Ethical Issues in Alzheimer's Disease Clinical Trials: Genetic and Biomarker Disclosure

Joshua Grill

Associate Professor of Psychiatry and Human Behavior

Alzheimer's Disease Research Center

Institute for Memory Impairments and Neurological Disorders

University of California, Irvine

Jason Karlawish

Professor of Medicine, Medical Ethics and Health Policy

Penn Neurodegenerative Disease Ethics & Policy Program

University of Pennsylvania

AD Prevention Trial Designs

1. Blinded enrollment – a proportion of participants who do not meet biomarker or genetic criteria are enrolled so that enrollment is not *de facto* disclosure of biomarker status. Those participants are non-randomly assigned to placebo and complete the entire protocol.
2. Transparent enrollment – only participants meeting biomarker or genetic criteria are enrolled and randomized to drug or placebo

What Makes Clinical Research Ethical?

- Informed consent
- Independent review
- Social value
- Scientific validity
- Fair selection of subjects
- Favorable risk-benefit ratio
- Respect for enrolled subjects

Emanuel et al. JAMA 2000.

Special Issues in Informed Consent

Blinded Designs

- Procedural risks (blood draws, neuroimaging, lumbar puncture) without potential benefit
- Unwanted disclosure of risk status, e.g., adverse events

Transparent Designs

- Risk of learning risk status but not receiving effective therapy or even qualifying for the trial
- Unknown what proportion become impaired or what timeline will impairment occur?

Is the Requirement of Disclosure Coercion?

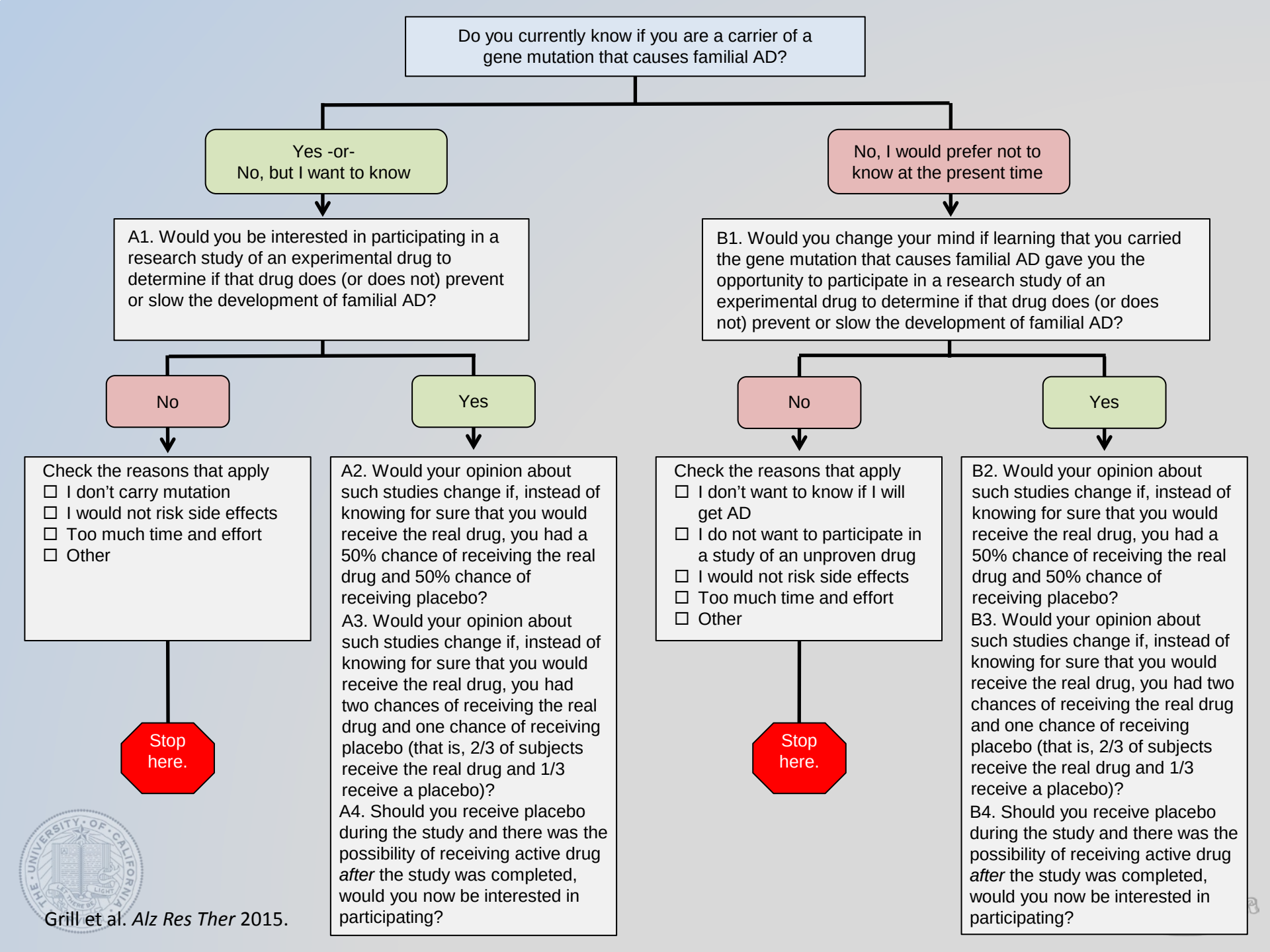
- Coercion: overt threat of harm to elicit compliance
- Undue influence: improper or inappropriate reward to elicit compliance
- Transparent enrollment is neither coercive nor does it offer undue influence
- Informed consent is critical to respect the autonomy of participants

The Belmont Report, 1978. Kim et al. *Neurology* 2015.

To Be Ethical, Prevention Trials Must Be Feasible

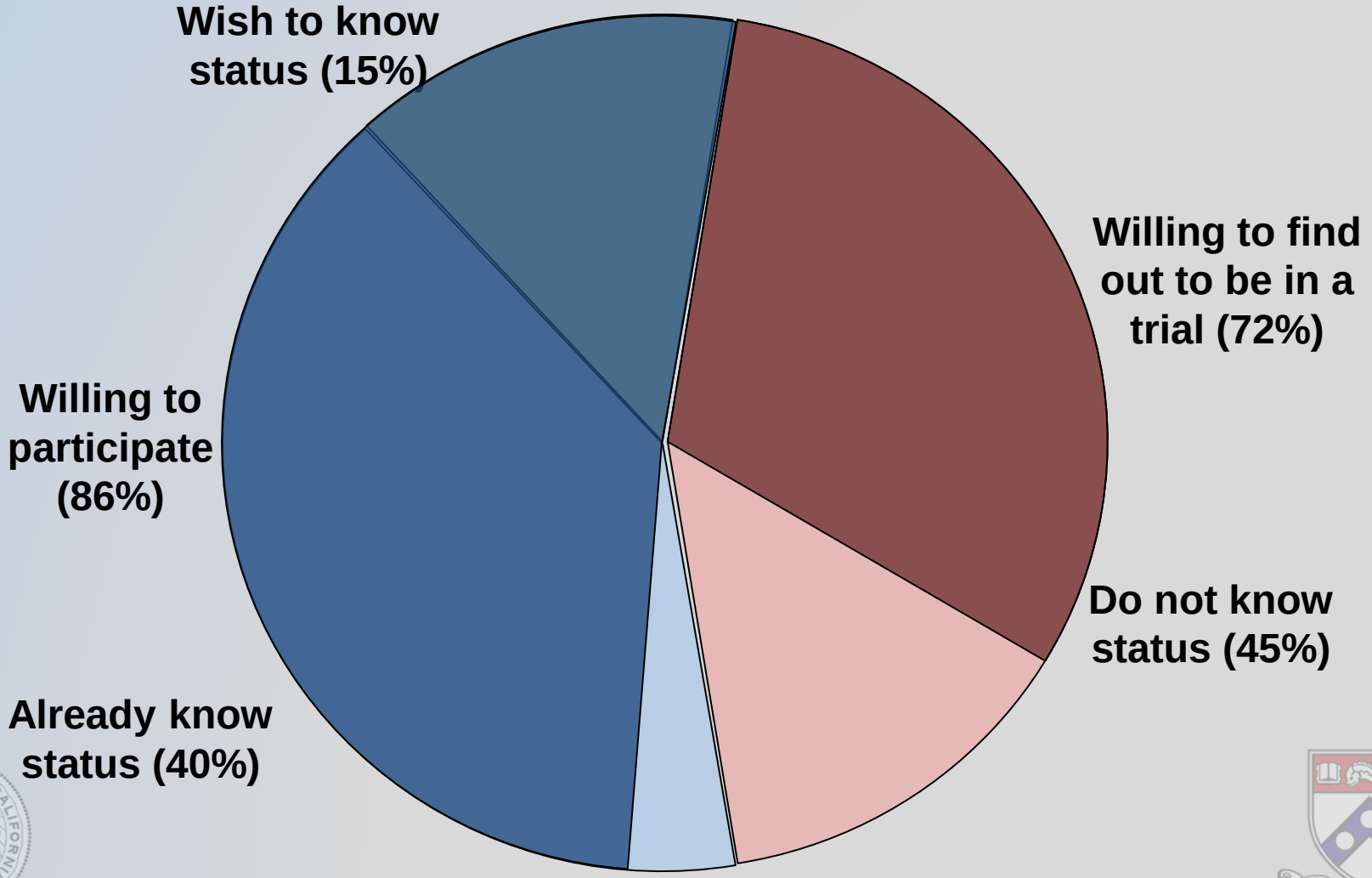
- *"…If persons who at baseline wish not to know their mutation [genetic/biomarker] status choose not to participate, then a majority of persons at risk for the condition would be excluded."*

Kim et al. *Neurology* 2015



Grill et al. *Alz Res Ther* 2015.

Genetic Testing in Autosomal Dominant AD Trials



Grill et al. *Alz Res Ther* 2015.

N=80 respondents from DIAN longitudinal study

Should Transparent Designs Be Implemented in DIAD?

- Hypothetical scenarios may not reflect actual behaviors

- Full informed consent and counseling (which were not part of the study) may reduce the desire to undergo testing

+ Taking action

+ Hope associated with research

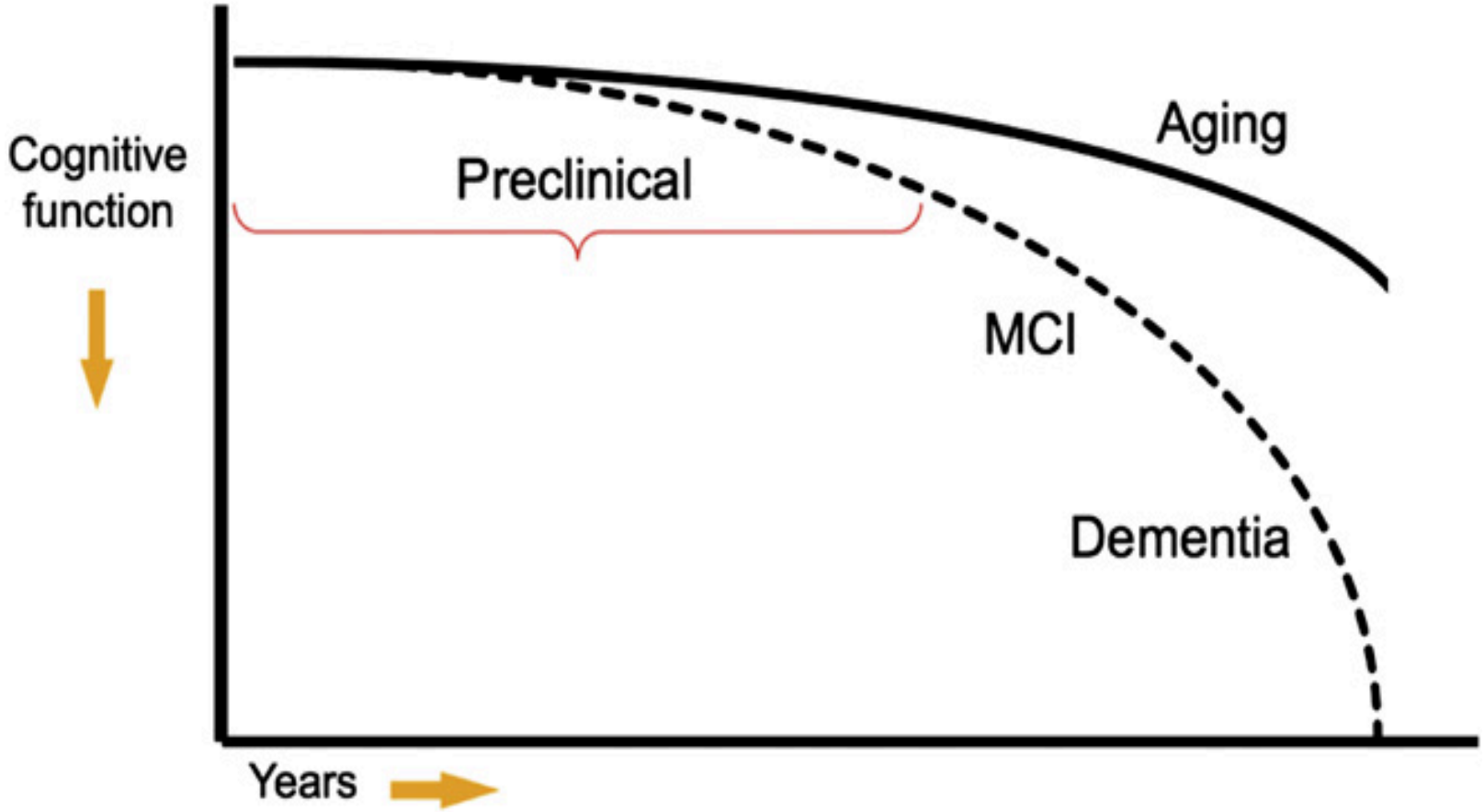
+ Contributing to science

Grill et al. *Alz Res Ther* 2015.

Thank You

- Participants are the heroes of the fight against Alzheimer's disease
- **Thank you!**
- jgrill@uci.edu

The Continuum of Alzheimer's Disease



Sperling et al. 2011 Alz & Dem

A4 Study:

Anti-Amyloid in Asymptomatic Alzheimer's

Amyloid Imaging Disclosure Process. Step by step education, assessment of mood and motivation, & monitoring of mood and well-being

Harkins et al. "Development of a process to disclose amyloid imaging results to cognitively normal older research participants." Alz Res and Therapy. (2015) 7:26.

Available as Open Access!

Telling others about your amyloid PET scan results

- Sharing the result
  - Who did you tell it to and how did they react?
  - Who didn't you tell it to and why?
- How do you feel about your future?

Types of Stigma

- **Anticipated**
  - Expectations of experiencing prejudice and discrimination among the stigmatized
- Received
  - Overt behaviors of rejection and devaluation experiences of negative interactions
- Enacted
  - Behaviors of differential treatment by stigmatizers
- **Self**
  - Internalized acceptance of stereotypes and prejudice

- Pescosolido and Martin 2015

Anticipated stigma

- Anticipated stigma
  - Expectations of experiencing prejudice and discrimination among the stigmatized
  - Influences willingness to seek treatment by people diagnosed with mental illness (Vogel 2006; 2007)
- Anticipated stigma associated with amyloid imaging might challenge the wisdom of amyloid imaging if the goal is to encourage people to get treatment when one is available
    - Will receiving elevated amyloid result lead some people to see themselves as less worthy? Will others see them as less worthy?

Harkins et al. “Development of a process to disclose amyloid imaging results to cognitively normal older research participants.”

Alz Res and Therapy. (2015) 7:26.

SOKRATES-I – amyloid disclosure

SOKRATES-II – ApoE disclosure

REVEAL-SCAN – impact of amyloid disclosure on cognition

Thank you!

JasonKarlawish@gmail.com

www.jasonkarlawish.com