Alzheimer's Disease Prevention Clinical Trials: Taking the Next Steps Responsibly

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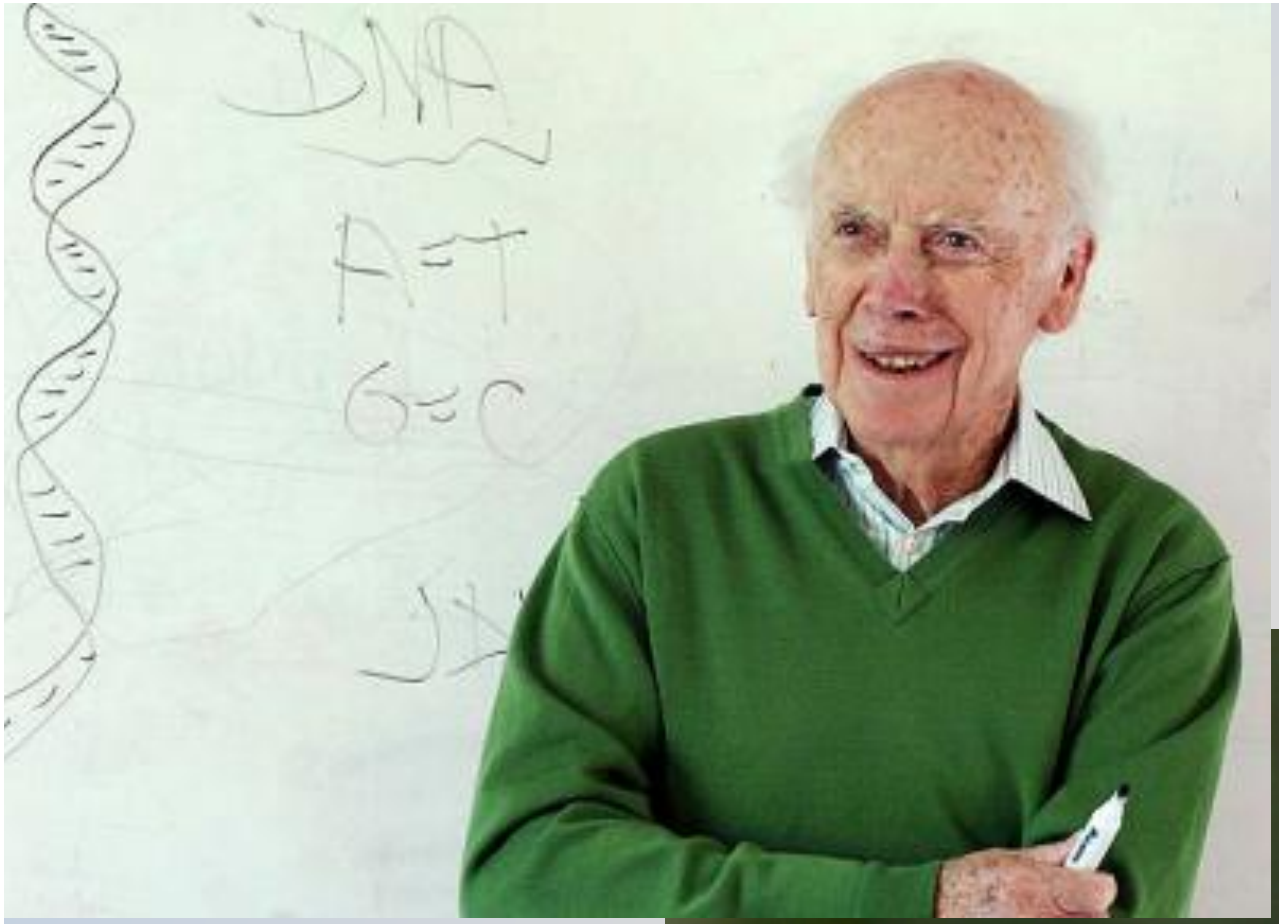

DNA
A=T
G=C

Agenda

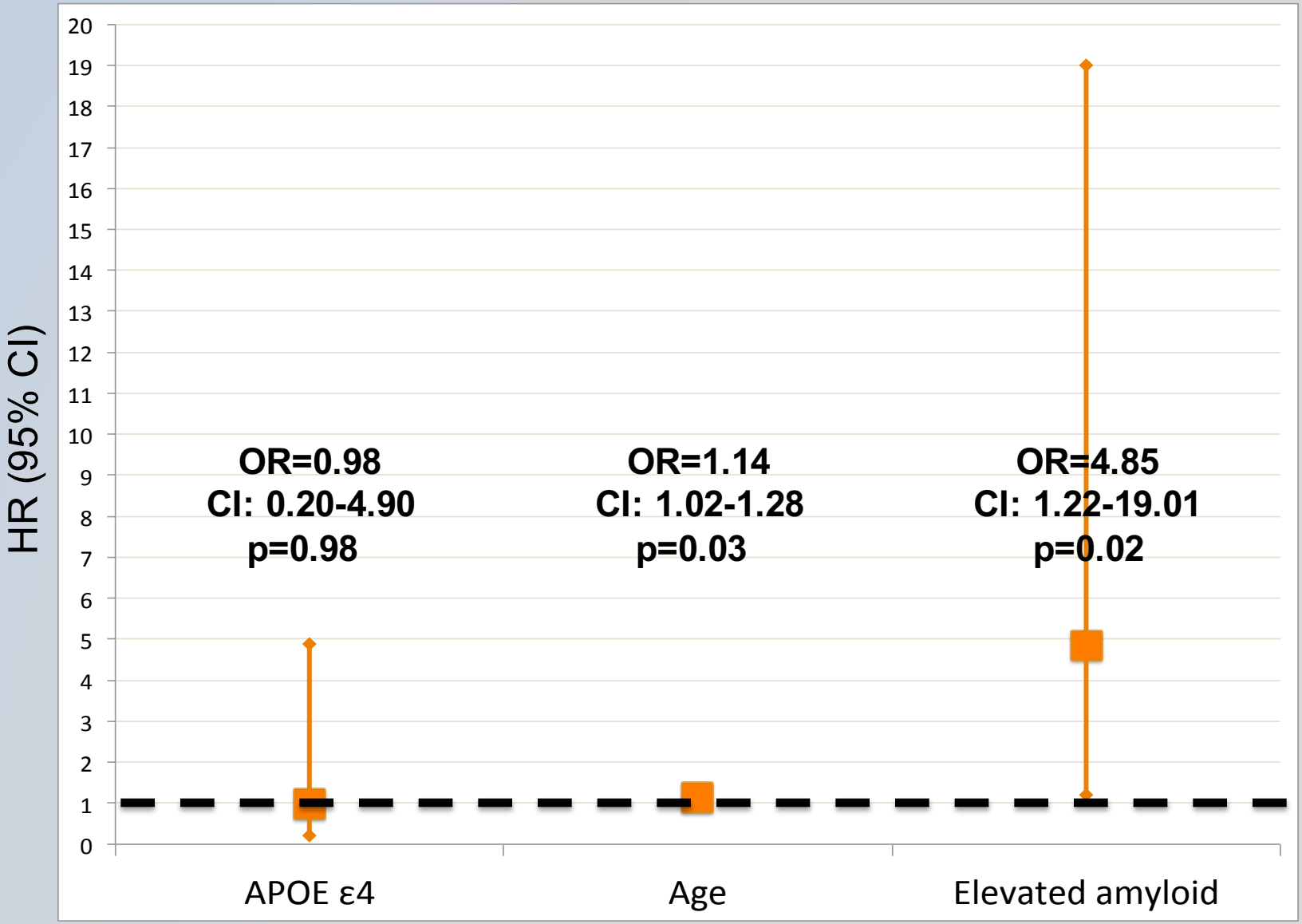
- Under what conditions is it acceptable to inform AD genetic/biomarker status?
- What are the ethical concerns for AD prevention trials?
- What data can instruct ethical AD prevention trial design and conduct?

Are Older Persons Willing to Learn AD Risk?

Study	Sample	Outcome
Neumann et al.	General population survey	85% of those 60 or older would take a predictive blood test for AD. 48% for partially predictive.
Cutler and Hodgson	108 adult children age 40-60 and a matched sample with no family hx	68% of adult children and 62% of controls (NS) were likely to take a 100% accurate predictive blood test
Neumann et al.	1463 US respondents (mean age=43)	>70% would take predictive AD blood test, even if imperfect
Wikler et al.	2678 US and European adults (82% <65)	67% were somewhat or very likely to get an early medical test
Roberts et al.	Health and Retirement Survey (mean age 64)	60% somewhat or strongly agreed that they wished to know their AD risk
Caselli et al.	Alzheimer's Prevention Initiative registrants	81% wanted genetic testing if it were paid for by insurance, 59% willing to pay. 80% wanted biomarker testing.

Neumann et al. *Health Affairs* 2001. Cutler and Hodgson, *Am J Alz Dis Other Dement*. 2003. Neumann et al. *Health Economics* 2012. Wikler et al. *Alz Res Ther* 2013. Roberts et al. *Alz Dement* 2014. Caselli et al. *Mayo Clin Proc* 2014.

Predicting AD Dementia



Morris et al. Arch Neurology, 2009.

Appropriate Use Criteria for Clinical Amyloid Imaging

Appropriate

1. Persistent or progressive unexplained MCI
2. Possible AD because of unclear clinical presentation, either an atypical clinical course or an etiologically mixed presentation
3. Atypical early age of onset (usually defined as 65 years or less in age)

Inappropriate

1. Patients with core clinical criteria for probable AD with typical age of onset
2. To determine dementia severity
3. Based solely on a positive family history of dementia or presence of apolipoprotein E (APOE)ε4
4. Patients with a cognitive complaint that is unconfirmed on clinical examination
5. In lieu of genotyping for suspected autosomal mutation carriers
6. In asymptomatic individuals
7. Nonmedical use (e.g., legal, insurance coverage, or employment screening)

Johnson et al. *J Nucl Med* 2013.

On-Going Preclinical AD Trials

Trial/Organizing group	Treatment	Population
Anti-Amyloid treatment in Asymptomatic AD / ADCS	Solanezumab	Preclinical sporadic AD (elevated brain amyloid PET signal with normal cognition)
AD Prevention through Exercise	Exercise	Preclinical sporadic AD
Crenezumab in PSEN1 E280 Mutation carriers	Crenezumab (subcutaneous)	PSEN1 mutation carriers and non-carriers
DIAN TU. A Study of Potential Disease Modifying Treatments in Individuals at Risk for or With a Type of Early Onset Alzheimer's Disease Caused by a Genetic Mutation	Gantenerumab and Solanezumab	Asymptomatic and mildly symptomatic carriers and non-carriers of ADAD mutations
Biomarker Qualification for Risk of Mild Cognitive Impairment (MCI) Due to Alzheimer's Disease (AD) and Safety and Efficacy Evaluation of Pioglitazone in Delaying Its Onset (TOMMORROW)	Pioglitazone	Biomarker risk algorithm (BRAA) composed of TOMM40 rs10524523 genotype, APOE genotype, and age
Alzheimer's Prevention Initiative APOE4 Treatment Trial	CAD-106, BACE inhibitor	APOE e4 homozygotes

Mills et al. Rev Neurol (Paris) 2013. Crenshaw et al. Clin Pharm Ther 2013. Rafii J Alz Dis 2015. ClinicalTrials.gov Identifiers: NCT02008357, NCT02000583, NCT01998841, NCT01760005, NCT01931566. Banneralz.org.

Trial Designs in Preclinical AD

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

Criteria for Ethical Research

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

Emanuel et al. *JAMA* 2000. Kim et al. *Neurology* 2015.

Special Issues in Preclinical AD Trial 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?

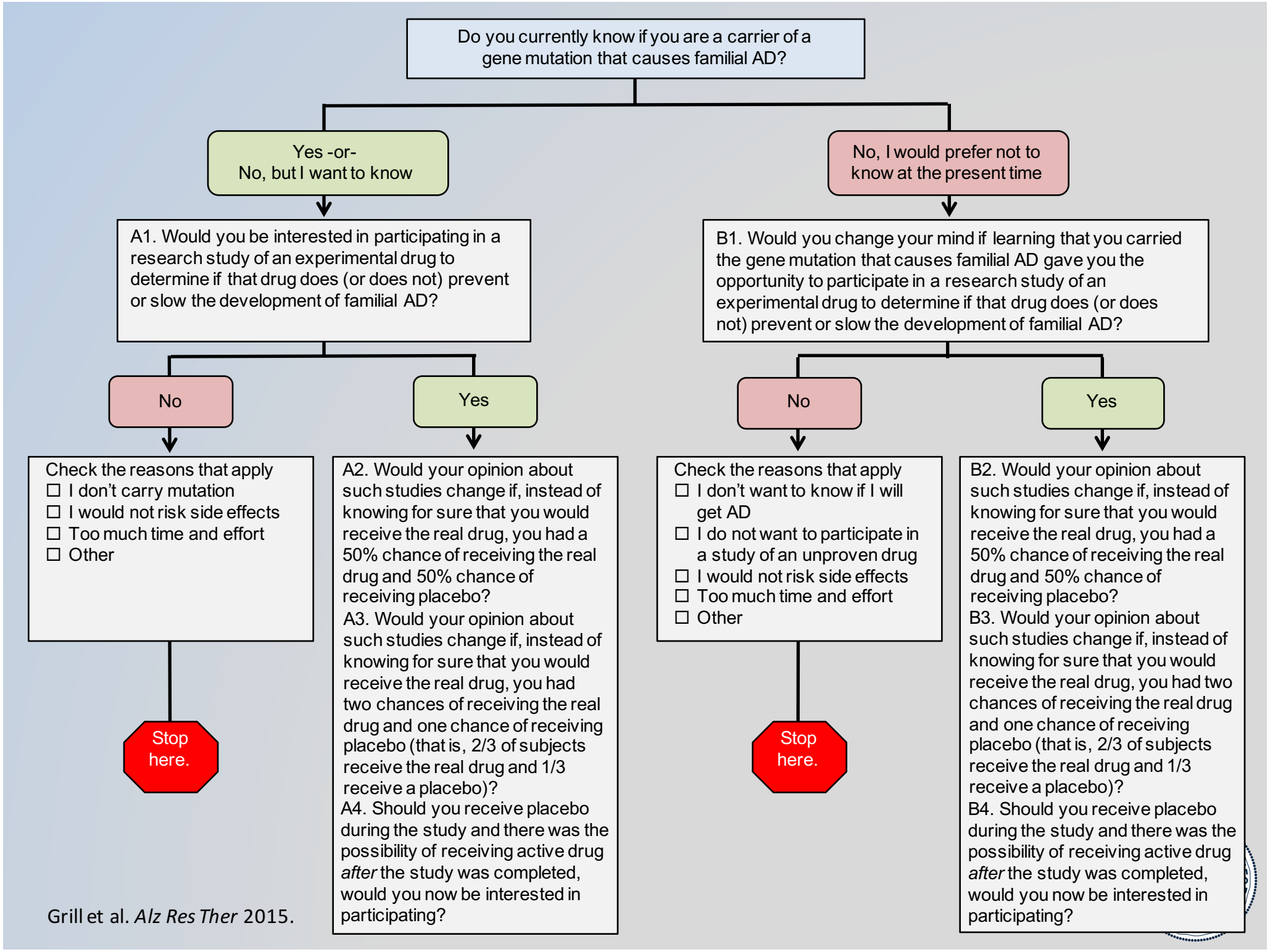
- Coercion: overt threat of harm to elicit compliance
- Undue influence: improper or inappropriate reward to elicit compliance
- Transparent enrollment is neither coercive nor does it offer undue influence
- Informed consent is critical to respect the autonomy of participants

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

To Be Ethical, Prevention Trials Must Be Feasible

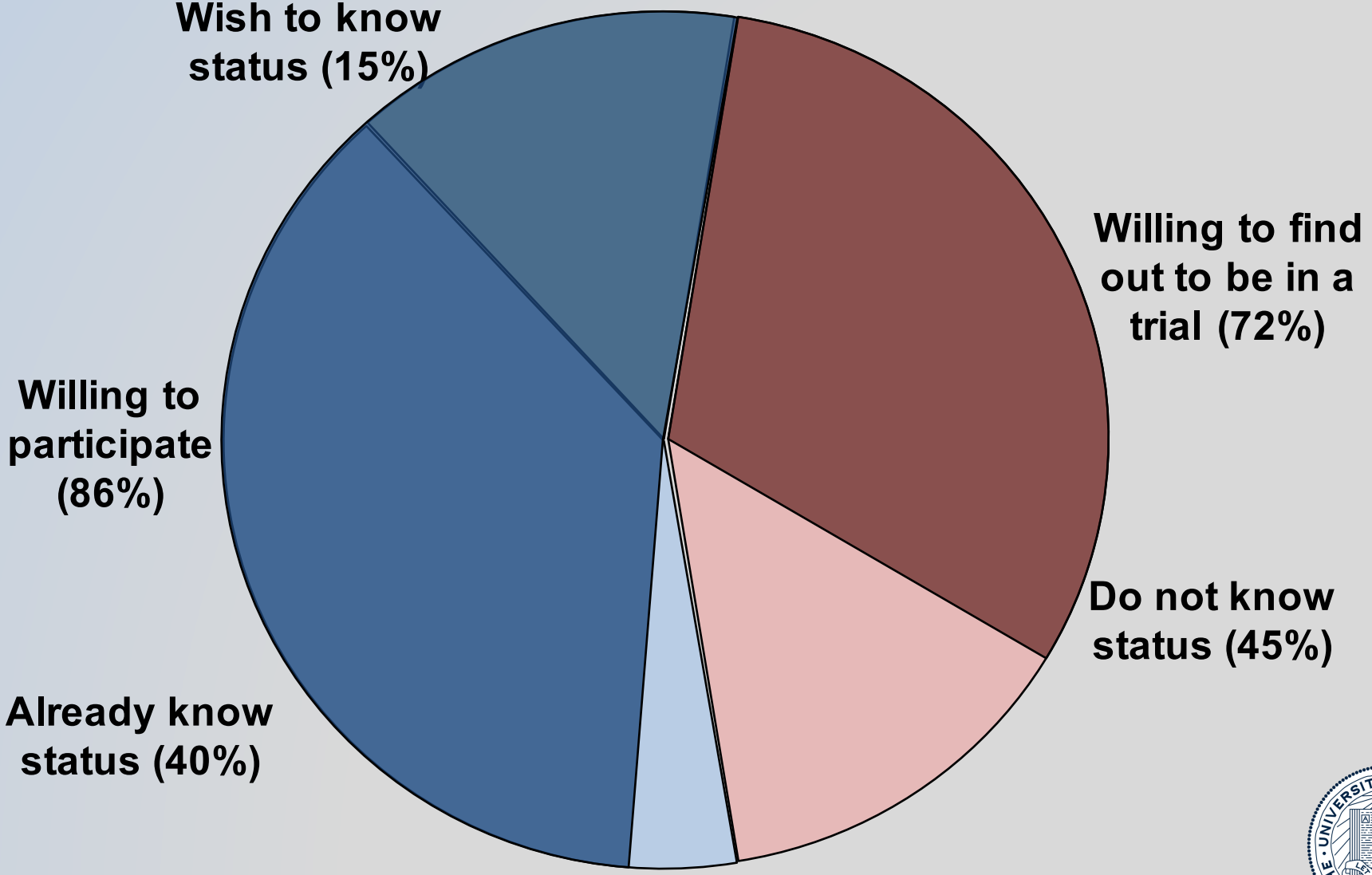
- *"…If persons who at baseline wish not to know their mutation status choose not to participate, then a majority of persons at risk for the condition would be excluded."*

Kim et al. *Neurology* 2015



Grill et al. *Alz Res Ther* 2015.

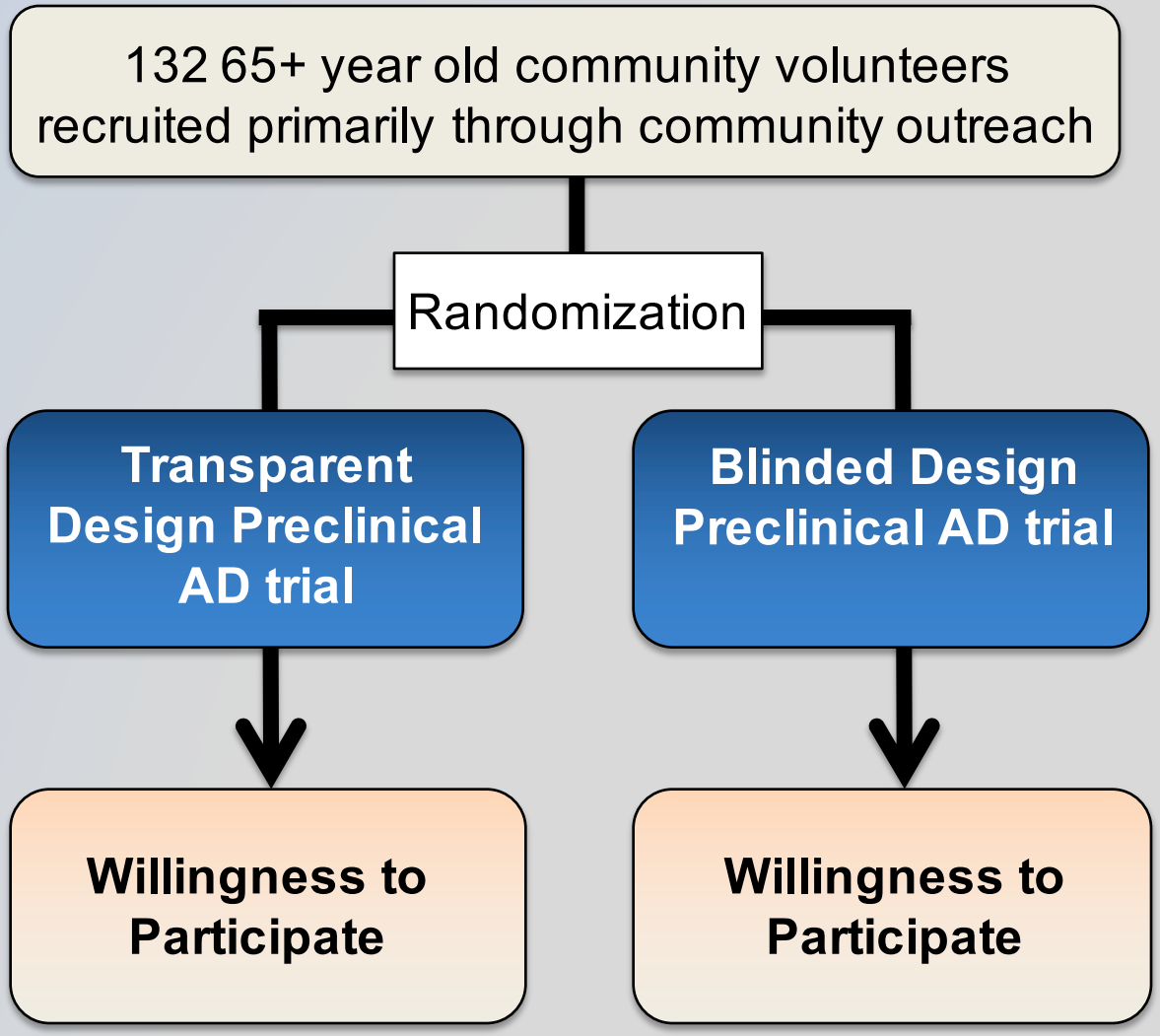
Genetic Testing in Autosomal Dominant AD Trials



Grill et al. *Alz Res Ther* 2015.

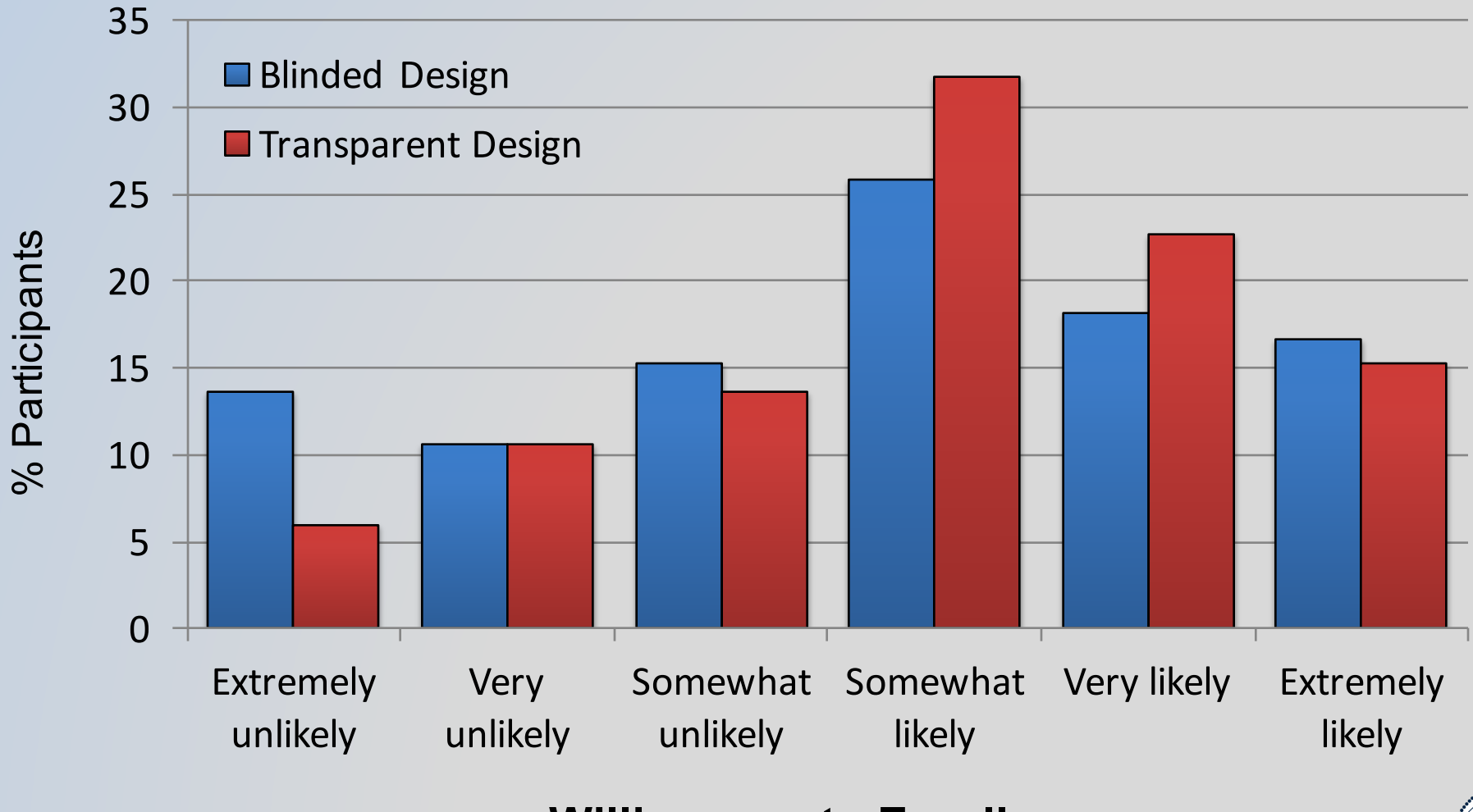
N=80 respondents from DIAN longitudinal study

A Randomized Study to Examine Recruitment in Transparent Enrollment Preclinical AD Trials



Grill et al. under review.

Transparent and Blinded Enrollment Rates Do Not Differ



Effect of group assignment; OR=1.30; 95% CI:0.71-2.38.

Grill et al. under review.

Amyloid Imaging Disclosure Process

Round 1:

Experts reviewed a slideshow presentation on PET amyloid imaging and its role in trials such as A4, and then completed telephone interviews designed to elicit amyloid imaging disclosure best practices and discussion topics

Transcribed responses were grouped and standardized for language consistency

Round 2:

Experts rated the necessity of each Round 1 item (include, unsure, do not include) through an online survey

Responses were compiled and items were categorized into three levels of support:

- consensus to include (support of ≥ 8 experts)
- mixed support (support of 5-7 experts)
- do not include (support of < 5 experts)

Mixed support items were included if the majority of remaining votes were "unsure" rather than "do not include"

Items with consensus support were included in a template brochure and disclosure process guidelines

Round 3:

Experts rated brochure sections for clarity (5 point scale) and provided comments through an online survey

We used comments for revisions, with attention to mean clarity ratings lower than 4

Harkins et al. *Alz Res Ther* 2015.

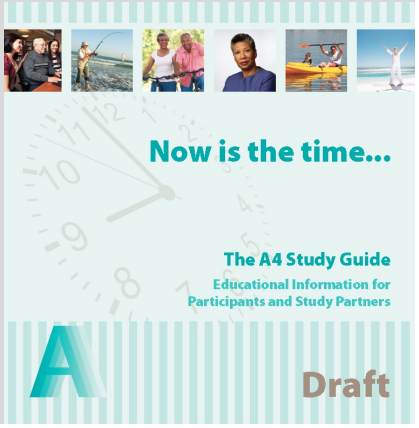
Amyloid Imaging Disclosure Recommendations

- A pre-consent education: verbal and written information covering what is and is not known about amyloid imaging, possible imaging results and their meaning, implications of results, and information about Alzheimer's disease and risk factors
- The person conducting the educational session should assess comprehension, specifically how well the individual understands amyloid imaging and its role in the study
- Participants should be queried about motivation for joining the study and willingness to learn amyloid status
- Participants should be screened for anxiety and depression
- The person conducting the educational and disclosure sessions should be skilled in communication and recognizing distress

Harkins et al. *Alz Res Ther* 2015.

Amyloid Imaging Disclosure Recommendations

- Imaging should occur on a separate day from consent and disclosure on a separate day from imaging
- At disclosure, investigators should first assess mood and willingness to receive results, and should provide a written report of results
- Disclosure should occur in person, with time for questions
- Telephone follow-up should occur within a few days of disclosure to assess participant mood and impact of disclosure
- Participants showing distress should receive additional monitoring and follow-up
- Periodic assessment of depression and anxiety should be scheduled following disclosure



Harkins et al. *Alz Res Ther* 2015.

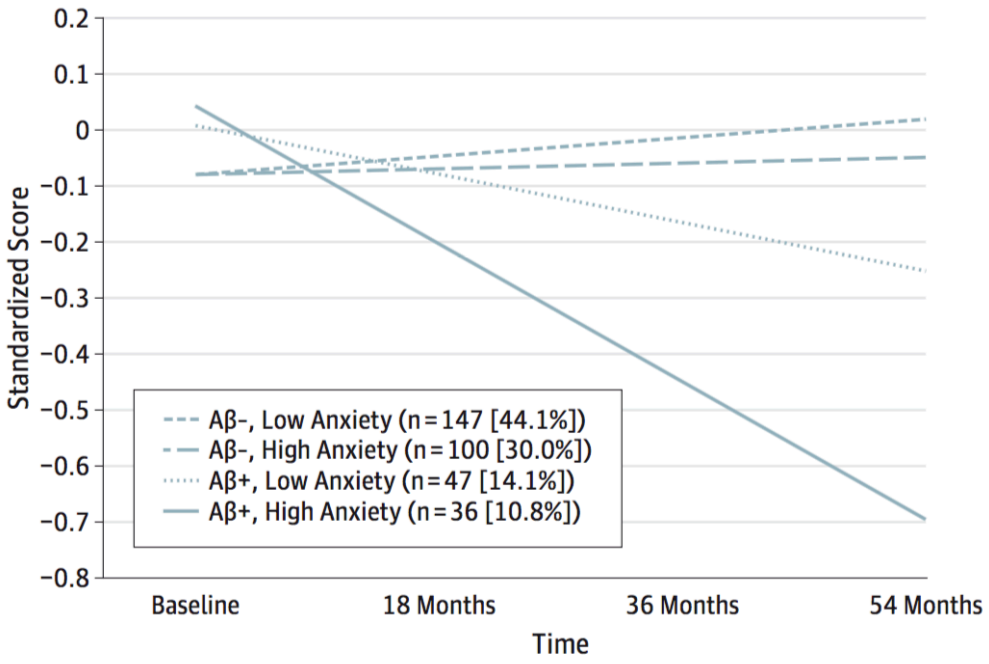
A4 Data Collection

Follow-up over the course of the study

- **Geriatric Depression Scale** (GDS), the **State Trait Anxiety Inventory** (STAI), and the **Columbia suicide severity rating scale** (C-SSRS) are administered at 3-6 month intervals
- Assessments of participant's understanding of amyloid status disclosure and concerns about AD
  - Perceived risk of AD dementia
  - Future Time Perspective
  - Reasons to undergo amyloid imaging

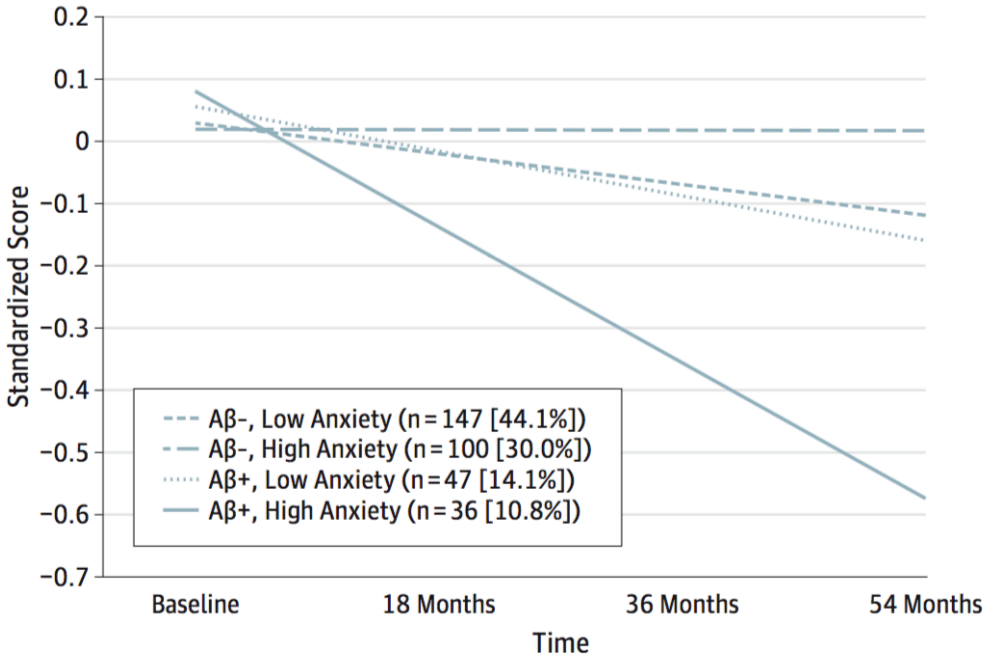
Anxiety and Cognitive Decline in Preclinical AD

Figure 1. Slopes of Change in Verbal Memory Composite Score by Amyloid-β (Aβ) and Anxiety Levels



Slopes are adjusted for age, educational level, full-scale IQ, *APOE* genotype, subjective memory complaints, number of vascular risk factors, and depressive symptoms.

Figure 2. Slopes of Change in Language Composite Score by Amyloid-β (Aβ) and Anxiety Levels



Slopes are adjusted for age, educational level, full-scale IQ, *APOE* genotype, subjective memory complaints, number of vascular risk factors, and depressive symptoms.

Pietrzak et et al. *JAMA Psychiatry* 2015.

Considering Suicide in Prevention Trials

	Genetic evidence of increased AD risk	Biomarker evidence of increased AD risk
Begin a healthier lifestyle	90.5 (3478/3841)	91.0 (3459/3798)
Get long-term care insurance	76.3 (2819/3693)	76.6 (2783/3634)
Spend all your money for pleasure	18.4 (683/3720)	18.7 (682/3656)
Seriously consider suicide	11.6 (427/3706)	10.2 (370/3639)

Caselli et al. *Mayo Clin Proc* 2014.

Considering Suicide in Prevention Trials

- At least some participants (and researchers) endorse risk information as a means to instruct planned suicide
  - To ensure the social value of the study (and future such studies) risk of suicide occurrence must be minimized.
- Long-term follow-up, even after study completion, perhaps especially in the setting of negative results, will be required
- The disclosure of risk information in the controlled, protocol-derived setting, with participants meeting pre-specified criteria, may not generalize to clinical care

Risk Factors for Suicide in AD

Male sex
Mild disease
High education
Insight into impairment
History of depression
Access to firearms

Ferris et al. *Alz Dis Assoc Disord* 1999. Vega et al. *Am J Geri Psychiat* 2002. Harwood and Sultzer *J Geriatr Psychiatr Neurol* 2002. Lim et al. *Alzheimer Dis Assoc Disord* 2005.

Risk Factors for Suicide in Predictive Testing for AD

Not currently married

Caselli et al. *Alzheimer Dis Assoc Disord* 2015.

Employment and Insurance

- Issues in employment and insurance
  - EMR mixes clinical and research data
  - AE's generate a record
- Possible protections
  - Genetic Information Nondiscrimination Act
  - HIPAA
  - Americans with Disabilities Act
- These issues need to be in the IC form

Arias and Karlawish, *Neurology* 2014.

Confidentiality in Preclinical AD trials

- Potential breaches
  - Neuroimaging that is incorporated to the EMR
  - Adverse events that lead to ED visits incorporated to the EMR
- Protections/Solutions
  - "sensitive orders"
  - Research Record Numbers (vs Medical Record Numbers)
  - Information redaction (consider data trails)

Arias and Karlawish, *Neurology* 2014.

Stigma in Preclinical AD

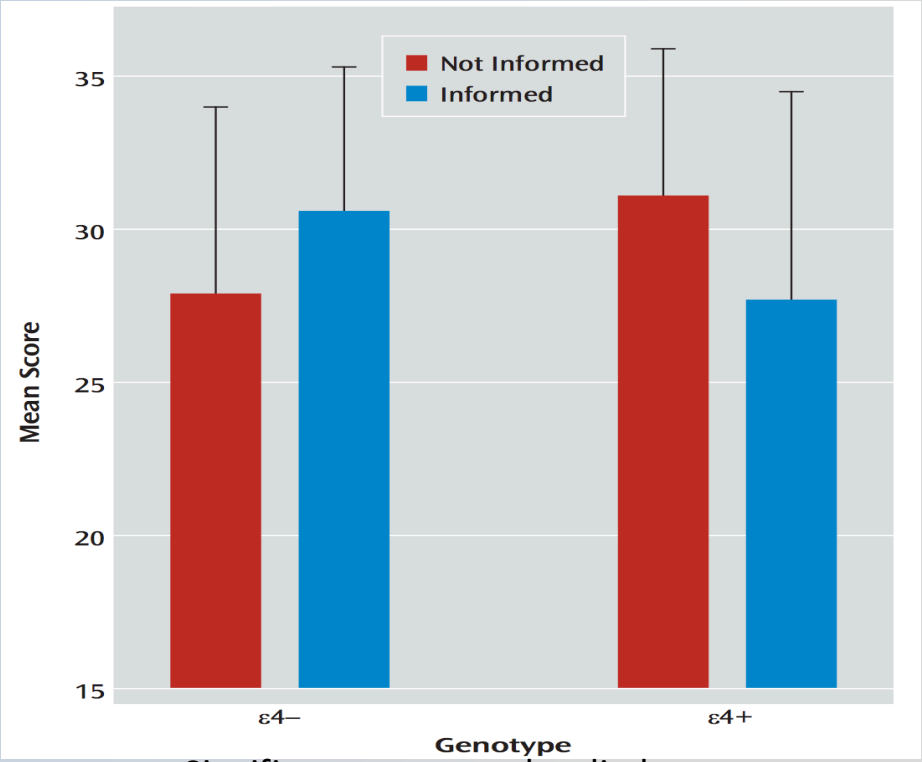
- Family and friends
- Employers
- Health care providers
- Self-stigma?

Garand et al. *Res Gerentol Nurs* 2009. Gauthier et al. *Prog Neurobiol* 2013. Beard and Neary, *Sociology Health Illness* 2013.

Impact of Knowing

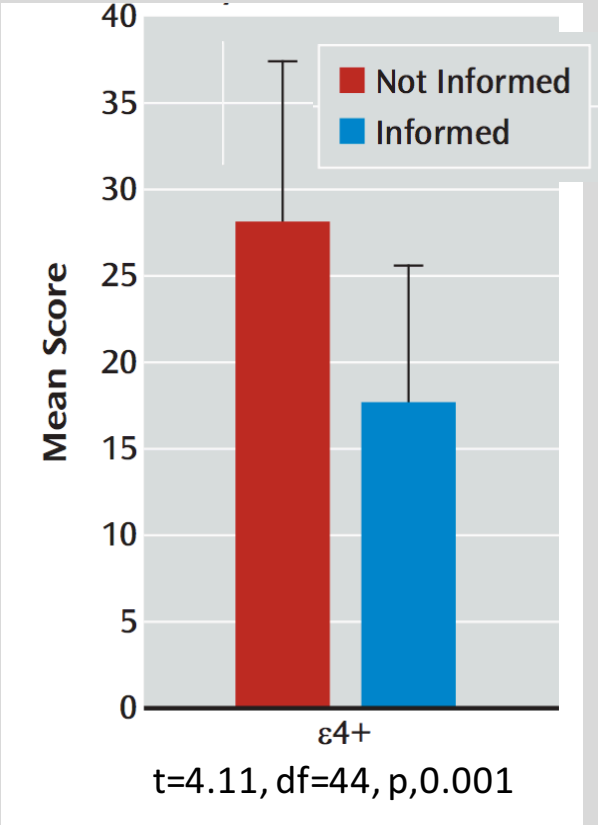
- Does telling an older adult he or she has elevated brain amyloid change subjective memory self-efficacy?

Capacity Scale of the Metamemory in Adulthood Questionnaire



Significant genotype-by-disclosure status interaction effect (F=9.3, df=1, 137, p,0.01)

Logical Memory Test, Delayed Recall



t=4.11, df=44, p,0.001

Lineweaver et al. *Am J Psychiatry* 2014.

Ethical Concerns if Trials Demonstrate Efficacy

1. The cost of diagnostic tests to screen for responders (e.g., amyloid PET scan or ApoE genotyping),
2. Refusal of treatment to persons who do not fit the responder profile (wrong genotype, too old, dementia stage too severe),
3. Access and cost of treatment (e.g., monthly intravenous infusions or injections)
4. Safety monitoring for brain edema and microhemorrhages using serial MRI
5. When to stop treatment

Gauthier et al. *Prog Neurobiol* 2013.

Summary

- Requiring disclosure of eligibility for preclinical AD trials is not unethical
- To be ethical, transparent enrollment trials must be feasible
  - Preliminary results suggest that these designs may be feasible in sporadic and even autosomal dominant preclinical AD
- Research is needed to better understand whether learning preclinical AD status
  - Is an incentive to enroll in sporadic AD trials
  - Alters the decision-making calculus in autosomal dominant AD trials or if therapeutic misconception could occur
  - Results in stigma or stereotype threat

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Preclinical AD barriers study

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