

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

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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



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



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.”*



Do you currently know if you are a carrier of a gene mutation that causes familial AD?

Yes -or-
No, but I want to know

No, I would prefer not to know at the present time

A1. Would you be interested in participating in a research study of an experimental drug to determine if that drug does (or does not) prevent or slow the development of familial AD?

B1. Would you change your mind if learning that you carried the gene mutation that causes familial AD gave you the opportunity to participate in a research study of an experimental drug to determine if that drug does (or does not) prevent or slow the development of familial AD?

No

Yes

No

Yes

Check the reasons that apply
 I don't carry mutation
 I would not risk side effects
 Too much time and effort
 Other

A2. Would your opinion about such studies change if, instead of knowing for sure that you would receive the real drug, you had a 50% chance of receiving the real drug and 50% chance of receiving placebo?
A3. Would your opinion about such studies change if, instead of knowing for sure that you would receive the real drug, you had two chances of receiving the real drug and one chance of receiving placebo (that is, 2/3 of subjects receive the real drug and 1/3 receive a placebo)?
A4. Should you receive placebo during the study and there was the possibility of receiving active drug *after* the study was completed, would you now be interested in participating?

Check the reasons that apply
 I don't want to know if I will get AD
 I do not want to participate in a study of an unproven drug
 I would not risk side effects
 Too much time and effort
 Other

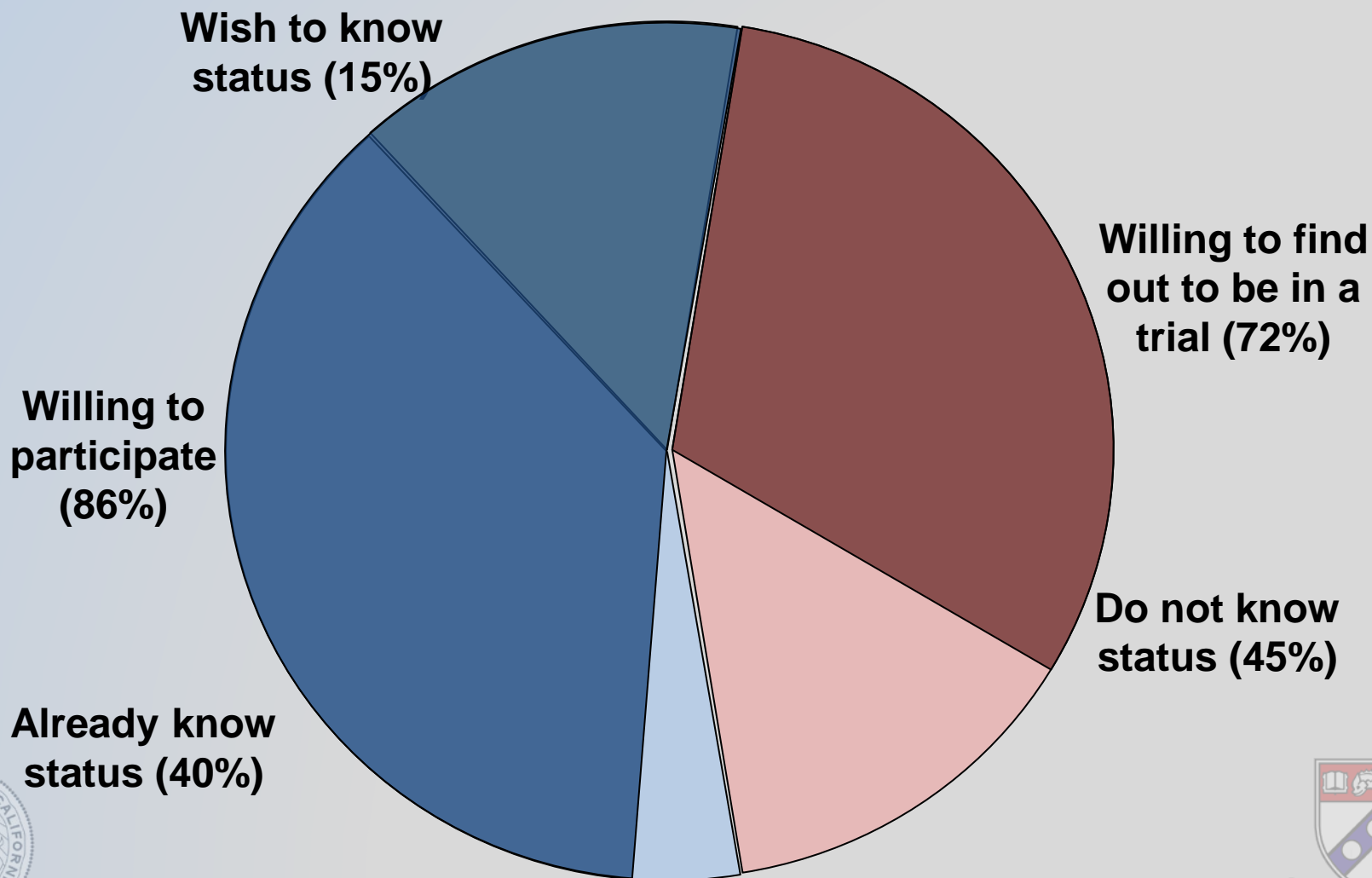
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Stop here.

Stop here.



Genetic Testing in Autosomal Dominant AD Trials



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

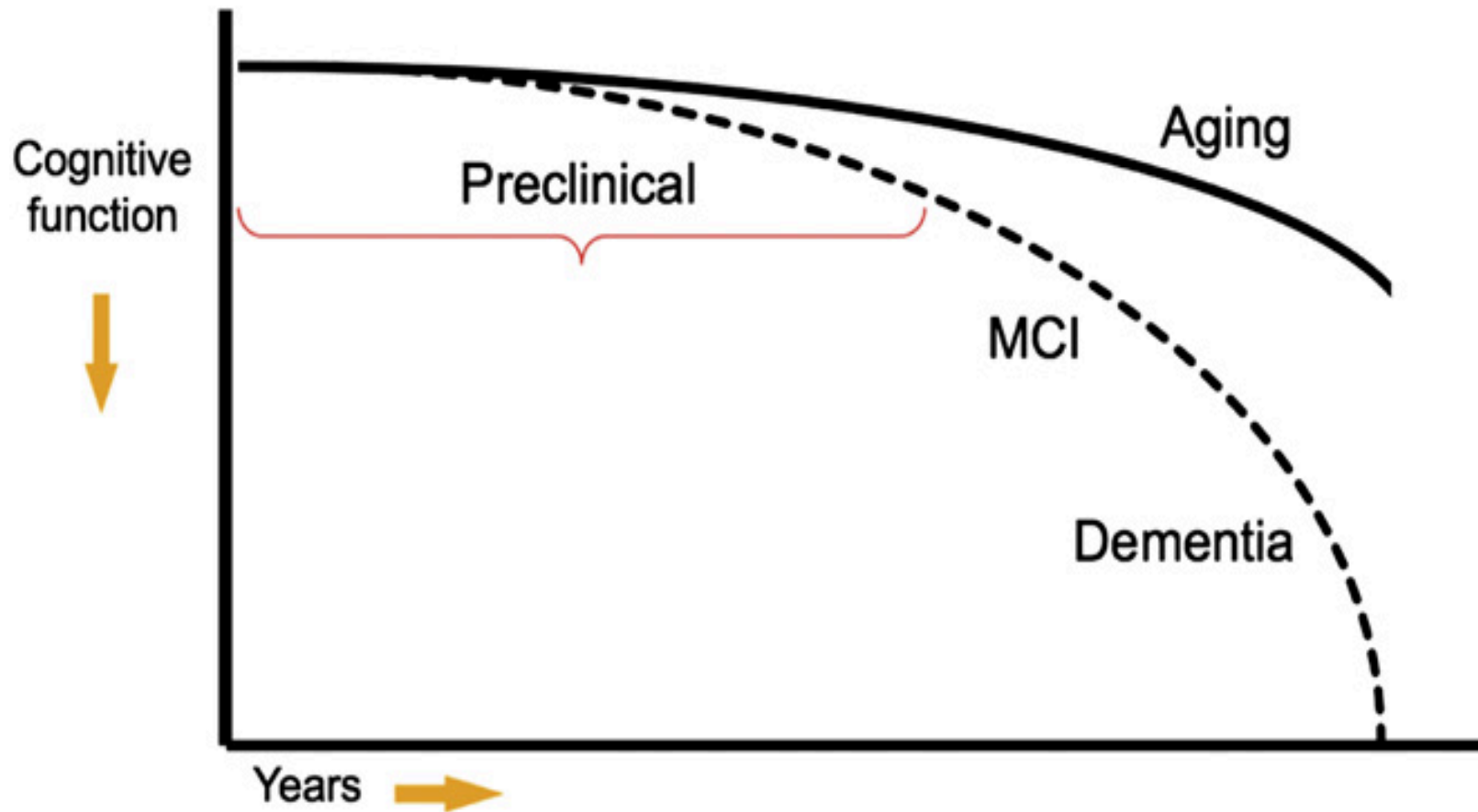


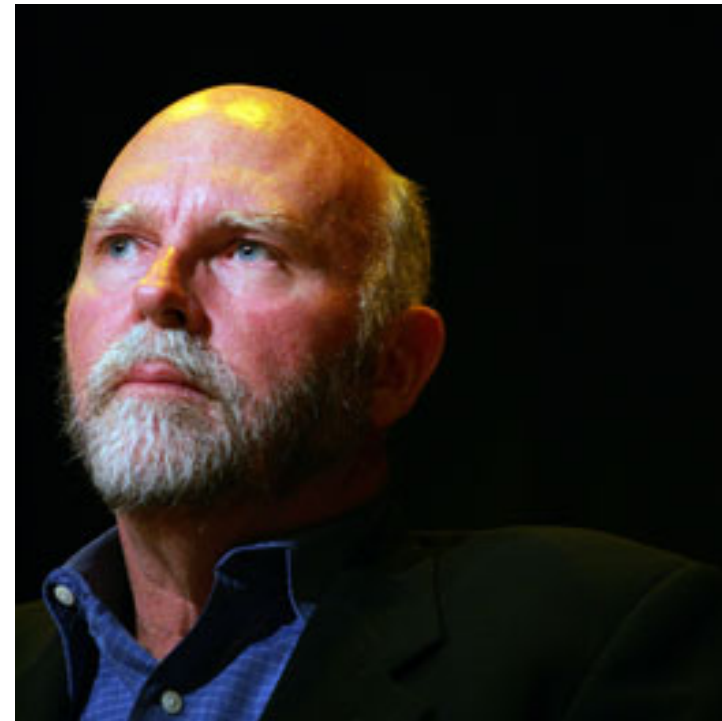
Thank You

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



The Continuum of Alzheimer's Disease





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!



The A4 study is a landmark clinical trial to prevent the memory loss associated with Alzheimer's disease for older individuals ages 65-85 who may be at risk but who have normal memory function.

Interested in learning more?
Phone: 844-A4STUDY (247-8839)
Email: A4-participate@usc.edu
A4study.org

The A4 Study
NOW IS THE TIME

NOW IS THE TIME
Join the fight to prevent memory loss associated with Alzheimer's disease.

A4 Study Organizers
The A4 study is a landmark public-private partnership, funded by the National Institute on Aging/NIH, Eli Lilly and Company, and several philanthropic organizations. The A4 trial is coordinated by the University of Southern California's Alzheimer's Therapeutic Research Institute, with study sites in multiple locations.

A4study.org

A4study.org

Version 2 | July 16, 2014

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.”

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SOKRATES-I – amyloid disclosure

SOKRATES-II – ApoE disclosure

REVEAL-SCAN – impact of amyloid disclosure on cognition

Thank you!

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