Consent for Revealing Biomarker Status in AD Prevention Trials

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Disclosures

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  - **National Institutes of Health (NHGRI)**
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  - **American Association for Cancer Research**

- No other disclosures to report

Risk Evaluation & Education for AD (The REVEAL Study; R.C. Green, PI)

An intervention trial where
risk information is the intervention:

What is the impact of
genetic risk assessment on
adult children of people with AD?

Consensus Statements: Predictive APOE Testing Should Not Be Offered

Alzheimer Disease and Associated Disorders
Vol. 9, No. 4, pp. 182–187

Consensus Statement on Predictive Testing for Alzheimer Disease

Medical and Scientific Advisory Committee, Alzheimer's Disease International*

1: JAMA. 1995 Nov 22-29;274(20):1627-9.

Statement on use of apolipoprotein E testing for Alzheimer disease. American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and Alzheimer disease.

[No authors listed]

OBJECTIVE--To evaluate the published data on the association betv genotype (APOE) and Alzheimer disease (AD) and determine wheth of genetic testing for diagnosis or prediction of disease. This staten neurologists, psychiatrists, geneticists, primary care providers, diag public. PARTICIPANTS--The joint American College of Medical Genet Society of Human Genetics (ASHG) Test and Technology Transfer Cc member ACMG/ASHG Working Group to assess available data on th APOE alleles. To ensure inclusion of clinical specialists primarily invo families, the American Academy of Neurology (AAN) and the America (APA) appointed liaisons to the Working Group. EVIDENCE--Peer-re obtained from an Index Medicus search or known to members of th source of data on which the statement is based. CONSENSUS PROC

GENETIC TESTING
Volume 3, Number 1, 1999
Mary Ann Liebert, Inc.

Genetic Testing and Alzheimer Disease: Recommendations of the Stanford Program in Genomics, Ethics, and Society*

LAURA M. McCONNELL,[1] BARBARA A. KOENIG,[1,2] HENRY T. GREELY,[1,3] THOMAS A. RAFFIN,[1,4] and MEMBERS OF THE ALZHEIMER DISEASE WORKING GROUP OF THE STANFORD PROGRAM IN GENOMICS, ETHICS, AND SOCIETY

THE LANCET

Consensus statement

Apolipoprotein E genotyping in Alzheimer's disease

*National Institute on Aging/Alzheimer's Association Working Group**

Apolipoprotein E (*APOE*=gene; apoE=protein) is the first identified genetic susceptibility factor for sporadic Alzheimer's disease (AD). The application of *APOE* genotyping to the prediction and diagnosis of AD has been a source of controversy for the public and for clinicians and scientists. These issues were explored by a 33 member working group in a two-day conference held in October, 1995, and sponsored by the National Institute on Aging, the Alzheimer's Association (USA), and other organisations. The group's conclusions are:

- The use of *APOE* genotyping to predict future risk of AD in symptom-free individuals is not recommended at this time.
- Insofar as patients with AD are more likely to have an *APOE-ε4* allele than are patients with other forms of dementia or individuals without dementia, physicians may choose to use *APOE* genotyping as an adjunct to other diagnostic tests for AD.
- Since genotyping cannot provide certainty about the presence or absence of AD, it should not be used as

Introduction

The association between apolipoprotein E (apoE=protein, *APOE*=gene) ε4 and risk of Alzheimer's disease (AD) was first reported in 1993,[1] and subsequent confirmations have established *APOE* genotype as the single most important genetic determinant of susceptibility to sporadic and late-onset familial AD yet identified.[2–29] The discovery of this genetic risk factor is an important step forward in Alzheimer research, but has posed dilemmas for individual physicians, patients, and investigators. Since *APOE* genotyping is already commercially available,[30] and tens of thousands of patients have previously undergone testing for cardiovascular risk assessment, patients are now requesting *APOE* genotyping and/or interpretation of previous *APOE* results as an indicator of their risk of AD. No broadly accepted guidelines for the use of *APOE* genotyping for diagnosis and risk assessment are available. By a consensus process (panel 1) a US National Institute on Aging/Alzheimer's Association working group has attempted to fill that gap, with the following position statement.

nature
International weekly journal of science

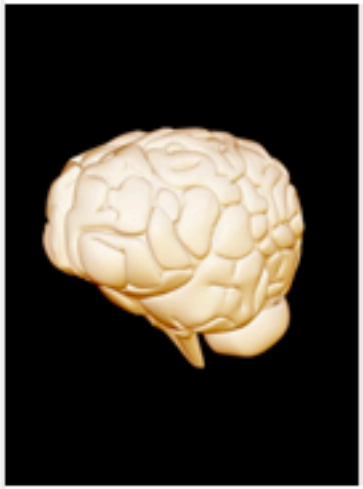
News

Nature **389**, 898 (30 October 1997) | doi:10.1038/39971

Genetic testing for Alzheimer's disease 'not appropriate'

Sally Lehrman, palo alto, california, palo alto, california

- Genes and health
- Conditions we cover
- Alzheimer's Disease
- Complete scan
- Cancer scan
- Cardio scan
- Advanced features



Alzheimer's Disease

Alzheimer's Disease is the most common form of dementia (brain disorder) accounting for about two-thirds of all dementia cases. The risk of developing Alzheimer's disease is in part genetically determined.

deCODEme can calculate your genetic risk for Alzheimer's Disease.

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A common genetic variant in the Apolipoprotein E (ApoE) gene called ApoE4 has been shown to increase risk of developing late-onset Alzheimer's disease.

The deCODEme Complete Scan analyzes your DNA for this variant and provides you with a personalized interpretation of your risk for Alzheimer's Disease.

deCODEme helps you assess your genetic risk for late-onset Alzheimer´s Disease

Alzheimer's Disease is characterized by progressive loss of memory
Classical symptoms of Alzheimer's Disease begin with loss of memory for recent events. With time, additional symptoms develop in individuals with the disease, including confusion, disorganized thinking, impaired judgment, trouble with expressing themselves and disorientation.

The main risk factor is increased age
Alzheimer's Disease primarily affects people over the age of 65 and it becomes more prevalent with advanced age. About 5% of individuals in the age range 65-74 are affected by the disease, but nearly half of all individuals over the age of 85.

Certain genes increase the risk of developing late-onset Alzheimer's Disease
The risk of developing Alzheimer´s Disease is in part genetically determined and rare mutations in three different genes are known to cause early-onset Alzheimer´s, affecting individuals before the age of 65. The risk of developing late-onset Alzheimer´s Disease is to a large extent mediated by a variant in the APOE gene referred to as APOE4.

Overview of REVEAL Trials

- Series of multi-site randomized clinical trials
  - BU, Cornell, Case Western, Howard, Michigan, Penn
- GC-delivered education/counseling protocols
- N = 699 1st-degree relatives of AD patients
  - Cognitive, psychiatric screening
- Longitudinal (up to 12 months) psychological, health behavior assessment

Does APOE testing cause psychological harm?

The NEW ENGLAND JOURNAL of MEDICINE

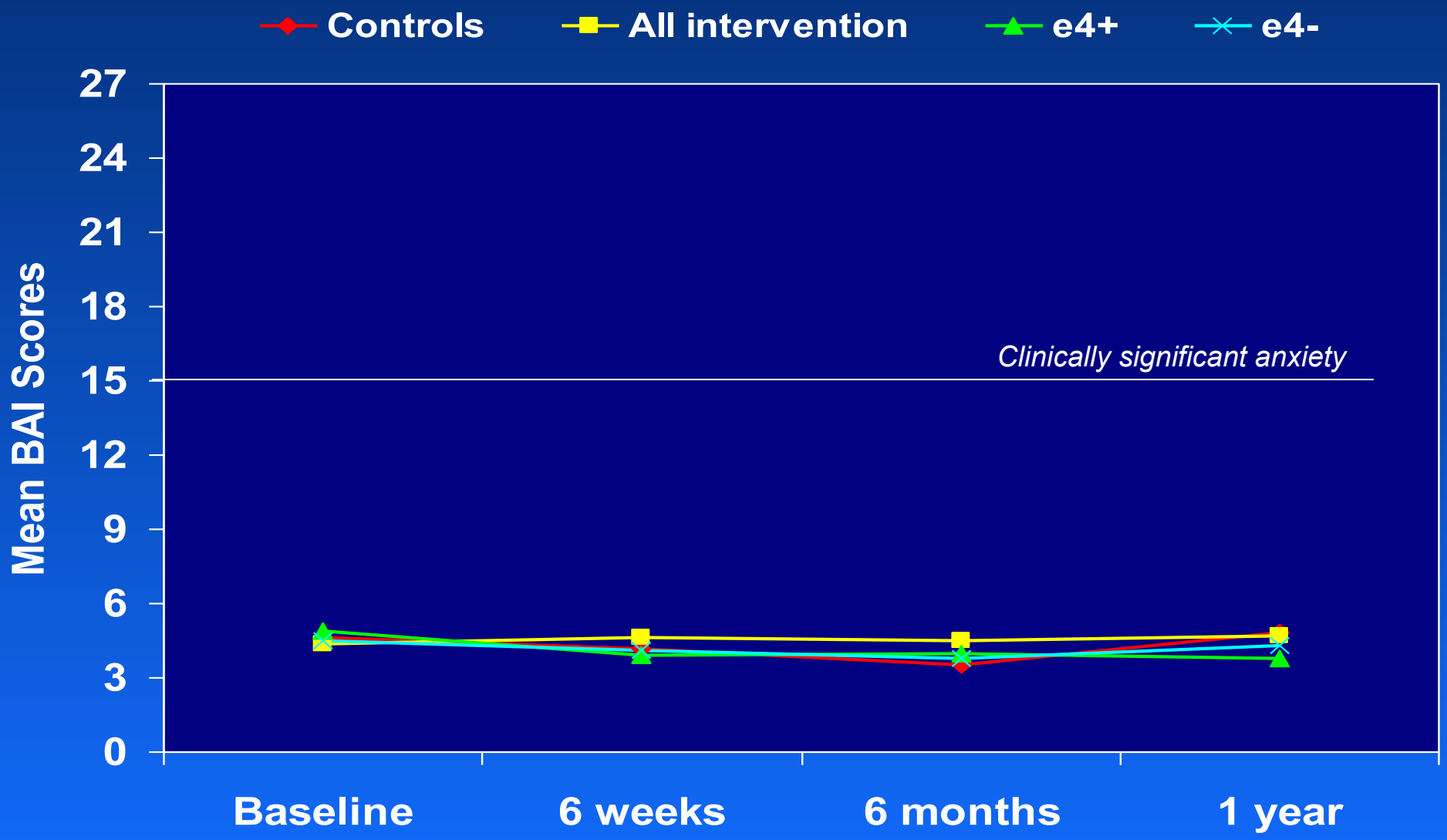
ORIGINAL ARTICLE

Disclosure of *APOE* Genotype for Risk of Alzheimer's Disease

Robert C. Green, M.D., M.P.H., J. Scott Roberts, Ph.D.,
L. Adrienne Cupples, Ph.D., Norman R. Relkin, M.D., Ph.D.,
Peter J. Whitehouse, M.D., Ph.D., Tamsen Brown, M.S.,
Susan LaRusse Eckert, M.S., Melissa Butson, Sc.M., A. Dessa Sadovnick, Ph.D.,
Kimberly A. Quaid, Ph.D., Clara Chen, M.H.S., Robert Cook-Deegan, M.D.,
and Lindsay A. Farrer, Ph.D., for the REVEAL Study Group*

Green, Roberts et al, *NEJM*, 2009

Anxiety Levels by Study Group



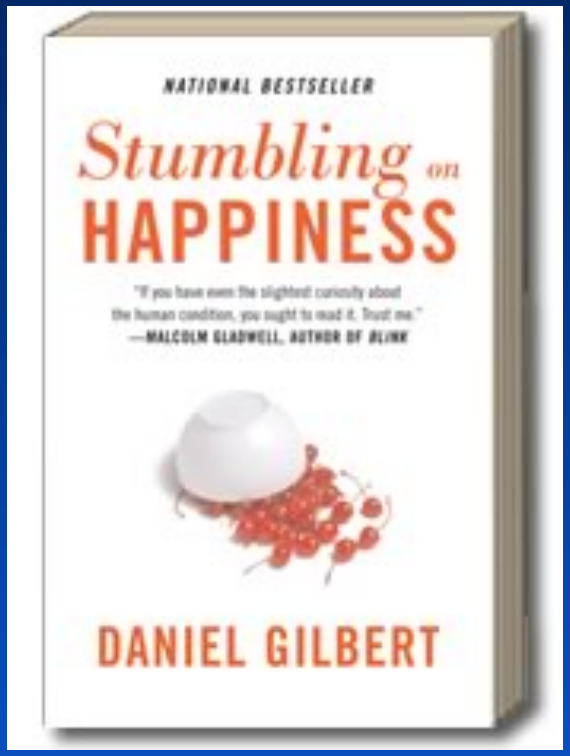
Subjective Impact of Disclosure

Impact of Risk Information		
Positive	Neutral	Negative
59%	27%	14%
Impact on Anxiety about AD		
Lower	Same	Higher
38%	53%	9%

Results differ by APOE status in expected directions

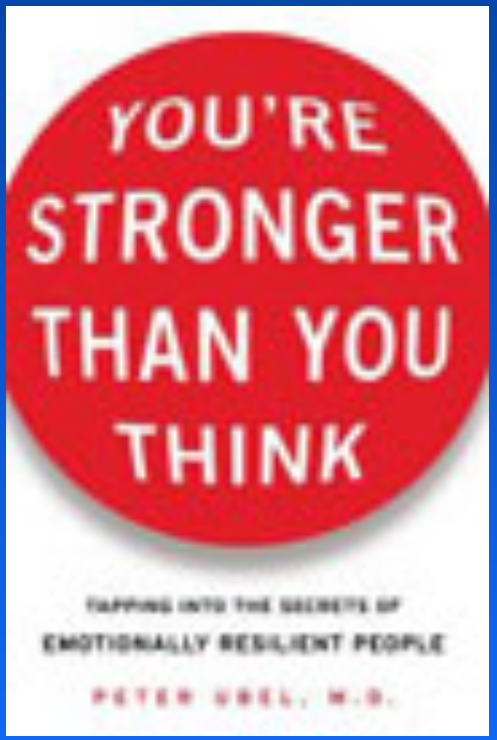
Carpenter et al (2008): Psychological Impact of a Diagnosis of AD or MCI

- No significant short-term (1-2 wks) increases in depression, anxiety following dx disclosure
  - Either in patients or their companions
- Anxiety often decreased following disclosure
- Need for larger studies, more sensitive measures, longer term follow-up

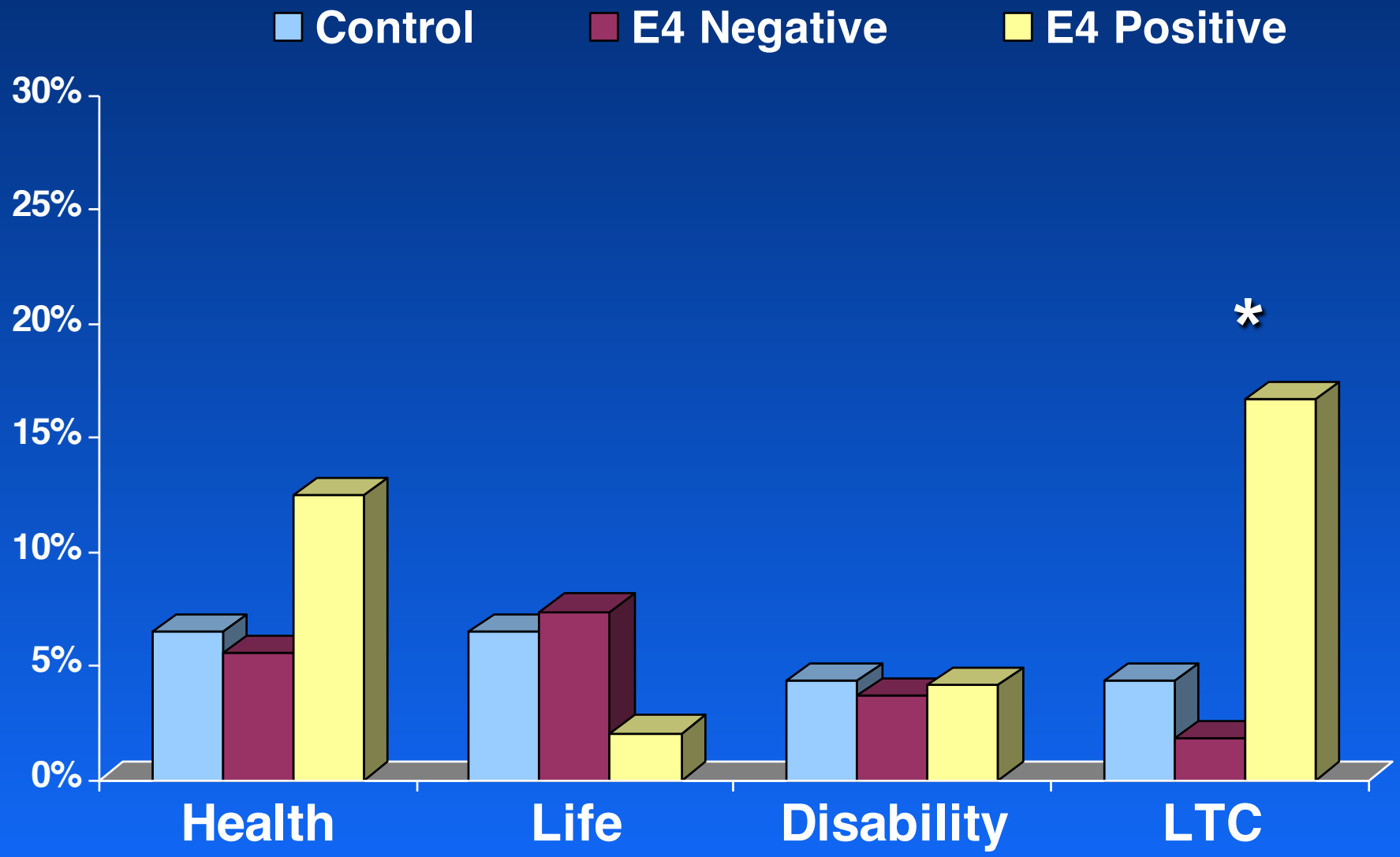


Cognitive biases in *affective forecasting* may influence response of patients, providers, policymakers

Impact bias: our tendency to overestimate the intensity, durability of reactions to negative events



Insurance Changes Reported at 12 Month Follow-Up



Zick, Mathews, Roberts et al., *Health Affairs*, 2005

REVEAL IV Overview

- Impact of APOE disclosure in population with mild cognitive impairment (MCI)
- More imminent risk information
- Combining genotype + phenotype info
- Cognitively vulnerable population
  - Dyadic disclosure
  - Decisional capacity assessment tool (CAT-GT)

REVEAL IV Flow chart

3-Year Estimates of Risk of AD

	55-70 years	71-77 years	78 years and older
a-MCI, *APOE* ε4 Absent	8%	21%	31%
a-MCI Alone	25%	34%	44%
a-MCI, *APOE* ε4 Present	42%	47%	57%

There are six possible **APOE** gene test results.

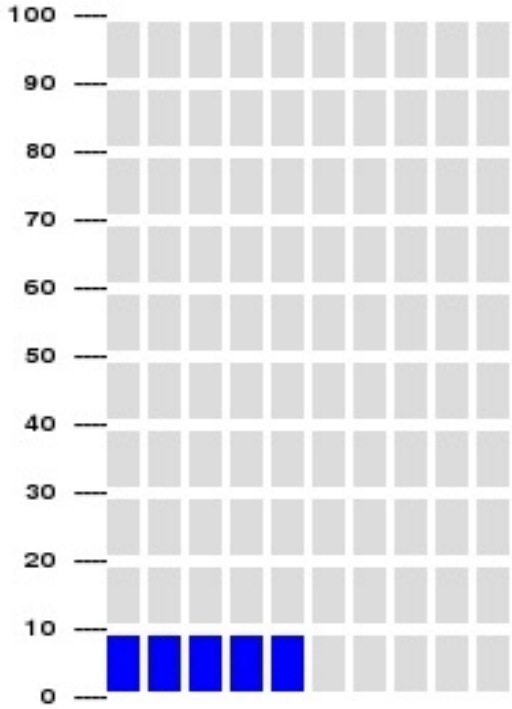
Individuals who have at least one copy of the **ε4** form have an **increased** risk of developing Alzheimer's disease.

Your risk estimate is based on the following factors:

- Your diagnosis of mild cognitive impairment (**MCI**)
- Your current **age** being between 71 and 77 years
- Your gene test result: ***APOE* ε4 present**

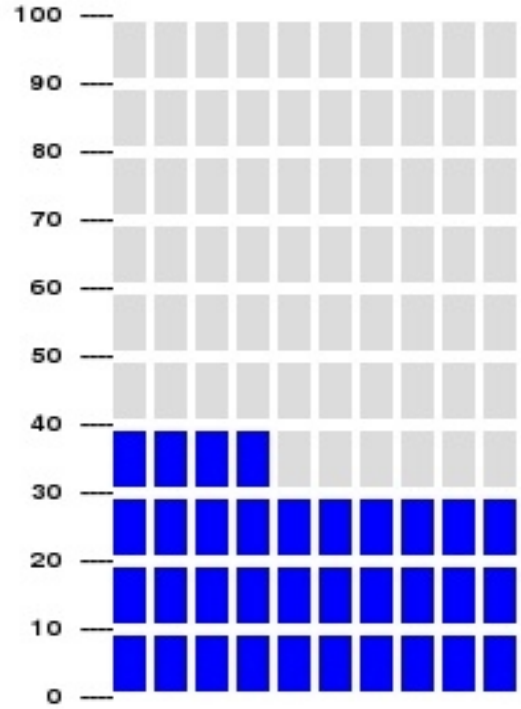
Risk of progressing to dementia of the Alzheimer's type

General Population



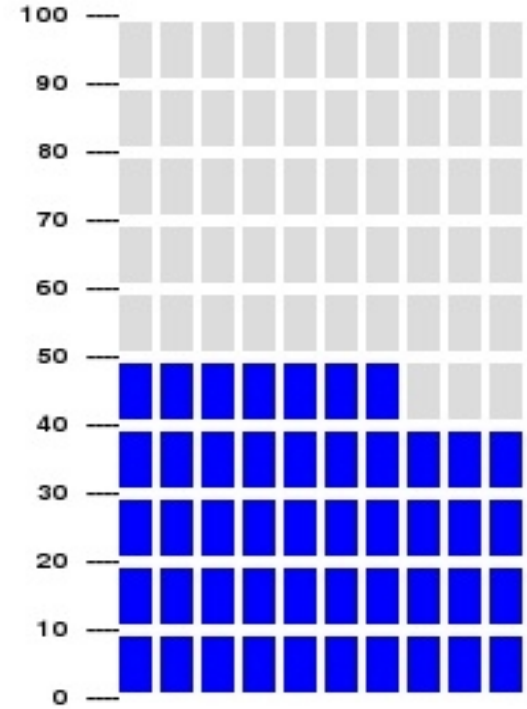
5% risk of progressing to dementia of the AD type in **3 years**

MCI



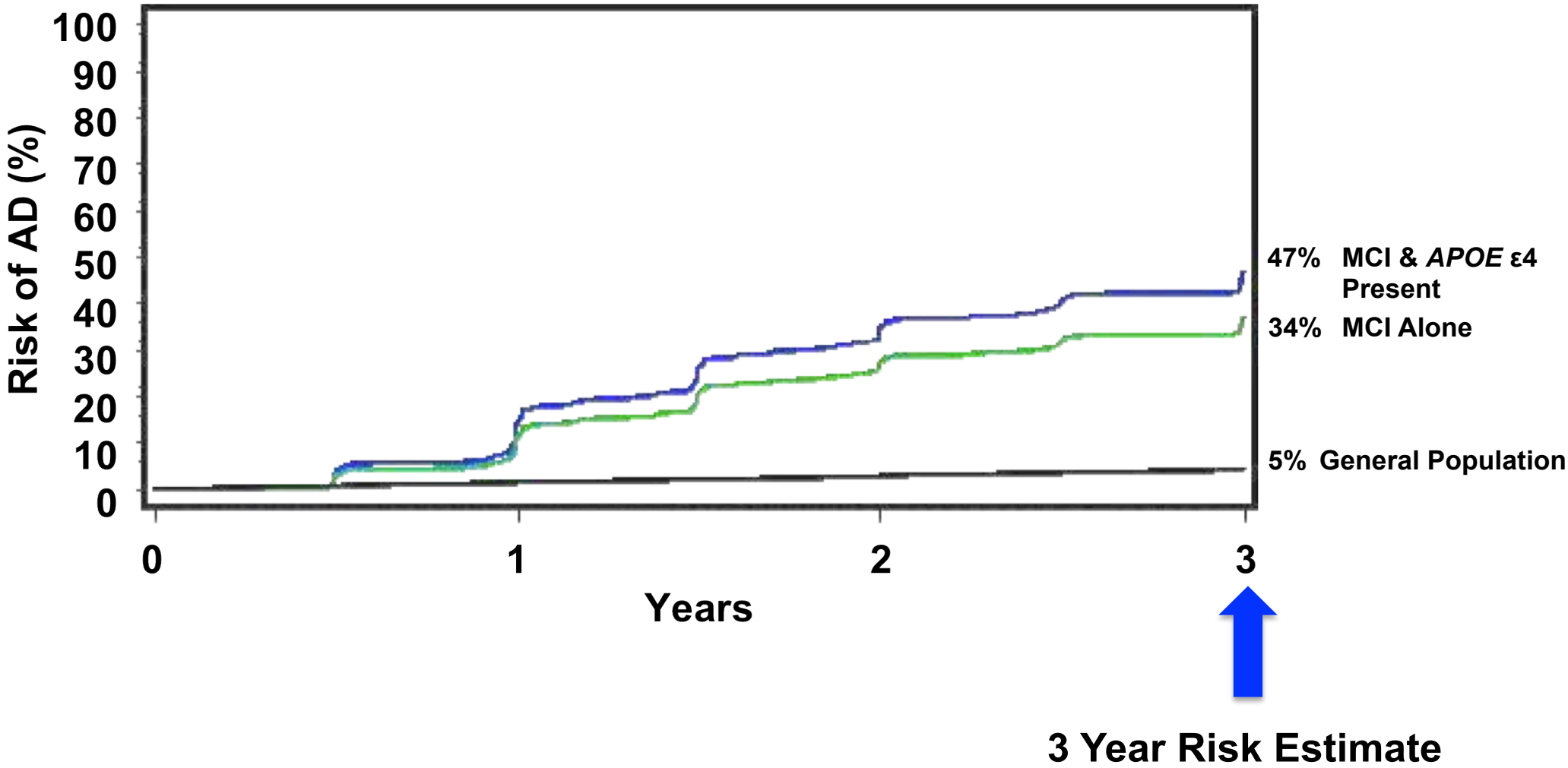
34% risk of progressing to dementia of the AD type in **3 years**

MCI and *APOE* ε4 Present



47% risk of progressing to dementia of the AD type in **3 years**

Risk increases over time



Other Topics

- Risk beyond three years
  - Elevated but no quantitative estimates
- Limitations of estimates
  - Not all risk factors accounted for
  - Lack of ethnic diversity in existing data

Future Directions

- Amyloid imaging results
- Other biomarkers
  - A-beta in CSF

Conclusions

- Risk assessment for AD will become increasingly important in clinical care, RCTs
- Disclosure of imminent risk info has wide-ranging implications
  - Ethical, psychological, behavioral, social
- Empirically validated methods of disclosing risk information can inform practice, policy

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