multiple AD/ADRD disease processes may be active in the brain of a given individual
- Overall paradigm shift of the field towards an understanding that there are multiple potential causal pathways to dementia, including cellular and molecular mechanisms as well as lifestyle, genetic, environmental, and psychosocial factors
- Requirements of trial design, for pharmacological and non-pharmacological interventions

In the Session II Presentation…

- In Session II, NIH program staff will share an overview of significant advances in the AD/ADRD prevention/treatment space.
- The Session II presentation will highlight ongoing work as well future directions, to aid the committee in evaluating progress to date.
- NIH is also eager to hear the committee's input on ways to strengthen our existing programs and investments and which new directions might hold most promise for the future.

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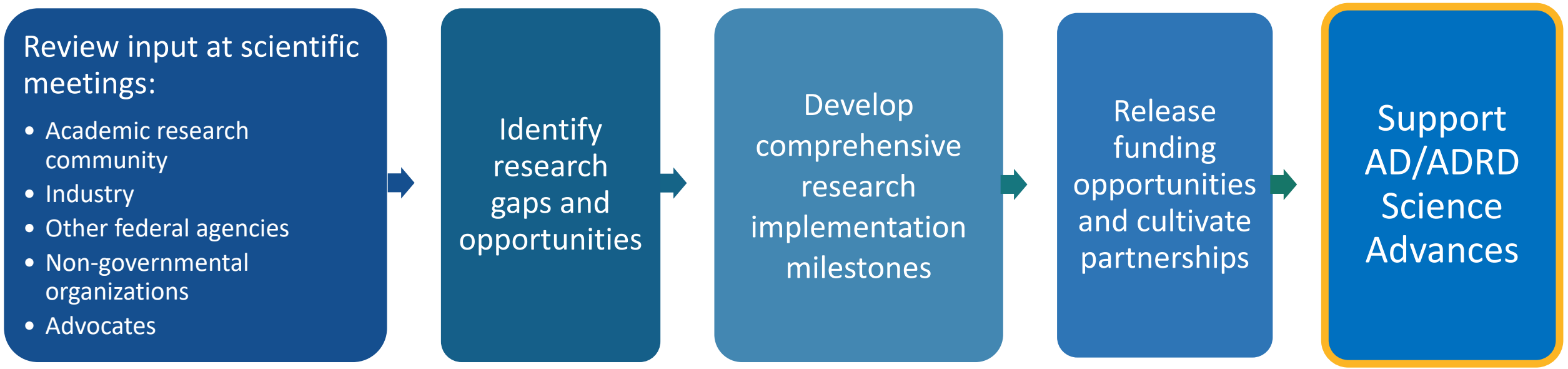
Overview of NIH AD/ADRD Strategic Planning Activities, Research Programs, and Outcomes

Dr. Eliezer Masliah, Dr. Suzana Petanceska, Dr. Sara Dodson, and Dr. Lis Nielsen

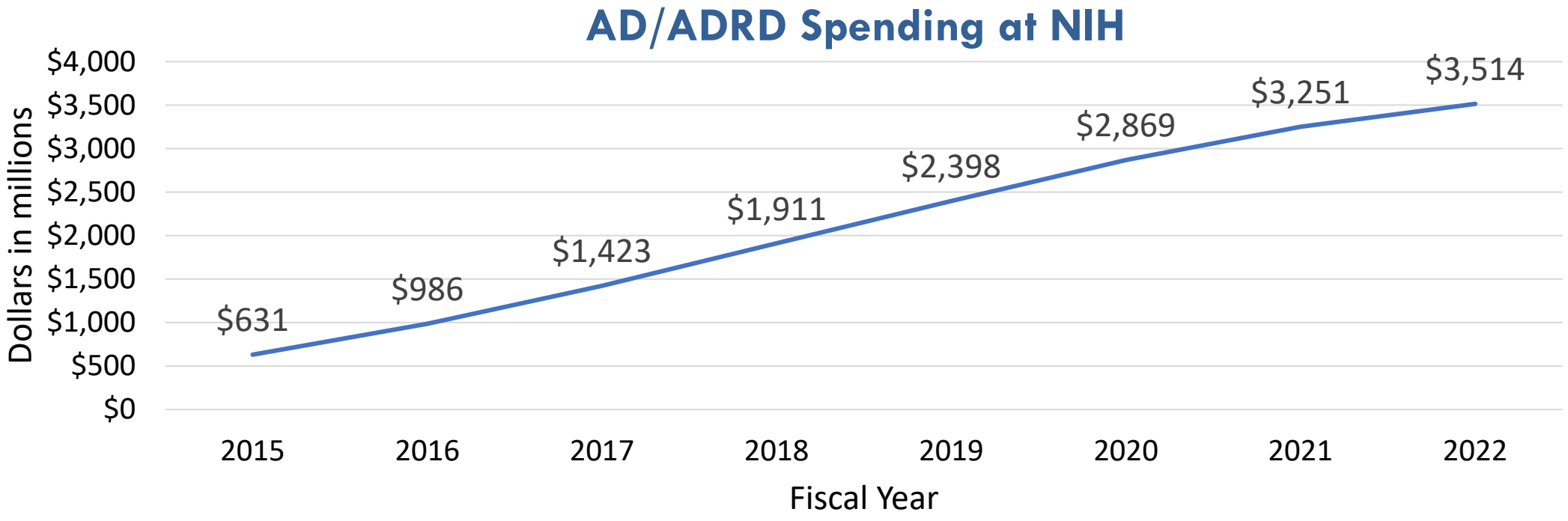
AD/ADRD Research Strategy Builds from External and Internal Input



Growth in Funding Leads to AD/ADRD Advances

- Over the past 10 years, NIH significantly expanded 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.

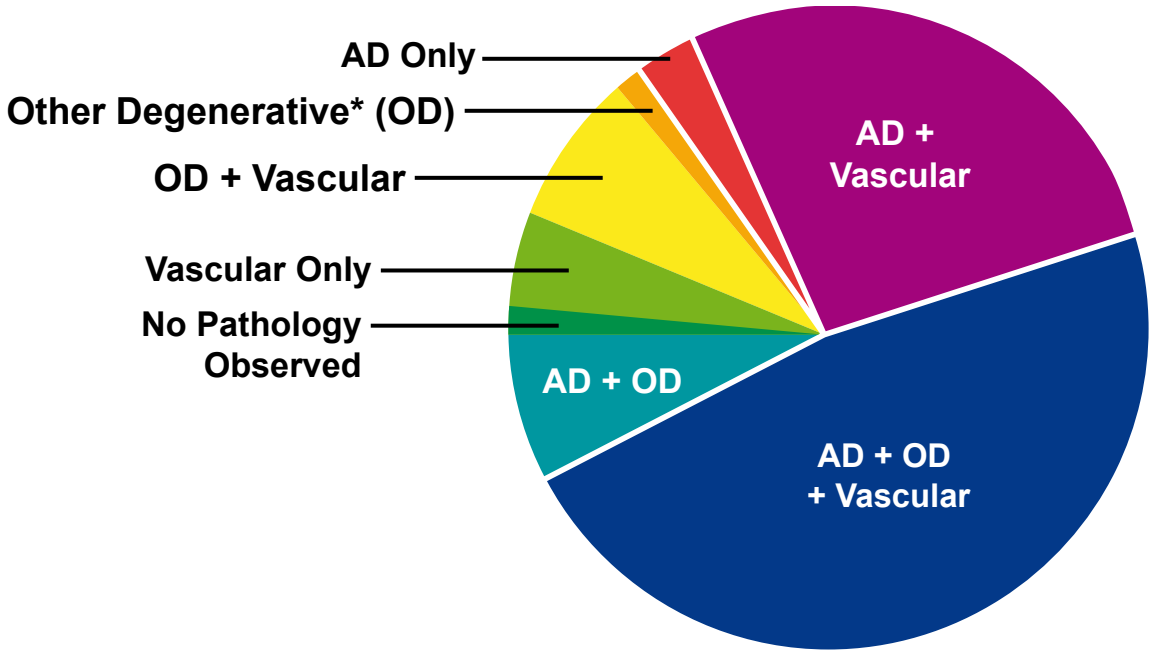


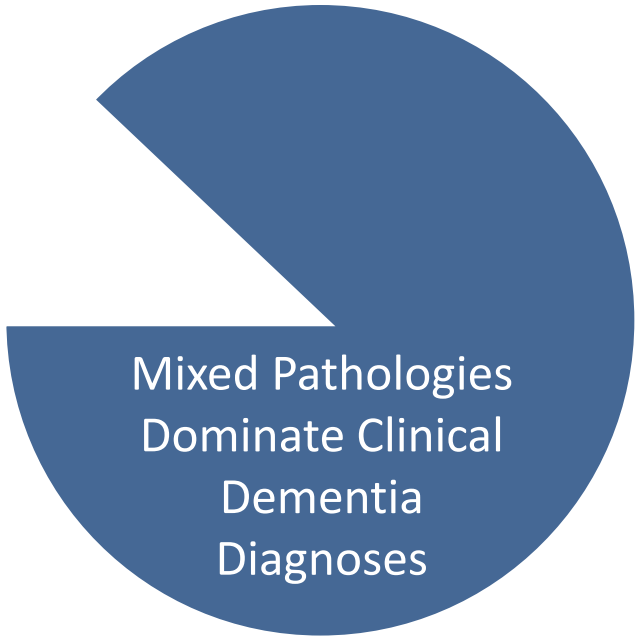
5.6-fold increase from 2015-2022

Traditional Perception of 1:1 Relationship Between Brain Pathologies and Clinical Dementia Diagnoses is the Exception, Not the Rule

CLINICAL DIAGNOSIS: PROBABLE ALZHEIMER'S DEMENTIA

PATHOLOGICAL DIAGNOSES:





THIS MATTERS FOR DEVELOPMENT OF PRECISION APPROACHES & BIOMARKERS

Increased recognition that more than one disease process is typically present in a person's brain should help move toward effective prevention and treatments.

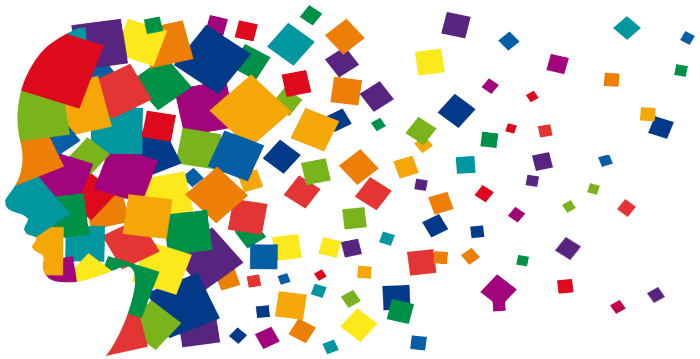
Adapted from KAPASI A, ET AL. ACTA NEUROPATHOL. 2017 AUG;134(2):171-186. ROS/MAP (N = 447)

*Other Degenerative (OD) included neurodegenerative disease pathologies: Lewy bodies, TDP-43, hippocampal sclerosis

Paradigm Shift: Multiple Potential Pathways to Dementia

COGNITIVE IMPAIRMENT and DEMENTIA DIAGNOSES

- **Alzheimer's Dementia**
- **Lewy Body Dementias**
- **Vascular Dementias**
- **Frontotemporal Dementias**
- **Limbic Predominant TDP**
- **Multiple Etiology Dementias**
- **Other Cognitive Impairment**
- **Other Dementias**



LIFESTYLE FACTORS
- Physical Activity
- Diet
- Drug/Alcohol Abuse
- Social Engagement
- Cognitive Stimulation

ENVIRONMENTAL FACTORS
- Education
- Head Trauma
- Toxins/Other

PSYCHOSOCIAL FACTORS
- Depression/Anxiety

OTHER MEDICAL RISKS
- Metabolic / Obesity / Diabetes
- Hypertension / Heart Disease / Stroke
- Inflammation
- Certain Infectious Diseases
- Certain Medications
- Unmanaged hearing loss

HEALTH DISPARITIES FACTORS

AGING

GENETIC

FACTORS

SEX F>M

MISFOLDED PROTEINS
- Beta-Amyloid
- Tau
- Alpha Synuclein
- TDP-43
- TMEM 106B

VASCULAR DISORDERS
- Injury, Infarct (Stroke)
- White Matter Disease
- Other Vessel Disease

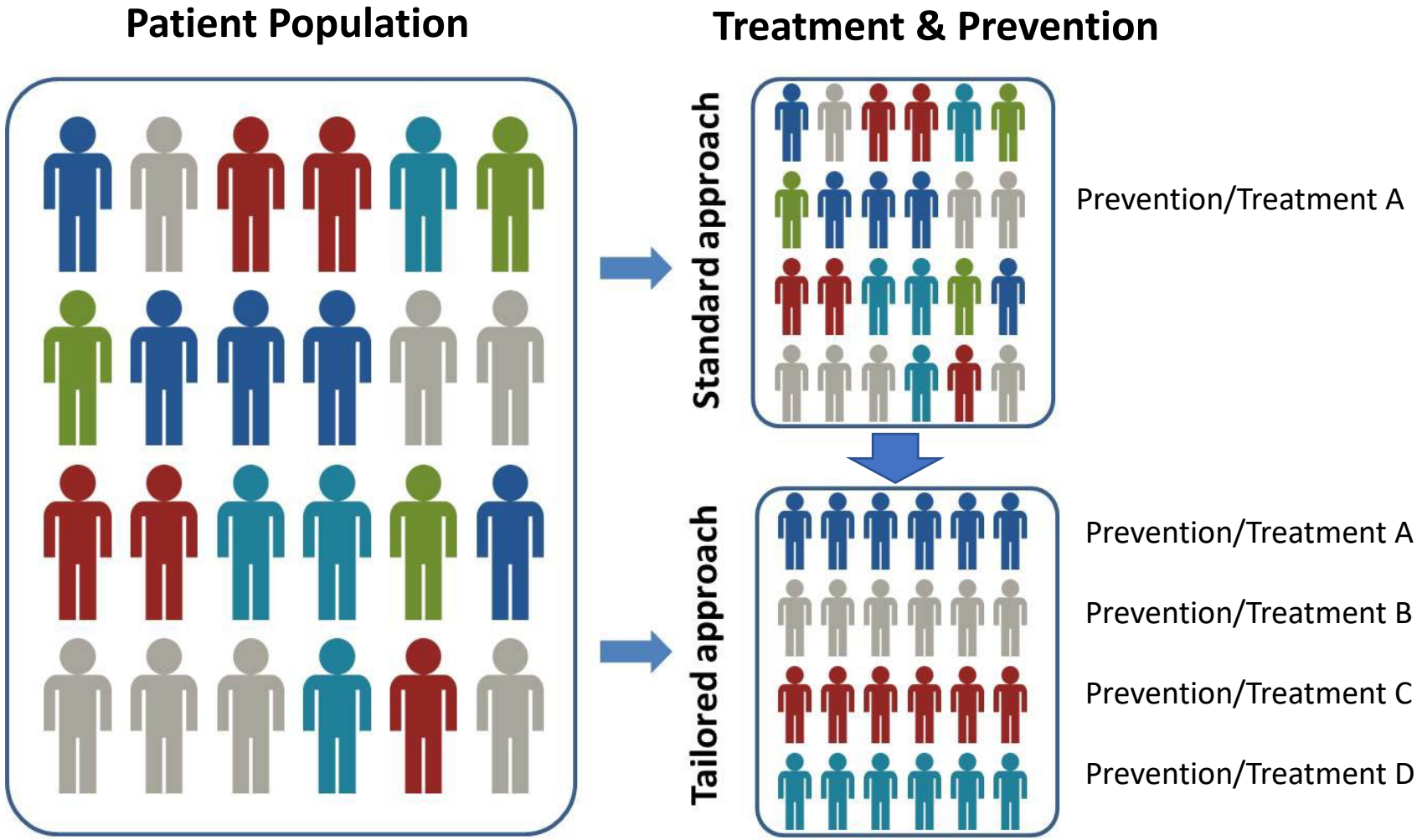
OTHER DISORDERS

Aiming to Develop a Precision Treatment & Prevention Approach

Multiple factors influence disease progression and leads to disease complexity

Multiple Etiologies
Multiple Prodromal Phenotypes
Multiple Progression Trajectories

For a specific individual,
RIGHT TARGET
RIGHT DRUG/INTERVENTION
RIGHT DOSE
RIGHT STAGE OF DISEASE



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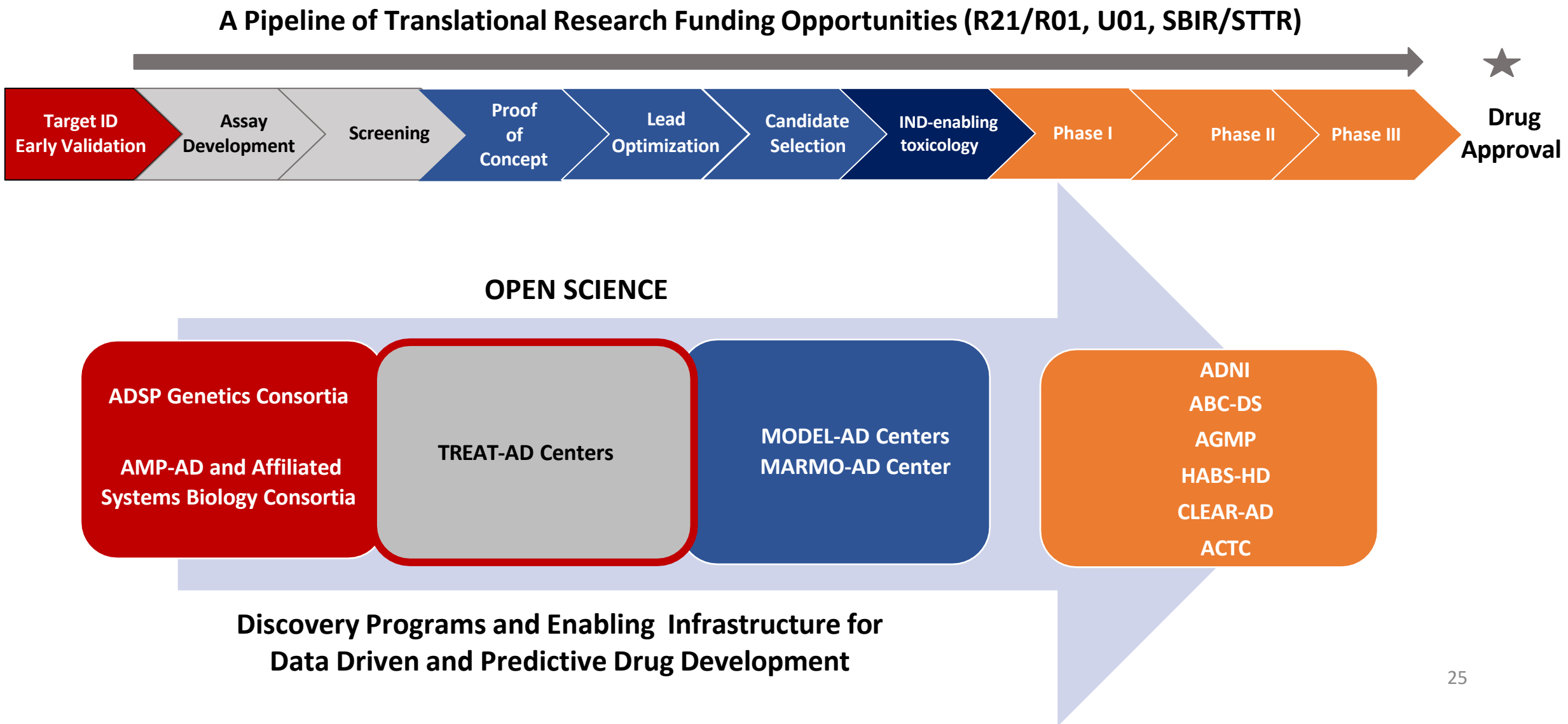
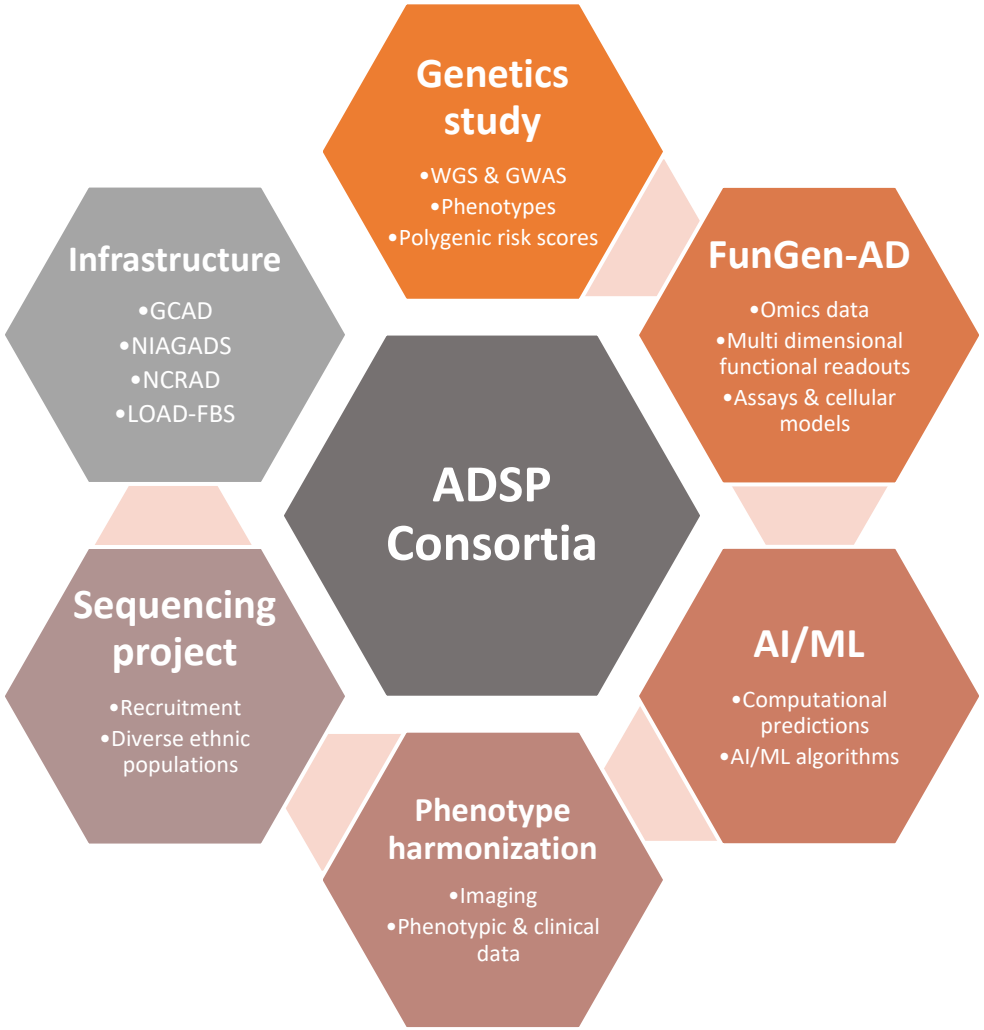
Accelerating Development of Treatment & Prevention for AD/ADRD

NIA AD/ADRD Translational Research Program

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



Resolving the Complex Genetics of AD

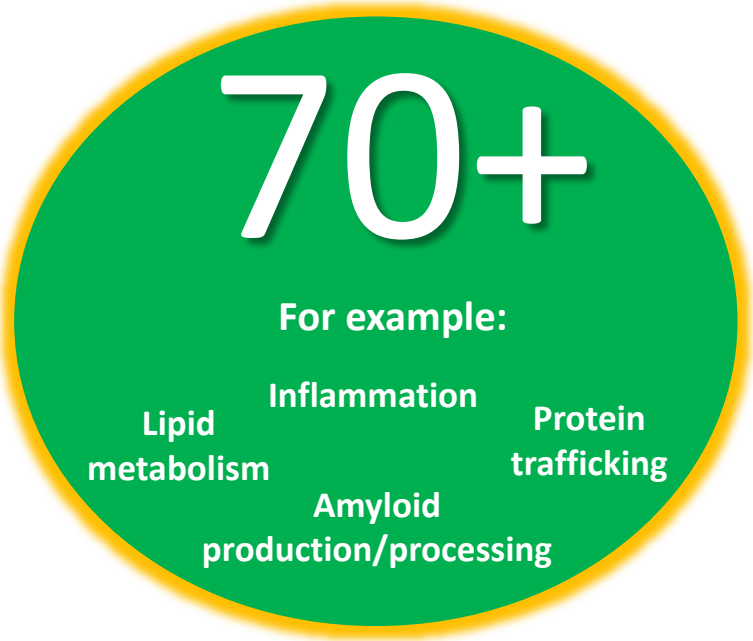


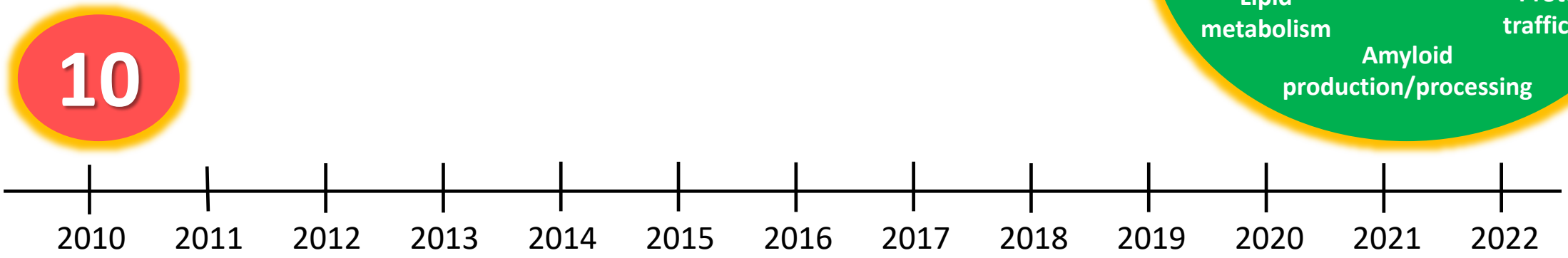
A Decade of Genetic Advancements in AD/ADRD

Advancing Understanding of AD/ADRD Genetics-

- Ten years ago, 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 70 genetic areas associated with Alzheimer's, leading to new approaches in developing potential dementia therapeutics.





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

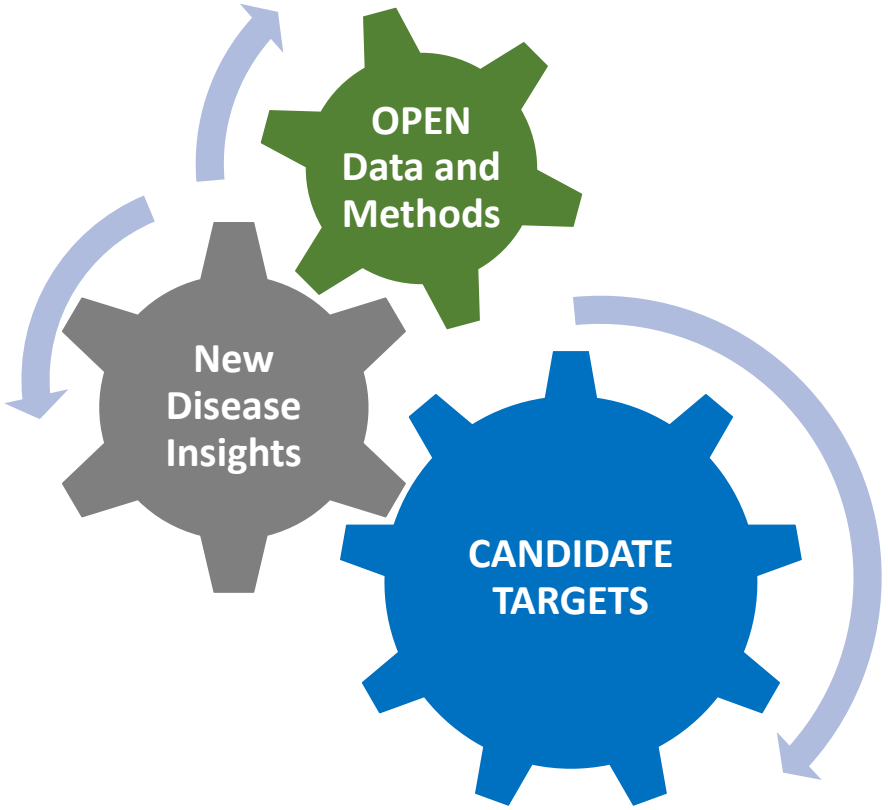
- Large scale team science
- Sharing of data, methods and results through centralized data infrastructure
- Integration of epidemiologic, genomic and mechanistic research
- Integration of data generation, computational analyses and experimental validation
- Cross-species analyses
- CNS - Peripheral systems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

ACCELERATING MEDICINES PARTNERSHIP FOR ALZHEIMER'S DISEASE (AMP-AD 1.0)

Target Discovery and Preclinical Validation Project

Key Achievements over the 5 years

- Centralized data resources/infrastructure: AD Knowledge Portal and Agora platform.
- Rich, human, multi-omic data (brain and blood) generated, made available and being widely used
- Molecular network models of disease pathways made available
- New mechanistic insights on the role of the genome, proteome, metabolome and microbiome
- Animal models phenotyped and evaluated relative to human molecular networks
- **Over 500 unique candidate targets nominated and made available through Agora along with the supporting evidence and extensive druggability information**



Translational Centers: Capacity Building for Data Driven Drug Development

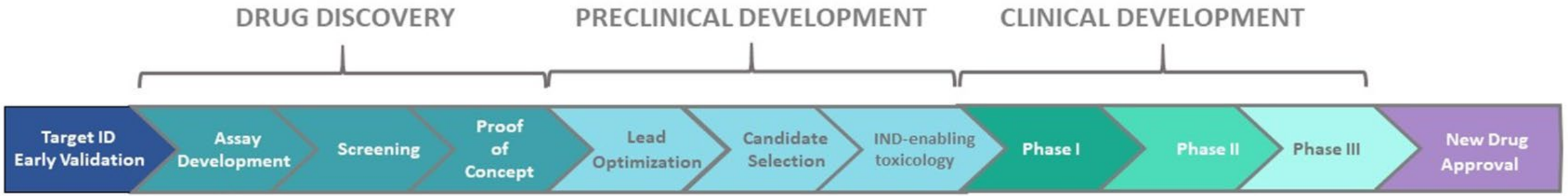
- Novel targets prioritization/preclinical validation.
- Open-source, target enabling tools for studying disease biology and as seeds for drug discovery for novel targets

https://treatad.org

- 50 new mouse models (knock-in) of Late Onset AD (LOAD)
- Multi-modal phenotyping and aligning with human AD phenotypes
- Pipeline for rigorous preclinical efficacy testing
- Open data and model distribution free of IP barriers

https://model-ad.org

Example: Milestone 4.0 Supports the Establishment of TREAT-AD Consortium



Milestone 4.0

De-risk novel candidate targets by supporting the development of high quality, open source, target enabling tools that can serve as starting points for drug discovery campaigns or as research tools to understand the biology of “dark targets”.

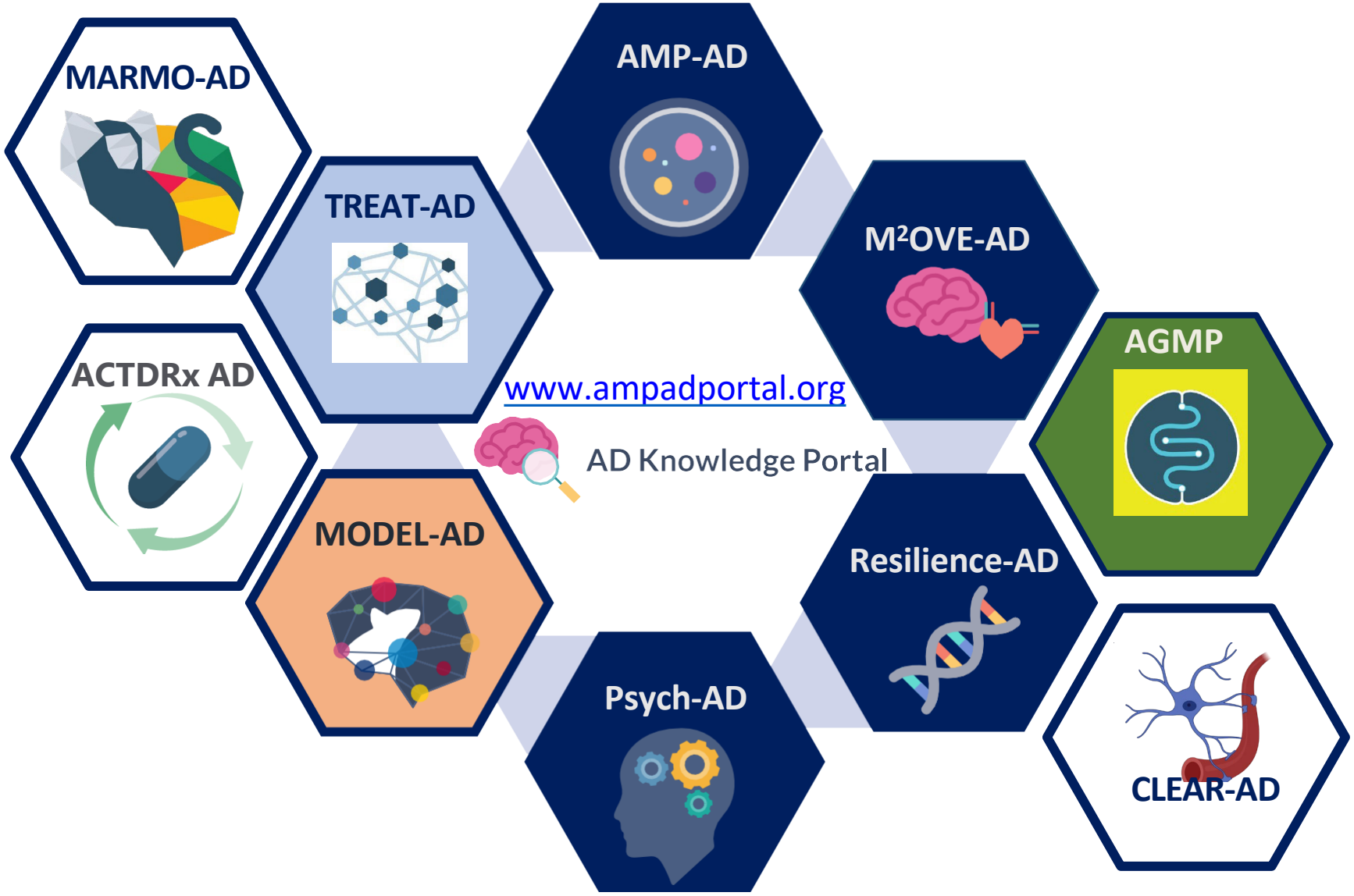
FUNDING INITIATIVE IN SUPPORT OF THIS MILESTONE:

RFA-AG-19-010
Alzheimer Centers for Discovery of New Medicines

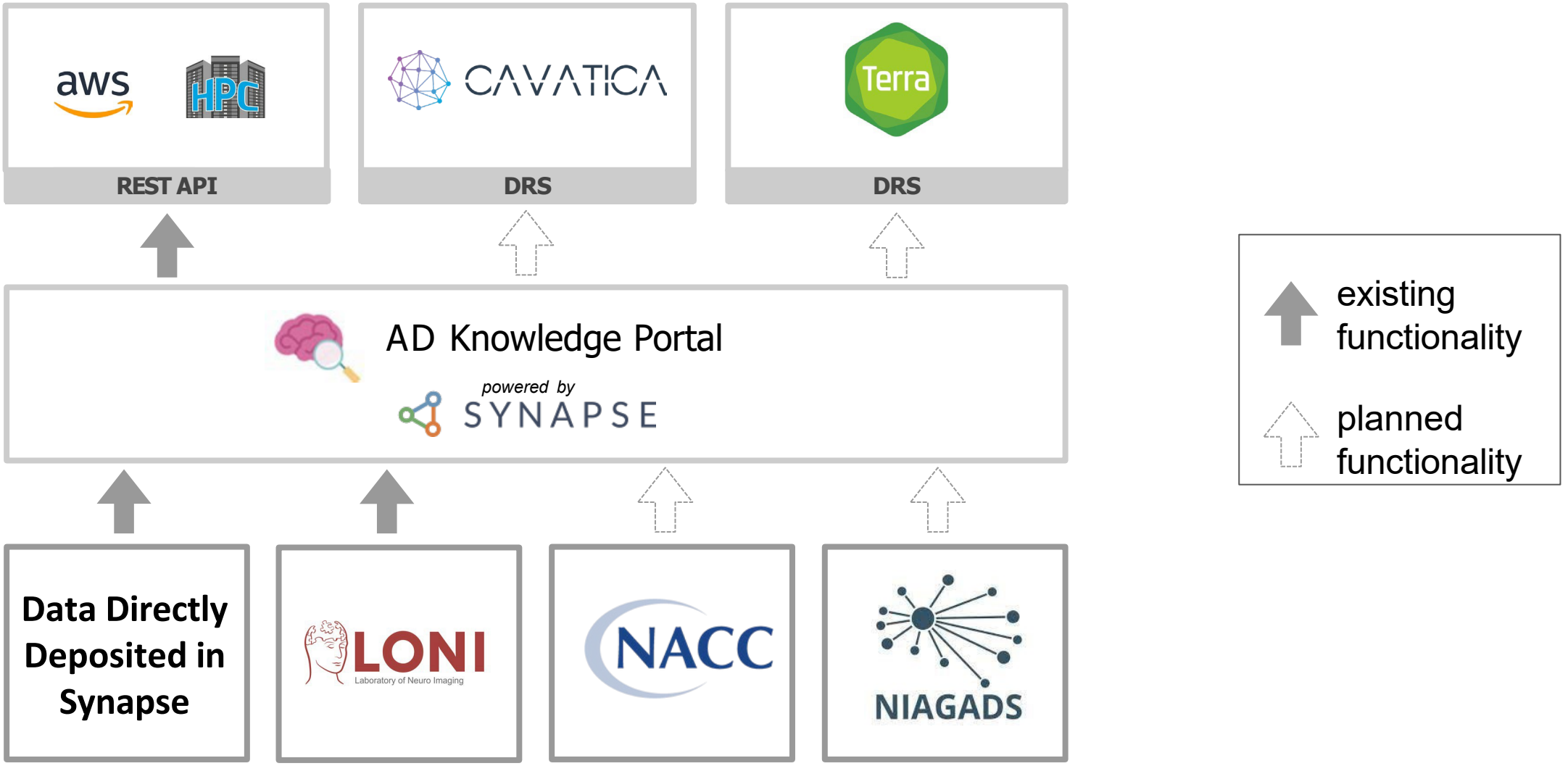
ACHIEVEMENTS:
2 New Centers established – TREAT-AD Consortium

The Centers are developing research tools known as target enabling packages (TEPs) that will serve as starting points for drug discovery against ~100 novel targets. To date, high-quality tools for ~40 novel targets have been made available to researchers in academia and in industry.

Open Science Programs Enabling a Precision Medicine Approach to Drug Development for AD

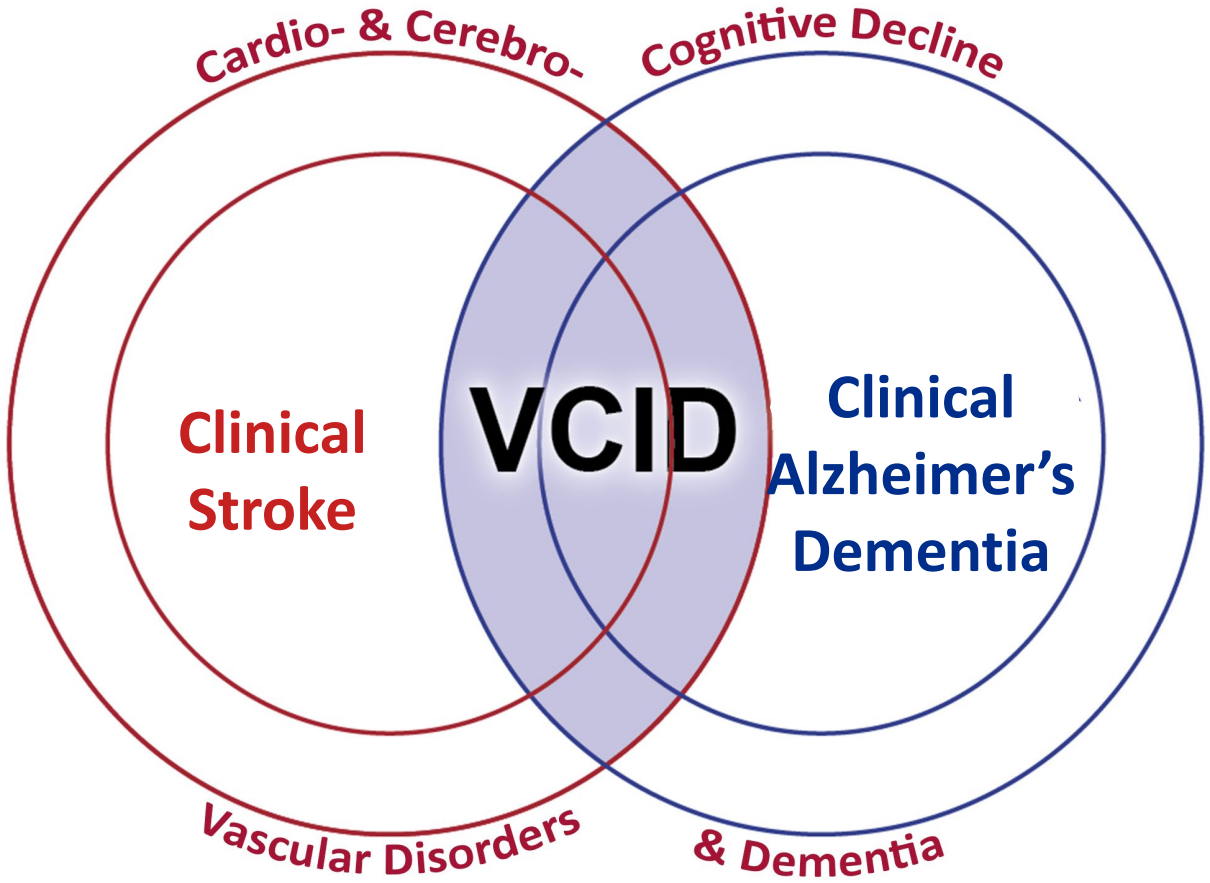


Enhancing the Interoperability of the AD/ADRD Data Infrastructure



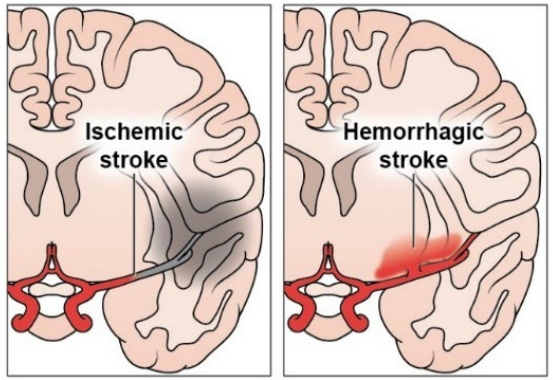
Disciplinary Term Proposed by NINDS and Adopted by the National Plan and the Research Community

- **Vascular Contributions to Cognitive Impairment and Dementia (VCID)**
- Field of research investigating hypothesis that significant AD/ADRD disease burden due to cognitive decline results from damage to brain function due to vascular insults of any type.
- First discussed at 2014 Alzheimer's Association International Conference; Published in 2016: Corriveau et al., Cellular and Molecular Neurobiology 2016 Mar;36(2):281-8.

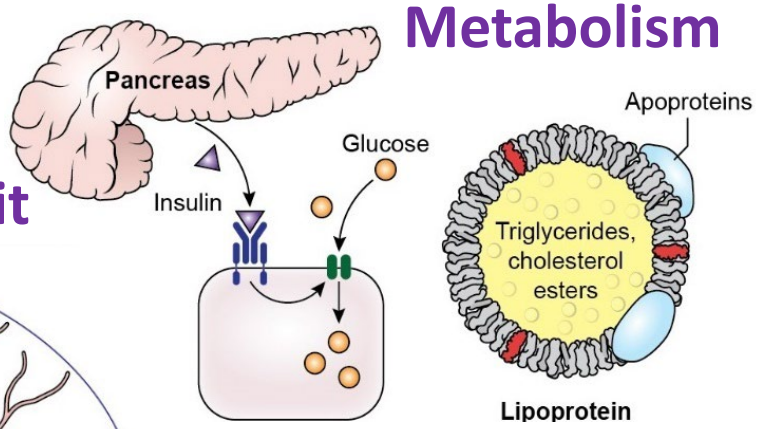


Complex Mechanisms Underlie VCID

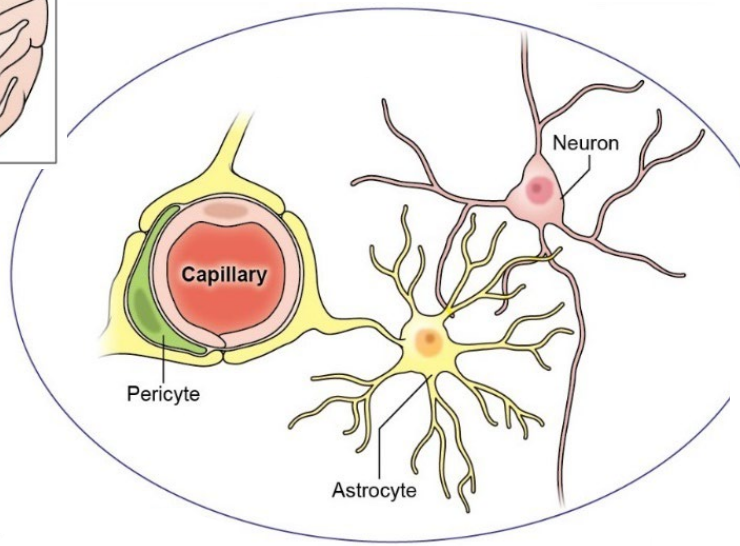
Cerebro- & Cardio-Vascular Biology

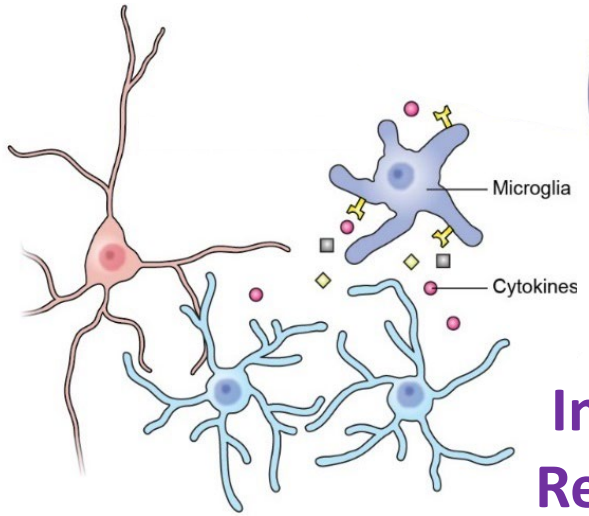


Metabolism

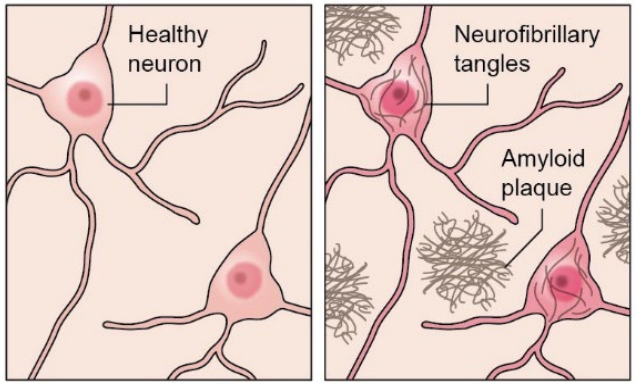


Neurovascular Unit





Immune Response



Dementia Proteinopathy (AD, Lewy, TDP-43)

Mechanism-oriented VCID research is best described as the neurovascular unit integrating, and failing to cope with, biological insults due to cerebro- & cardio-vascular disease, proteinopathy, metabolic disease, & immune response.

Looking Forward: Taking VCID Science to the Next Level

FY24 Funding Announcement: VCID Center Without Walls for Understanding and Leveraging Small Vessel Cerebrovascular Disease Mechanisms in ADRD (R01)

Purpose:

- Generate a foundational VCID knowledge needed for future development of interventions that prevent, treat, and decrease the burden of dementia

This funding opportunity will support research:

- Designed to utilize in parallel human-based & model-based studies
- Focused on molecular mechanisms of cerebral small vessel disease (SVD)
- Intended to use multi-faceted approaches to understand cerebral SVD cross-sectionally and over time

Looking Forward: Mechanism-Focused Research to Promote Adherence to Healthful Behaviors to Prevent MCI & AD/ADRD

RFA-AG-22-016

Funding Opportunity Title

Mechanism-Focused Research to Promote Adherence to Healthful Behaviors to Prevent Mild Cognitive Impairment (MCI) and Alzheimer's Disease and Related Dementias (AD/ADRD) (R61/R33 Clinical Trial Required)

- Address psychological and interpersonal mechanisms driving adherence to behaviors or lifestyle changes relevant to prevention of cognitive decline, MCI, and AD/ADRD.
- Seek to identify malleable, mechanistic, psychological, or interpersonal targets that, if modified, will strengthen adherence to, maintenance of, and continued/renewed engagement in behaviors that may promote cognitive health and prevent AD/ADRD.

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Biomarkers & Other Assessments

Breakthroughs in Biomarkers

- Before the early 2000s, autopsy was the only sure way to diagnose Alzheimer's.

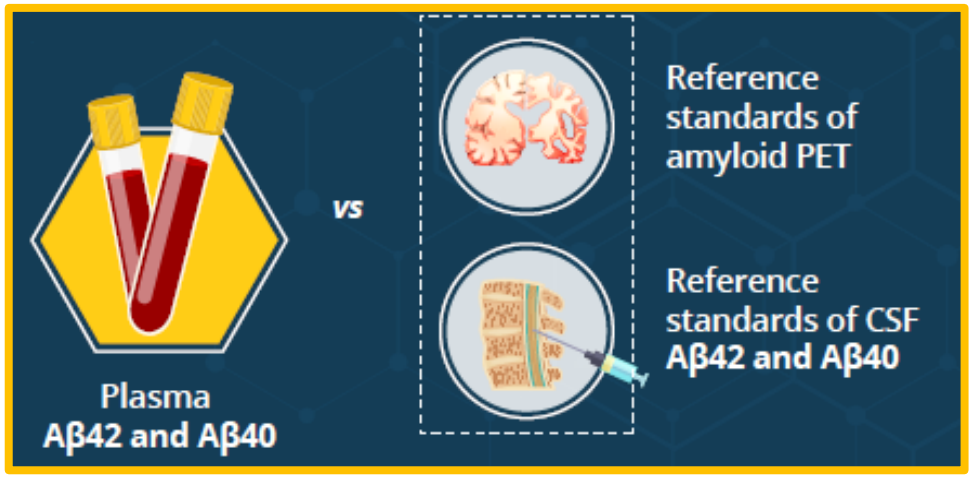
- Now, biomarkers — which are often found in body fluids or with imaging — are helping researchers:
  - **Diagnose risk of clinical dementia earlier**
  - **monitor its progression**
  - **gauge response to treatments**

First Blood Test of Beta-Amyloid Now Available

- Blood-based biomarkers are a **less expensive and less invasive** option.

PrecivityAD™

- The **first commercial blood test of beta-amyloid**, PrecivityAD, became available to doctors for use with patients in 2020. The test produces an Amyloid Probability Score to suggest the likelihood of amyloid plaques in the brain with comparable accuracy as current diagnostic standards (i.e., PET scans).



NIA supported this work from early foundational research through test development.

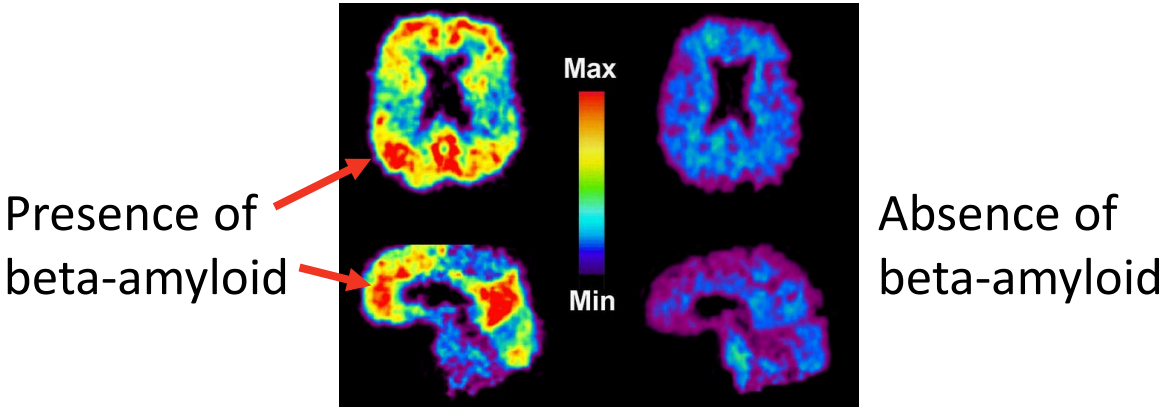
Li, Y., et al. (2022). *Neurology.* 98(7): e688-e699.

PET Imaging for Alzheimer's Pathology Diagnosis

- Imaging allows doctors and scientists to see factors that may help diagnose Alzheimer's.

- Positron emission tomography (PET) uses small amounts of a radioactive substance, called a tracer, to measure specific activity or a specific molecule in different brain regions.

- Amyloid PET scans measure beta-amyloid deposits and have been a standard procedure for helping to diagnose Alzheimer's since 2012.



Amyloid PET Brain Scan
Adapted from Klunkwe/Wikimedia Commons

First Tau Biomarker Approved for Alzheimer's Evaluation

- Amyloid PET is now complemented by tau PET, which detects abnormal accumulation of the tau protein.
- In May 2020, the FDA approved the **first PET tracer for tau imaging.**
- NIA supported a key study used to validate this biomarker.

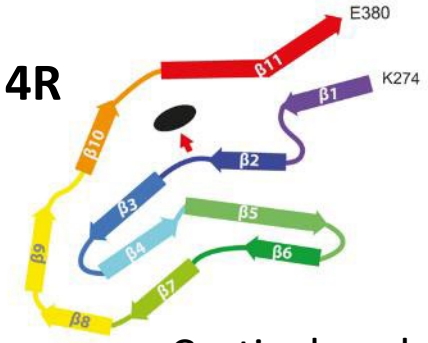
FDA-Approved Tracers and Diagnostic Tests

FDA Approved PET Tracers and *In Vitro* Diagnostic Tests

PET Tracers Amyloid and Tau	In vitro Diagnostic Tests - CSF
Amyvid (Florbetapir F-18) Amyloid; 2012	**Lumipulse G** Aβ 42/40 CSF 2022
Vizamyl (Flutemetamol F 18) Amyloid; 2014	**Elecsys β-Amyloid** (1-42) CSF II **Elecsys Phospho-Tau** (181P) CSF 2022
Neuraceq (Florbetaben F-18) Amyloid; 2014	**Elecsys β-Amyloid** (1-42) CSF II **Elecsys Total-Tau** CSF 2023
Tauvid (Flortaucipir F18) Tau 2020	

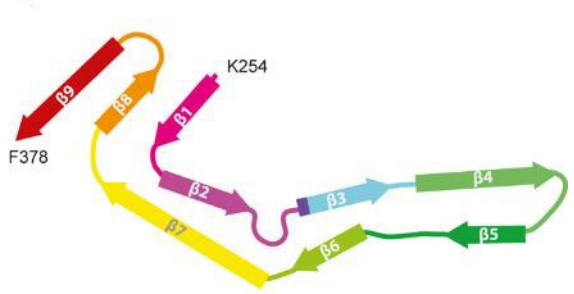
Next Generation Tau Biomarkers: Specific Tauopathies Have Been Reported to Feature Different Structural Forms of Tau Filaments

4R



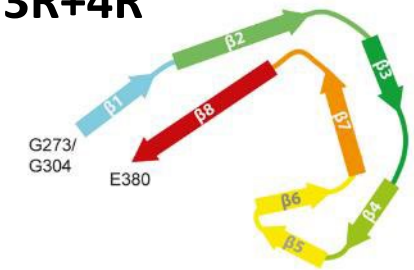
Corticobasal Degeneration

3R



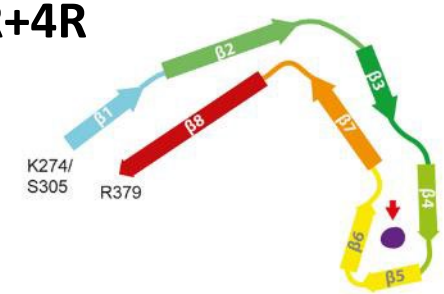
Behavioral Variant FTD

3R+4R



Alzheimer's Disease

3R+4R

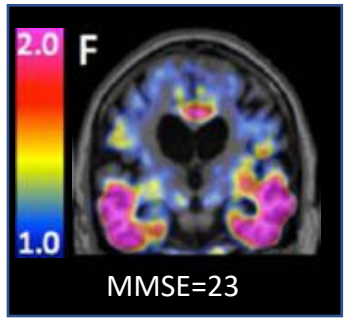


Chronic Traumatic Encephalopathy

Zheng et al., Nature 2020 Apr; 580(7802):283-287.
Johnson et al. Ann Neurol. 2016 Jan;79(1):110-9.

FDA-approved PET ligand 18F-flortaucipir/Tauvid:

High affinity for mixed 3R/4R PHF-tau in pathological AD, and lower affinity for predominately 3R or 4R isoforms.



NINDS is leading structural biology (cryoEM, cryoET) and PET ligand programs to inform development of new PET ligand biomarkers that selectively bind distinct forms of misfolded tau associated with different tauopathy diagnoses.

RFA-NS-18-015, PAR-22-208: NS110438, NS110437, NS133651, NS110436. RFA-NS-19-014 RFA-NS-24-011, U19NS110456-01A1.

Evaluating Disease Heterogeneity in Diverse Cohorts and in Special Populations to Discover New Precision Medicine Biomarkers

HEALTH & AGING BRAIN STUDY

1,500 Mexican Americans/1,500 African Americans/1,500 non-Hispanic Whites

LEADS Longitudinal Early-Onset Alzheimer's Disease Study

500 amyloid positive APP/PSEN1/PSEN2 mutation negative EOAD individuals and 100 age-matched individuals

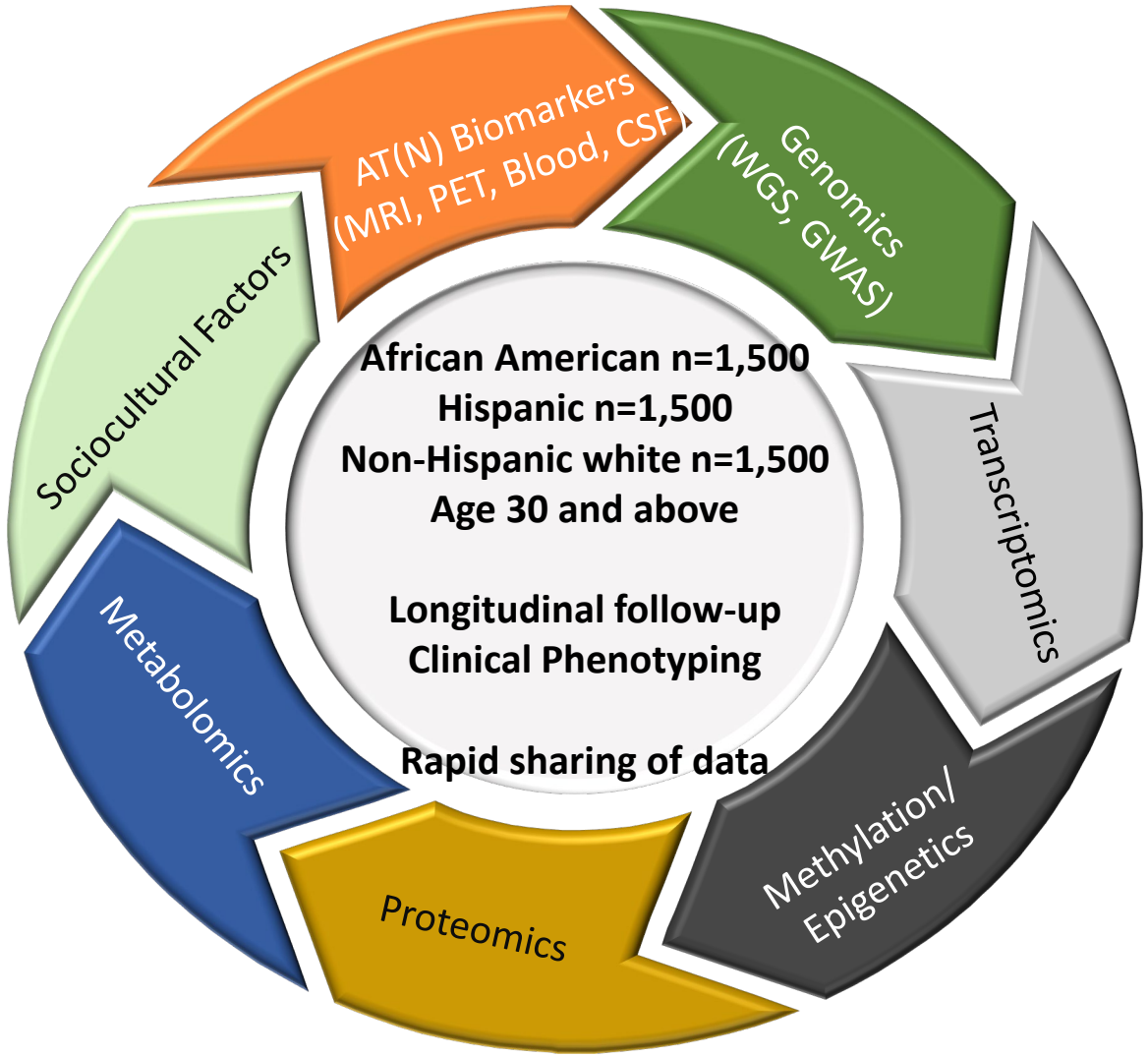
ABC-DS

Alzheimer's Biomarker Consortium - Down Syndrome

~500 adults with Down syndrome (25-85 years old)

Emphasis on participants engagement, longitudinal data collection, rigorous evaluation of AT(N), and rapid sharing of data

Examining AT(N) Biomarkers within a Health Disparities Framework: The Health & Aging Brain Study – Health Disparities (HABS-HD)



HEALTH & AGING BRAIN STUDY

- Functional exam
- Clinical labs
- Sociocultural, environmental and behavioral factors
- Item-level data entry
- Neuropsychological assessment
- Biorepository (n>500,000 aliquots available)
- Multi-level “omics”
- Amyloid and Tau PET Scans
- 3T MRI

MarkVCID Biomarker Consortium

Consortium of Cooperative Agreements of Coordinating Center and Nine Sites

MarkVCID (Y1-2)

Proposed (47)
- Feasibility
- Building consortium
- Standardized, optimized protocols; core clinical data
- Sharing agreements

MarkVCID (Y3-5)

Instrumental Validation (11)
- Multi-site reproducibility
- Inter-operator reproducibility
- Precision
- Sensitivity

MarkVCID 2 (Y6-11)

We are here

Clinical Validation (5)

Pre-specified: protocols, hypotheses, FDA Biomarker Category & Context of Use

1. **Arteriolosclerosis (ARTS)**
2. **Cerebrovascular Reactivity**
3. **MRI Free Water**
4. **Peak Skeletonized Mean Diffusivity**
5. **Neurofilament Light (NfL)**

Validated VCID biomarkers ready for large scale clinical trials (informs on individuals)

GOAL

MarkVCID 2: NS100591 (CC), NS100614, NS125513, NS100598, NS125417, NS100588, NS125512, NS100608, NS100599, NS125488; >1000 participants enrolled

External Advisory Committee
GJ Biessels, S Catalano
H Gonzalez, R Gottesman,
C Iadecola, K Krudys, SX Xie

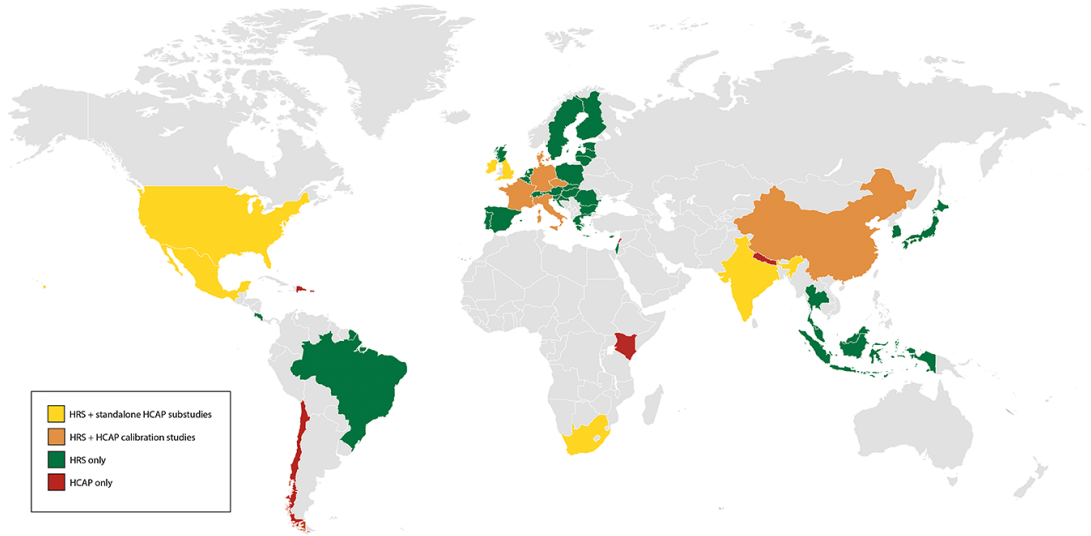
Developing Consistent Cognitive Outcome Measures to Inform the Design of Future Primary Prevention Trials

MOBILE TOOLBOX

Northwestern University · SageBionetworks · PennState · Massachusetts General Hospital · UC San Diego · UCSF University of California San Francisco · University of Delaware · Washington University in St. Louis

https://www.mobiletoolbox.org/

Harmonized Cognitive Assessment Protocol



https://hrs.isr.umich.edu/data-products/hcap

NIH Concept for Potential Future Funding Initiative: Open Measurement Coordinating Network for Non-Pharmacological AD/ADRD Primary Prevention Trials

https://www.nia.nih.gov/approved-concepts#openmeasure

Assessing Early Psychological and Functional Changes in AD/ADRD

- The field also requires precise measures of cognitive and functional change, to know whether we are altering the trajectory of cognitive decline or preventing decline.

- The NIA is supporting **ARMCADA,** a research network to catalyze and integrate research efforts to develop, validate, norm, and disseminate standardized measurements to assess decision-making functionality among the aging population.

- NIA also led The Landscape of Early Neuropsychological Changes in AD/ADRD Project by convening experts to discuss gaps in measuring early changes in AD/ADRD.

ARMCADA: Advancing Reliable Measurement in Cognitive Aging and Decision-making Ability

https://www.scholars.northwestern.edu/en/projects/armcada-advancing-reliable-measurement-in-cognitive-aging-and-dec

https://www.nia.nih.gov/research/dbsr/landscape-early-neuropsychological-changes-ad-adrd-webinar-series

FDA-Approved Drugs for AD/ADRD

Symptomatic	Disease Modifying
Donepezil **Aricept; 1996**	**Aducanumab** **Aduhelm** Anti-amyloid; 2021 *Accelerated approval*
Rivistagimine **Exelone; 2000**	**Lecanemab** **Leqembi** Anti-amyloid; 2023 *Full approval*
Galantamine **Razadyne; 2001**	
Memantine **Namenda; 2003**	
Donepezil and Memantine **Namzaric; 2014**	

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Clinical Trials for AD/ADRD Treatment and Prevention

AD/ADRD Active Research: Lecanemab

NIA is funding three trials to evaluate lecanemab in treating different stages of AD

Trial Name	Drug Description	Phase	Population	Funding End Date
The A3 Study: Anti-Amyloid Prevention of Alzheimer's Disease (AHEAD STUDY)	**Lecanemab**, anti-amyloidβ antibody	III	Cognitively healthy older adults with "intermediate" amyloid levels on screening PET. Ages 55-80; Adults 55-64 must also carry at least one APOE ε4 allele.	2024
The A-45 Study: Anti-Amyloid Therapy for Preclinical Alzheimer's Disease (AHEAD STUDY)	**Lecanemab**, anti-amyloidβ antibody	III	Cognitively healthy older adults with "elevated" amyloid levels on screening PET. Ages 55-80; Adults 55-64 must have an additional risk factor.	2025
DIAN-TU: Tau Next Generation Prevention Trial	Combination of an anti-tau immunotherapy with **Lecanemab**, anti-amyloidβ antibody	III	Cognitively healthy or mildly impaired adults who are Alzheimer's disease genetic mutation carriers.	2025

Expanding the Clinical Trial Pipeline for AD/ADRD Treatment & Prevention

Pharmacological

66 TRIALS

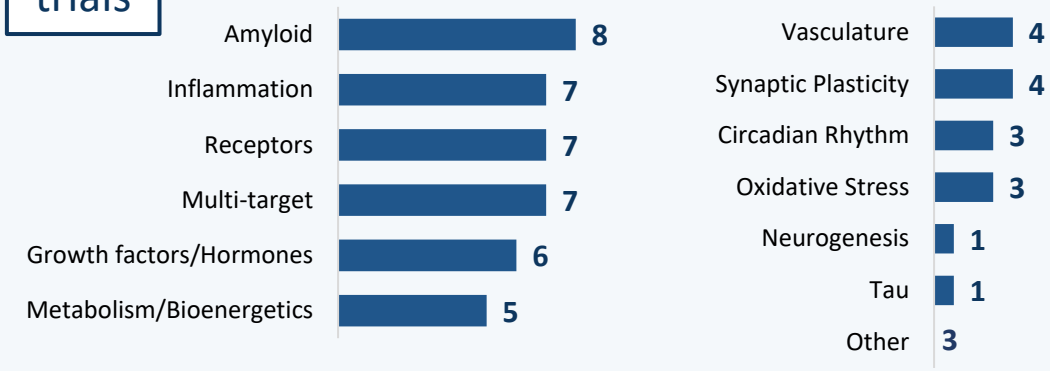
Non-Pharmacological

152 TRIALS

59 trials

Phase I & Phase II

Targeted Disease Process

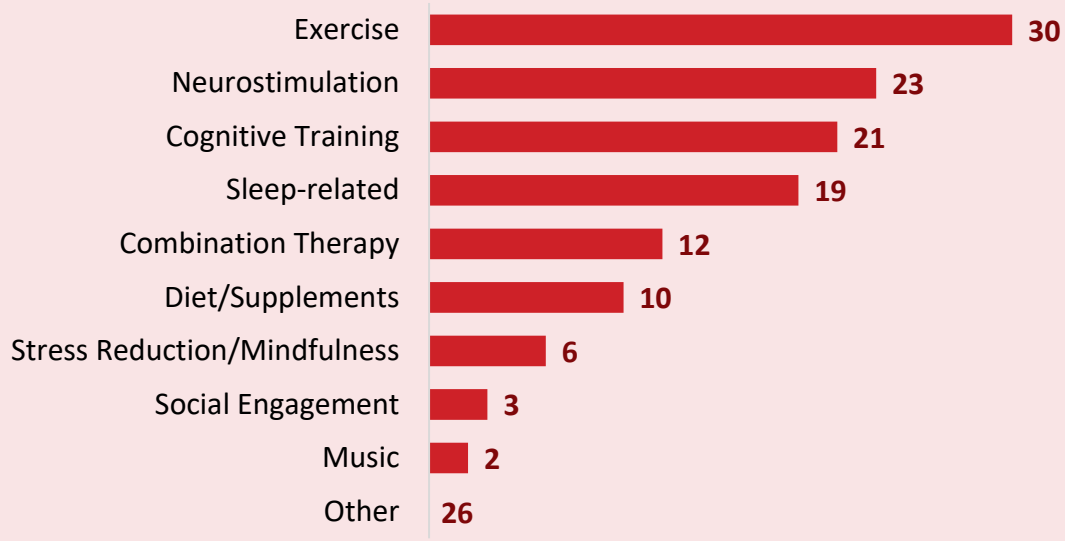


7 trials

Phase II/III & Phase III

Targeted Disease Process

Modality



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

NIH National Institute on Aging

Data last updated: September 2022.

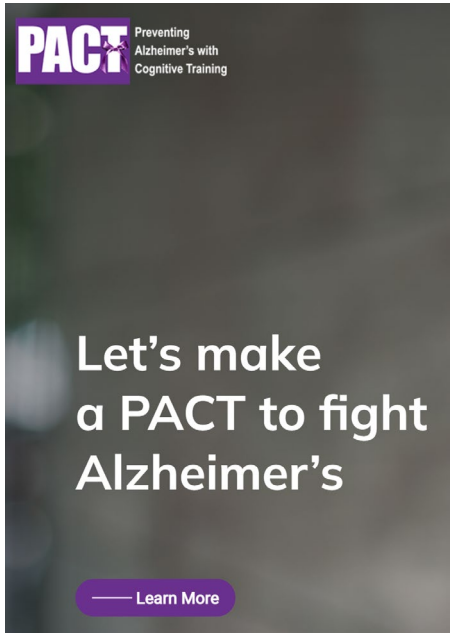
Trial Design is Essential

- Outcomes of the AHRQ-NASEM “Preventing Cognitive Decline: A Way Forward” study included elevating the importance of trial design.
- Accordingly, prior to scaling up to larger, well-powered interventions, NIA has been empowering and funding researchers to conduct mechanistic and/or feasibility studies.
- These studies focus on trial designs that justify the means used to assess cognition and to explore the underlying mechanisms of change.
- Such methods as structural and functional neuroimaging with biomarkers justified by an underlying model of change, CSF fluids, and blood biomarkers are appropriate candidate tools.

EXAMPLE:

RFA-AG-18-031
Towards Implementing Novel Training Methods to Enhance Cognition in Aging (U01 Clinical Trial Required)

Examples of Non-Pharmacological Approaches to Prevention



SMARRT

Health Equity, Prevention

Public Health Campaign: Mind Your Risks®

mindyourrisks.nih.gov

https://www.youtube.com/watch?v=mJi9srnvI3Q

National Institute of Neurological Disorders and Stroke

Created By: NINDS ONCE Office

Continued Investment in Early and Late-Stage Clinical Trials Across the AD/ADRD Spectrum

- NIA released funding opportunities to **enable the collection of pilot data to support early-stage testing** of promising pharmacological and non-pharmacological interventions
- In particular, NIA is interested in supporting researchers aiming to test interventions for cognitive and neuropsychiatric changes associated with age-related cognitive decline and AD/ADRD **across the spectrum from pre-symptomatic to more severe stages of disease**
- Furthermore, this work is aiming to stimulate studies to enhance trial design and methods.

Funding Initiative:

PAR-23-081 & PAR-23-083 Early and Late Stage Clinical Trials for the Spectrum of Alzheimer's Disease/Alzheimer's Related Dementias and Age-Related Cognitive Decline (R01 and R61 Clinical Trial Optional)

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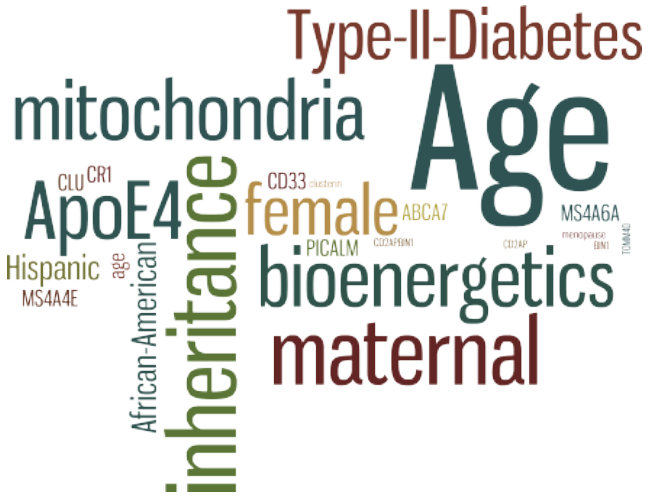
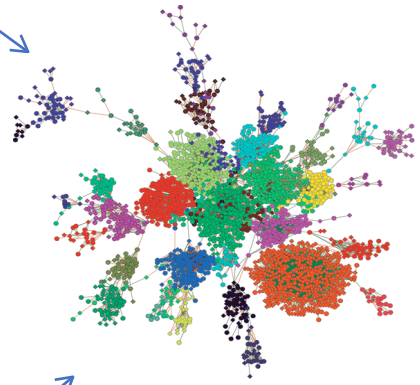
Impact of the Exposome on AD/ADRD



Multiple Etiologies
Multiple Prodromal Phenotypes
Multiple Progression Trajectories

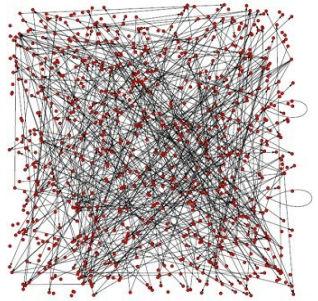
Genetics

Genetics



Disease progression

Disease modifying therapy



Healthy State

Disease State

Environment

Environment

Ecosystems

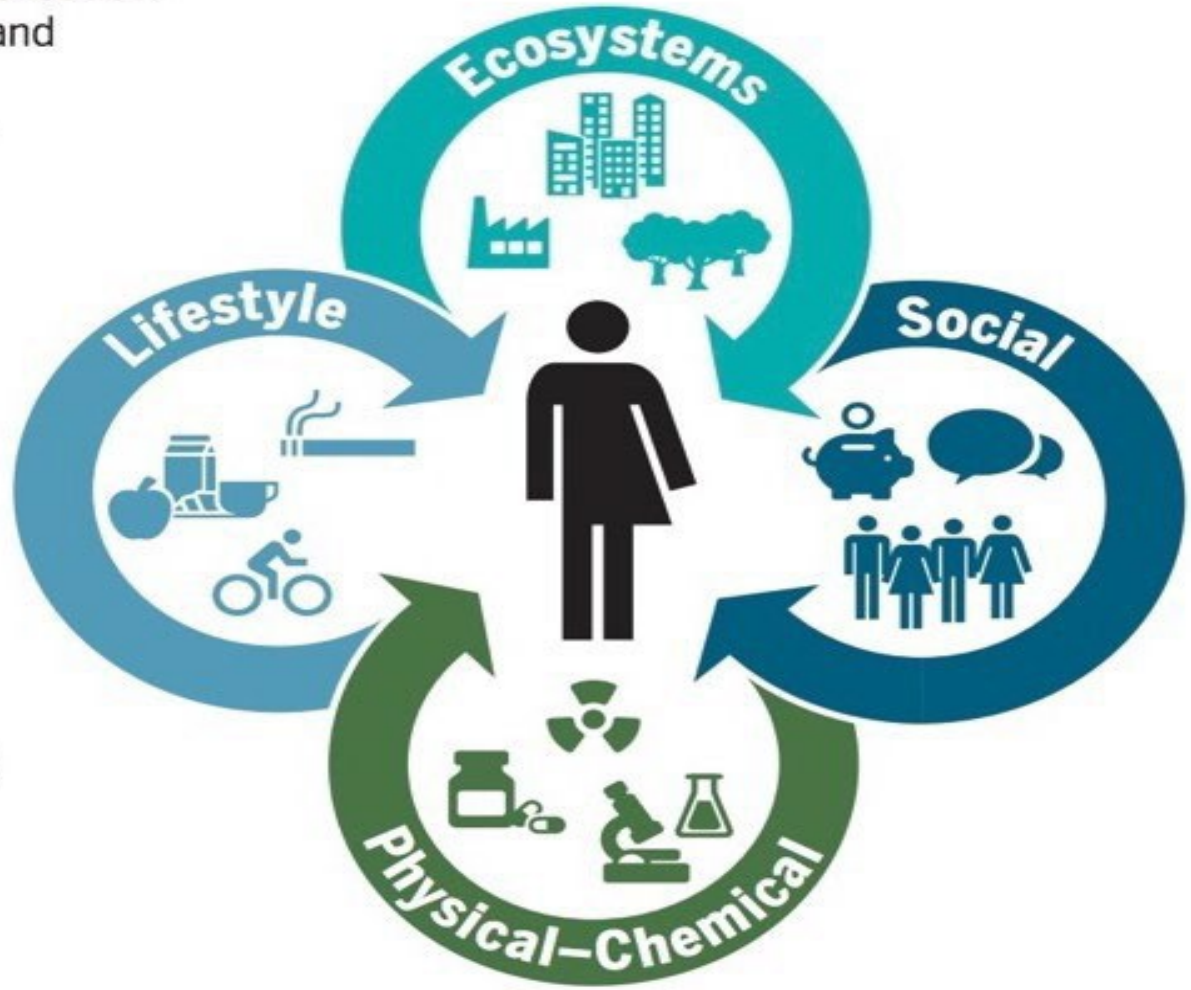
Food outlets, alcohol outlets
Built environment and urban land uses
Population density
Walkability
Green/blue space

Lifestyle

Physical activity
Sleep behavior
Diet
Drug use
Smoking
Alcohol use

Social

Household income
Inequality
Social capital
Social networks
Cultural norms
Cultural capital
Psychological and mental stress



Physical–Chemical

Temperature/humidity
Electromagnetic fields
Ambient light
Odor and noise
Point, line sources, e.g. factories, ports
Outdoor and indoor air pollution
Agricultural activities, livestock
Pollen/mold/fungus
Pesticides
Fragrance products
Flame retardants (PBDEs)
Persistent organic pollutants
Plastic and plasticizers
Food contaminants
Soil contaminants
Drinking water contamination
Groundwater contamination
Surface water contamination
Occupational exposures

Vermeulen, et al. (2020) Science. 367: 392-396.

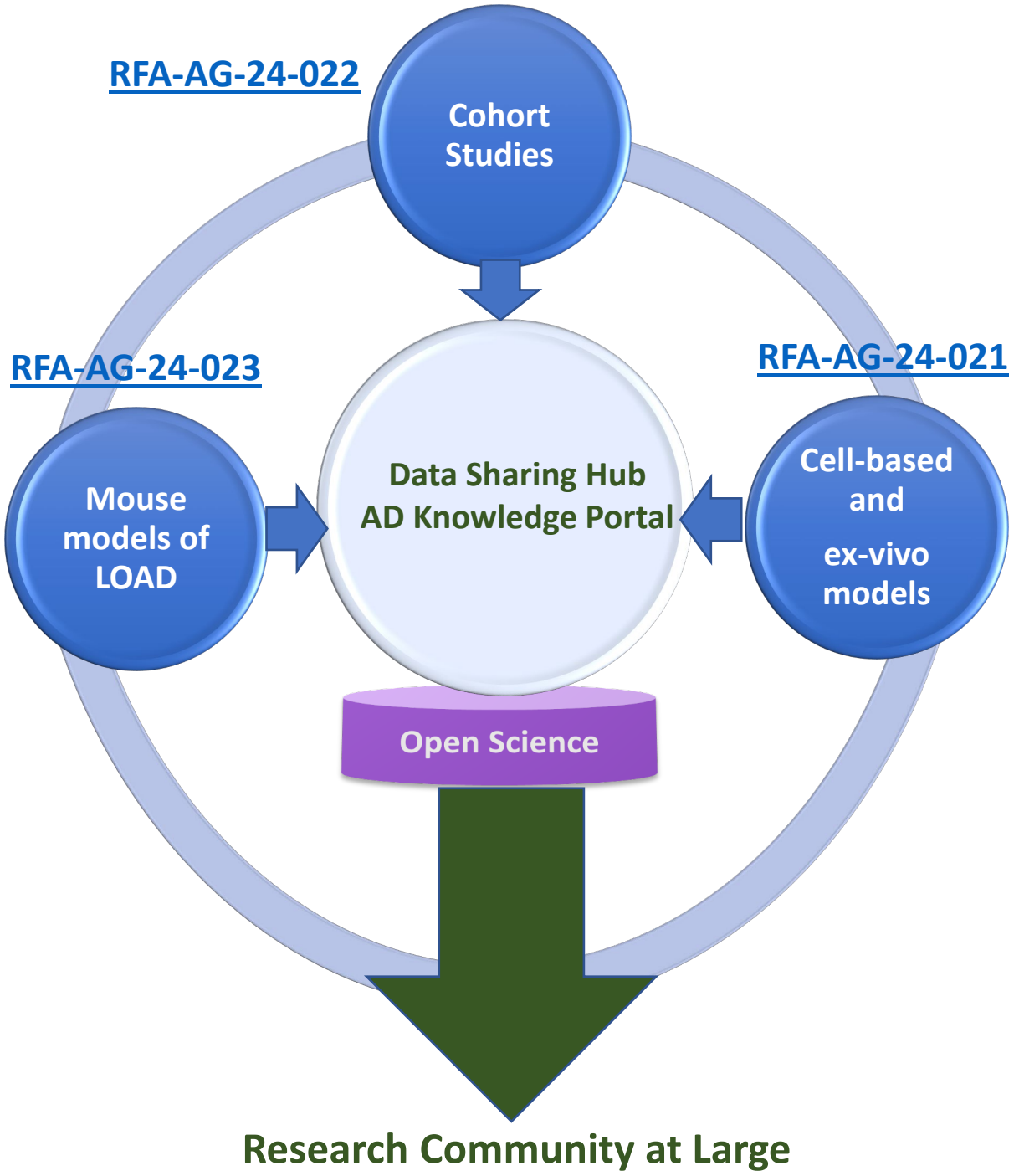
Precision Environmental Health Approach to AD/ADRD Prevention

RFA-AG-24-011: Research Coordinating Center on the Exposome and Alzheimer's Disease and Related Dementias: Elucidating the Role of Social and Behavioral Determinants of Health

RFA-AG-24-022: Quantifying the Impact of Environmental Toxicants on Alzheimer's Disease and Related Dementias Risk in Cohort Studies *Human cohort studies*

RFA-AG-24-021: Understanding Gene-Environment Interactions in Brain Aging and AD/ADRD *Cell based and ex-vivo models*

RFA-AG-24-023: Preclinical Studies to Characterize the Impact of Toxicants on Brain Aging and AD/ADRD *Mouse models of LOAD*



AD/ADRD Implementation Milestones

1B. Quantify the exposome in existing and new AD cohorts to gain a more precise measure of environmental exposure factors and their relationship to AD risk and individual trajectories of disease progression.

1F. Support the inclusion of measures of AD-related phenotypes and environmental exposures in non-AD cohorts to enable new discovery research and to accelerate cross-validation of discoveries made in AD cohorts

2Y. Support research that utilizes animal models of LOAD and iPSC-derived cerebral organoids from human donors, to understand the molecular mechanisms by which a variety of exposures influence the heterogeneity of AD/ADRD.

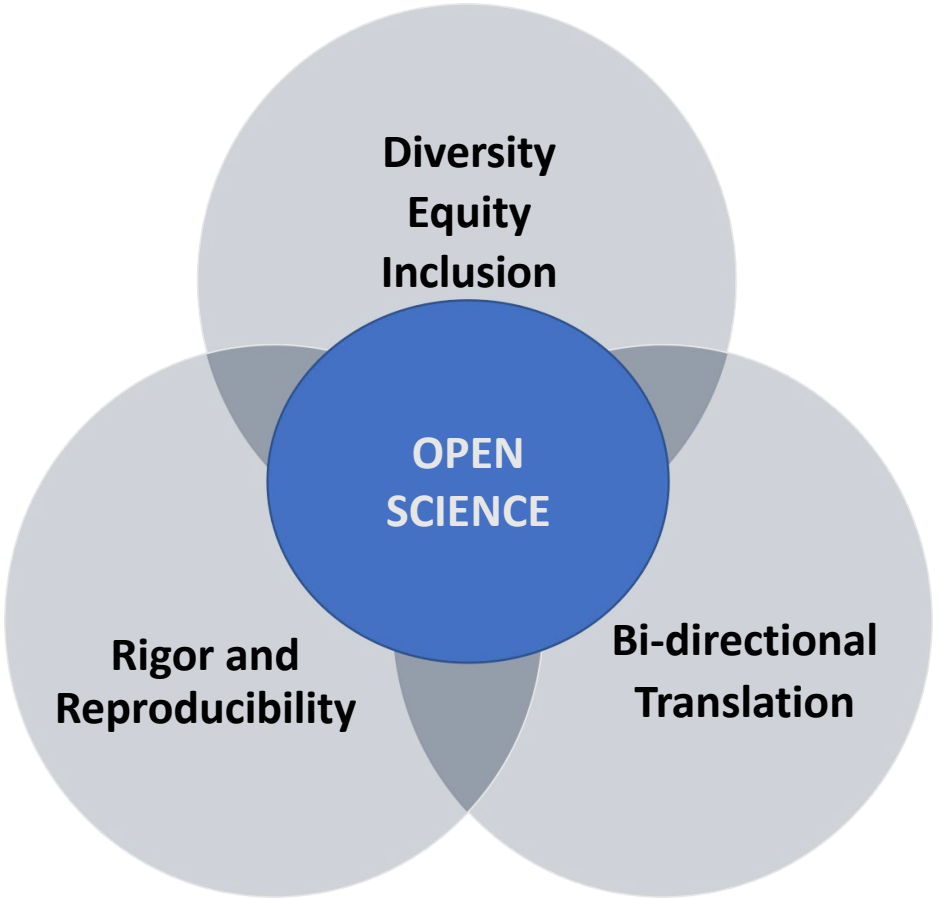
Ensure that all data and analytical outputs are made widely available according to open-science and FAIR data practices and encourage the adoption of exposomics-related ontologies for data interoperability.

National Institutes of Health

Future Directions

Future Directions

- Continue to build an integrated and interoperable infrastructure for AD/ADRD research
- Propagate open science practices across the research continuum and expand translational capabilities to accelerate the development of precision treatment and prevention strategies
- Integrate computational and experimental approaches to advance drug repurposing and combination therapies/interventions
- Elevate the critical need for representative samples and inclusion of more diverse study populations in AD/ADRD clinical trials



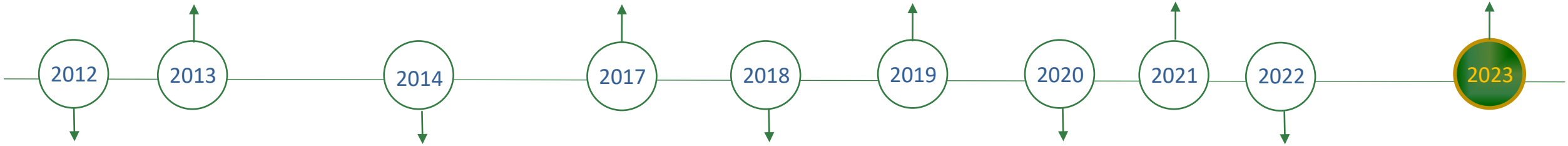
National Institutes of Health

Thank you

National Institutes of Health

Reference Slides

AD/ADRD Precision Treatment & Prevention



2012

» National Plan to Address Alzheimer's Disease unveiled

» NIH convenes first Alzheimer's Disease Research Summit

» First amyloid positron emission tomography (PET) imaging agent approved by the U.S. FDA, enabling detection and tracking of Alzheimer's in living humans

2013

» NIH holds first Alzheimer's Disease Related Dementias Research Summit

2014

» NIH partners with industry, nonprofit organizations, and FDA to launch the Accelerating Medicines Partnership® Program for Alzheimer's Disease

» NIH-funded ACTIVE Study shows that cognitive improvements from cognitive training in older adults can last 10 years

2017

» NASEM releases the Preventing Cognitive Decline and Dementia: A Way Forward, which reports "encouraging but inconclusive evidence" for three intervention types: blood pressure, cognitive training, and physical activity

2018

» NIA-Alzheimer's Association (AA) biological research framework incorporates use of brain imaging and cerebrospinal fluid biomarkers

2019

» NIH SPRINT MIND study demonstrates that intensive high blood pressure control may reduce occurrence of mild cognitive impairment (MCI)

2020

» First blood test for amyloid, developed with funding from NIH, made available for clinical use

» First tau tangle PET imaging agent approved by FDA

2021

» NIA funds the Preventing Alzheimer's with Cognitive Training (PACT) study.

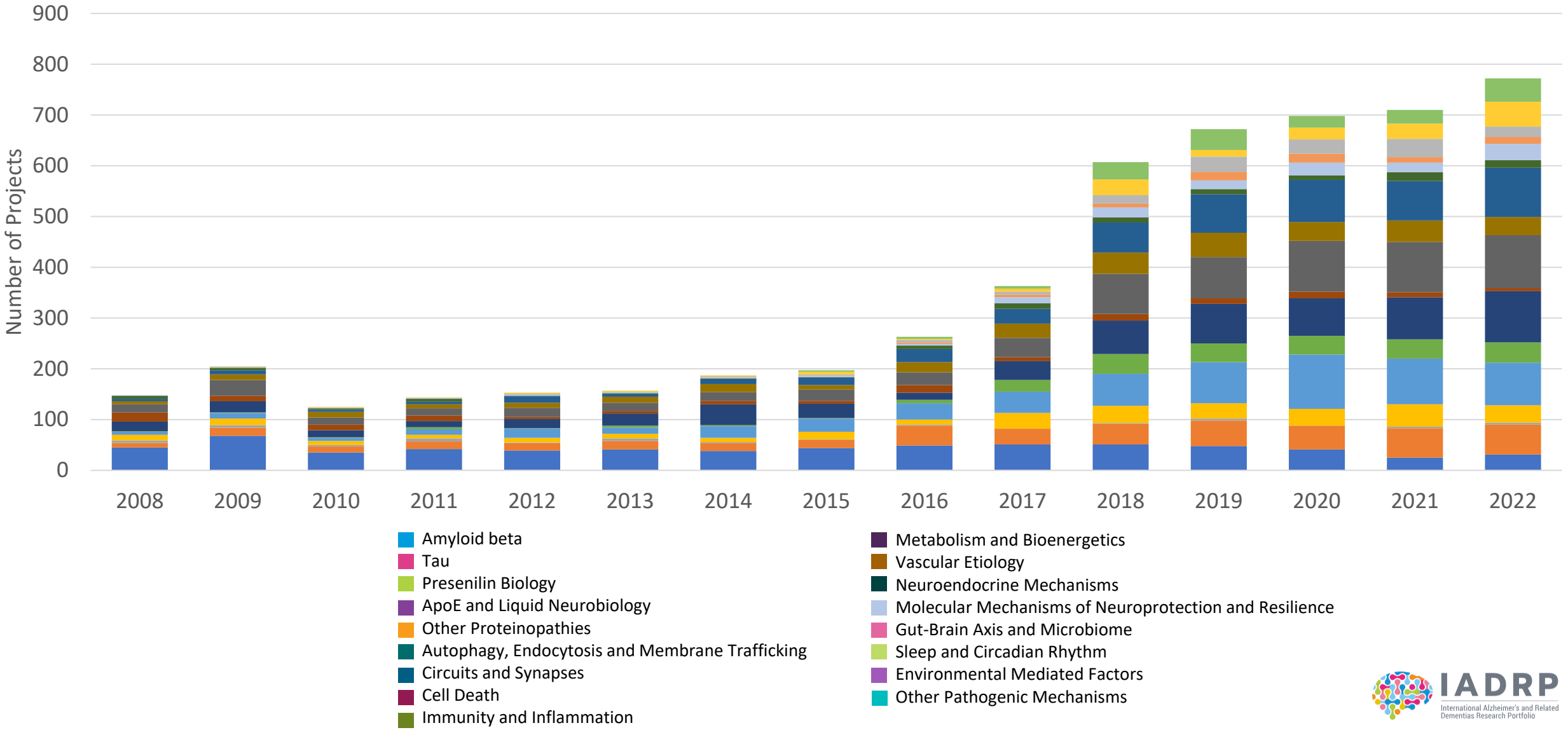
2022

» First estimates of dementia prevalence reported for Black, Hispanic, and White Americans from a longitudinal nationally representative sample

2023

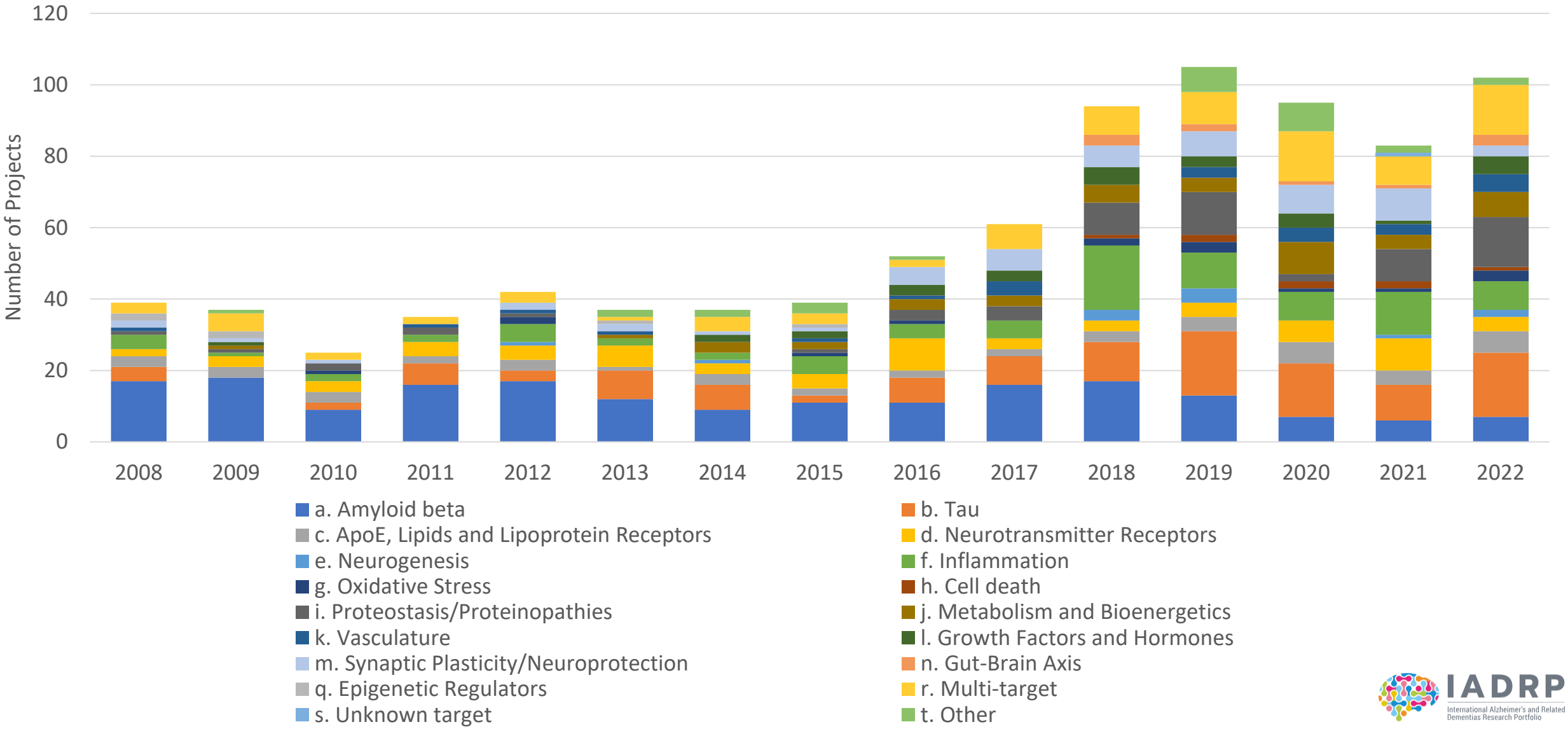
» Disease-modifying therapy lecanemab-irmb (Leqembi) granted FDA approval

Trends in Number of New NIH-Supported Projects: Molecular Pathogenesis and Physiology of AD/ADRD



IADRP
International Alzheimer's and Related Dementias Research Portfolio

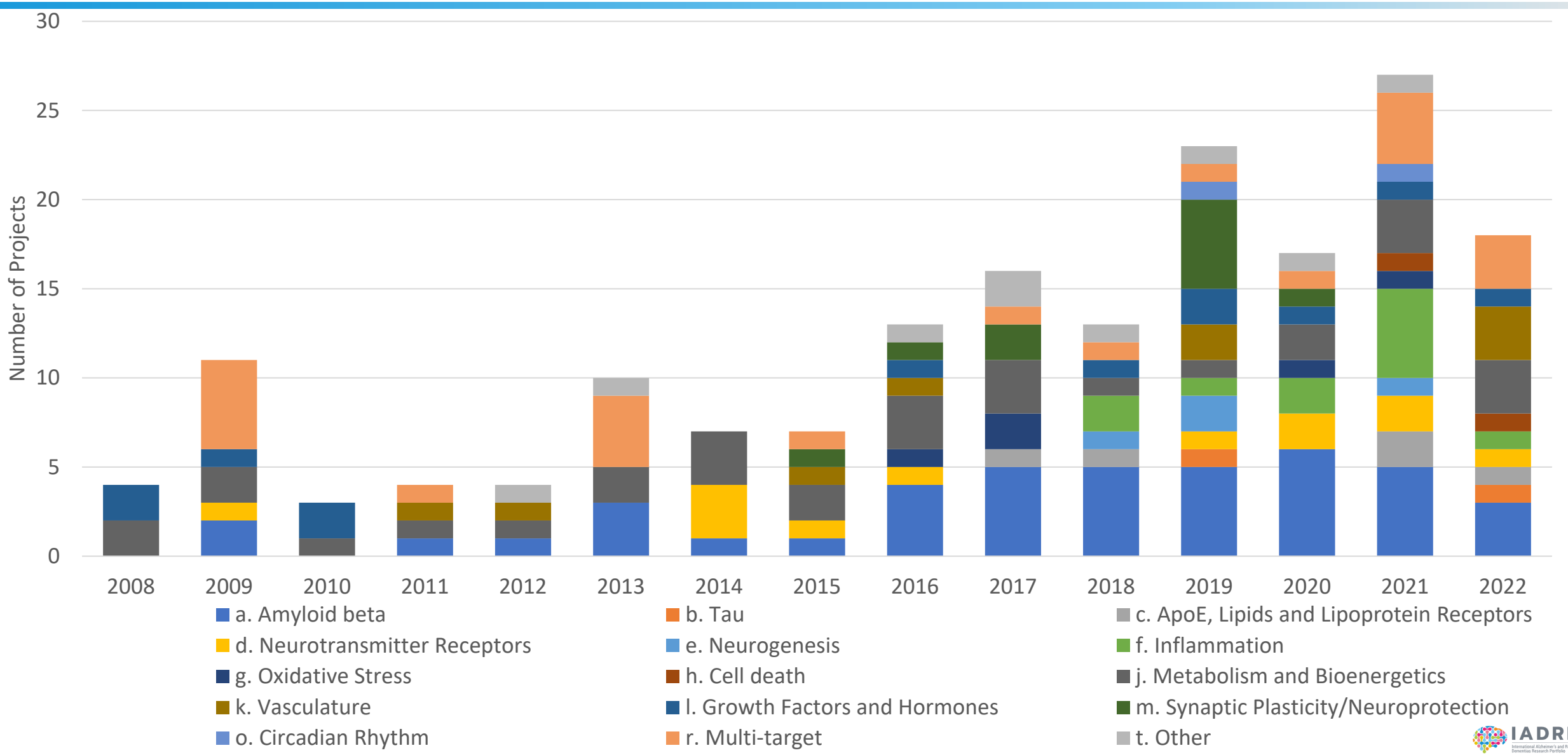
Trends in Number of New NIH-Supported Projects: AD/ADRD Drug Discovery and Preclinical Drug Development



IADRP
International Alzheimer's and Related Dementias Research Portfolio

Trends in Number of New NIH-Supported Projects:

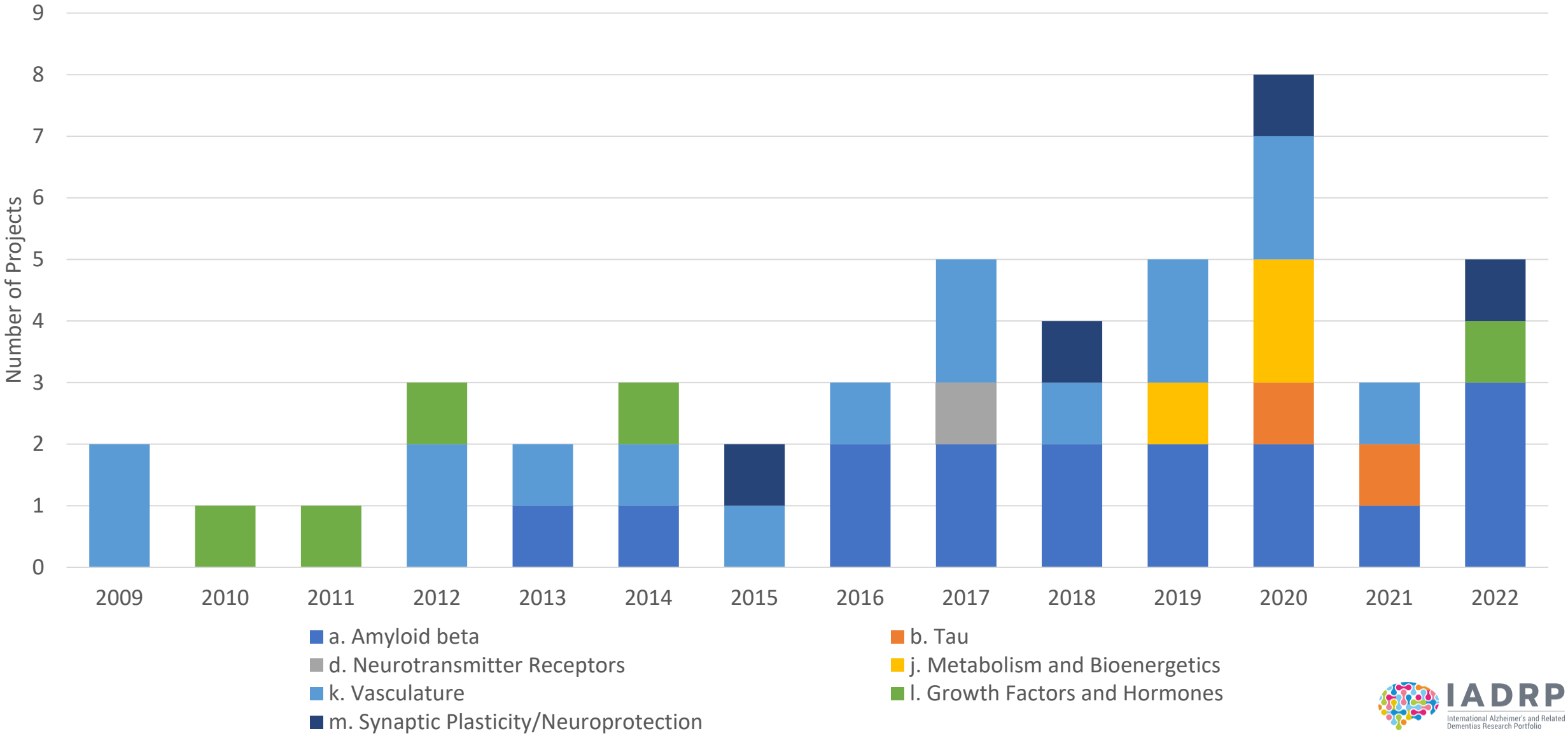
AD/ADRD Early-Stage Clinical Drug Development (Phase I and Phase II Clinical Trials)



IADRP
International Alzheimer's and Related Dementias Research Portfolio

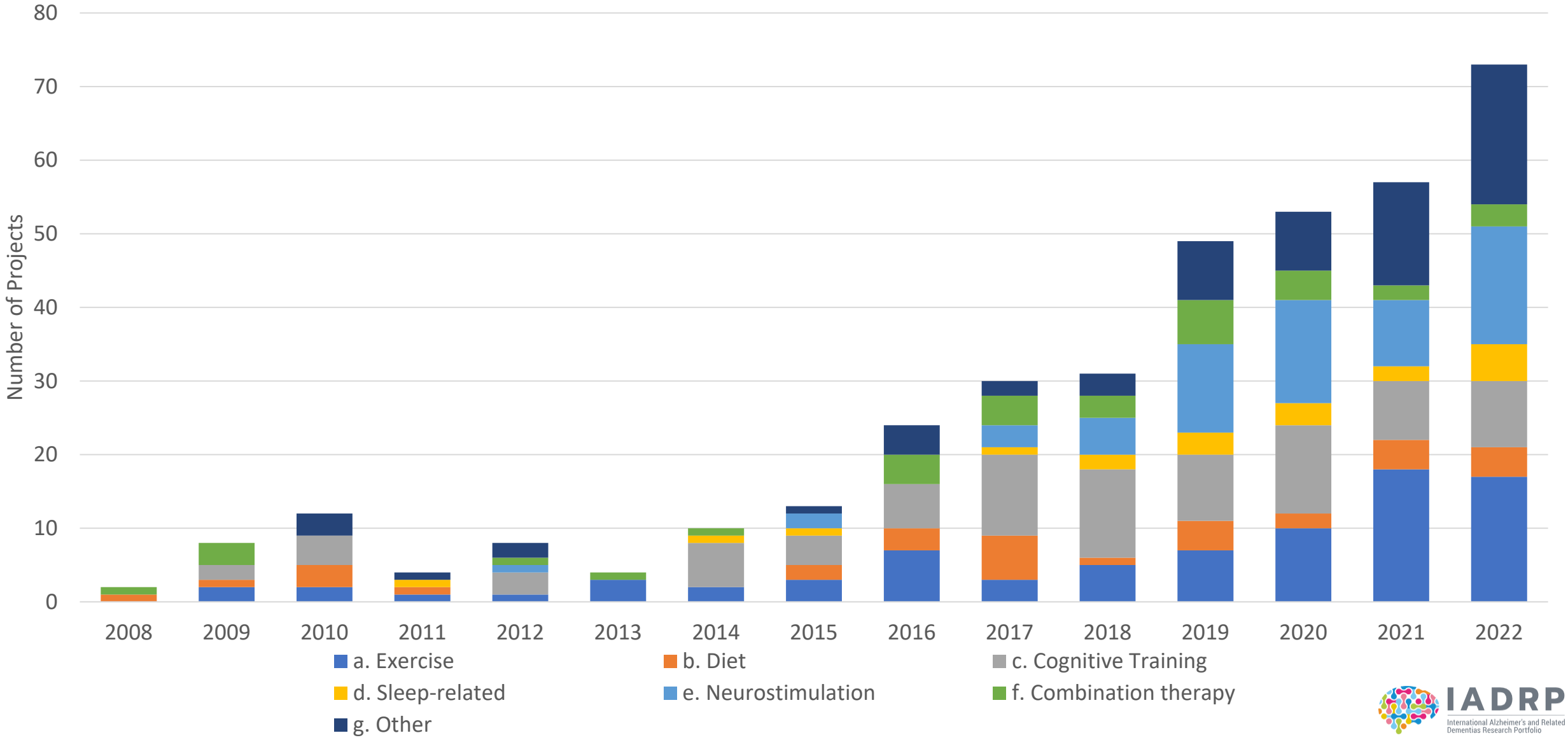
Trends in Number of New NIH-Supported Projects:

AD/ADRD Early-Stage Clinical Drug Development (Phase II/III & Phase III Clinical Trials)



IADRP
International Alzheimer's and Related Dementias Research Portfolio

Trends in Number of New NIH-Supported Projects: AD/ADRD Non-Pharmacological Intervention



IADRP
International Alzheimer's and Related Dementias Research Portfolio

18 Drug Candidates Developed with NIA Support Have Advanced to Human Trials

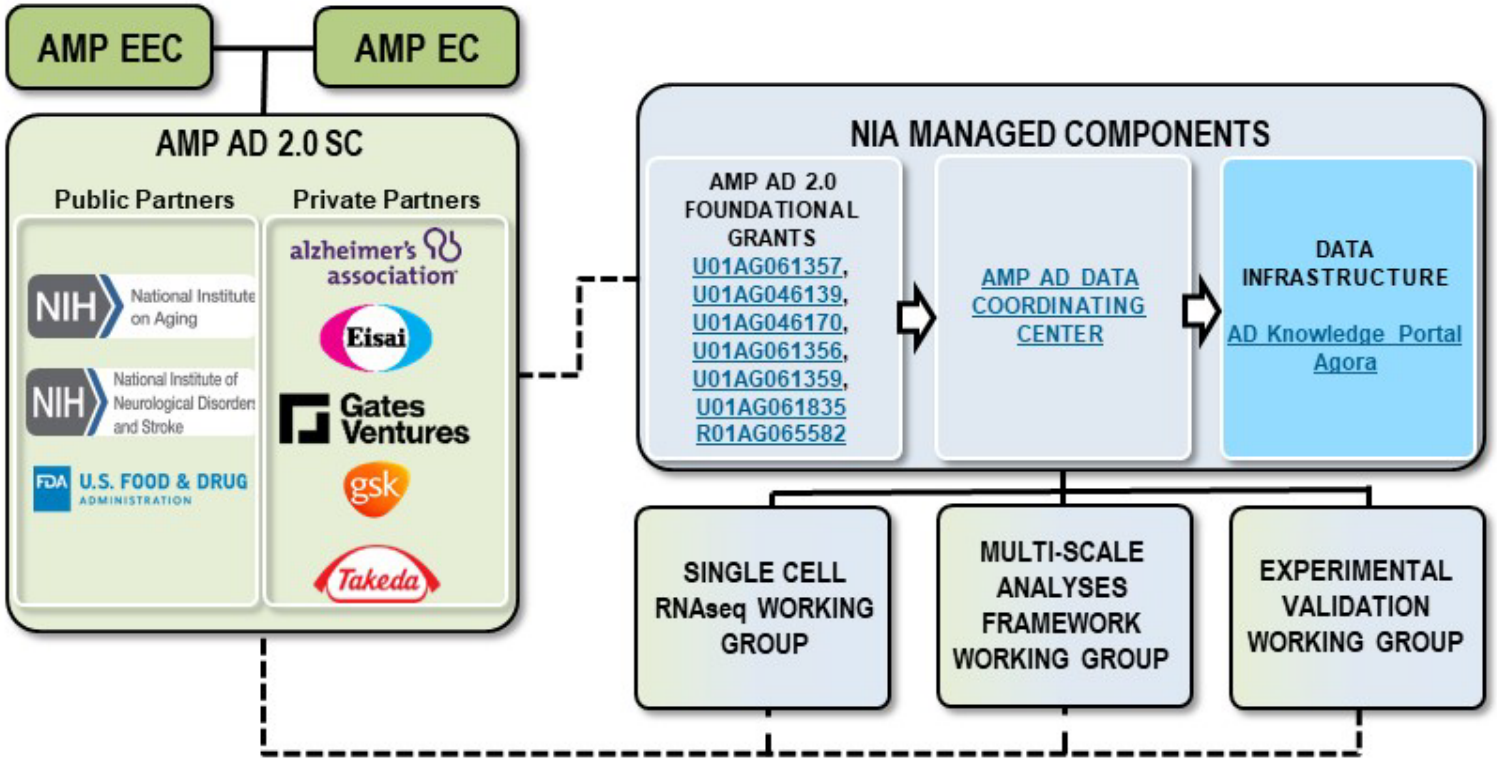
Drug Candidate/Therapy Type	Targeted Biology (IADRP/CADRO Theme)	Current Development Stage
Allopregnanolone	Multi-target	Phase 2
PU-AD/PU-HZ151/Icapamespib	Proteostasis/Proteinopathies	Phase 2
MW150	Inflammation	Phase 2
MW189	Inflammation	Phase 2
LM11A-31	Growth Factors and Hormones	Phase 2
CT1812	Amyloid beta	Phase 2
BPN14770/Zatolmilast	Neuroprotection/Resilience	Phase 2
AV-1959D (DNA vaccine)	Amyloid beta	Phase 1
AAV2-BDNF (Gene Therapy)	Growth Factors and Hormones	Phase 1
ACU193 (Immunotherapy - Monoclonal Antibody)	Amyloid beta	Phase 1
BMS-984923	Neurotransmitter Receptors	Phase 1
MW151	Inflammation	Phase 1
Posiphen	Proteostasis/Proteinopathies	Phase 1
OLX-07010	Tau	Phase 1
CS6253	ApoE, Lipids and Lipoprotein Receptors	Phase 1
NNI-362	Neurogenesis	Phase 1
J147	Metabolism and Bioenergetics	Phase 1
CMS121	Multi-target	Phase 1

AMP AD 2.0: Enabling a Precision Medicine Approach to Target and Biomarker Discovery

Launched March 2021

NIA Press Release | FNIH Press Release

- Expand multi-omic profiling in samples (brain, CSF, blood) from diverse cohorts (African American and Hispanic American)
- Generate longitudinal immunologic profiling data across diverse cohorts (Caucasian, African American, and Hispanic American)
- Expand the existing sn/sc molecular profiling efforts to multiple brain regions and in samples from diverse cohorts



ALZHEIMER GUT MICROBIOME PROJECT

Project 1: 1200 Subjects x 2 time points
Blood, & Feces

NACC

AD Research Centers

Wisconsin · UCD · UCSD · Wake Forest · IU · NYU · Stanford

Project 2: 1724 Diet subjects
Blood, & Feces

US POINTER (1000) · BEAT-AD (120) · MIND (604)

Project 3: Mice Studies with (Human Fecal Transplants 200)
Mouse Blood, Feces, Urine, Liver, Brain

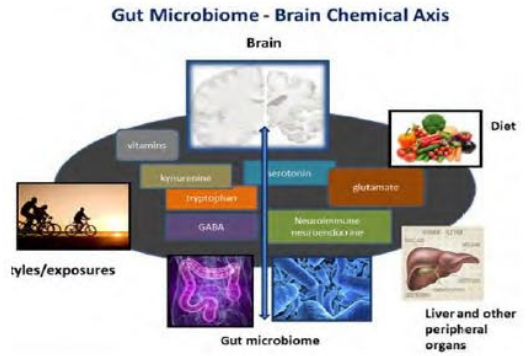
NCRAD Sample Coordination

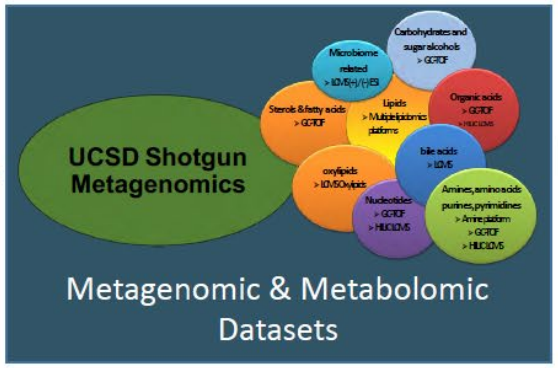
- *Receives fecal/blood samples*
- *Subaliquots blood*
- *Sample Inventory*
- *Creates blinding codes*
- *Distributes*

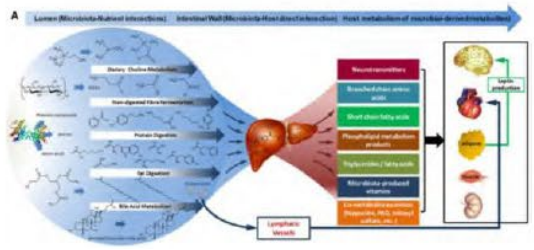
Duke Database & BOX

Contains:

- *De-identified Merged Data*
- *Limited Data Sets*
- *Sociodemographic, clinical, sample, genetic and imaging data*
- *Analysis results*







Overall Aims

Examine the association between the gut microbiome and AD phenotypes.

Define the biochemical axis of communication between the gut microbiome and the brain and identify metabolites that contribute to AD endophenotypes.

Examine mechanistic links between the activity of the gut microbiome and AD pathogenesis, and identify new approaches for AD prevention that target the gut-brain axis.

https://alzheimergut.org