The Impact and Utility of Personalized Genomic Information: Insights from the REVEAL Study

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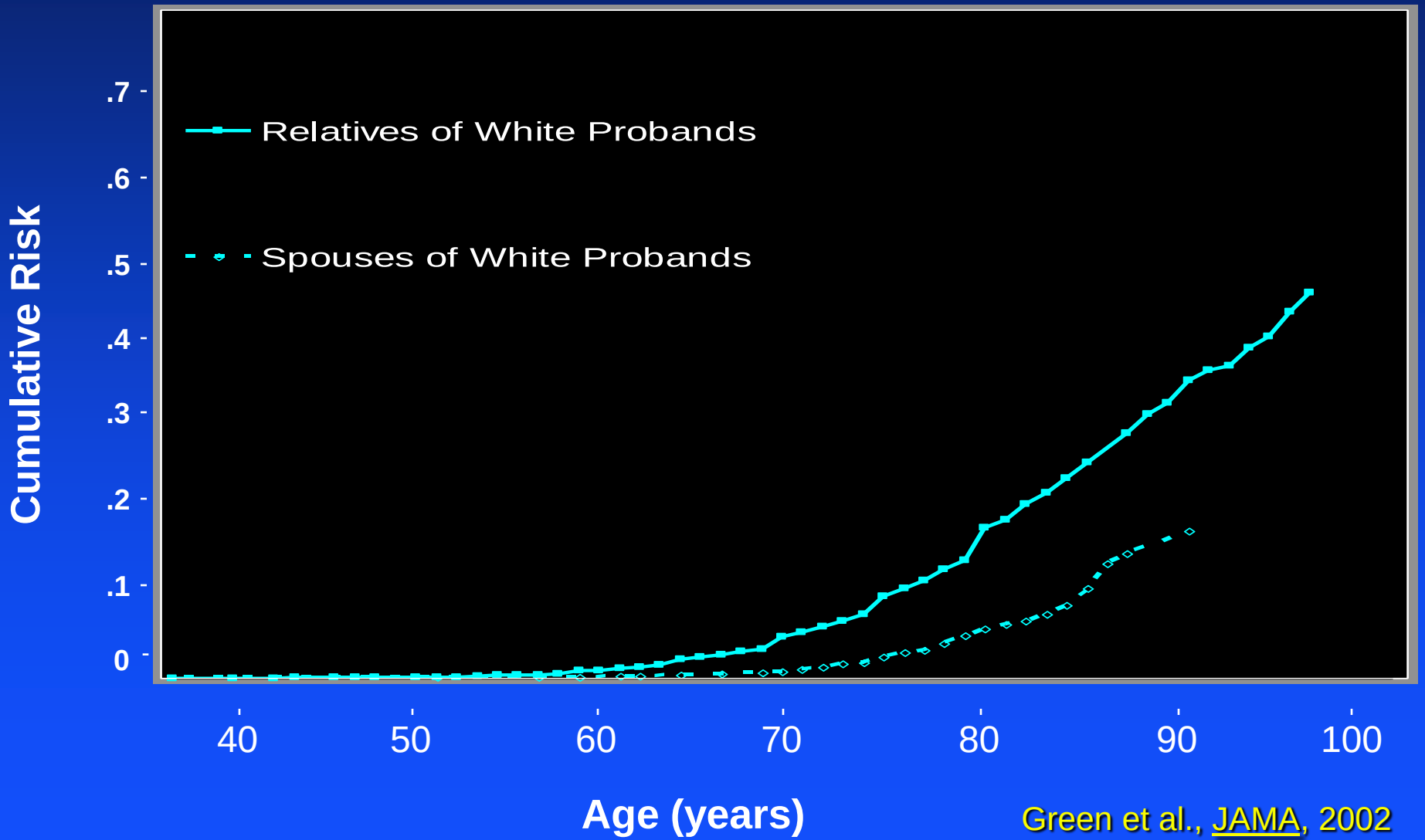
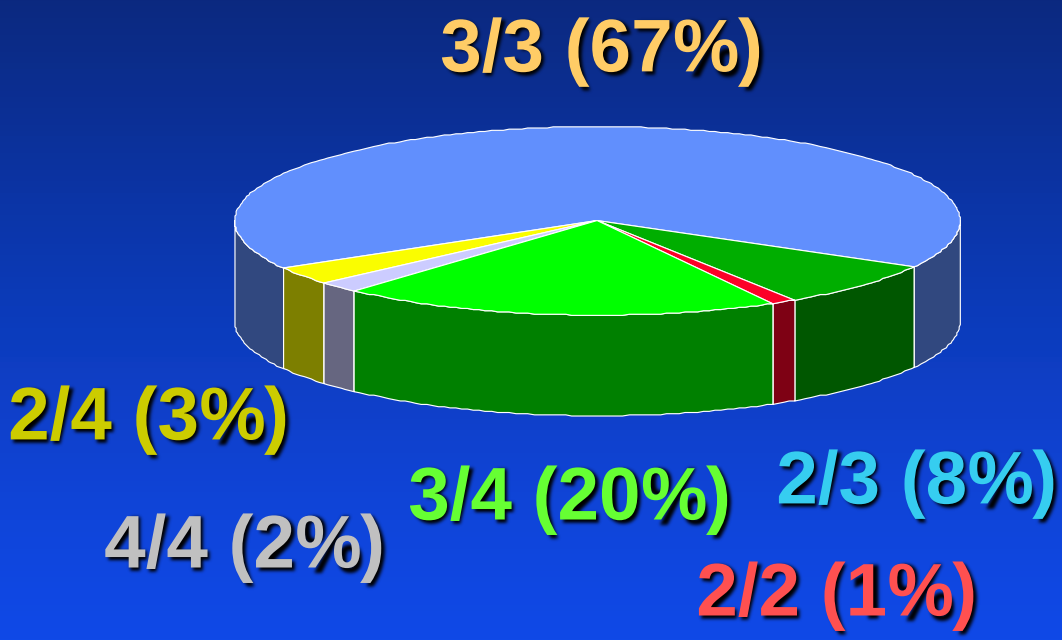
Advisory (uncompensated):	23andMe, Navigenics, Myriad Pharmaceuticals, SmartGenetics
Equity:	None

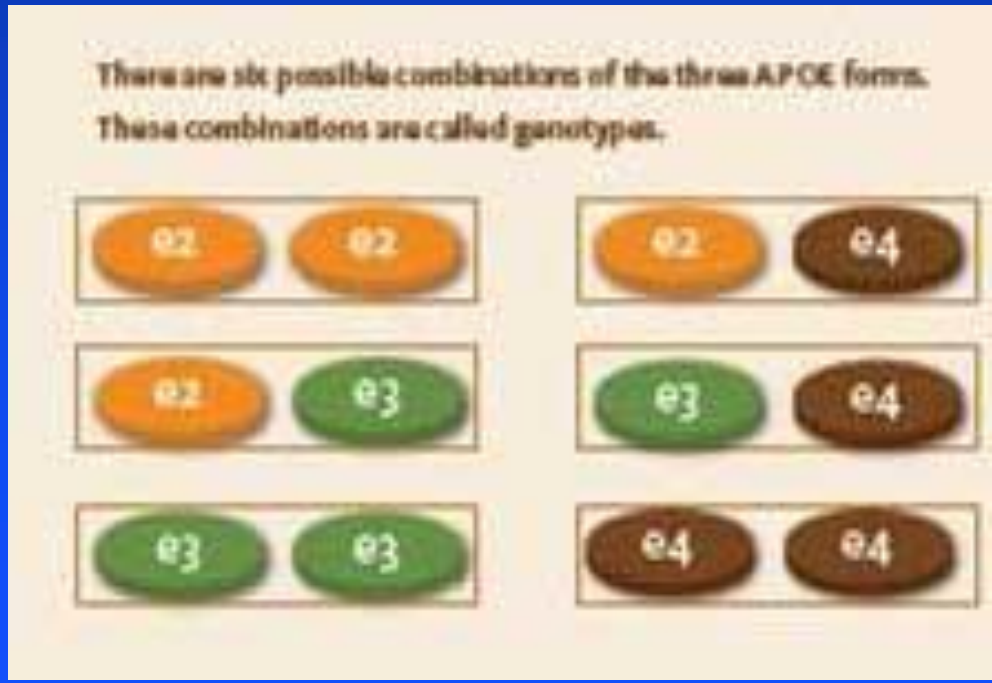
Cumulative Risk of Dementia in First-Degree Relatives of Patients with AD



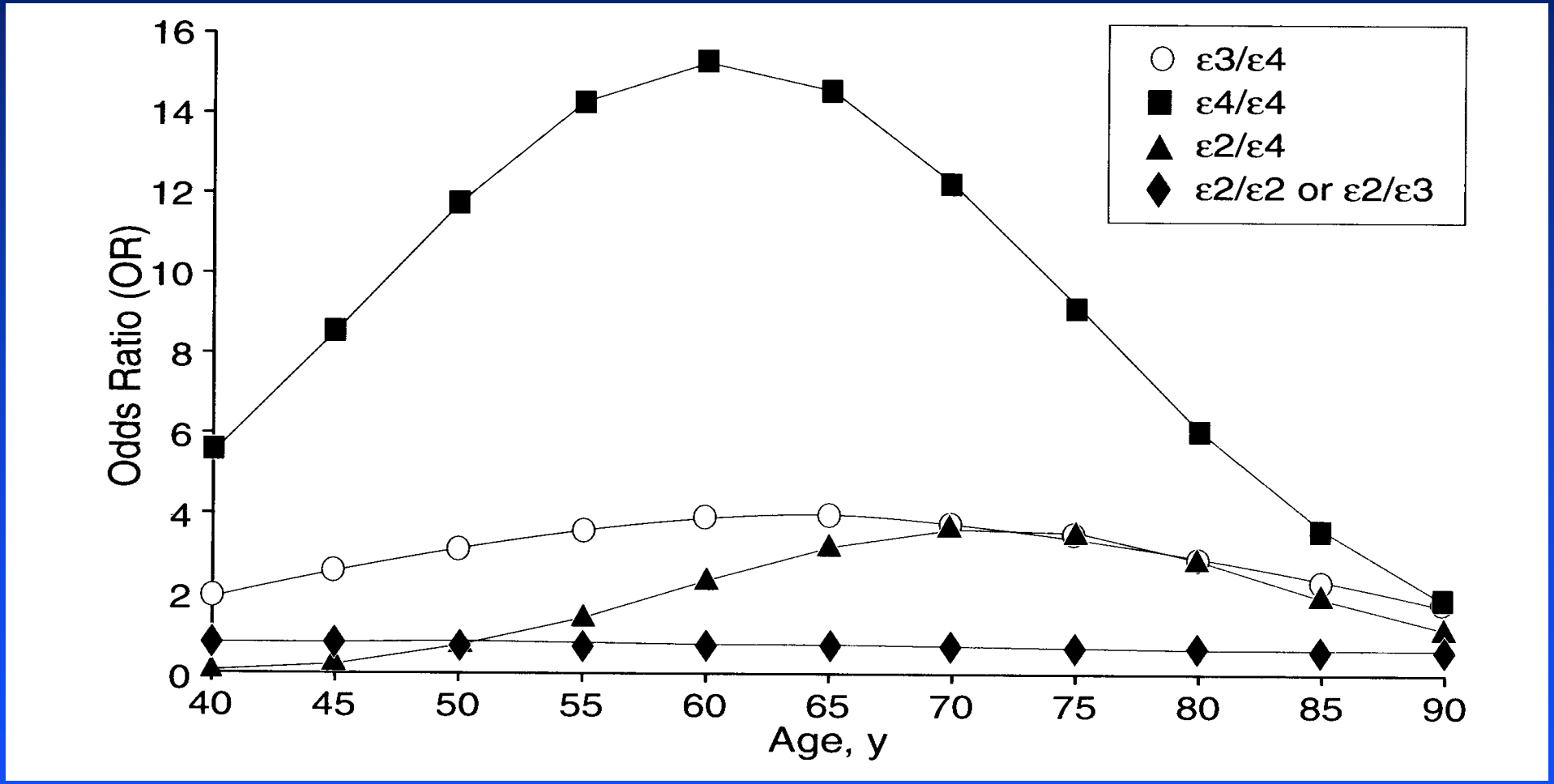
Green et al., JAMA, 2002

APOE Genotypes in the General Population





Odds of Alzheimer's Disease by APOE and Age: Highly Credible Epidemiology



Farrer et al., JAMA, 1997

APOE Genotyping for Risk Assessment Conventional Wisdom in 2000

Why we should NOT do risk assessment for Alzheimer's Disease with APOE?

- Psychological harm or discrimination may occur
- No treatment available to prevent AD
- Five (!) consensus conference recommendations

APOE Genotyping for Risk Assessment
The REVEAL "Rationale" in 2000

Why should we EXPLORE risk assessment for Alzheimer's Disease using APOE?

- Define at-risk persons to enrich prevention trials
- Explore responsive or vulnerable sub-populations
- Respond to self-interested family members
- Develop clinical paradigms for the use of susceptibility markers in common disorders

APOE and Alzheimer's Disease: A Unique Model for Exploring Clinical Utility and ELSI

- Excellent Analytic Validity
- Well documented Clinical Validity
- No treatments (and no market pressures!)
- Terrifying disease
- People still want to know their risk

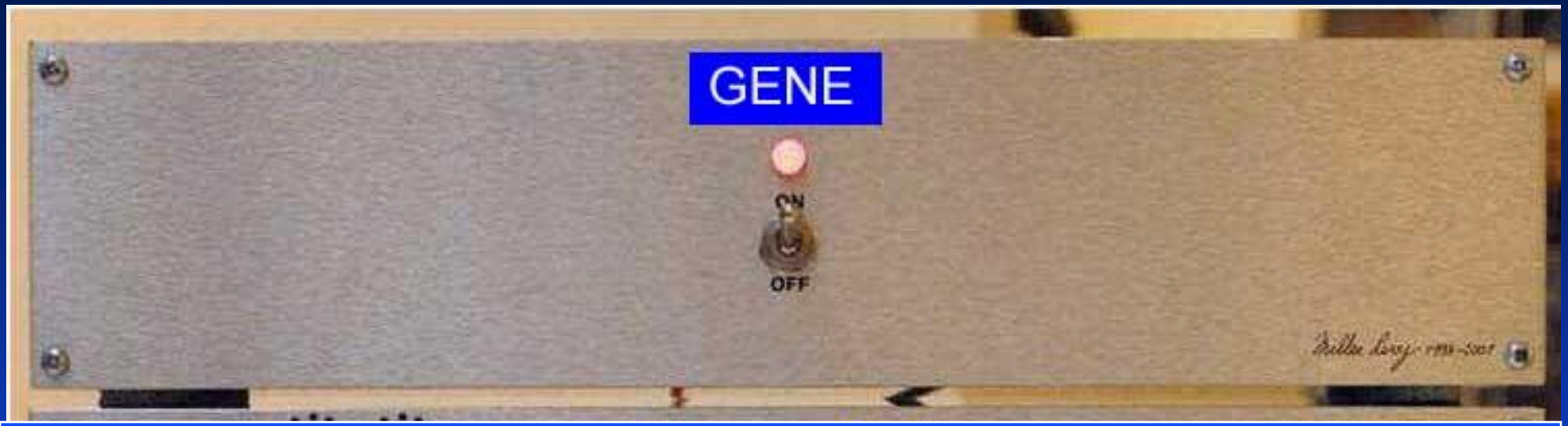
The REVEAL Study

Is risk information beneficial or toxic?

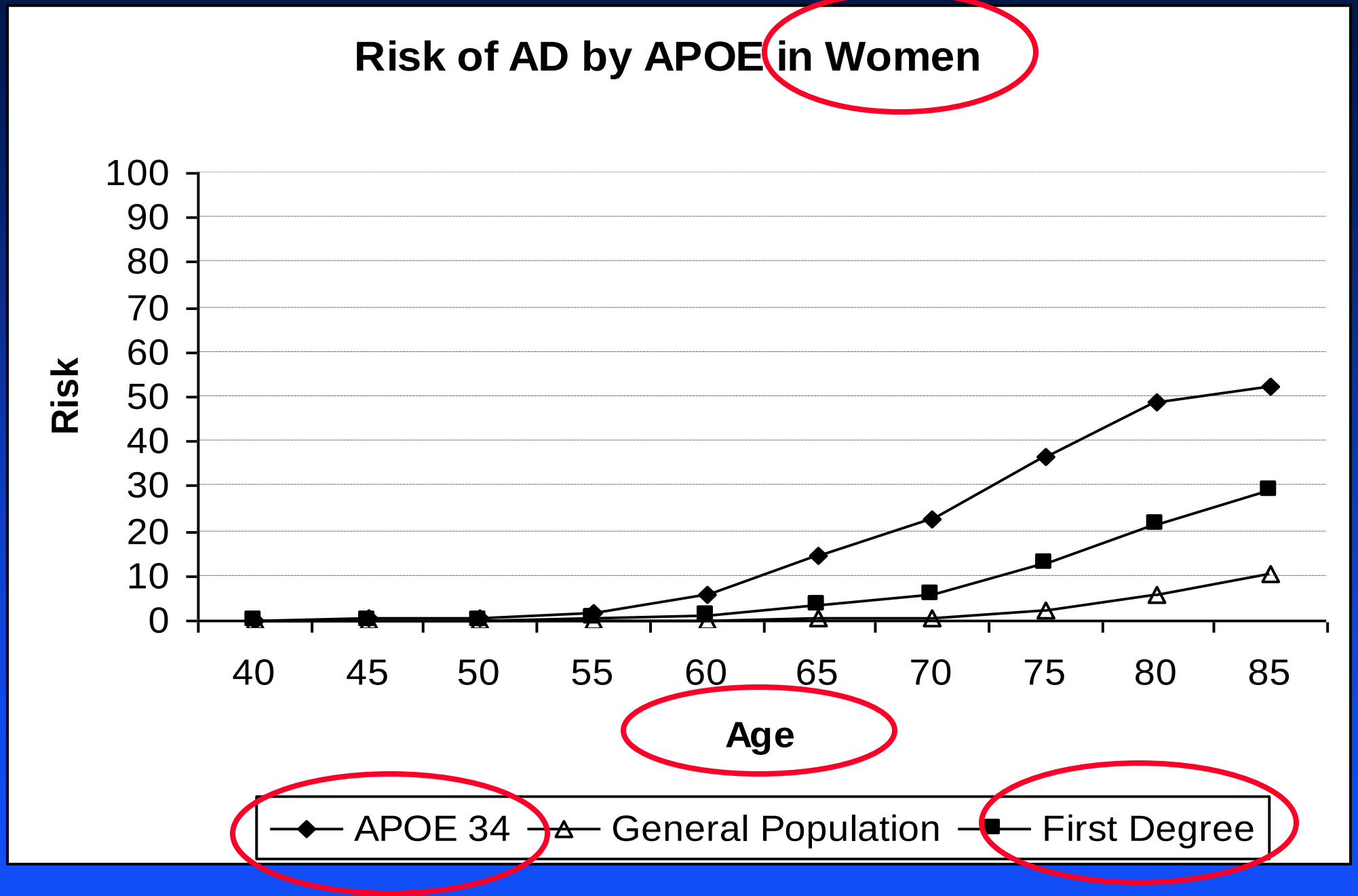
Empirically measure the benefits and risks of genetic susceptibility testing…

REVEAL Questions

How can we clearly communicate risk information based on genetics?



Cupples et al. Genetics in Medicine, 2004



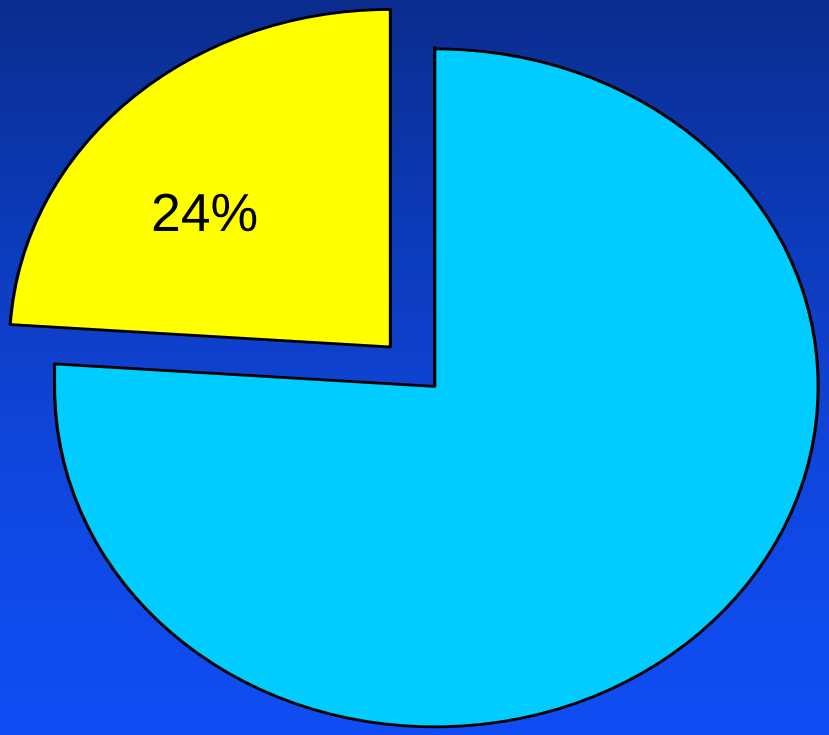
Cupples et al., Genetics in Medicine, 2004

REVEAL Questions

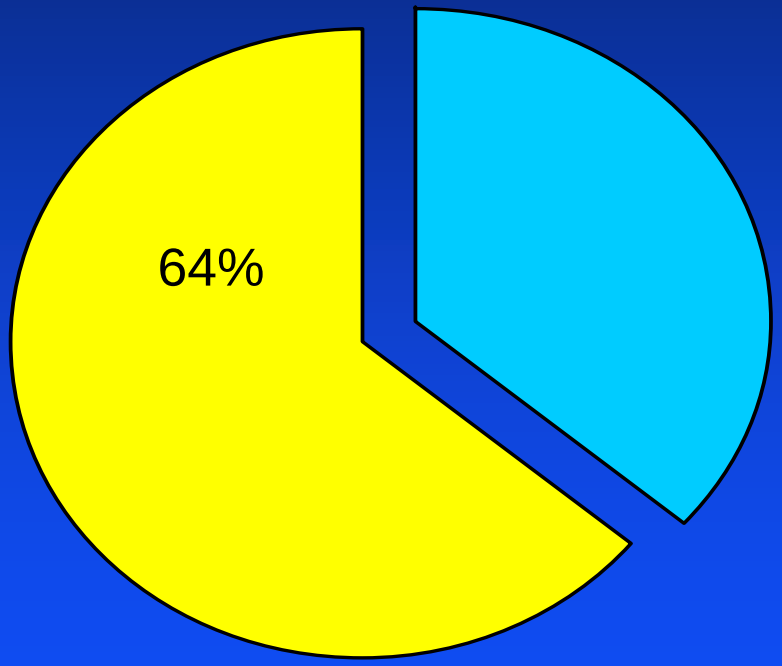
Who wants to know?

Persons Agreeing to Participate in REVEAL

Systematically Ascertained



Self Referred



Roberts et al. Genetics in Medicine, 2004

REVEAL Questions

Why do people want to know?

Reasons Associated with Enrollment (note that none of these are medically actionable)

Strongly endorsed reason for seeking testing as predictor of study enrollment	*Odds ratio*
To prepare family for AD	3.33
To arrange personal affairs	2.62
To arrange long-term care	2.52
To learn information for family planning	2.25

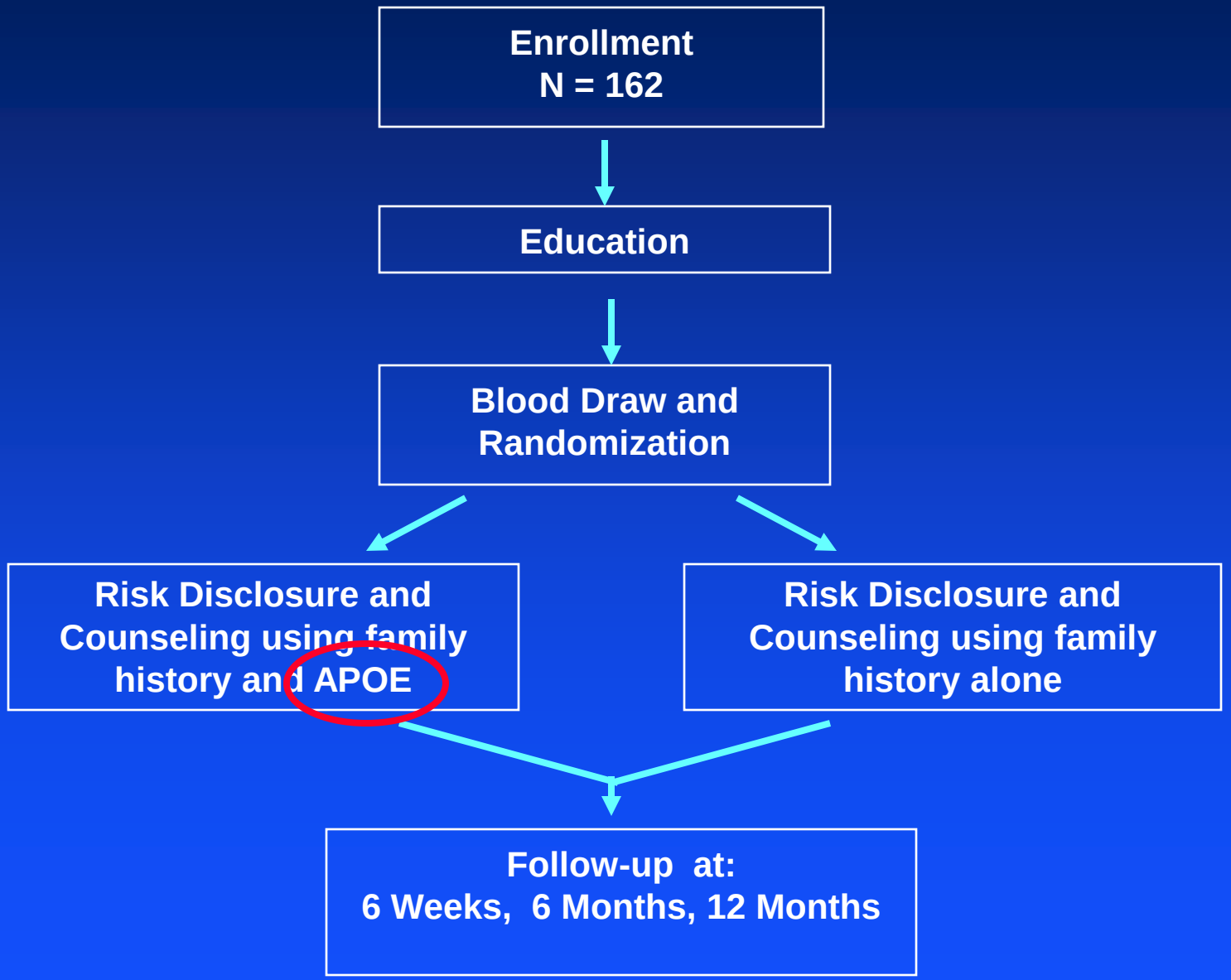
Women strongly endorsed more reasons for seeking testing than men, p = .01

Roberts et al., Alz Dis Rel Dementias, 2003

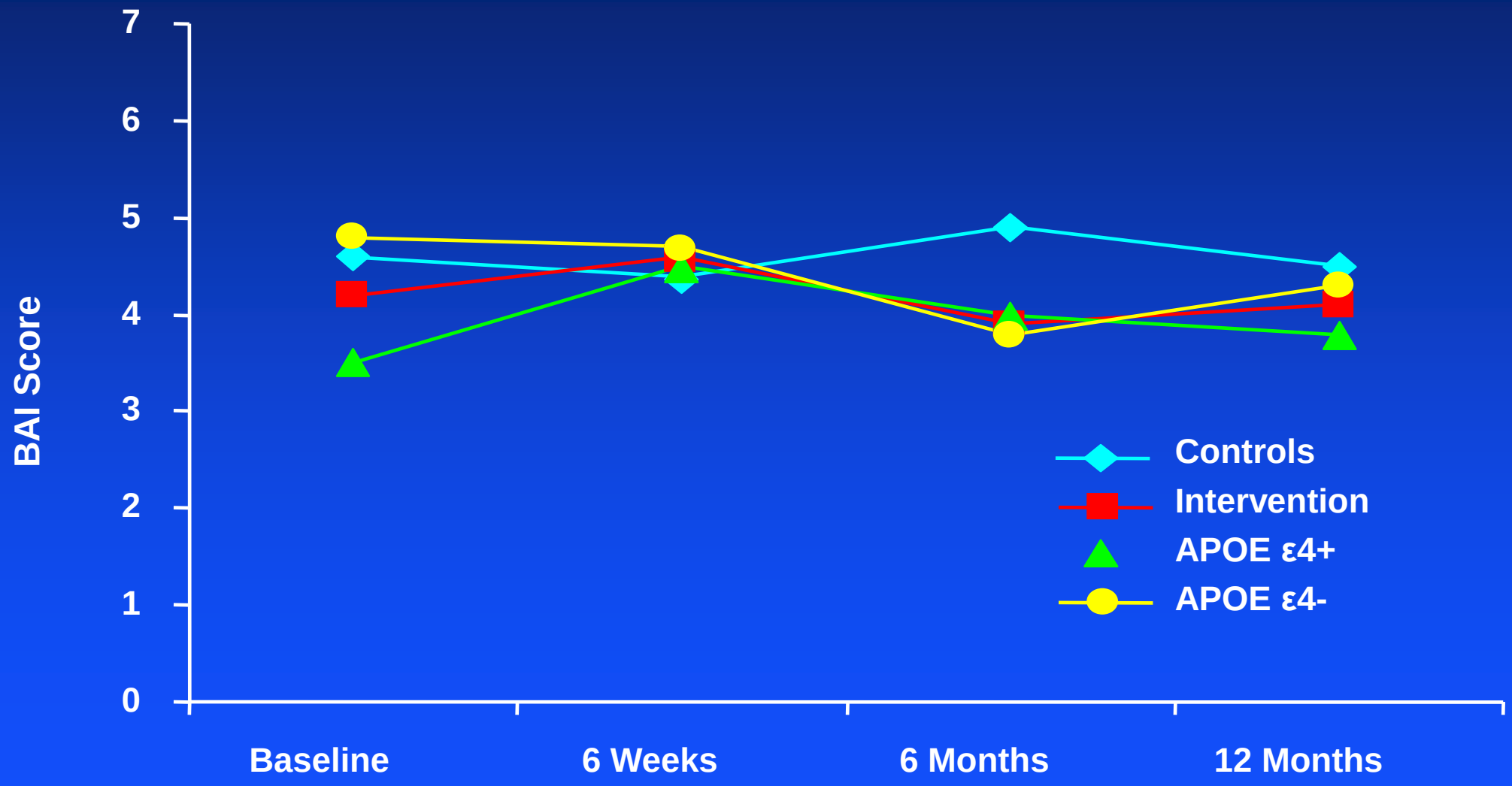
REVEAL Questions

What is the impact of learning genetic risk information?

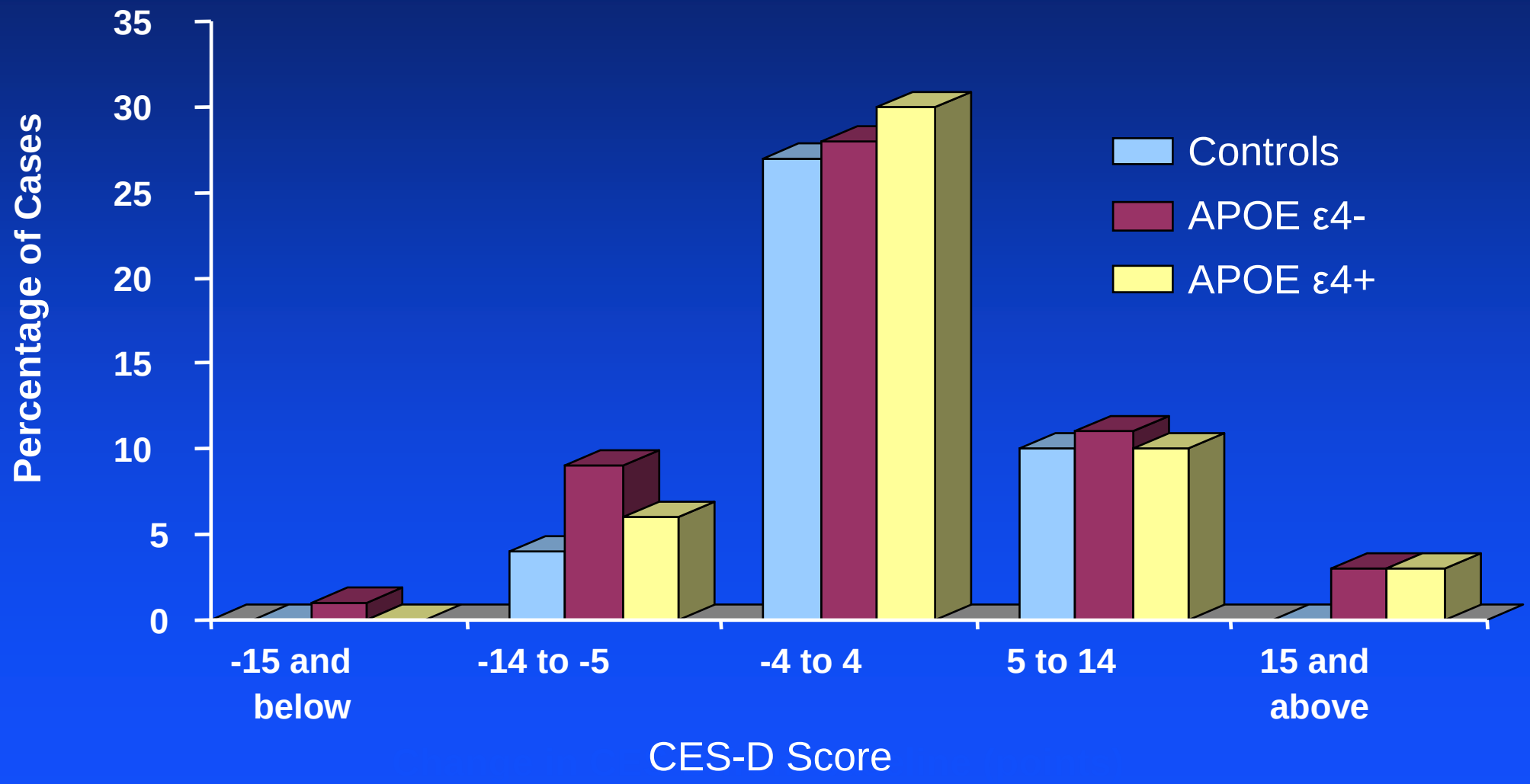
REVEAL I - Randomized Clinical Trial



REVEAL Study: Mean Anxiety Scale Score



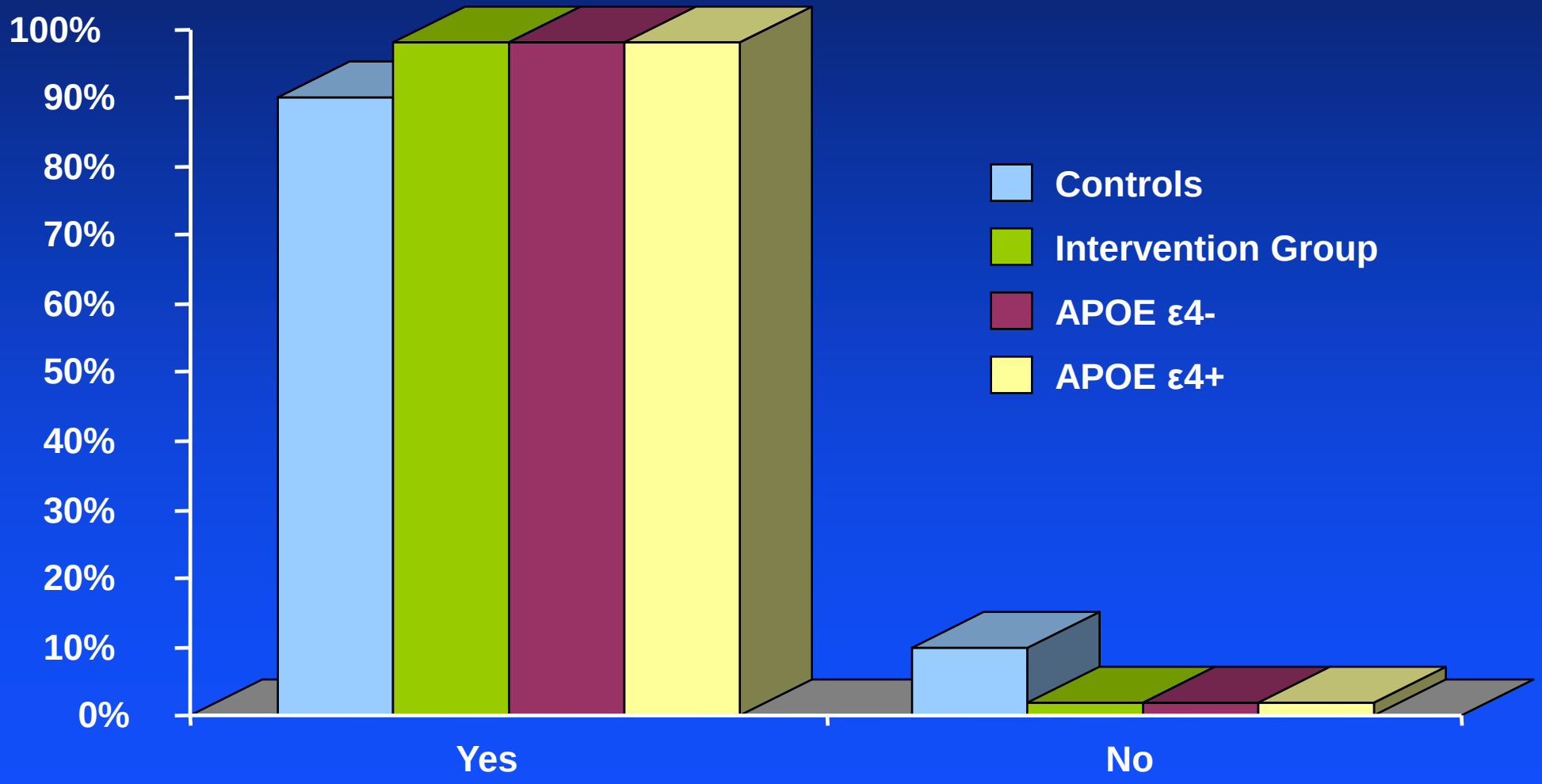
Post-Disclosure Change to Depression Symptoms: 1 year



REVEAL Questions

Are they satisfied with the information?

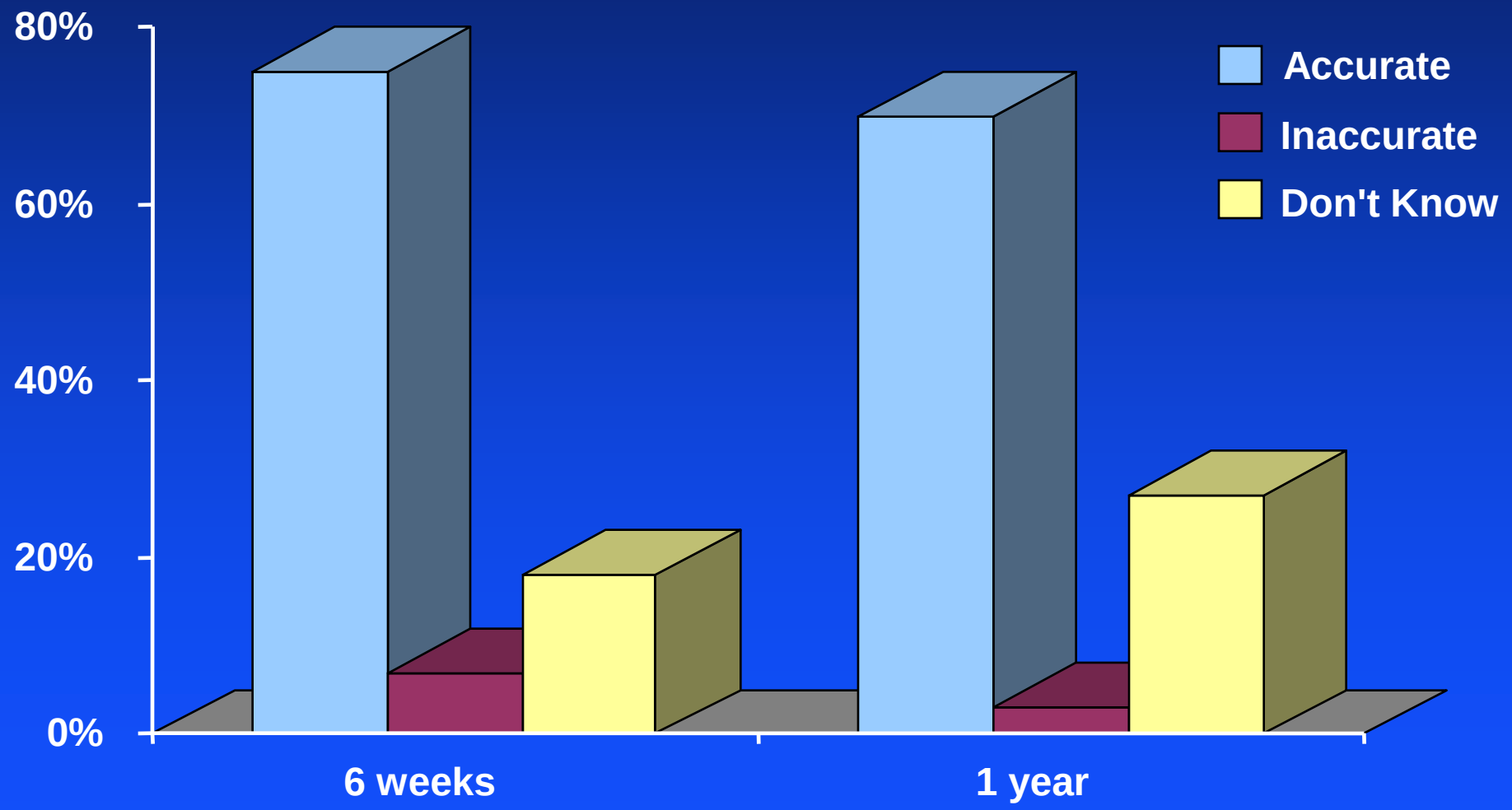
Would Do Risk Assessment Again…



REVEAL Questions

Can they recall the information?

Recall of Disclosure Information
APOE Status (positive or negative)

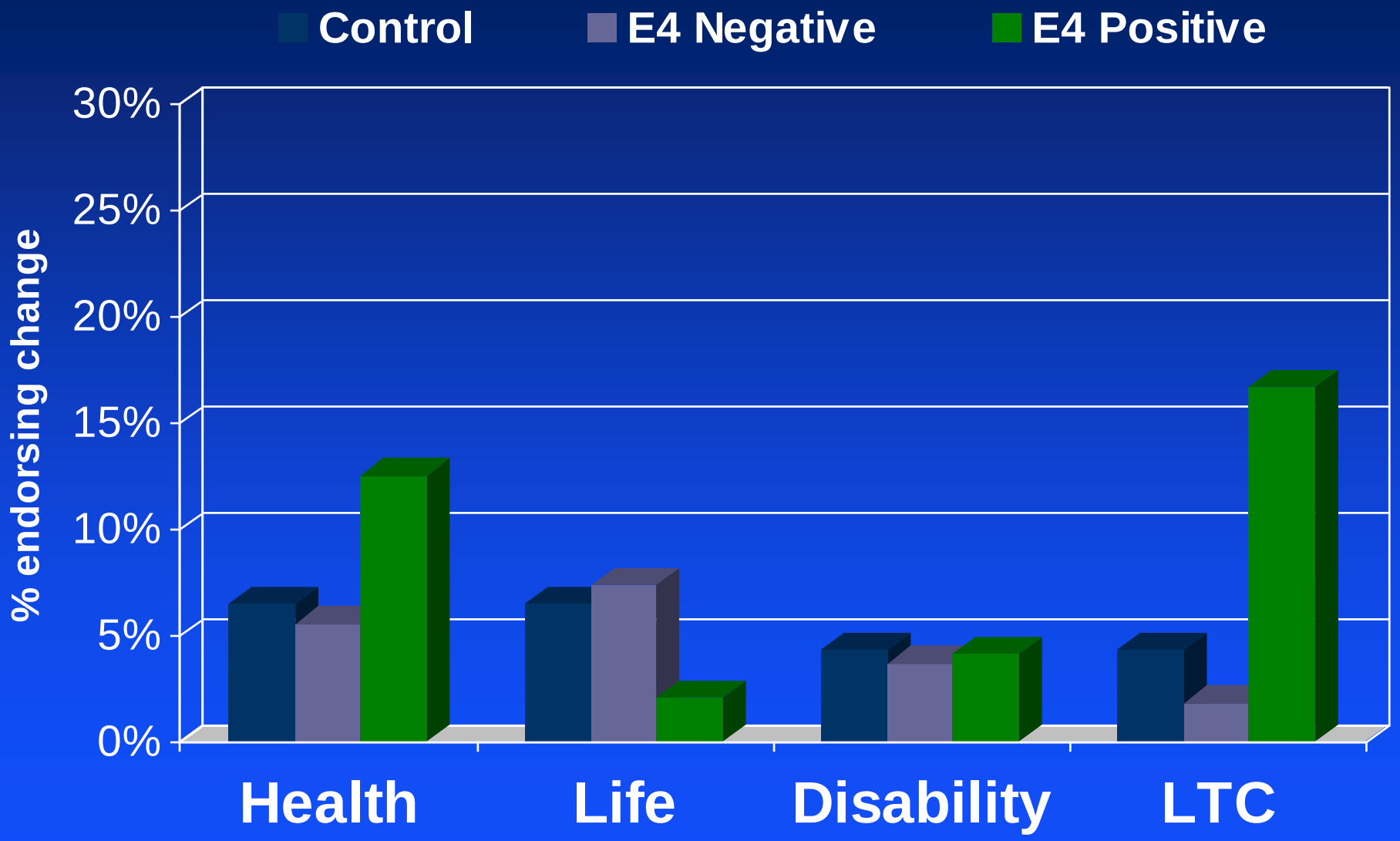


Eckert et al., Genetics in Medicine, 2006

REVEAL Questions

Does the information change their behavior (insurance purchasing)?

Insurance Changes 1 Year After APOE Disclosure

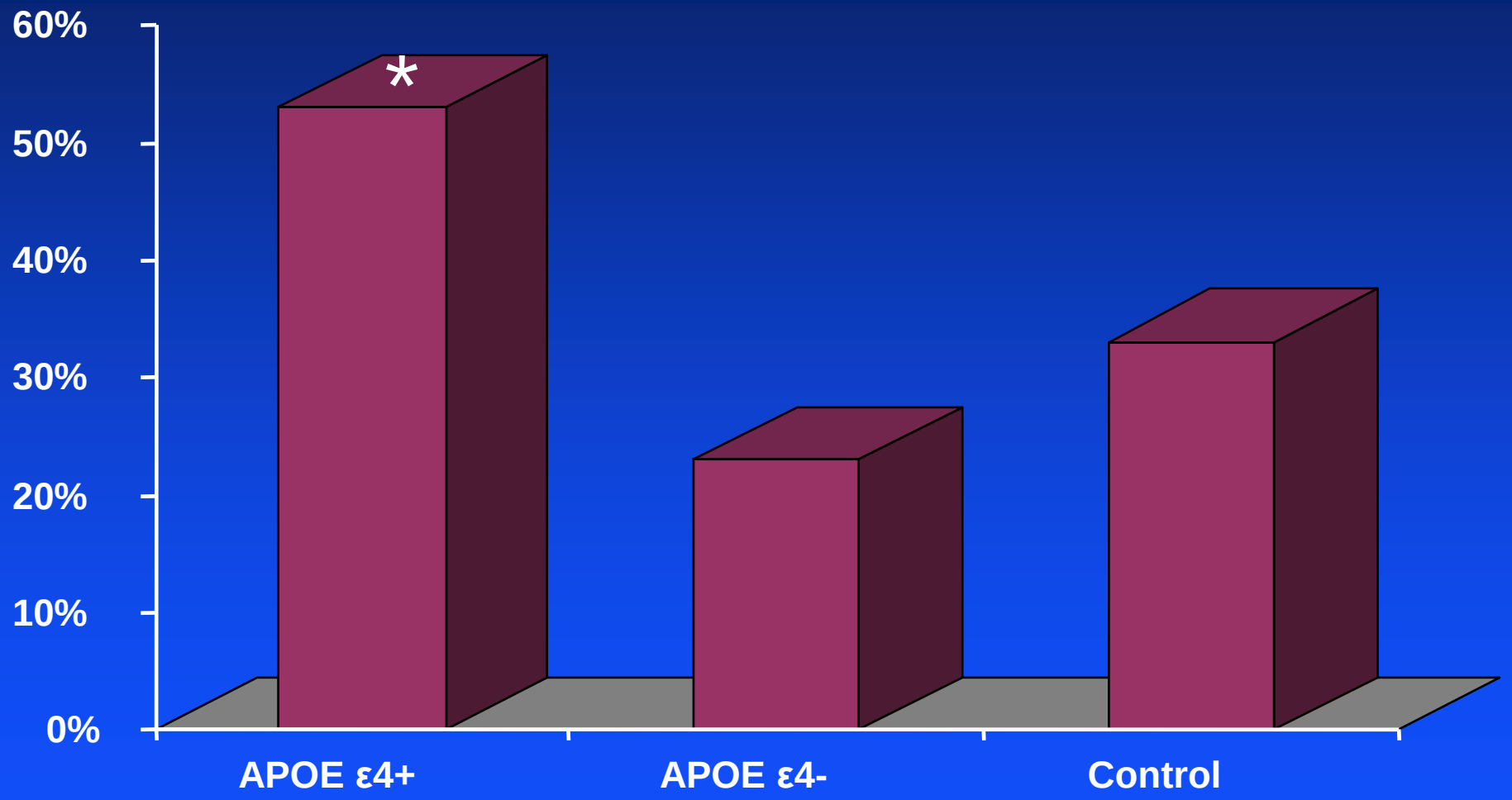


Zick et al., Health Affairs, 2005.

REVEAL Questions

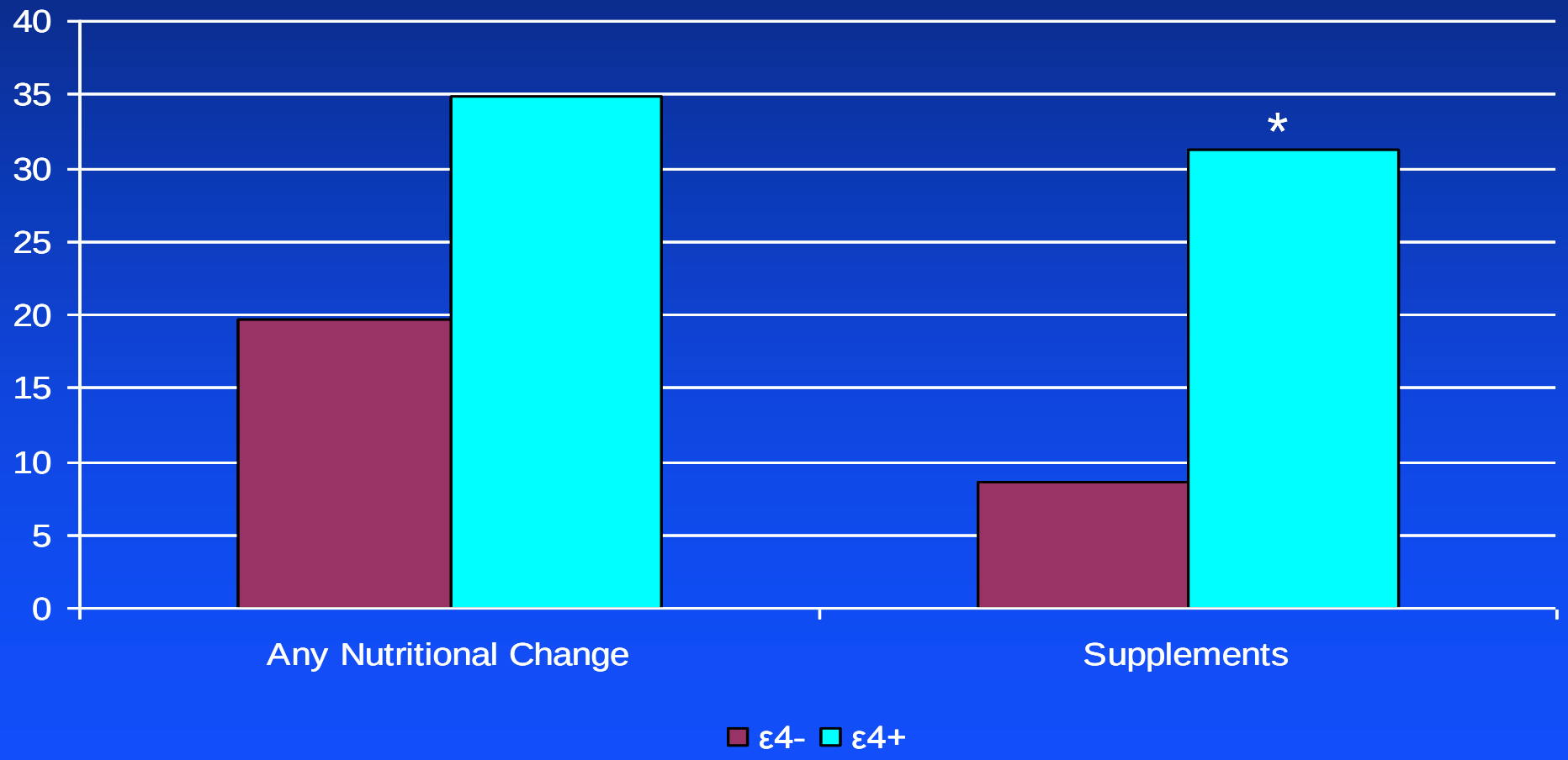
Does the information change their behavior (health behavior)?

Health Behavior Changes at 1 Year (Vitamins, Exercise, Medications)



Chao, et al. Alz Dis Assoc Dis, 2008

Health Behavior Changes at 6 Weeks (Nutrition and Supplements)



REVEAL Questions

How should we handle ethnicity?

ORIGINAL CONTRIBUTION

Risk of Dementia Among White and African American Relat of Patients With Alzheimer

Robert C. Green, MD, MPH
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Rodney Go, PhD
Kelly S. Benke, AB
Timi Edeki, MD, PhD
Patrick A. Griffith, MD
Mary Williams, EdD, PAC
Yvonne Hipps, PhD
Neill Graff-Radford, MD
David Bachman, MD

Context Evidence exists that the attributable to specific genetic fact vary considerably among ethnic g opportunity to evaluate lifetime ri

Objective To compare lifetime d African American probands with

Design and Setting Risk analys mental records between May 199 ing to the Multi-Institutional Rese

Participants A total of 17 639 fi 2339 white AD probands, and 22 of 255 African American AD prob

among populations in other countries have been less thoroughly studied, but there is evidence that the incidence of disease, as well as the risk attributable to specific genetic factors such as *APOE* genotype, may vary considerably among ethnic groups.[2,7-10]

by the probability of having an *APOE* ε4 allele app white families. These data provide estimates of de counseling to family members of patients with AD

JAMA. 2002;287:329-336

Author Affiliations and Members of the MIRAGE (Multi- Institutional Research in Alzheimer's Genetic Epidemiology) Study Group are listed at the end of this article. Corresponding Author and Reprints: Robert C. Green,

Comparison of Alzheimer's disease risk factors in white and African American families

D.L. Bachman, MD; R.C. Green, MD, MPH; K.S. Benke, AB; L.A. Cupples, PhD; and L.A. Farrer, PhD; for the MIRAGE Study Group*

Alzheimer Disease and Associated Disorders
Vol. 17, No. 1, pp. 19–26

Differences Between African Americans and Whites in Their Perceptions of Alzheimer Disease

:Yvonne G. Hipps,
n

rsity School of Medicine, and the
usetts; the †Department of Health

Incorporating ethnicity into genetic risk assessment for Alzheimer's disease: the REVEAL study experience

Kurt D. Christensen, MPH[1], J. Scott Roberts, PhD[1], Charmaine D. M. Royal, PhD[2], Grace-Ann Fasaye, ScM, CGC[3], Thomas Obisesan, MD[4], L. Adrienne Cupples, PhD[5,6], Peter J. Whitehouse, MD, PhD[7], Melissa Barber Butson, ScM, CGC[7], Erin Linnenbringer, MS, CGC[1], Norman R. Relkin, MD, PhD[8], Lindsay Farrer, PhD[5,6,9,10], Robert Cook-Deegan, MD[2], and Robert C. Green, MD, MPH[6,9]

Differences Between African Americans and Whites in Their Attitudes Toward Genetic Testing for Alzheimer's Disease

YVONNE G. HIPPS,[1] J. SCOTT ROBERTS,[2] LINDSAY A. FARRER,[3] and ROBERT C. GREEN[3]

REVEAL Questions

Are preparatory genetic counseling protocols necessary for safe disclosure?

The REVEAL II Study: Condensed "Education"

Alzheimer's Disease and the APOE Gene

Inheriting a specific form of the APOE gene can increase the risk of getting Alzheimer's disease. The role of the APOE gene in Alzheimer's disease is still being studied. Some studies have shown that it may be related to other conditions in addition to Alzheimer's disease.

We do know that the APOE gene comes in three different forms: E2, E3, and E4. Every person has two copies of the APOE gene—one inherited from each parent. Because there are three different forms of the APOE gene and there are two APOE genes in every person, an individual posesses one of six unique APOE combinations (pictured below).

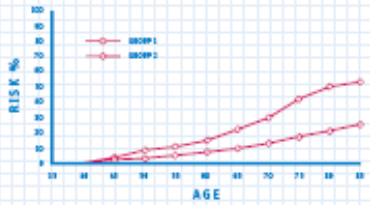
If an individual has one or two copies of the E4 form of the APOE gene, it increases his or her risk of developing Alzheimer's disease. However, this does not mean that he or she will definitely get Alzheimer's disease.

APOE Genetic Testing

As part of your risk assessment, we provide APOE testing. There are three basic steps to APOE testing. First, you will meet with a genetic counselor to review any questions or concerns about having an Alzheimer's disease risk assessment, including APOE testing. Next, you will provide a small blood sample for APOE testing. Finally, you will meet with a clinician to learn and discuss your test result and risk assessment. Test results are typically available within a few weeks of the blood draw.

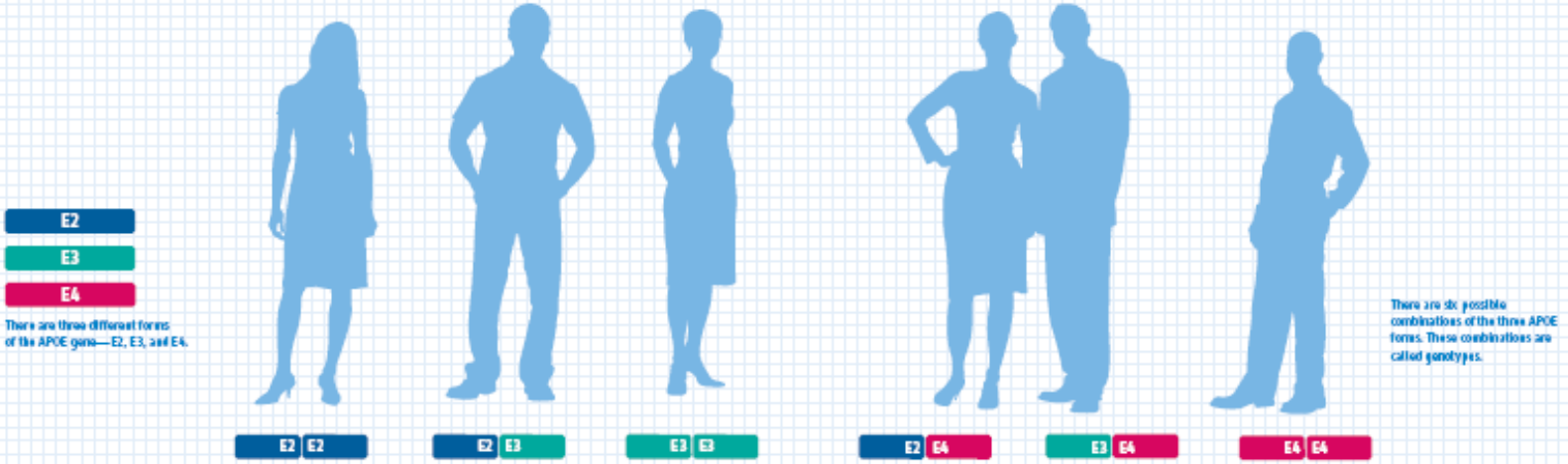
Understanding Your Risk Assessment

You will be given an estimate of your risk of developing Alzheimer's disease by the time you are 85 years old. Depending on your risk factors, you will be given a risk number between approximately 15% to 75%. Your risk estimate will also be shown on a graph, similar to that pictured below.

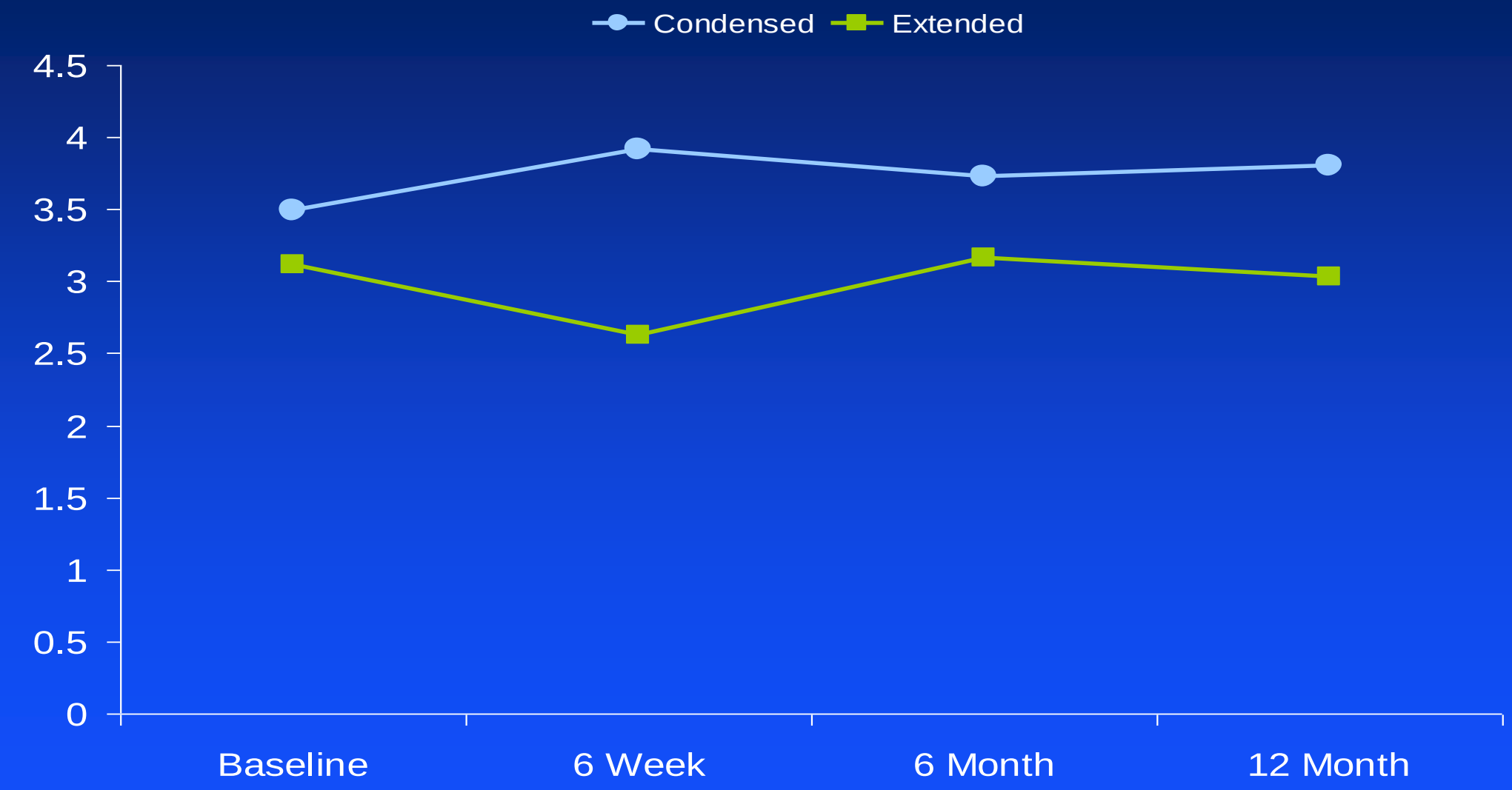


The characteristics taken into account in the risk assessment include your age, gender, race, APOE test result, and whether or not you have a parent, brother, or sister with Alzheimer's disease.

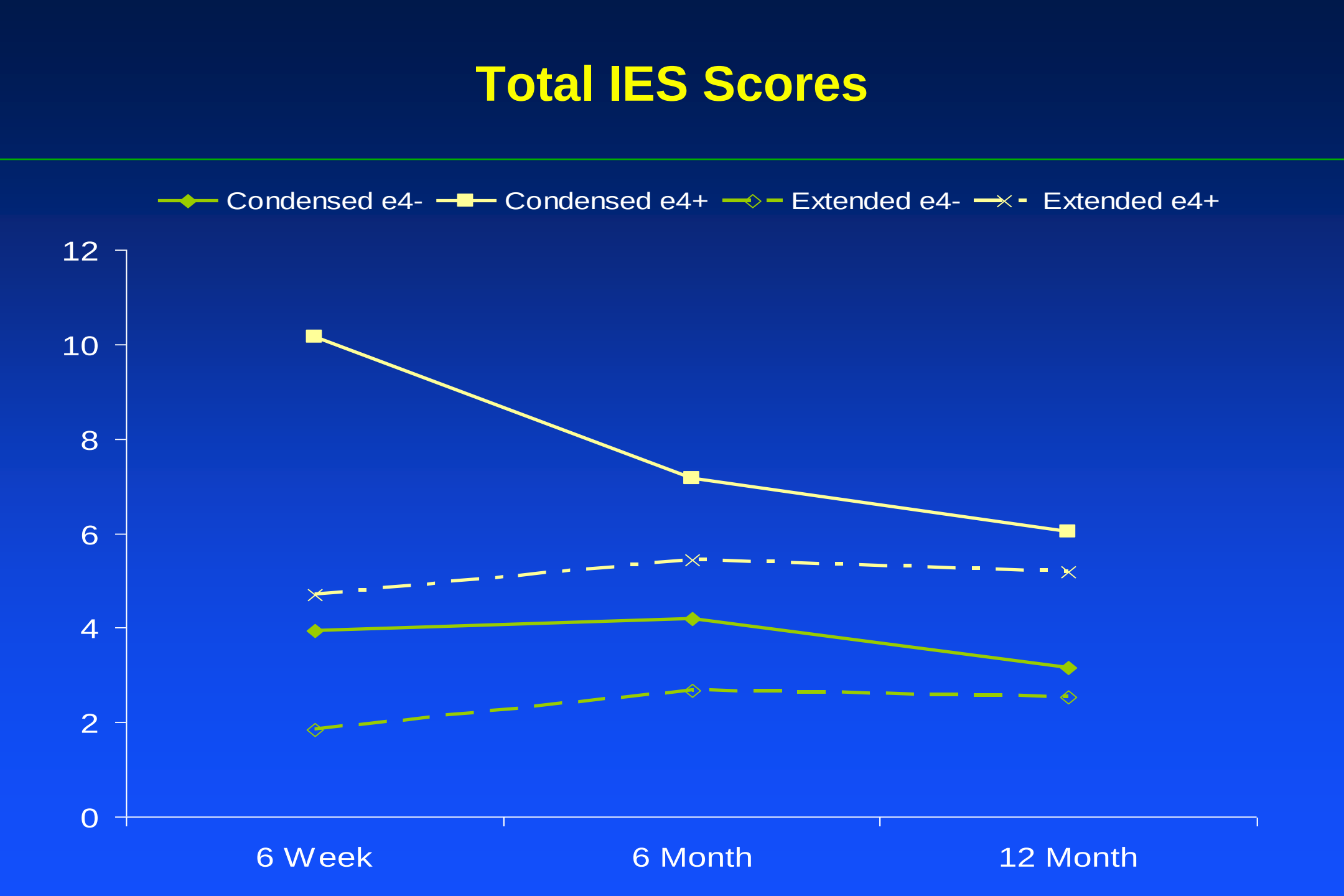
We are still learning about many other genetic and non-genetic factors that are involved in the development of Alzheimer's disease. As scientists learn more about what causes Alzheimer's disease, this new information may alter your risk assessment.



BAI Scores


Condensed
Extended
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Baseline
6 Week
6 Month
12 Month

Total IES Scores



REVEAL Questions

What features predict willingness to pay for such testing?

Multivariate analysis: Correlates of Willingness to Pay >$100 for Testing

	Odds Ratio	95% Confidence Interval		p value (multivariate)
		Lower	Upper	
Age	1.009	0.978	1.040	0.5815
Sex (Female)	0.756	0.393	1.455	0.4028
Race (African American)	0.881	0.394	1.969	0.7575
Education	1.083	0.957	1.226	0.2076
Income (≥$50K)	3.030	1.399	6.564	**0.0049**
APOE status (e4 positive)	1.145	0.641	2.043	0.6475
Baseline Self-Perceived Risk	1.004	0.991	1.018	0.5351
Interested in Knowing Results	3.071	1.476	6.387	**0.0027**

Kopits et al., in submission

What do participants say they would pay for AD risk assessment?

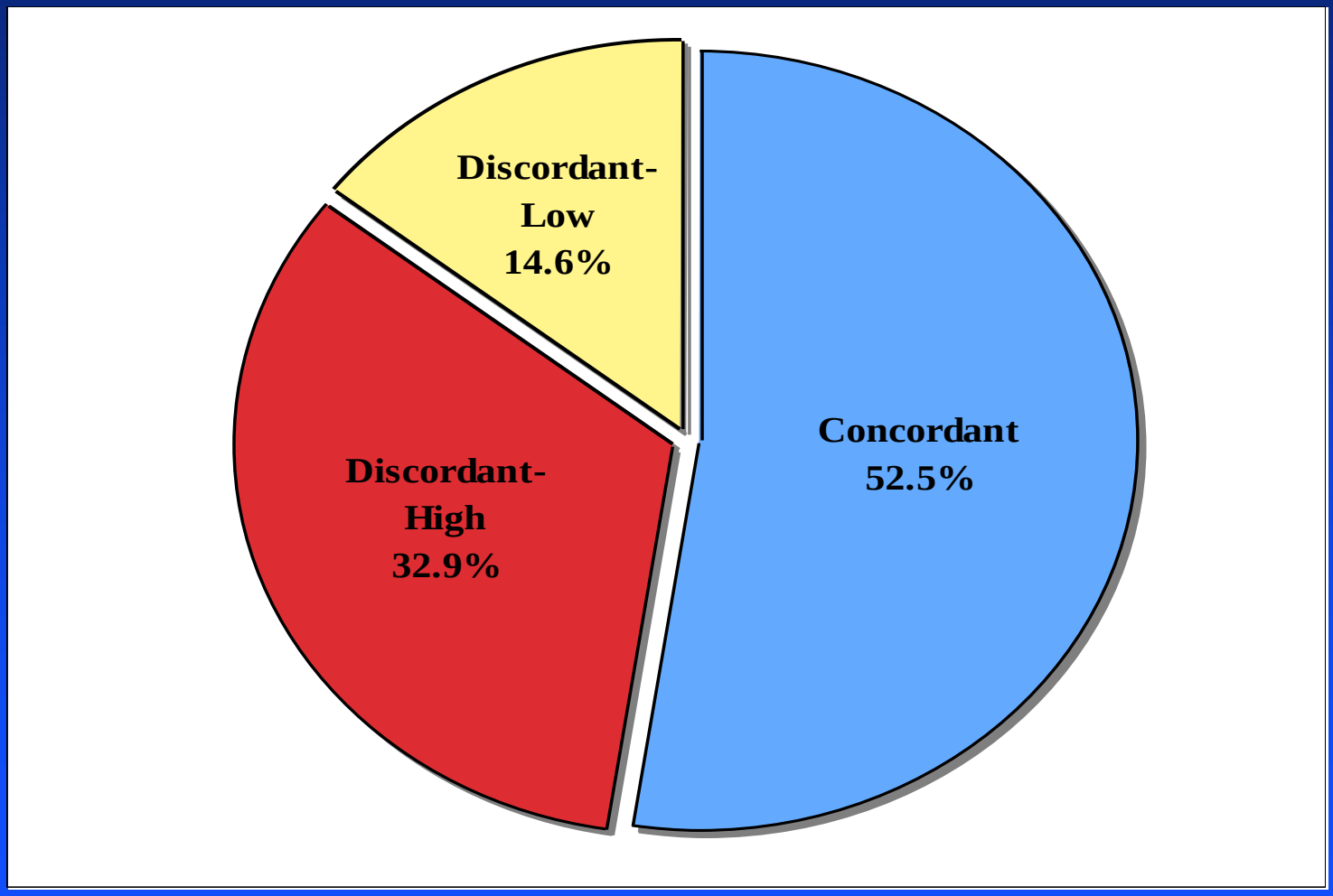
Amount Willing to Pay	Percentage
$0	3.1
$25	14.5
$50	11.7
$100	29.3
$200	21.5
$500	14.1
$1000	2.3
More than $1000	3.5

Kopits et al., in submission

REVEAL Questions

Does genetic testing change self-perceived risk?

Among those who accurately recall their risk disclosure numbers (n = 158) 47.5% continue to believe otherwise!



Multinomial logistic regression results examining the differences among concordant, discordant-high, and discordant-low groups

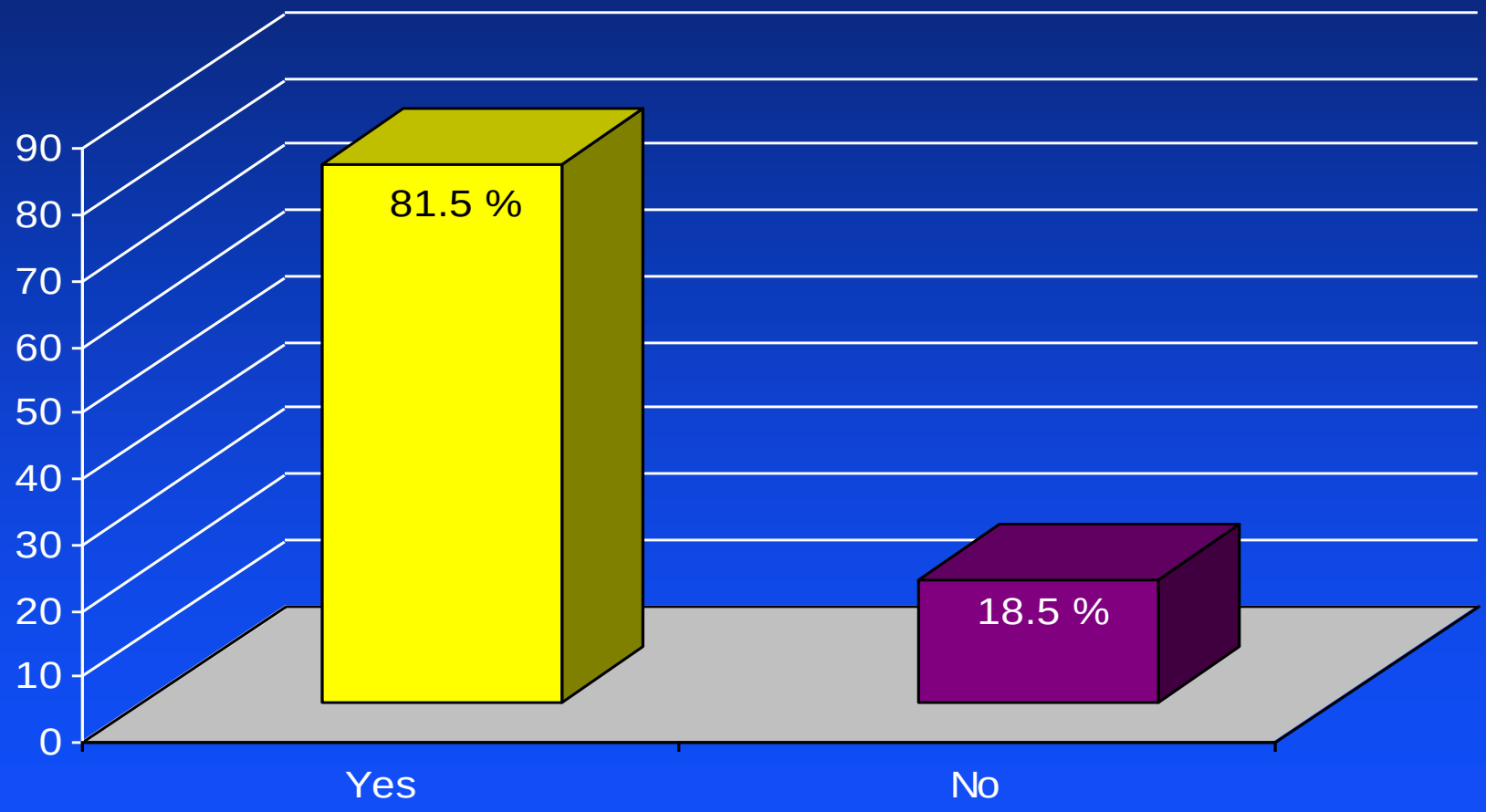
	Likelihood ratio chi-square	P-value	Odds ratio for discordant-high vs.concordant (95% CI for Exp b)	Odds ratio for discordant-low vs. concordant (95% CI for Exp b)
Demographics:				
APOE status (e4 negative)	10.06	0.01[b]	1.34 (0.57 – 3.17)	**0.17 (0.05 – 0.60)**
Racial group (Black)	6.23	0.04	0.27 (0.05 – 1.52)	2.75 (0.71 – 10.63)
Gender (female)	3.61	0.16	0.56 (0.23 – 1.38)	2.54 (0.51 – 12.64)
Age (less than 60)	0.59	0.75	0.95 (0.37 – 2.42)	0.60 (0.16 – 2.22)
Baseline attitudes & mood:				
AD risk perception	26.46	<0.01[a]	**1.06 (1.03 – 1.09)**	0.97 (0.94 – 1.00)
AD controllability	7.27	0.03[b]	1.08 (0.94 – 1.23)	**1.31 (1.05 – 1.64)**
Anxiety (BAI)	2.78	0.25	0.97 (0.84 – 1.13)	1.14 (0.95 – 1.38)
Depression (CES-D)	1.92	0.38	1.08 (0.96 – 1.21)	0.97 (0.84 – 1.16)
AD concern	0.54	0.97	0.93 (0.44 – 1.96)	0.93 (0.36 – 2.37)

a Concordant ≠ Discordant-high, $p < 0.05$ b Concordant ≠ Discordant-low, $p < 0.05$

REVEAL Questions

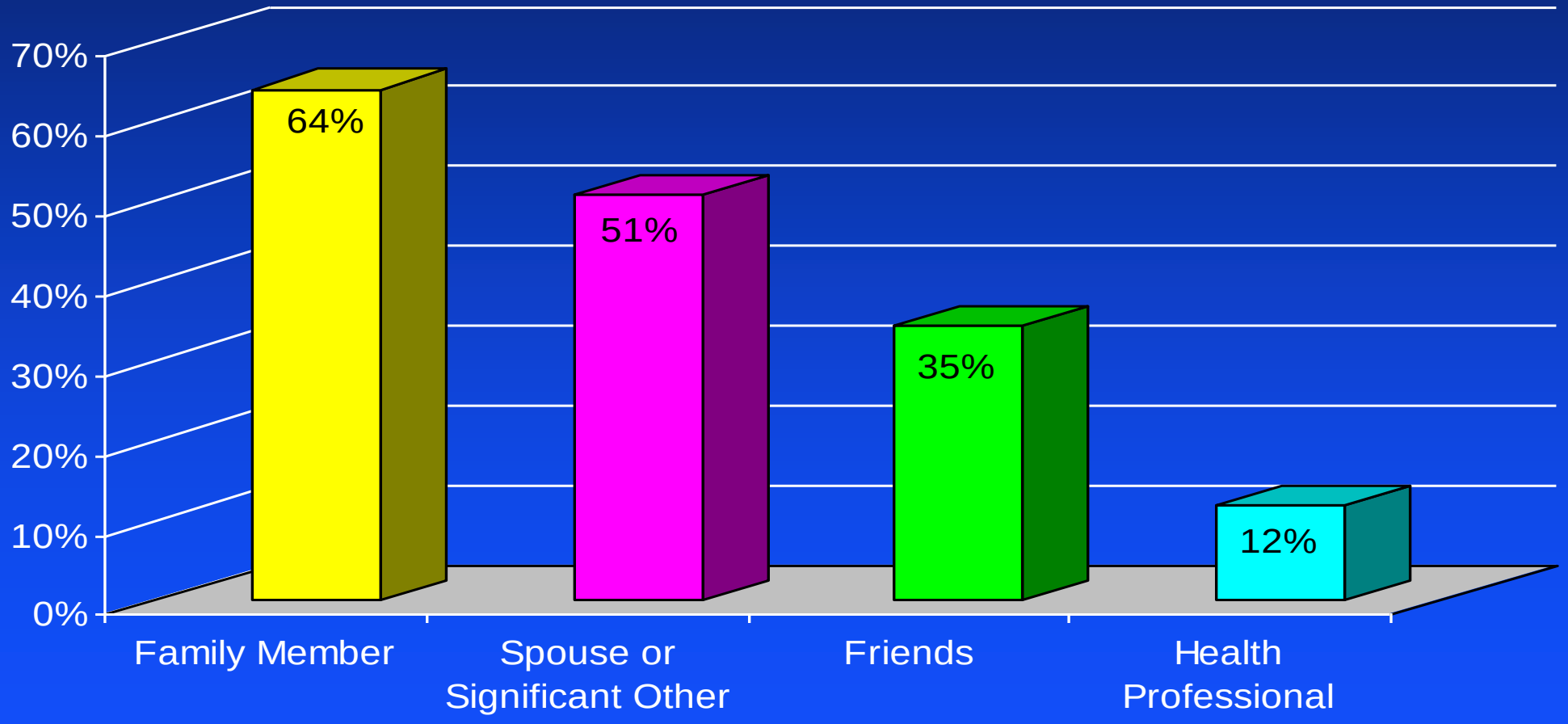
Whom do people tell about their genetic results?

Have you told anyone about your results?



Ashida et al., in submission

Whom did you tell about the results of your test?



Ashida et al., in submission

What Variable Predict Telling Anyone?

Characteristic	OR
Age: 60 and older	1.33
Education: 16 years and up	2.25* (1.13, 4.50)
Female	1.44
White	2.01
Married	1.09
Long-term care insurance	0.61
Caregiving experience	1.53
Carrier of *ε4* allele	0.75
Condensed disclosure	1.31
Benefits of genetics testing	1.61* (1.08, 2.40)
AD optimism	NS
Causal attribution to lifestyle	NS

*$p < .05$

Ashida et al., in submission

Stay Tuned for These Analyses from REVEAL

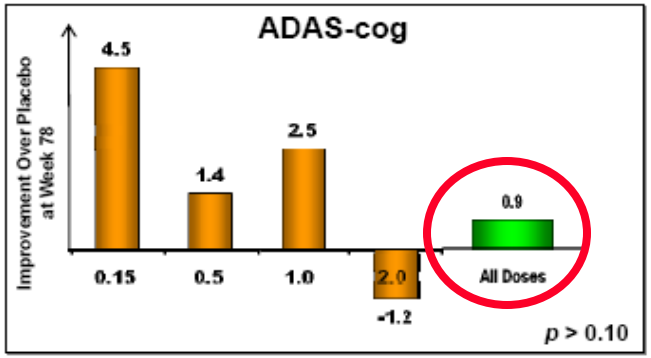
- What happens with telephone disclosure or on-line disclosure with minimal GC involvement?
- What happens when non-family members seek and receive genetic risk information
- What happens when participants receive risk information about a disease they did not expect to learn about (pleiotropy) ?
- What happens when you combine genotype information and phenotype information (early memory loss) to offer individual more imminent risk information?

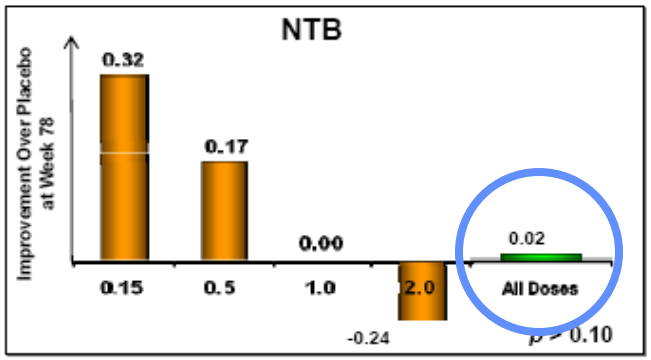
REVEAL Questions

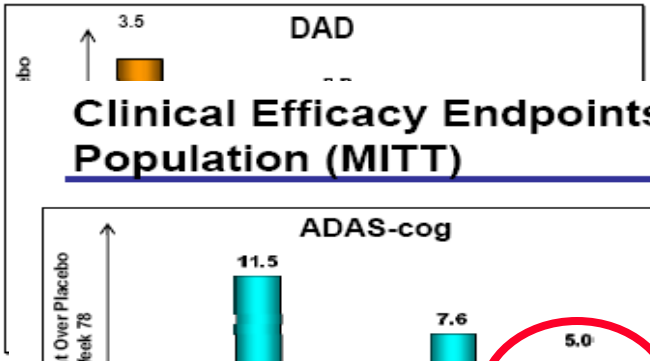
Will APOE become ‘actionable’?

Bapineuzumab for Alzheimer's Disease

Clinical Efficacy Endpoints: ApoE4 Carrier Population (MITT)

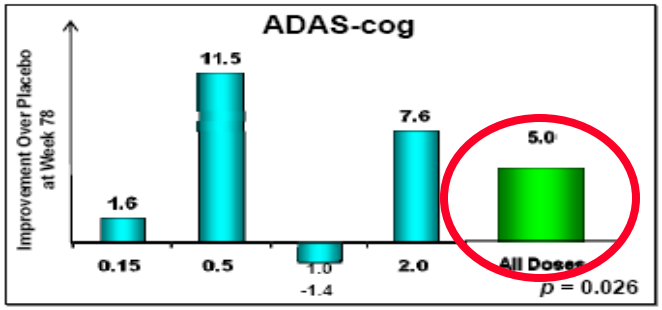


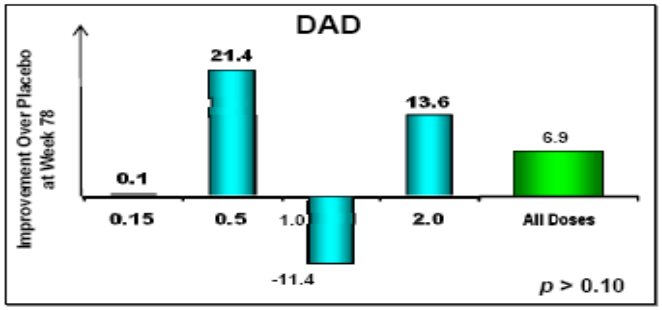


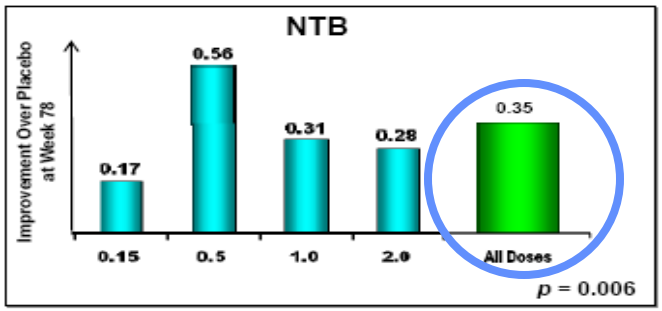


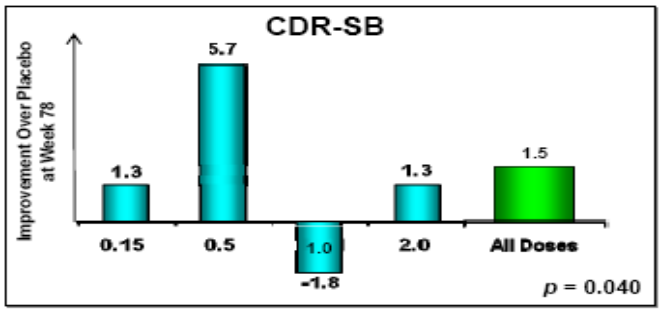
MITT analyses using RM model without assumption of linearity
Bars above zero indicate improvement relative to placebo
Patient populations for "all doses" comparisons: bapineuzumab range,

Clinical Efficacy Endpoints: ApoE4 Non-carrier Population (MITT)









MITT analyses using repeated measures model without assumption of linearity
Bars above zero indicate improvement relative to placebo
Patient populations for "all doses" comparisons: bapineuzumab range, N = 46-47; placebo range, N = 30-32

Points to Consider

- Individuals find “personal utility” in risk information, apart from whether or not the information is “medically actionable”.

- Inactionable may become actionable on short notice.

- Indirect public health benefits are possible.

- Individuals self-select for receiving and understanding risk information and are anchored to pre-disclosure risk perceptions.

- There is dangerous potential for the intrusion of pseudo-science, particularly if academic authorities merely resist, rather than guide, the integration of novel technologies.

REVEAL Study Collaborators

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