NAPA Research Subcommittee
Historical Recommendations and Progress

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Dr. Randall J. Bateman – Disclosure

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DIAN-TU Pharma Consortium: Active: Biogen, Eisai, Eli Lilly & Co., Janssen, Roche/Genentech. *Previous: AbbVie, Amgen, AstraZeneca, Forum, Mithridion, Novartis, Pfizer, Sanofi, United Neuroscience*
DIAN-TU Trial Companies: Eli Lilly and Co., Roche, Janssen, Eisai, Avid Radiopharmaceuticals, Cerveau Technologies
Companies:

Invited Speaker (12 months):
Editorial Board: Alzheimer's and Dementia, Alzheimer's Research and Therapy, The Journal of Prevention of Alzheimer's Disease
Consulting Relationships (12 months): Roche – GSMs for Autosomal Dominant AD Committee (unpaid)

- Dr. Randall J. Bateman co-founded C2N Diagnostics and receives income from C2N Diagnostics for serving on the scientific advisory board. Washington University has equity ownership interest in C2N Diagnostics.
  - Dr. Bateman is an inventor of the stable isotope labeling kinetics, blood plasma assay, methods of diagnosing AD with phosphorylation changes, neurofilament light chain assays and materials, and newer tau assays technologies licensed by Washington University to C2N Diagnostics. Through these relationships, Washington University, Dr. Bateman is entitled to receive royalties and/or equity from the license agreement with C2N.
  - C2N Diagnostics will be analyzing samples from the Knight Family DIAN-TU-001 trial of E2814 for primary, secondary, and exploratory endpoints. Should the DIAN-TU trials impact the value of C2N Diagnostics, Washington University (WU) and Dr. Randall Bateman could directly benefit.
- Dr. Holtzman is an inventor on patents for one of the treatments (solanezumab), previously 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.

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Theme of 2023 NAPA Spring Meeting:
Progress, Challenges, and Opportunities in Translating Research into Clinical Impact

- Perspectives from:
  - Food and Drug Administration
  - Center for Medicare and Medicaid Services
  - Veterans Affairs
  - NAPA Advisory Council
  - Industry (Biogen and Eisai)
  - Healthcare systems (Mass General Brigham)
- Discussion on Coordination of NAPA goals: Challenges & Opportunities
  - How do we implement optimal access and utilization of disease-modifying treatments?

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Current landscape of Alzheimer's disease treatments and diagnostics

- FDA accelerated approval of two anti-amyloid monoclonal antibodies, aducanumab (Aduhelm) and lecanemab (Leqembi)
  - VA coverage decision based on FDA accelerated approval March 13th
  - FDA full approval decision on lecanemab July 6th
  - CMS decision on lecanemab to be made
- Positive results from Phase 3 study of donanemab (May 3rd)
- Blood-based biomarkers (amyloid-β 42/40, p-tau217, and others) identify amyloid pathology with high accuracy and are on market for clinical use, but not yet FDA or payer approved, or used routinely in practice

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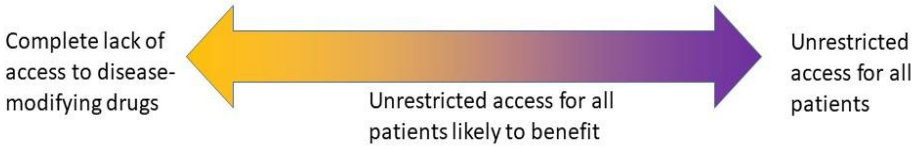
Disease-modifying treatments for Alzheimer's disease are available for the first time.

What happens now?



How do we implement optimal access and utilization of disease-modifying treatments?

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What are some factors that could influence decision-making for drug access in addition to individual medical considerations?

- Individual level factors: insurance status, access to specialized medical centers, family and caregiver support, demographic factors
- Capacity of medical systems to deliver treatments and treatment monitoring
  - Capacity of providers (neurologists and other specialists, primary care providers)
  - Infrastructure (PET and MRI scanners, infusion centers)
- Education and implementation of appropriate diagnosis and treatments
- Policy or Payer restrictions
  - E.g., restriction of subgroups of patients, providers, diagnostic access, requirement to enter studies or registries, reimbursement rates

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Summary of NAPA research subcommittee historical recommendations (2012-2022)

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Developing a scientific road map (2012-2022)

- The annual National Plan should encourage a sense of urgency about providing a robust, comprehensive, collaborative and transformative scientific road map for achieving the goal of preventing, effectively treating, and providing effective care and services for AD/ADRD by 2025, as well as continuous progress and improvement thereafter (including interim milestones).
  - This recommendation continues to be relevant.

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Increased research funding (2012-2022)

- A top priority remains the urgent need for Congress to continue to increase annual federal research and implementation science funding (by NIH and other agencies) sufficient to meet NAPA goals across biomedical, clinical, long-term services and supports, and public health settings. In developing their professional judgment budget, the NIH should identify the total science-driven funding needs for the budget year and also address the scale of needs anticipated through 2025.
  - Substantial progress in the last decade, however, further increased future funding still needed.

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Standardization of terminology (2016-2021)

- Emphasis should be given to the standardization of terminology across the spectrum of cognition in neurocognitive disorders by all agencies involved in the National Plan, to reduce ambiguity over confusing or overlapping terms, reduce stigma associated with AD/ADRD, and improve public awareness of AD/ADRD and access to relevant resources and services.
  - This has been partially addressed.
  - NIA has participated in an ongoing effort (i.e., a terminology working group) led by previous members of the NAPA Council (Ron Petersen and Angela Taylor). Updates have been shared during previous research summits.

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Enhancement of recruitment efforts, representation, and health equity (2017-2022)

- A major area of emphasis by all federal agencies involved in the National Plan should be the enhancement of recruitment efforts for research involving those with, or at risk of developing, AD/ADRD. NAPA federal agencies should investigate and propose successful models for increasing involvement of people with AD/ADRD in clinical research studies, including trials.
  - NIA led an effort to develop comprehensive goals and strategies to enhance recruitment into clinical research, particularly focusing on underrepresented communities.
  - NIH has begun - and will continue - to closely track enrollment and retention in clinical studies to ensure investigators are meeting requirements and adequately planning (which includes setting appropriate recruitment goals).

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Infrastructure for sharing research data and samples (2018-2021)

- Federal agencies should develop a strategy and infrastructure to increase ethical and open sharing of, access to, and utilization of research data and samples, in collaboration with academia, biotech and information system industries.
  - This has been partially addressed at this time. NIH released a new NIH Data Management and Sharing Policy, effective January 25, 2023. This new policy will effectively increase open sharing of and access to research data.

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Engagement of AD/ADRD community (2018-2022)

- All AD/ADRD research should establish the engagement of the AD/ADRD community as a standard practice in both participating in setting national research priorities for AD/ADRD and throughout all stages of clinical research and care, services and support research.
  - NIH encourages input from the AD/ADRD community in numerous ways. The primary way the NIA seeks input from the community is through the triennial summits. External stakeholders, including patients and care partners, have served on planning committees for these events and have contributed to the development of "gaps & opportunities" (i.e., output from the summits).

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Early detection of AD (2012-2017, 2022)

- The National Plan should continue to promote early detection and diagnosis of AD/ADRD by encouraging cognitive assessment while at the same time CMS works to confirm measurement strategies to track progress through the implementation of new quality measures. CMS should redesign Medicare coverage and physicians' and other health care providers' reimbursement to encourage appropriate diagnosis of AD, provide care planning to diagnosed individuals and their caregivers, and active referral to long-term services and supports.
- High-priority areas of research include early detection of cognitive decline and precursors of dementia at an individual level, identification of the pathology(s) causing a person's trouble, and development and testing of treatments targeted appropriately at the biologic underpinnings in a given individual.
  - This has become an even greater area of need with the advent of blood-based biomarkers and disease-modifying treatments.

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Increase research into care implementation, improving quality of life (2022, 2015-2016)

- Research into implementation of dementia care to provide best care models should continue to be increased. Federal agencies in partnership with national organizations and states, support research to identify standards and best practices to improve quality of life and long-term support services for individuals and families affected by AD/ADRD.
  - There continues to be a great need for implementation research. Some work is being done by external groups, foundations, etc.
  - NIA's Division of Behavioral and Social Research has been working to expand research on intervention development and lay groundwork for real-world implementation of these interventions. Other groups could further research this with funding support.

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2022 NAPA Scientific Research Sub-committee 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.

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Primary recommendation from 2022:

Increase synergies among all federal agencies involved in the National Plan to facilitate faster and more comprehensive translation of research into clinical practice of evidence-based advancements and approved diagnostic, treatment, and care paradigms to improve outcomes for people with dementia.

A. Federal agencies responsive to NAPA should work together to identify areas with the opportunity for translation of research to clinical practice to occur more rapidly.
   a. Examples include:
      i. ***Coordination in the review of clinical studies*** that demonstrate effectiveness of treatments and tests to determine the standards of clinical utility and approval for access and payment.

      ii. Collaboration by the agencies responsible for approval for access and payment on an ***agreed set of measures, analytic tools, and standards of clinical benefit*** for functional, clinical, cognitive, patient reported, and other outcomes applicable for review is needed to guide clinical studies.

      iii. NAPA agencies should also evaluate opportunities to better implement research supported strategies to improve the health and care of AD/ADRD and ***report recommendations to NAPA and the appropriate government bodies to make needed changes to implement improvements***.