# 2024 Spring ADRC Meeting
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NIH
National Institute on Aging
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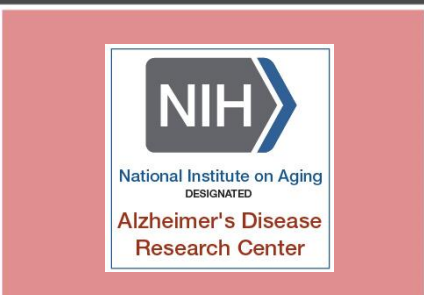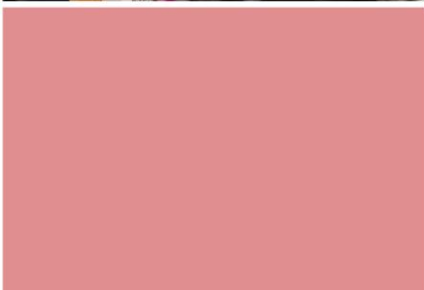
Disclosures

- I have received grants from NIA/NIH, Department of Veterans Affairs, State of Wisconsin, and UW-Madison to support my research program

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- UW-Madison has received grants from pharmaceutical companies for me to serve as a site PI to conduct treatment trials involving patients with MCI and dementia
- I have no conflicts of interest for this presentation

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Overarching Scientific Themes

A) **Non-amyloid mechanisms of AD/ADRD – TDP-43**

B) **Generalizability of AD/ADRD Research**

- The scientific themes permeate nearly all the sessions of this 2-day meeting

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TDP-43: Rationale for Selection as a Scientific Theme

Converging evidence that TDP-43 is an integral or co-occurring pathology among multiple neurodegenerative diseases, including Alzheimer's disease

Regulates gene expression through involvement in RNA splicing, trafficking, stabilization, and microRNA synthesis

Seen on brain autopsy in between 50-60% of decedents diagnosed with AD and other neurodegenerative disease including LBD, Parkinson's disease, Huntington's disease, CBD, and CU older adults

Contributes to cognitive, behavioral, language, and psychiatric symptoms, and mortality

TDP-43: Rationale for Selection as a Scientific Theme

Primary proteinopathy in patients with ALS, FTLD-TDP, and LATE-NC

Significant advances in understanding the genetics, structure, and molecular mechanisms underlying prion-like propagation of TDP-43

New disease modifying treatments are being tested for FTLD and ALS-*C9orf72*

TDP-43 Focused Presentations

A) Basic Biology of TDP-43
Speaker - Margaret Flanagan, MD
South Texas ADRC

B) Advances in Clinical Definitions and Biomarker Development for LATE
Speaker - David Wolk, MD
Penn ADRC

Generalizability of AD/ADRD Research: Rationale for Selection as a Scientific Theme

Generalizability and translation of research findings from the ADRC-network to larger marginalized populations across the US is a notable limitation and must be addressed

Enhancing generalizability is a top priority for the field of dementia research

Sociocultural and genetic diversity of cohorts will improve generalizability and help examine the effects of genetics, lifestyle, and environmental factors on risk and resilience to ADRD

Limitations in generalizability of AD/ADRD research is multifactorial.

1. "Selection bias" due to creation of "convenience" rather than "population-based" cohorts and "Survival bias" due differences in survivability between races

2. Limited diversity of ADRC research cohorts due to problems in recruiting URG participants
   ○ Legacy of unethical and abusive treatment of URGs in medical research
   ○ Exclusion of participants due to medical comorbidities, especially vascular diseases
   ○ Limited access to specialty clinics at academic hospitals

Generalizability of AD/ADRD Research: Rationale for Selection as a Scientific Theme

Generalizability can also be enhanced by using Real-world data (RWD), especially from electronic health record (EHR)

Real world data (RWD) from EHR provides evidence that is clinically meaningful and enhances generalizability

RWD using EHR allows creation of sophisticated algorithms and computational models that, among other outcomes, can help to:

- ○ Identify a research cohort for AD outcomes research
- ○ Examine various risk factors for ADRD, including clinical characteristics (age, gender, race, ethnicity, insurance, BMI, etc.), medical comorbidities, SDOH, etc.
- ○ Calculation of time-to-event outcome of interest
- ○ Examine response to treatments and care related outcomes

Generalizability Focused Presentations

A) Tackling the Landscape of Selection Bias and Representation in AD/ADRD Research: WHO We Study Matters
Speaker – Rachel Whitmer, PhD
UC Davis ADRC
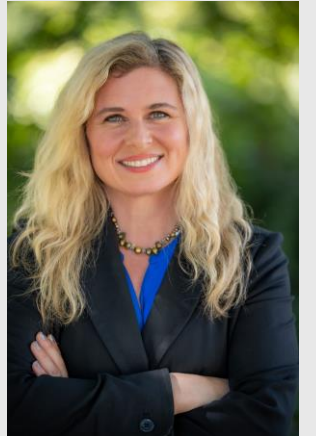
B) Generalizability - Real World Data / EHR Focus
Speaker - Robert Califf, MD
Commissioner Food and Drugs, FDA