Disease-Modifying Treatments for Alzheimer's Disease: Research Questions to Address

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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

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)

Companies:
- 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.

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Identification of patients who would benefit from anti-amyloid therapy

- Questions remain about the magnitude of benefit of anti-amyloid therapy on the following groups:
  - Stage of disease
  - Women
  - *APOE ε4* homozygotes
  - Racial and ethnic minority groups
  - People with mixed pathologies
  - People with a variety of comorbid diseases and conditions
    - E.g., superficial siderosis, macrohemorrhages, >5 microhemorrhages
  - People with cognitive decline and evidence of amyloid deposition in brain, but who were not eligible for clinical trials
    - E.g., Down syndrome, very early onset Alzheimer's disease, familial autosomal dominant Alzheimer's disease caused by mutations, etc.

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Side effects and adverse reactions

- What are the range and frequency of side effects and adverse reactions in people treated with anti-amyloid therapy and how to best monitor and manage these?
- Identification of people at high risk for serious adverse reactions (e.g. *APOE* ε4 alleles, MRI scans for cerebral amyloid angiopathy, other factors)
  - Missing data on many risk parameters and current practice guidelines are not based on comparative results, but instead on inclusion criteria of trials.
- Risk of anti-coagulation
- Risks of co-morbidities, age, and other factors

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Management of patients on DMTs – how to optimize benefits?

- How to manage patients treated with anti-amyloid therapy over time
  - Optimal dose
  - Optimal duration
  - Stage of disease and disease progression while on treatment
  - Effects of multiple co-morbidities and medications
  - Biomarker testing after a certain duration on treatment
    - Should blood/CSF/PET be repeated? If so, when?
  - What about people who participated in clinical trials of DMTs and then are prescribed DMTs in the clinic?
  - Switching medications – serial or concurrent treatments?

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How to implement DMTs for the population

- How to identify populations who will benefit
  - Specialty practices don't have capacity for the millions who could benefit
  - Primary care practices will be needed as part of the solution
  - How to integrate primary care into screening, diagnosing, treating, and referring to specialty clinics?
  - Inclusion of under-represented groups in clinical trials, clinical testing, and treatments
- How to test for Alzheimer's disease?
- Implementation of blood, CSF and PET scans – how to coordinate and cover these?
- Infrastructure for treatment and monitoring
  - Access to dementia specialists, infusion centers, MRI, radiologists
- How to account for the time window of benefit of DMTs in implementation plans (thousands a day advancing out of benefit window)?

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Estimating the impact of AD DMTs

- How much long term benefit is achieved in delaying disease progression or disability? (e.g., years to disability)
- What is the relative magnitude of benefit of treating at different stages of disease, including asymptomatic presence of pathology?
- What percent of eligible patients benefit under different diagnostic and treatment models?

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Future directions

- Can anti-amyloid treatment of cognitively normal people identified as high risk for AD based on biomarkers help prevent or delay cognitive decline?
  - Pending results of AHEAD and Trailblazer-3 trials
- Can combination treatments provide more beneficial effects compared to DMT monotherapy (e.g., combined anti-amyloid and anti-tau treatments or combined anti-amyloid treatments)?
- Can precision medicine approaches detect the disease earlier, tailor treatment plans to an individual's unique disease and risk profile, and improve outcomes?

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