# NAPA Scientific Research Sub-committee: Scientific Advances to 2025 goal

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## Sources of Research Support:

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<tr>
<th>Sources of Research Support</th>
<th>U1LTR02345 (WU ICTS, CTSA)</th>
<th>NIH U01AG042791 (DIAN-TU)</th>
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<tr>
<td>NIA/RF1AG061900 (Plasma Aβ Blood Test)</td>
<td>NIA R01000954 (Mass Spectrometry Resource)</td>
<td>NIH U01AG042791-S1 (DIAN-TU)</td>
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<td>NIA R01AG061900 (Plasma Aβ Blood Test)</td>
<td>NIH P41GM103422 (Biomed Mass Spec)</td>
<td>NIH U01AG046179 (DIAN-TU-AFT)</td>
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<td>NIA R01NS055667 (SILK AB)</td>
<td>NIH R01NS055773 (CNS Tau)</td>
<td>NIH R56AG058267 (DIAN-TU NeXGen)</td>
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<td>NIA R01AG0267670351 (FACS)</td>
<td>NIH U19AG010483 (A4)</td>
<td>NIH R01AG053267 (DIAN-TU NeXGen)</td>
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<td>NIA U54AG056681 (ADRC)</td>
<td>NIH R01AG053798 (A4-TRCPAD)</td>
<td>NIH U01AG059798 (DIAN-TU Primary Prevention)</td>
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<td>NIA R01AG03991 (HAD)</td>
<td>NIH U19AG032438 (DIAN)</td>
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Alzheimer's Association Zenith Grant, American Health Assistance Foundation, Glenn Foundation, Ruth K. Broad Biomedical Research Foundation, Anonymous Foundation, Merck research collaboration, Alzheimer's Association, Association for Frontotemporal Degeneration TDF Biomarkers Initiative, BrightFocus Foundation, Cure Alzheimer's Fund, Foundation for Barnes Jewish Hospital, GHR Foundation, MetLife Foundation, Rainwater Charitable Foundation, Tau SILK Consortium (AbbVie, Biogen, Lilly, Novartis), Centene, the Tracy Family Silo Center (established by the Tracy Family, Richard Frimel and Gary Werths, GHR Foundation, David Payne, and the Willman Family), NF Consortium (AbbVie, Biogen, Roche, UCL, BMS).

**DIAN-TU Pharma Consortium:** (Active: Biogen, Eli Lilly & Co., Janssen, Roche/Genevant, United Neuroscience. Previous: AbbVie, Amgen, AstraZeneca, Forum, Mithridion, Novartis, Pfizer, Soroptimist)

**DIAN-TU Trial Companies:** Eli Lilly and Co., Roche, Janssen, Avid Radiopharmaceuticals

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### Companies:

- **Drs. Randall J. Bateman and David M. Holtzman** are co-owners of CZN Diagnostics. Washington University has equity ownership interest in CZN Diagnostics.
  - Dr. Bateman, Dr. Holtzman, and Dr. Kavari Mawuenyega are co-inventors of the stable isotope labeling kinetics and blood plasma assay technology licensed by Washington University to CZN Diagnostics. Through these relationships, Washington University, Drs. Bateman, Holtzman, and Mawuenyega are entitled to receive royalties and/or equity from the license agreement with CZN. Drs. Bateman and Holtzman receive income from CZN Diagnostics for serving on the scientific advisory board.
  - Dr. Holtzman is an inventor on a patent licensed by Washington University to CZN Diagnostics on the therapeutic use of anti-tau antibodies. CZN has licensed certain anti-tau antibodies to AbbVie for therapeutic development. Washington University and Dr. Holtzman are entitled to royalties from the sale and distribution of the licensed and sublicensed anti-tau antibodies.
  - Dr. Holtzman is an inventor on patents for one of the treatments (solanezumab), currently being tested in the DIAN clinical trials. If solanezumab is approved as a treatment for Alzheimer’s disease or Dominantly Inherited Alzheimer’s Disease, Washington University and Dr. Holtzman will receive part of the net sales of solanezumab from Eli Lilly, which has licensed the patents related to solanezumab from Washington University.
Alzheimer’s disease – the challenge

- The most common form of dementia
- No cure (or disease modifying treatment) currently for Alzheimer's (universally fatal)
- Personal and societal impact
  - >30 million patients suffering from Alzheimer’s worldwide.
  - 6th leading cause of death and only increasing major cause of death.
  - >$200 billion annual cost in US.
  - Undiagnosed or misdiagnosed in half of all patients

NAPA 2025 Goals – 10 year anniversary

- 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
Signature Lesions of Alzheimer’s Disease:
Neuritic amyloid-beta plaque and Neurofibrillary Tau Tangle

amyloid-beta plaque

Tau tangle

Modified Bielschowsky silver impregnation

amyloid deposition, hypometabolism, and cortical atrophy by estimated years to symptom onset

DIAN
Dominantly Inherited Alzheimer Network

Estimated Age of Onset = -25

Estimated Years to Onset = -25.0

Bateman et. al NEJM 2012

Benzinger et. al 2015 PNAS
A brief history of diagnostic development in Alzheimer’s disease

2017 – blood Aβ biomarkers of AD
2018 – blood tau biomarkers of AD
2019 – abundant blood biomarkers of AD
2012 – FDA approval of amyloid PET tracers, tau PET tracers in development
2004 – Amyloid plaque PIB PET tracer developed for AD
1993/1995 – CSF tau and Aβ42 discovered as biomarkers of AD
1993 – ApoE risk factor allele for Alzheimer’s discovered
1991 – Amyloid Precursor Protein mutations discovered that cause autosomal dominant Alzheimer’s disease

1991 – Tau identified as major protein in tangles
1984 – Aβ the major protein in amyloid plaques sequenced
1906-2012 – autopsy the final diagnostic for Alzheimer’s disease
1906 – Dr. Alois Alzheimer describes first Alzheimer’s disease patient – disease of brain – plaques and tangles
Senility known throughout history

100 years of Alzheimer’s disease (AD)

1900 AD is named by Prof. Emil Kraepelin, after his mentor Dr. Alois Alzheimer
1906 Dr. Alois Alzheimer first describes “a peculiar disease”
1930s Advances in microscopy allow detailed study of the brain
1960s Advances in measurement scales allow assessment of functional decline
1976 AD recognized as the most common form of dementia
1984 Beta amyloid identified
1987 First AD drug trial (Tacrine)
1991 First AD risk factor gene identified (APOE-ε4)
2002 Memantine
2004 First report on PIB
2012 First major AD prevention trial
2011 New criteria for diagnosis
2010 Jack et al. publish biomarker model
2011 Aducanumab approved (accelerated approval)

APOE=apolipoprotein E; PIB=Pittsburgh Compound B

Courtesy of Ali Atri
Challenges for disease modification

- **Wrong target?** Which Aβ species, tau species, other? Not all targets may be safe to maximal effect (e.g. general gamma secretase inhibitors)

- **Too little?** Biomarker engagement in the human CNS of the mechanism of action has been inconsistently shown in many trials. No drug has ‘normalized’ AD biomarkers

- **Too late?** Focus on earlier stages of the disease including secondary prevention.

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Gantenerumab Affected Biomarkers of Disease Activity

- **Amyloid plaques substantially reduced**

- **Asymptomatic CDR 0 Participant**
  - Baseline
  - Year 4

- **Symptomatic CDR 0 Participant**

Source: Roche outputs, DMTU calculations/efficient Roche visual/graphics

The DIAN-TU, adapted from Salloway et. al, Nature Medicine 2021
How do we accelerate delivery of scientific advancements to patients sooner and impactfully?

- Discoveries are accelerating due to increased investments from all stakeholders.
- *Unprecedented breakthroughs*: Alzheimer’s disease can now be accurately diagnosed at an early stage, predicted with biomarkers and imaging, and drugs can reverse and normalize some Alzheimer’s disease pathology.
- There are *limitations* in the speed and scale at which these discoveries can be delivered to patients, families, and medical systems, and *opportunities* to improve processes to deliver on the promise of effective preventions and treatments of Alzheimer’s disease by 2025.

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**NAPA Advisory Council Research Subcommittee draft recommendations**

1. A major area of emphasis by all federal agencies involved in the National Plan should be to increase synergies and translation across research, clinical practice, and implementation of care for diagnostic, treatment, and care paradigms that could improve patient outcomes. Stakeholders should *design and implement pipelines for faster translation* of research findings to clinical care, accounting for the entire continuum from research studies through regulatory review and approval, payer review and approval, and delivery of improved diagnosis and care.
2. A top priority remains the urgent need for Congress to continue to increase annual federal research and implementation science funding sufficient to meet these goals across biomedical, clinical, LTSS, and public health settings.
3. Representation and diversity in clinical trials should continue to be increased to address health equity and representation in research.
4. Research into implementation of dementia care to provide best care models should continue to be increased.
5. An understudied area that should be prioritized is the impact of stigma on health-seeking behaviors to improve access to health services.
6. A cross-cutting recommendation across all NAPA subcommittees is to increase research into neurological effects of Covid-19 and development of emergency preparedness programs.
7. Research into causes and relationships between delirium (including Covid delirium) and dementia should be increased, with a focus on how to reduce delirium risk.