Gene Therapy for Alzheimer's Disease and Ethical Aspects of Genome Editing

DUKE UNIVERSITY | BASS CONNECTIONS

Brain & Society

Angela Wei[1], Anna Yang[1], Ishika Gupta[3], Mohanapriya Cumaran[2], Natalie Asmus[2], Sahil Malhotra[2], Suraj Upadhya[1], Boris Kantor[2], Misha Angrist[3], Ornit Chiba-Falek[1]

[1]Division of Translational Brain Sciences, Department of Neurology, Duke University Medical Center;
[2]Center for Genomic and Computational Biology, Duke University Medical Center;
[3]Initiative for Science and Society and Social Science Research Institute, Duke University

Mission: To develop a disease modifying therapy (DMT) for late onset Alzheimer's disease (LOAD) using gene therapy.

Introduction:

- Alzheimer's disease (AD) is a progressive neurodegenerative condition that causes memory loss and cognitive decline
- AD currently affects 5.8 million Americans.
- Mechanisms and causes behind onset and progression remain unknown; no cure currently exists.
- E4 variant of *APOE* gene is the strongest reproducible genetic risk factor for LOAD, making it an ideal target for gene therapy
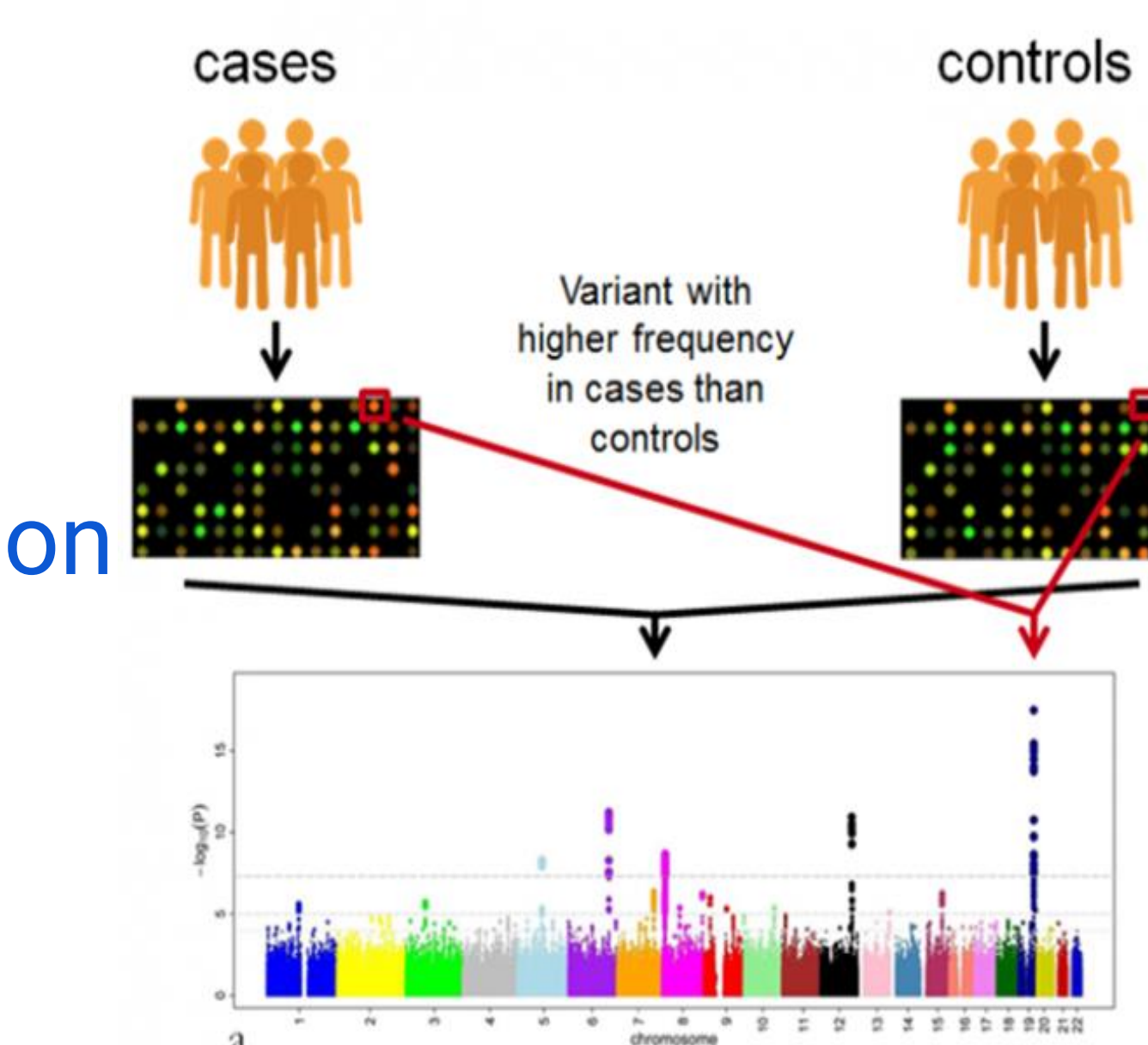
Genetic Risk Variants of LOAD
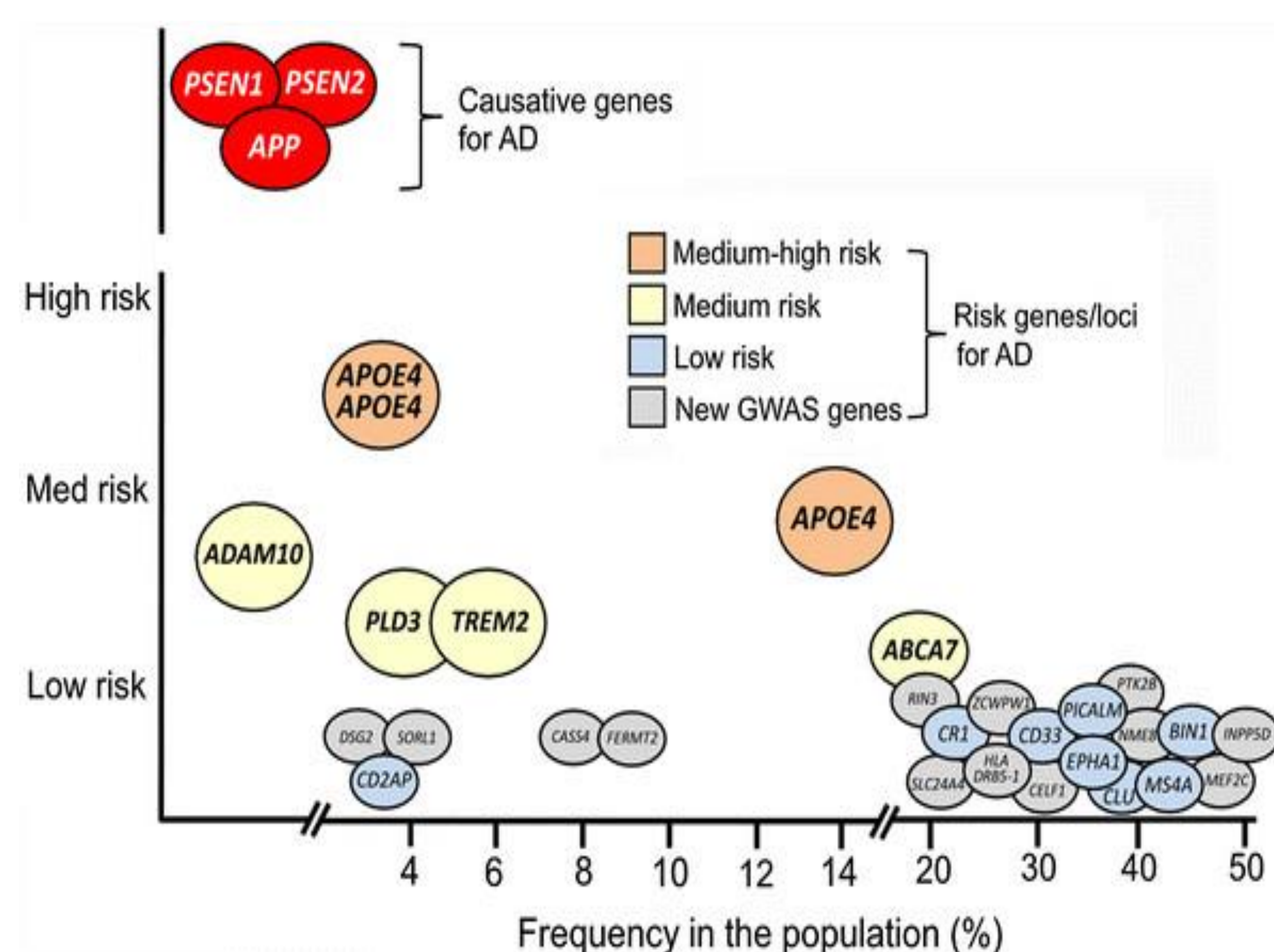
Methods

Identify high-risk genetic variants

Genome-wide Association Studies
Polygenic Risk Scores
APOE E4

Study variant function & mechanisms

Human Stem Cell Models
Animal Models
Organoid (3D) Models

Target variants with gene therapy tools
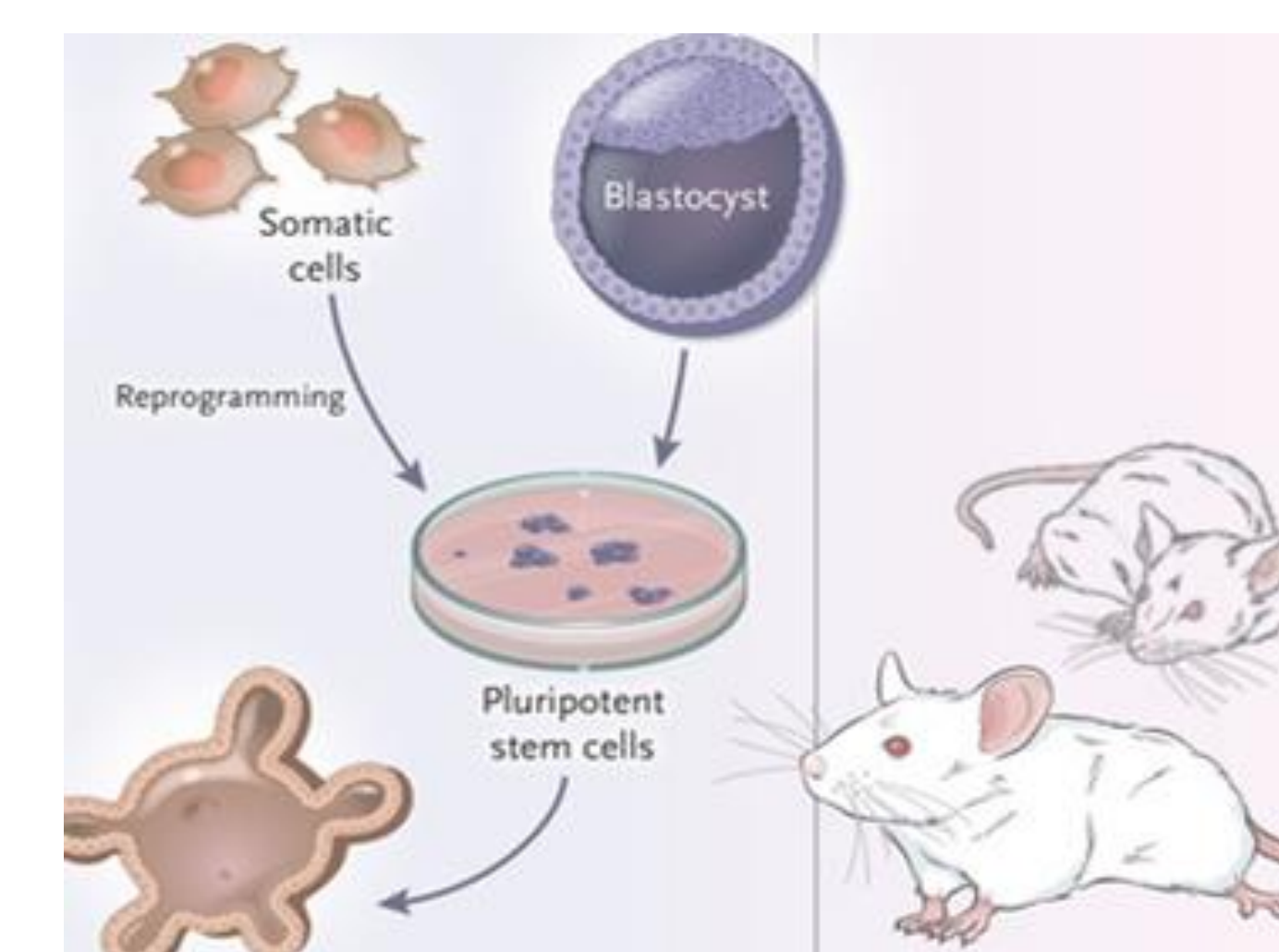
CRISPR-Cas9 Editing
Epigenetic Manipulation
Viral Vectors

Prepare for real-world roadblocks
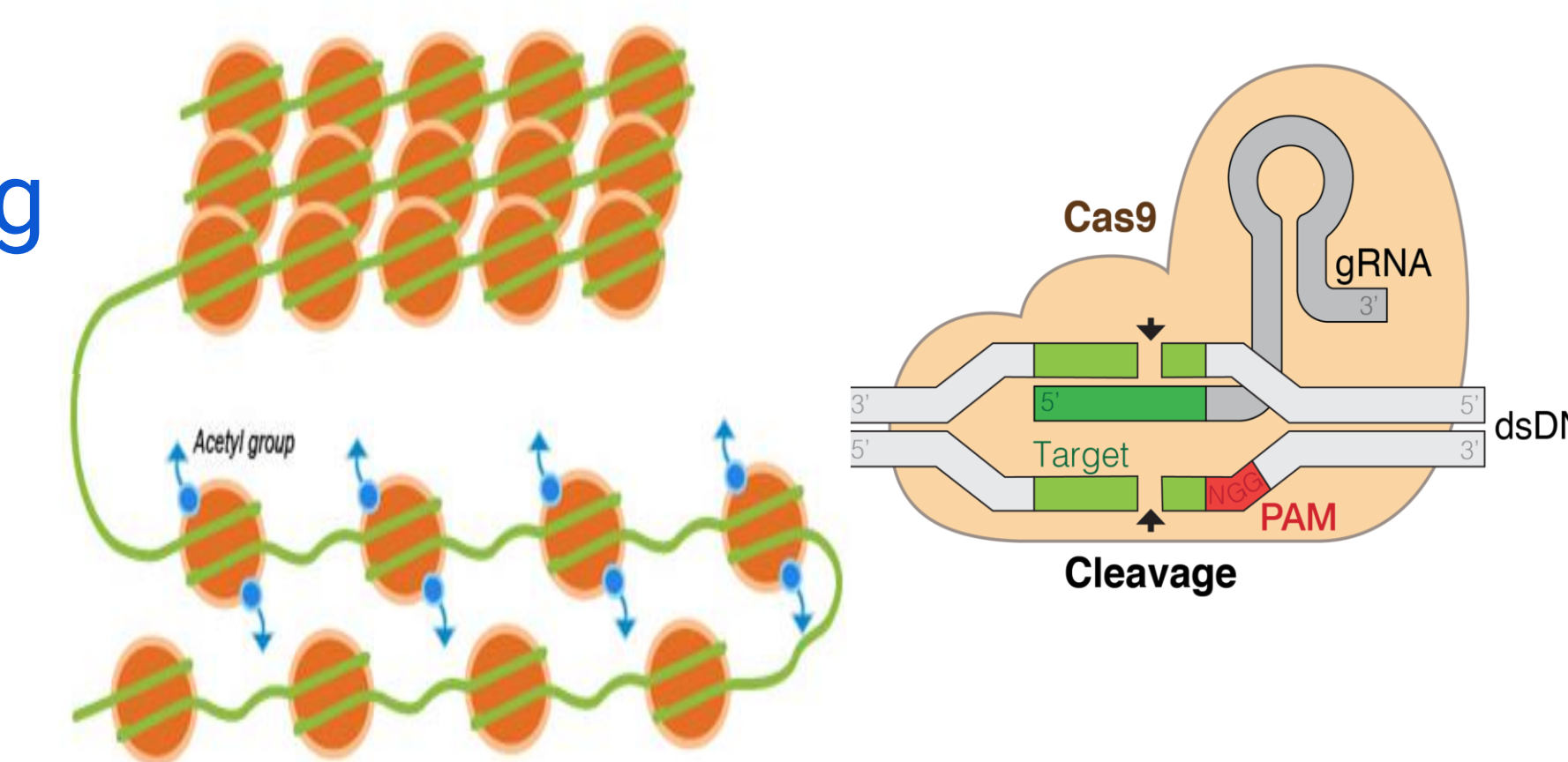
Financial Toxicity
Payment Programs
Price Inflation

Future Directions:

- Shift the paradigm of AD drug development towards precision methods using: Antisense Oligonucleotides (ASO), Monoclonal Antibodies (mAbs), and Gene Editing
- Develop additional gene therapy tools that allow for high levels of temporal and spatial control
- Generate more robust modeling systems for screening therapeutics
- Predict neuropsychiatric symptoms (e.g. depression) in AD patients using polygenic risk scores
- Predict and combat the ethical and financial difficulties AD patients will face once gene therapies arrive, using Multiple Sclerosis (MS) as a lens

Increasing Costs of MS DMTs
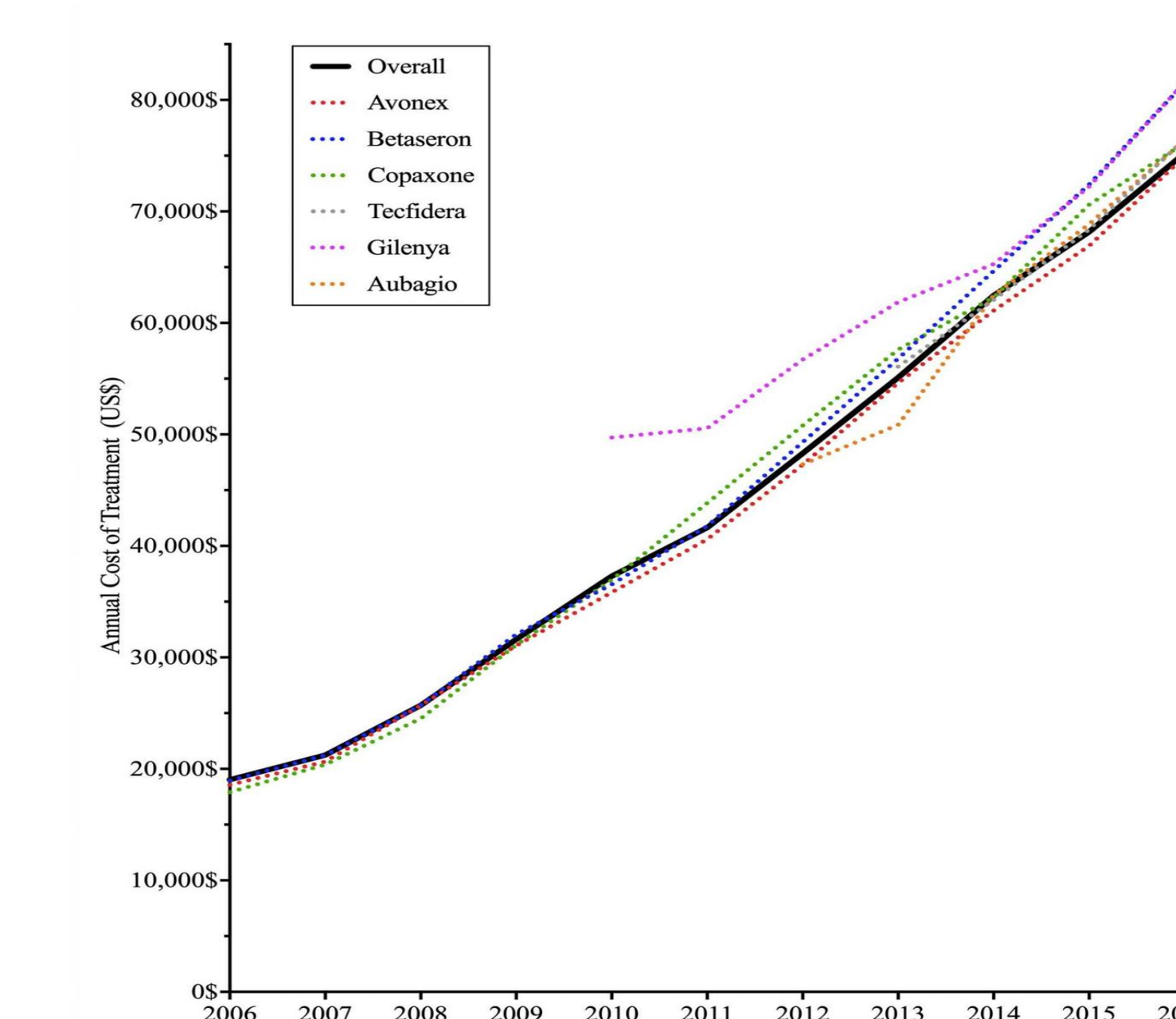
References
Li et al., 2019; Walter 2017; San-Juan-Rodriguez 2019; Yamazaki et al., 2017