

# The Personal Utility of Non-Actionable Genetic Information: The REVEAL Study

---

September 29, 2009

Robert C. Green  
Genetic Alliance

Posted in the Resource Repository at:  
<http://www.resourcerepository.org/documents/1691/thepersonalutilityofnon-actionablegeneticinformation:therevealstudy/>

# The Personal Utility of Non-Actionable Genetic Information: The REVEAL Study

Robert C. Green, MD, MPH

Fellow in Genetics, Harvard Medical School  
Professor of Neurology, Genetics and Epidemiology  
Boston University Schools of Medicine and Public Health

Supported by  
National Human Genome Research Institute and National Institute on Aging  
RO1 HG 02213 (The REVEAL Study)  
National Institute on Aging RO1 AG09029 (The MIRAGE Study),  
K24 AG027841 and P30 AG13846 (BU ADC)

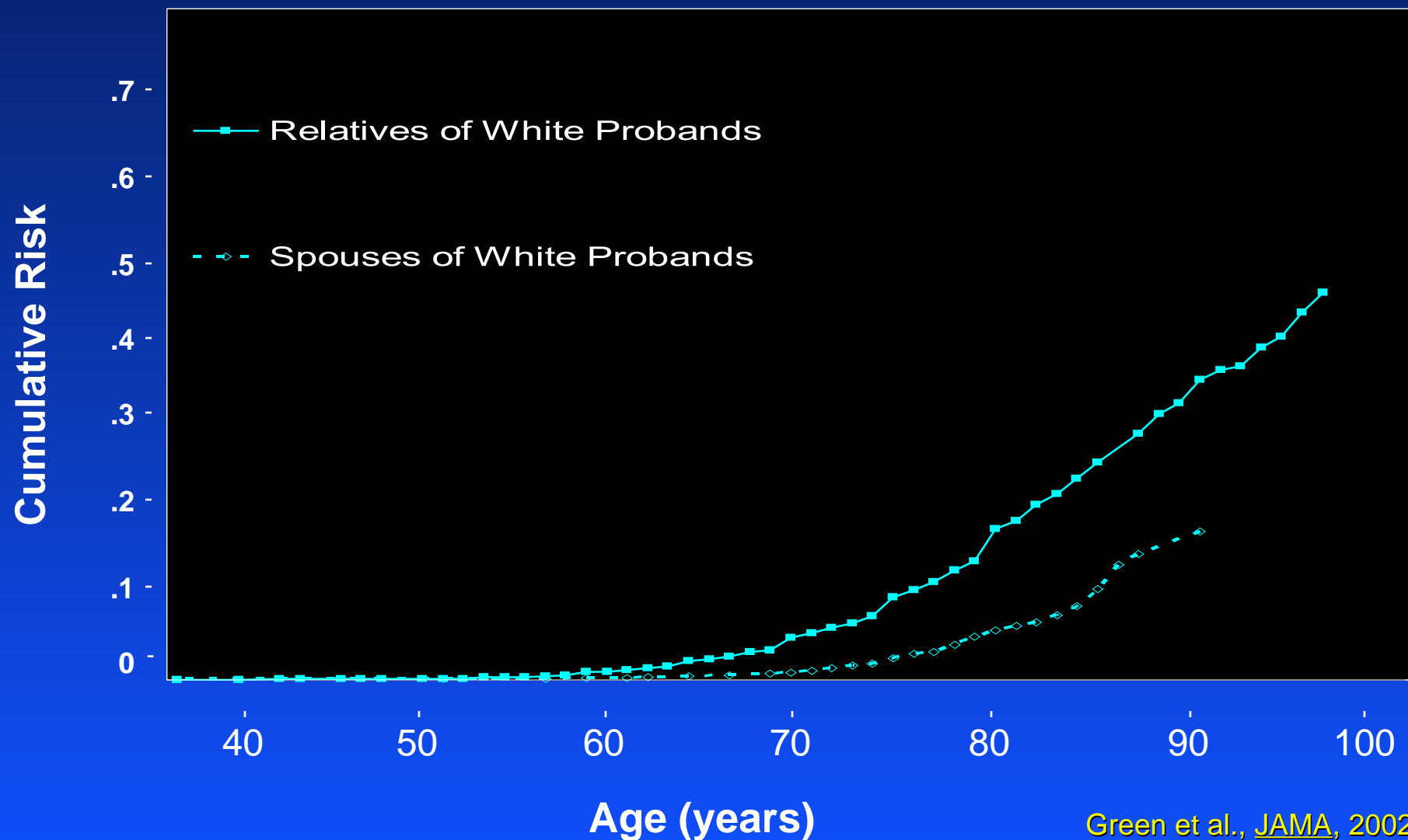
# Financial Disclosures in the Past 5 Years

Research Grants:	NIH, Myriad, Elan, Lilly
Speaking (compensated*):	Pfizer, Forest
Advisory (compensated*):	Schering-Plough, GlaxoSmithKline
Advisory (uncompensated):	23andMe, Navigenics, Myriad
Equity:	None

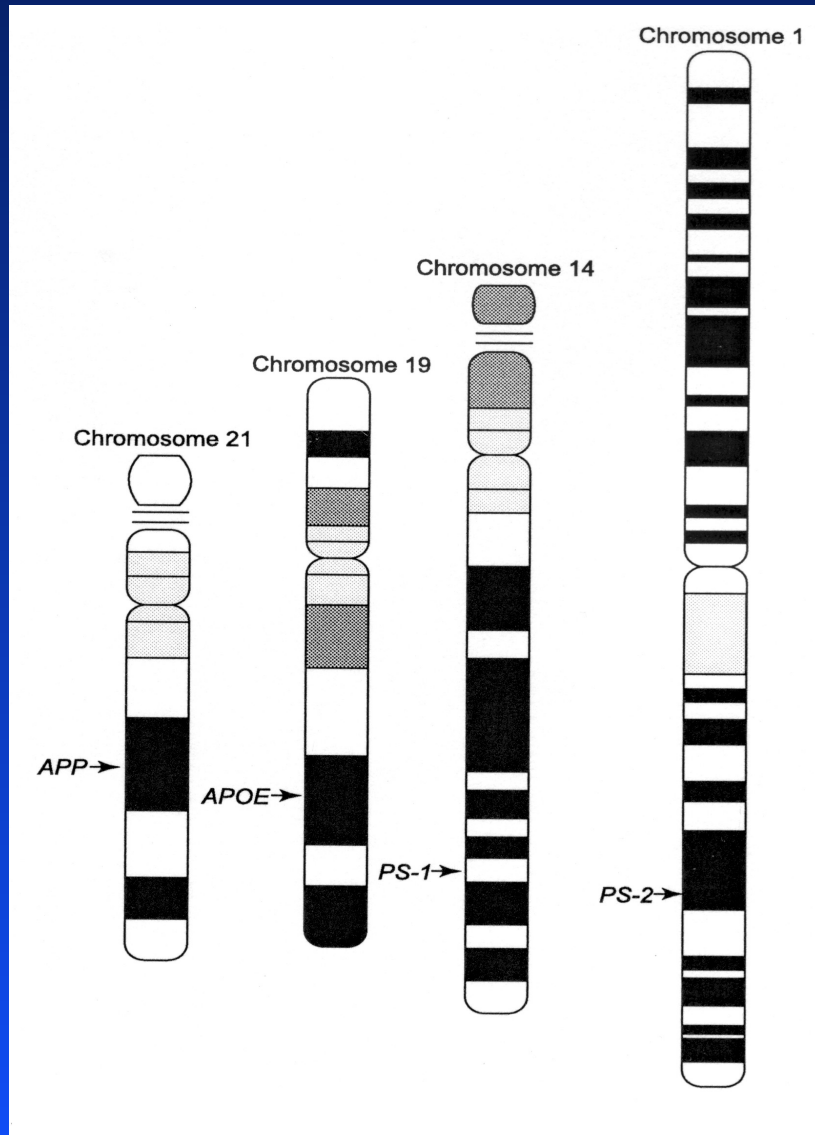
\*less than \$5,000/year



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



# Established Gene Markers for Alzheimer's Disease



## Deterministic Mutations:

Amyloid Precursor Protein (APP)

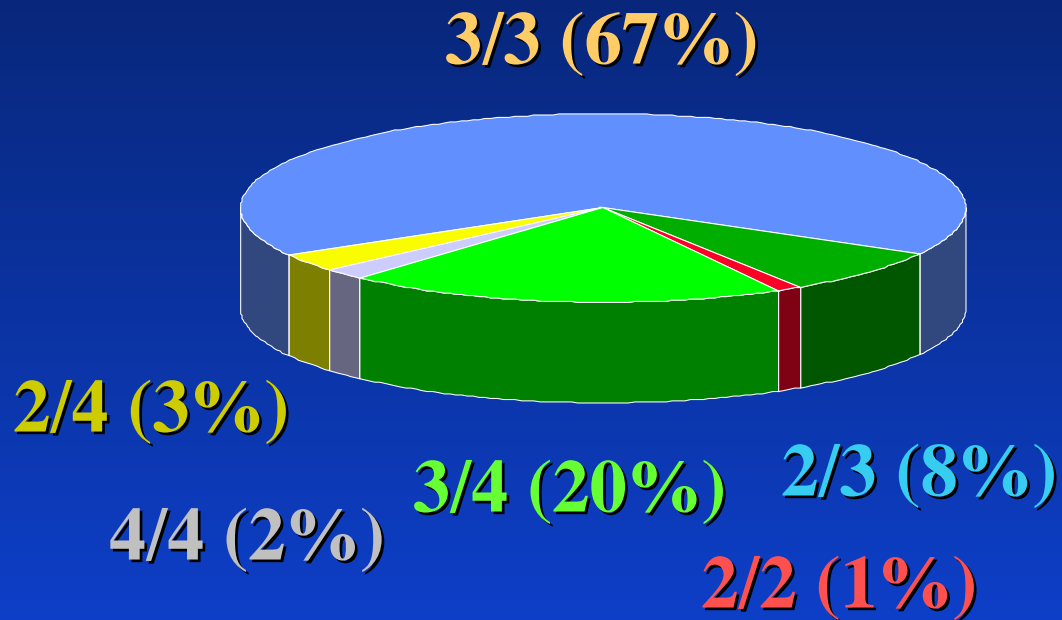
Presenilin-1 (PS-1)

Presenilin-2 (PS-2)

## Susceptibility Polymorphism:

Apolipoprotein E (APOE)

# APOE Genotypes in the General Population



There are six possible combinations of the APOE forms. These combinations are called genotype.

$\epsilon 2$	$\epsilon 2$	$\epsilon 2$	$\epsilon 4$
$\epsilon 2$	$\epsilon 3$	$\epsilon 3$	$\epsilon 4$
$\epsilon 3$	$\epsilon 3$	$\epsilon 4$	$\epsilon 4$

# 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

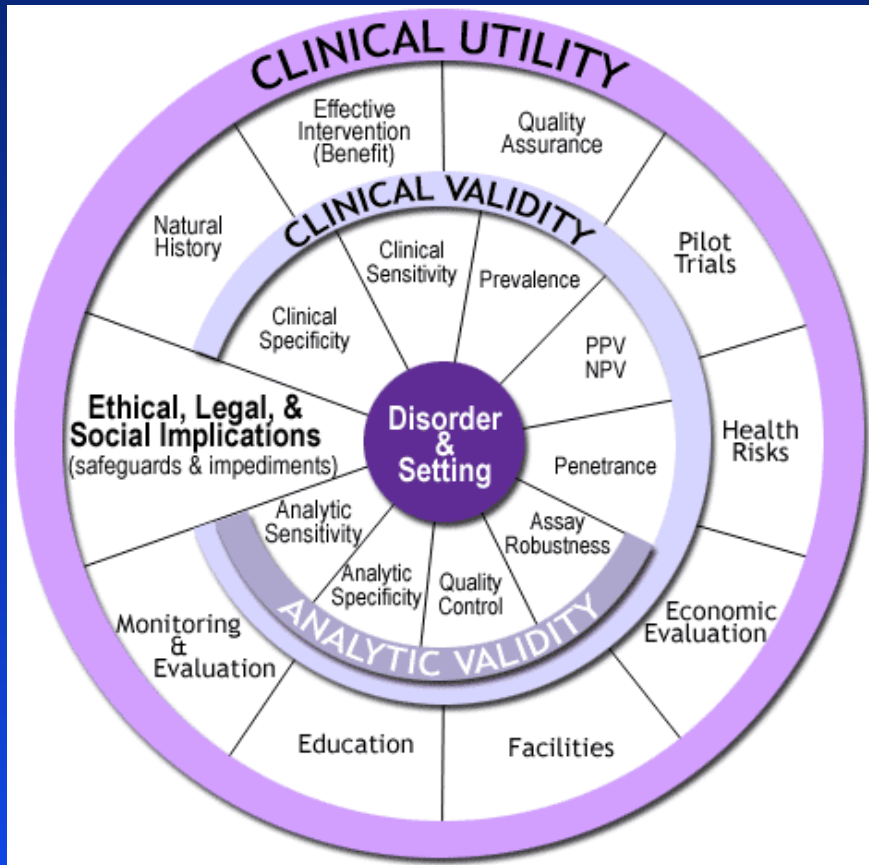
## The REVEAL “Rationale” in 2000

---

Why we should 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

# The ACCE Model for Genetic Testing



- Alytic Validity
- Clinical Validity
- Clinical Utility
- ELSI

# 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?



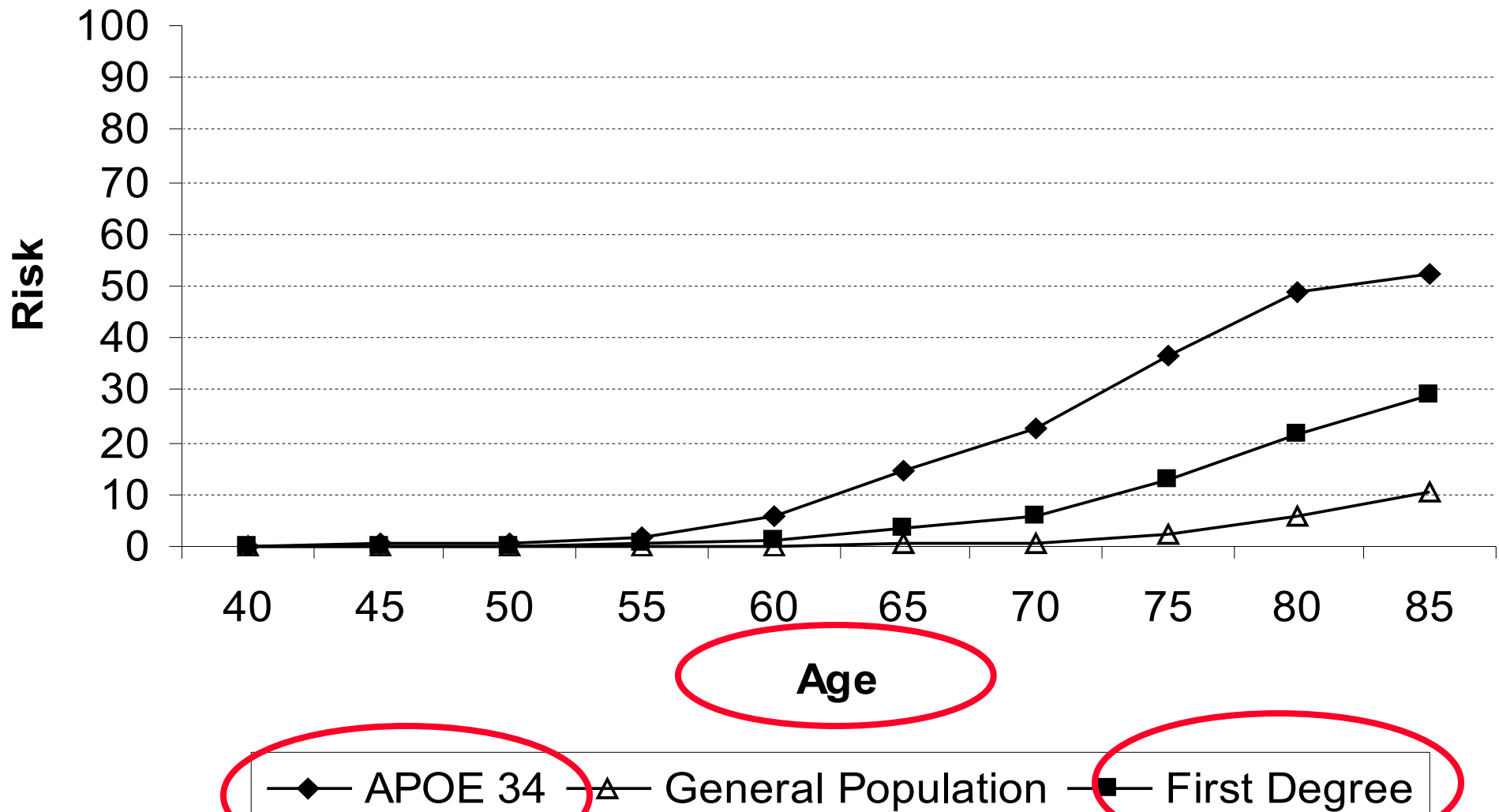
GENE

RISK

## Estimating risk curves for first-degree relatives of patients with Alzheimer's disease: The REVEAL study

*L. Adrienne Cupples, PhD<sup>1,2</sup>, Lindsay A. Farrer, PhD<sup>1-5</sup>, A. Dessa Sadovnick, PhD<sup>6</sup>, Norman Relkin, MD, PhD<sup>7</sup>, Peter Whitehouse, MD, PhD<sup>8</sup>, and Robert C. Green, MD, MPH<sup>2-4</sup>*

# Risk of AD by APOE in Women





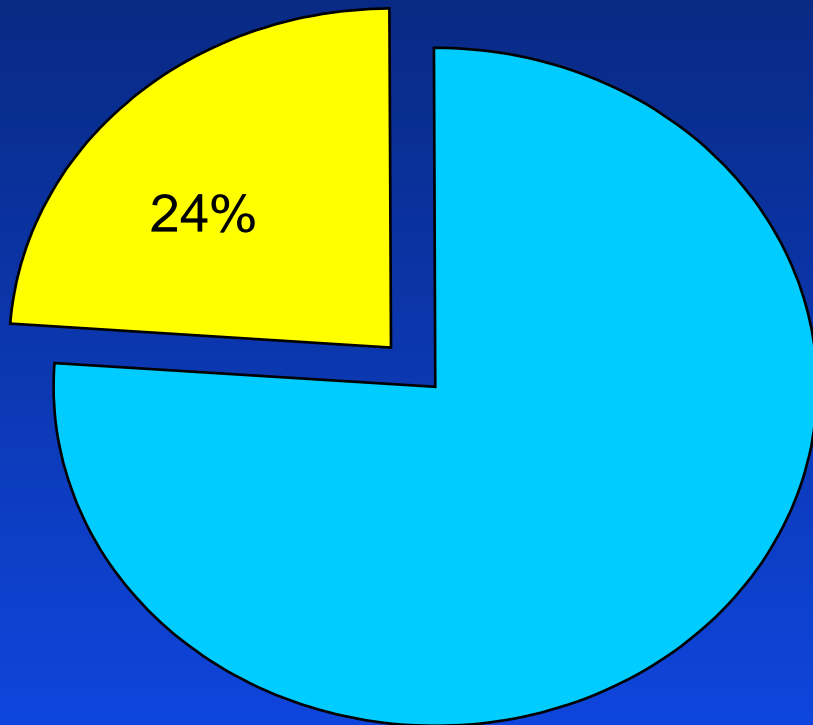
# REVEAL Questions

---

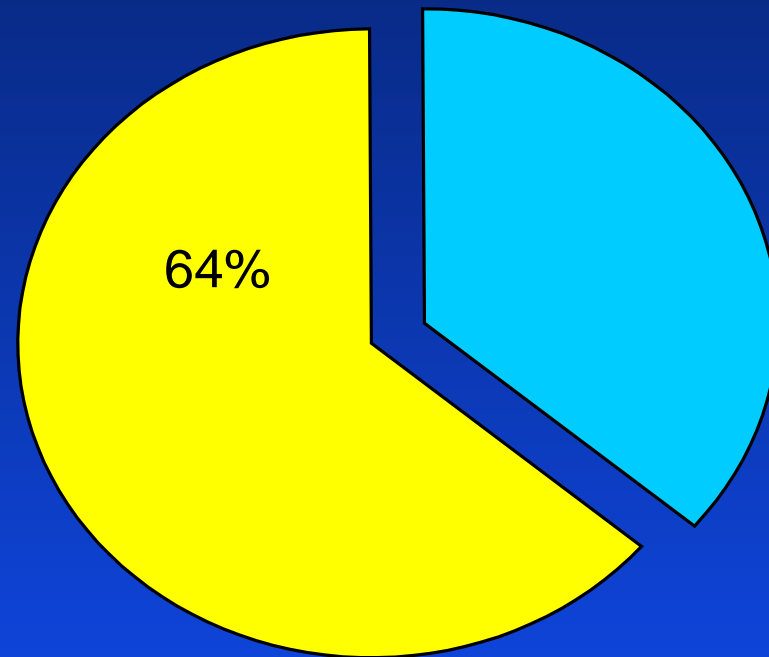
Who wants to know?

# Persons Agreeing to Participate in REVEAL

Systematically Ascertained



Self Referred



# REVEAL Questions

---

Why do people want to know?

# Reasons Associated with Enrollment

---

<i>Strongly endorsed reason for seeking testing as predictor of study enrollment</i>	<i>Odds ratio</i>
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

---

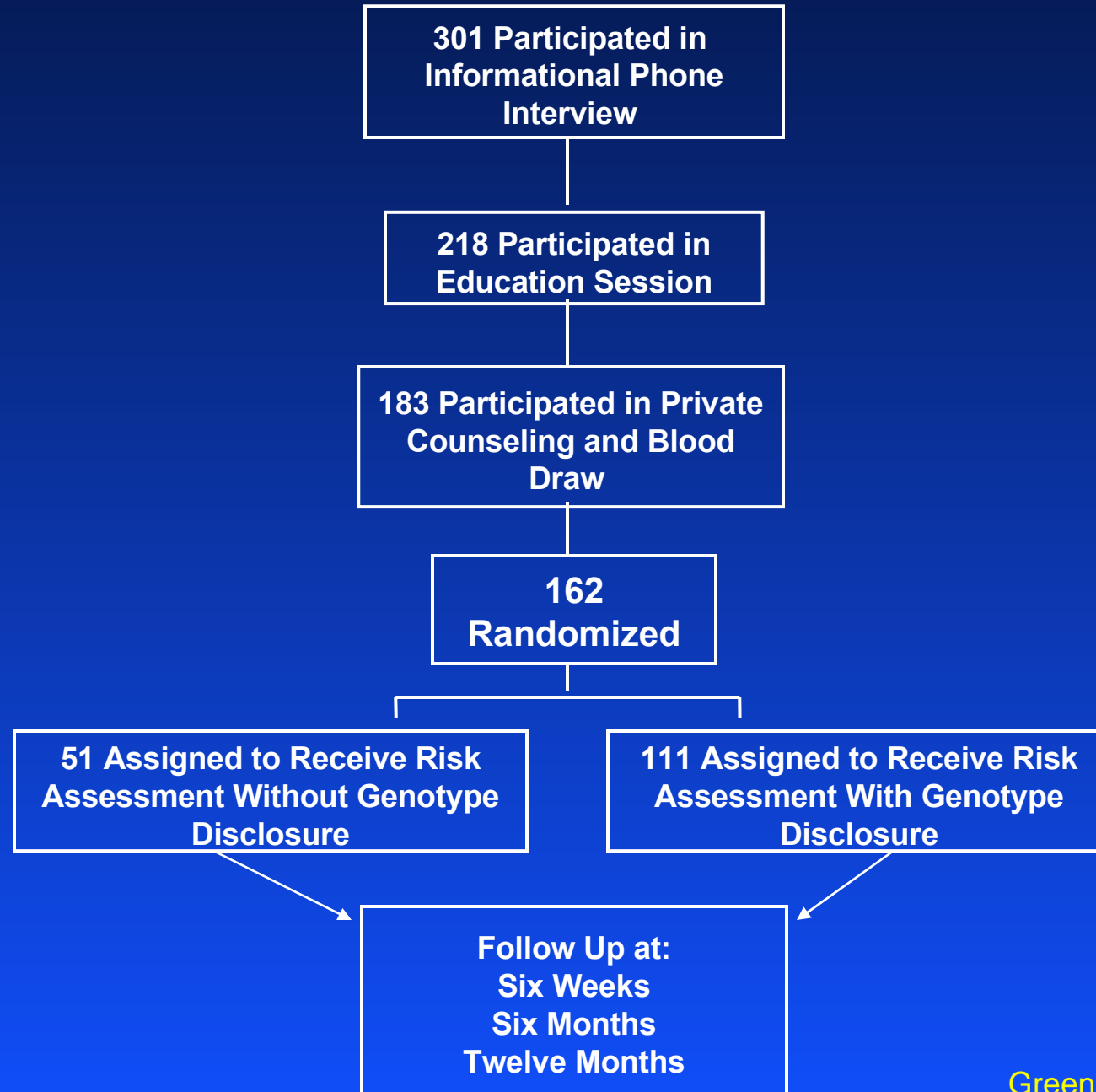
***Women strongly endorsed more reasons for seeking testing than men,  $p = .01$***

# REVEAL Questions

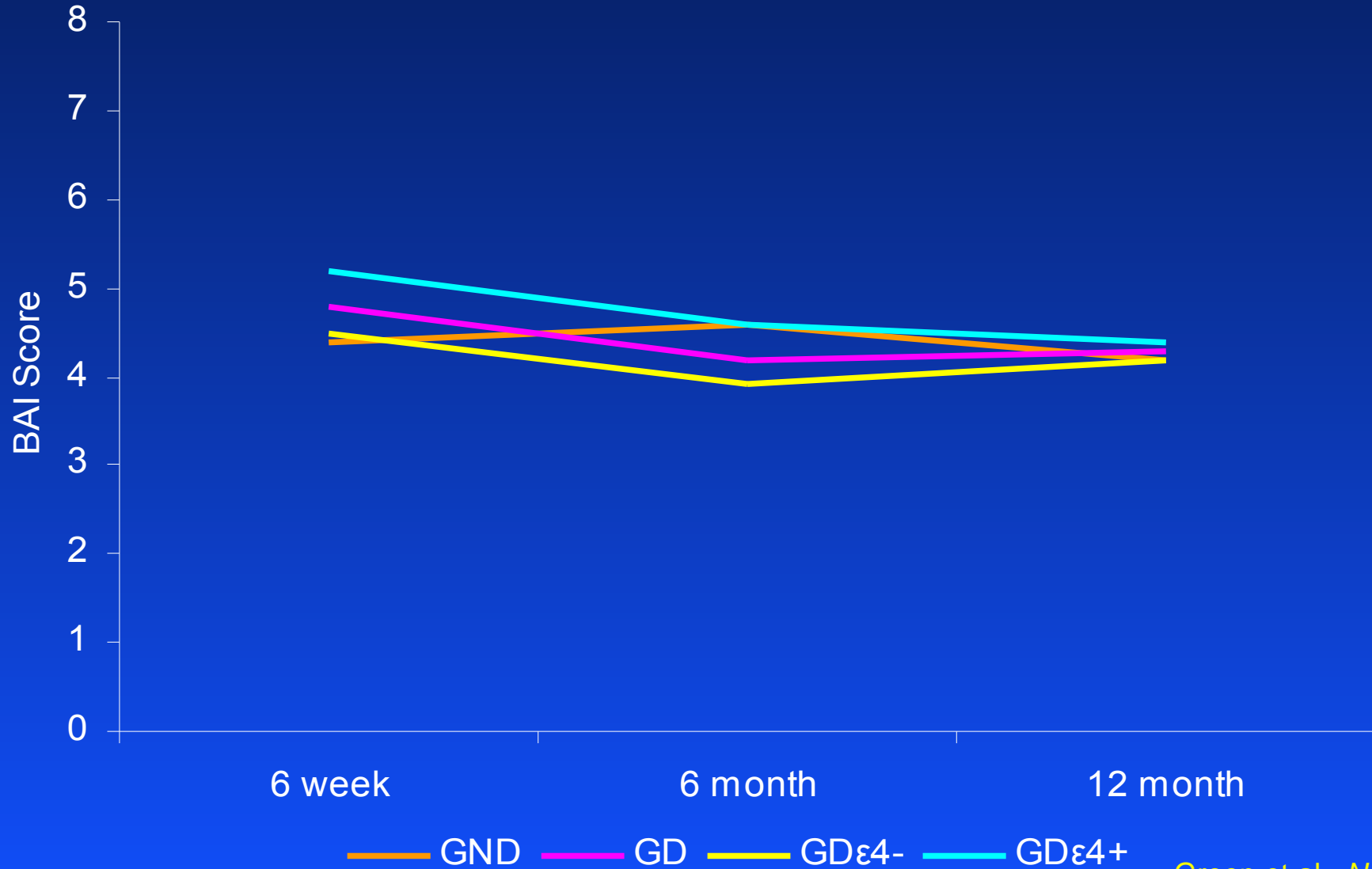
---

What happens to them when they find out?

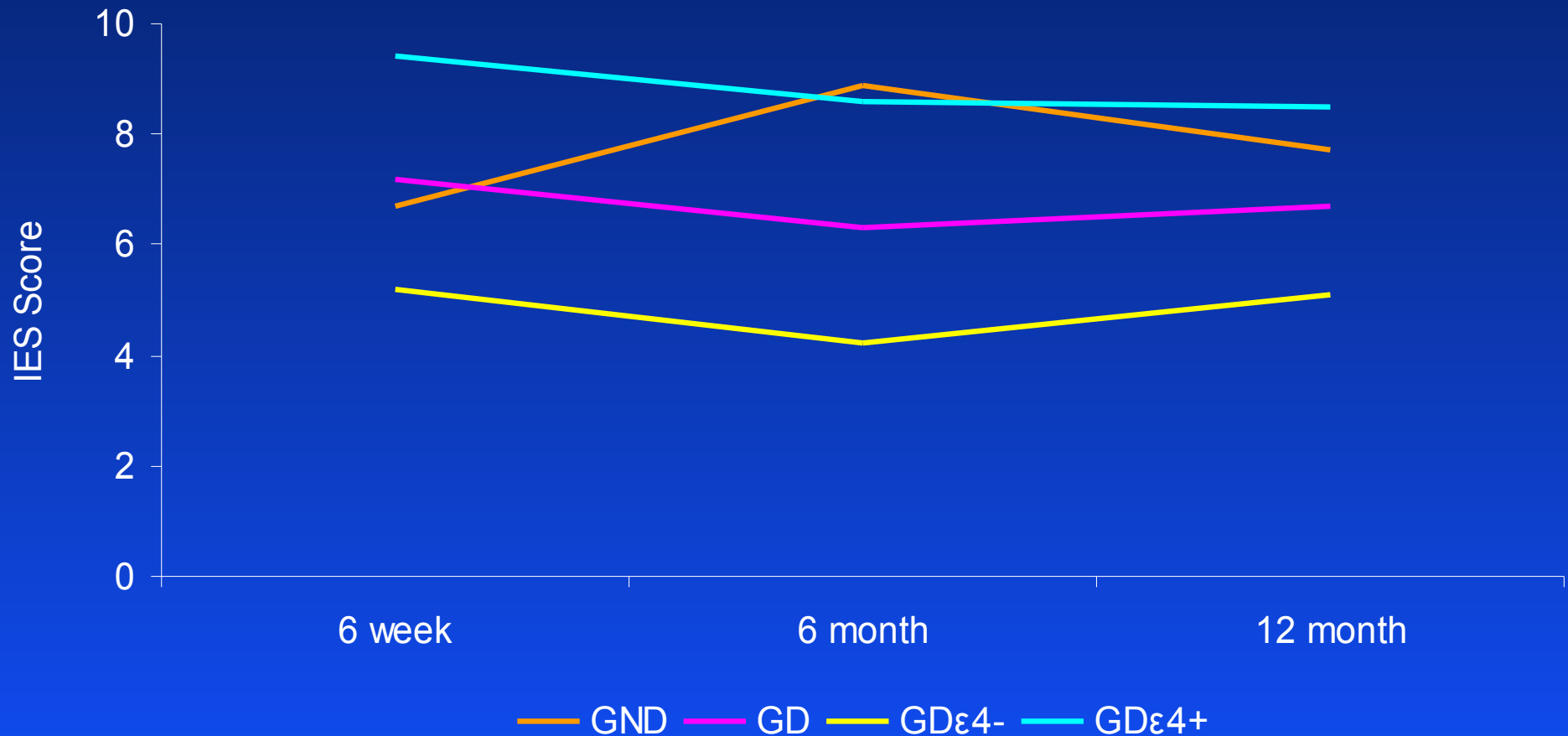
# REVEAL I: Randomized Clinical Trial



# REVEAL I Study: Mean Anxiety Scale Score

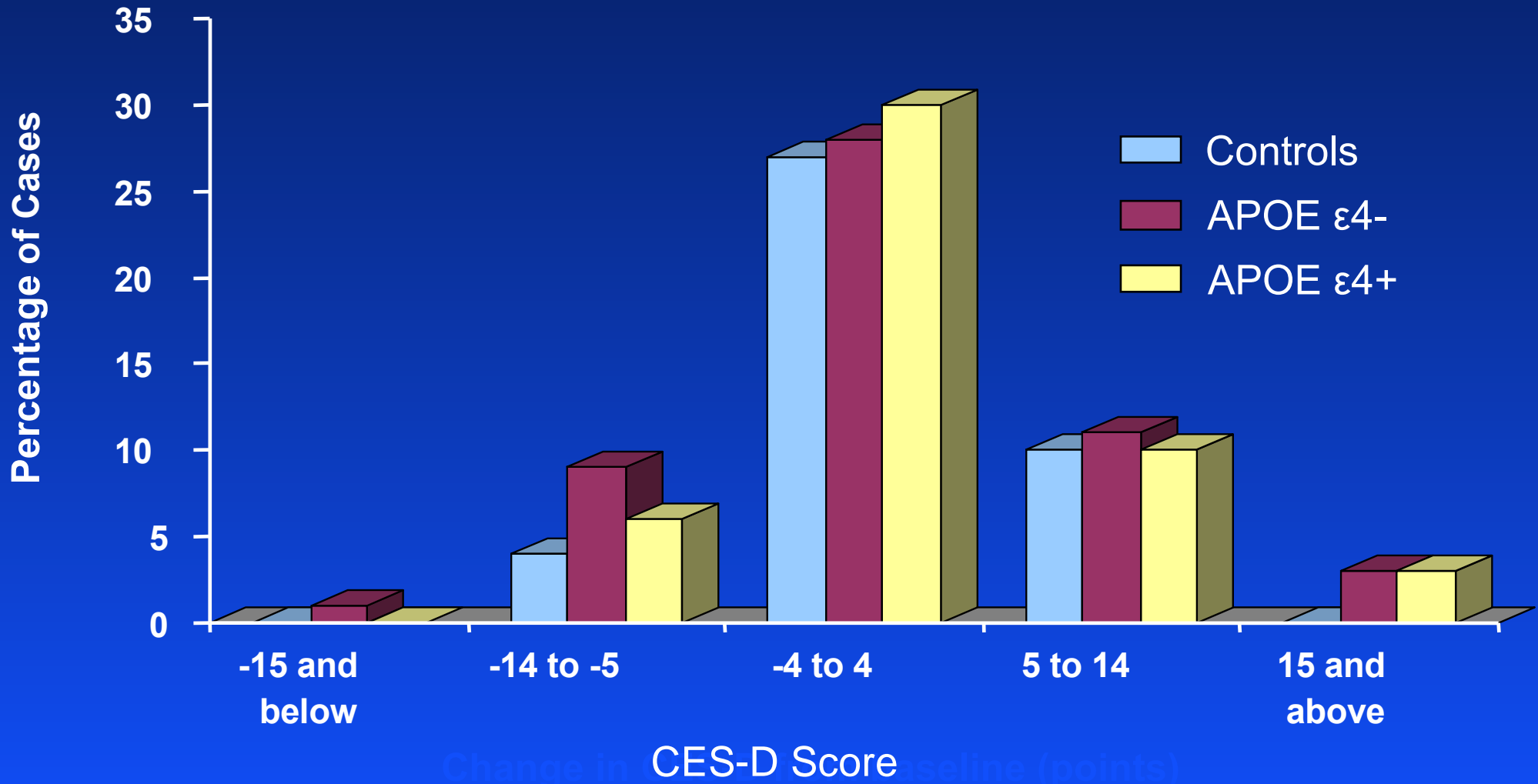


# REVEAL I Study: Adjusted Impact of Event Scores





# Post-Disclosure Change to Depression Symptoms: 1 year

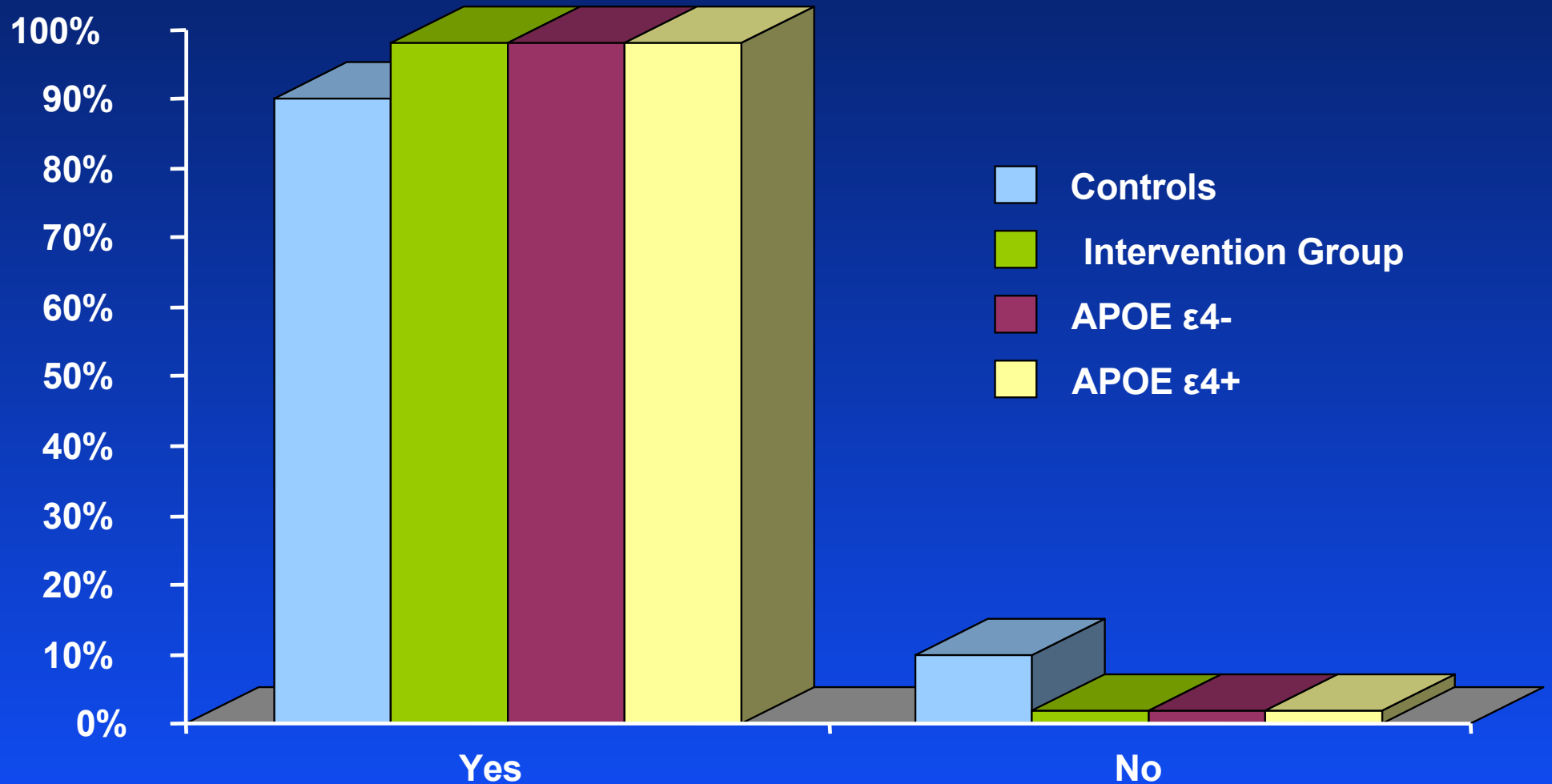


# REVEAL Questions

---

Are they satisfied with the information?

# Would Do Risk Assessment Again...

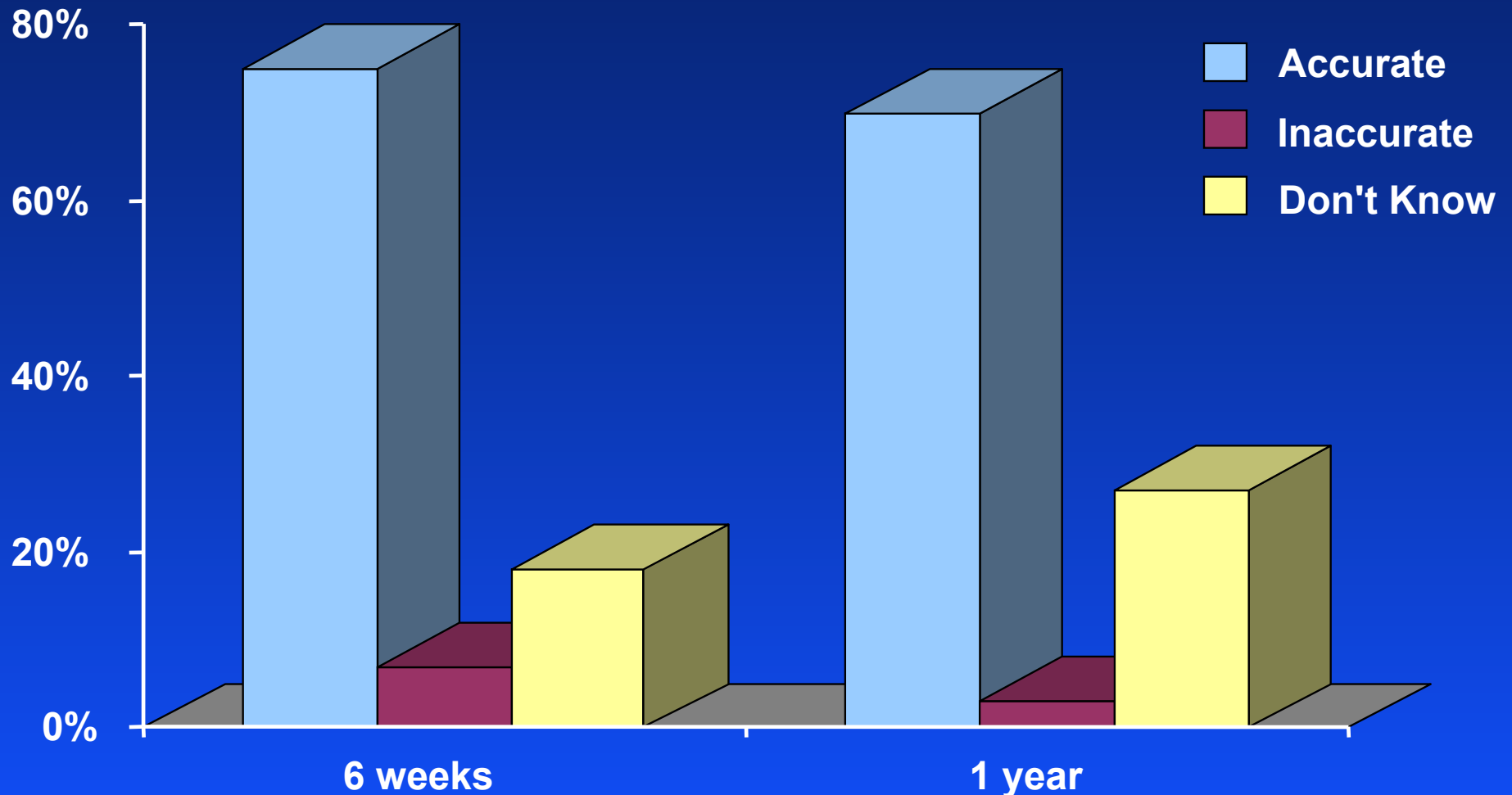


# REVEAL Questions

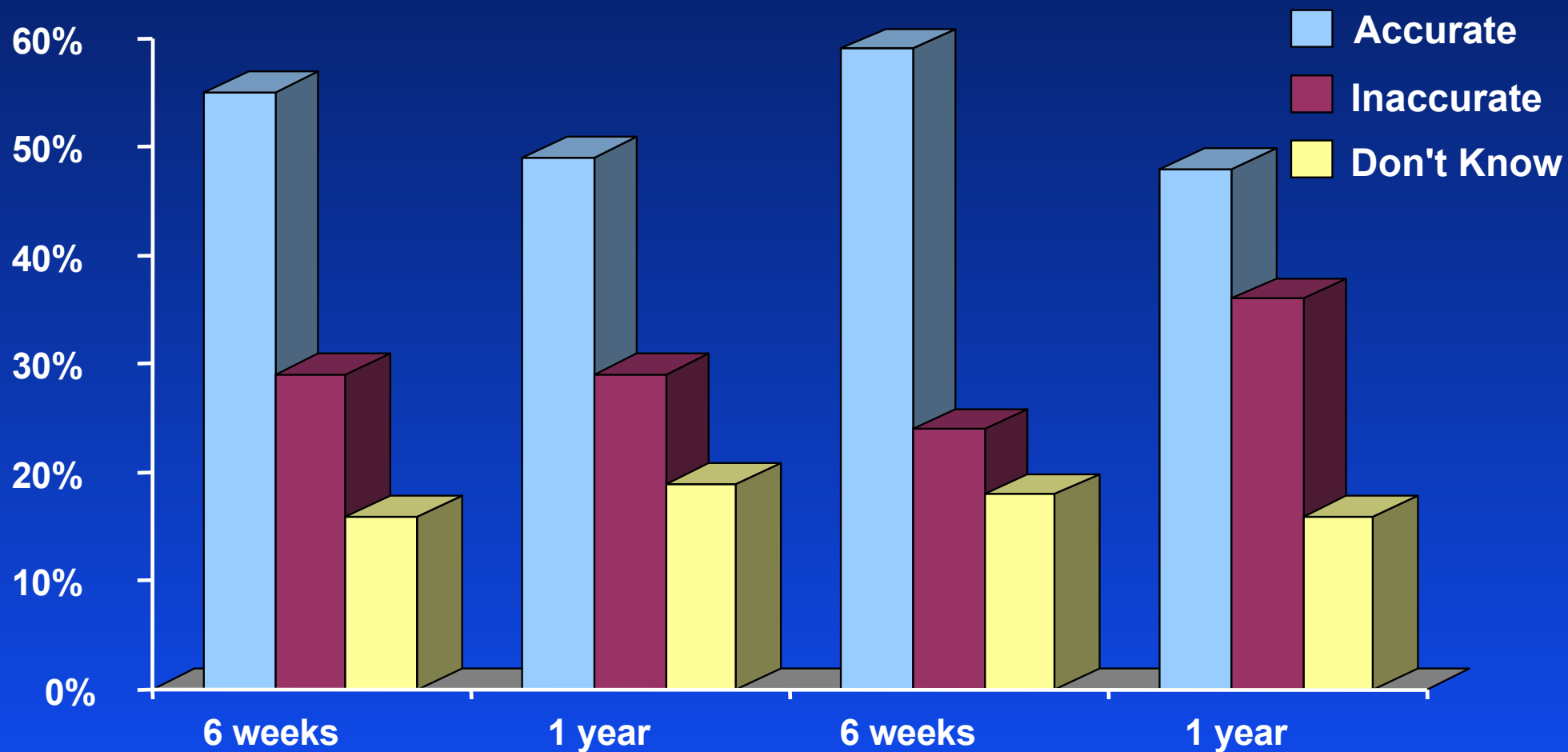
---

Can they recall the information?

# Recall of Disclosure Information APOE Status (positive or negative)



# Recall of Risk Information: Lifetime Risk Figures within 5 Points

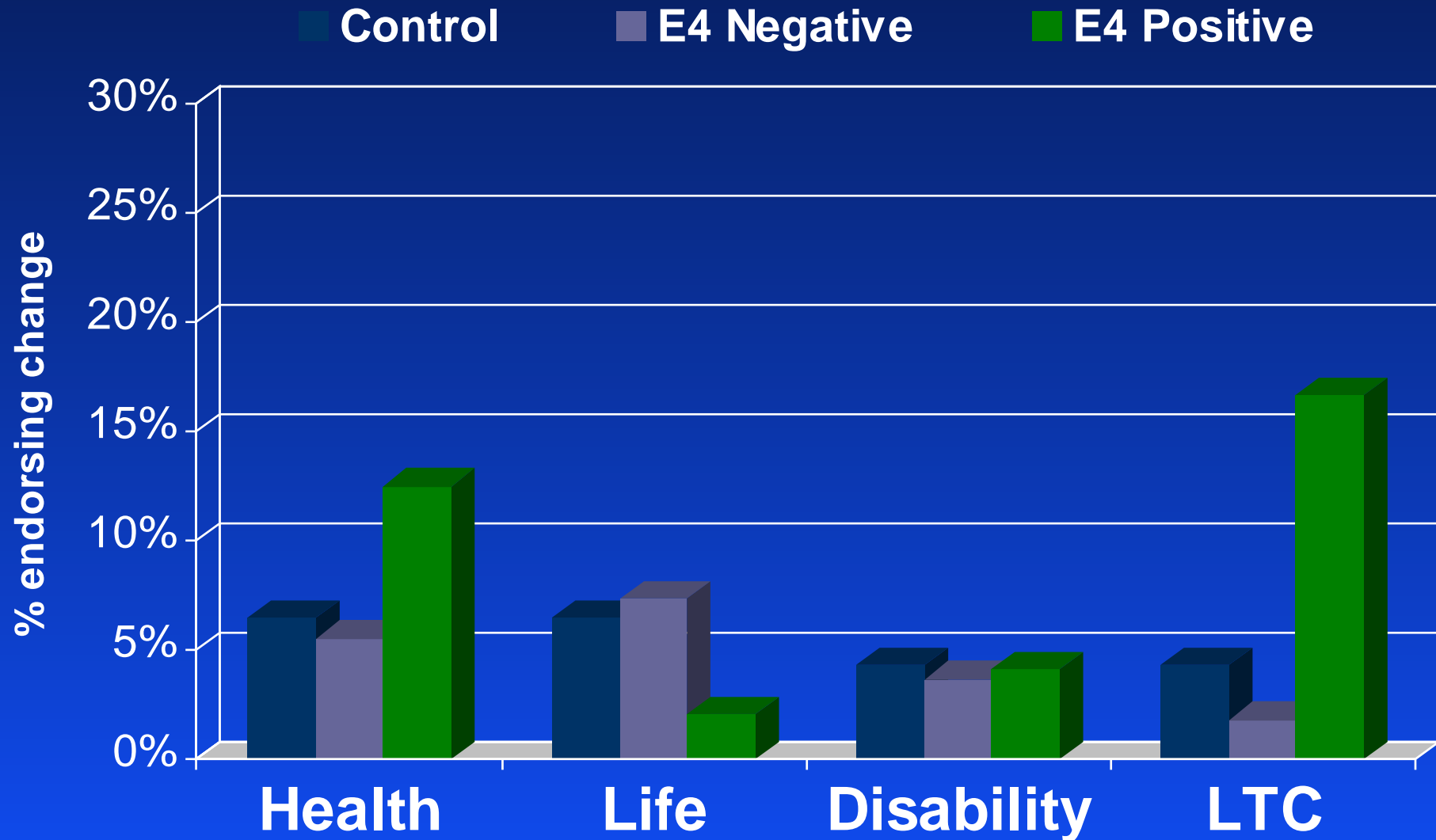


# REVEAL Questions

---

Does the information change their behavior  
(insurance purchasing)?

# Insurance Changes 1 Year After APOE Disclosure



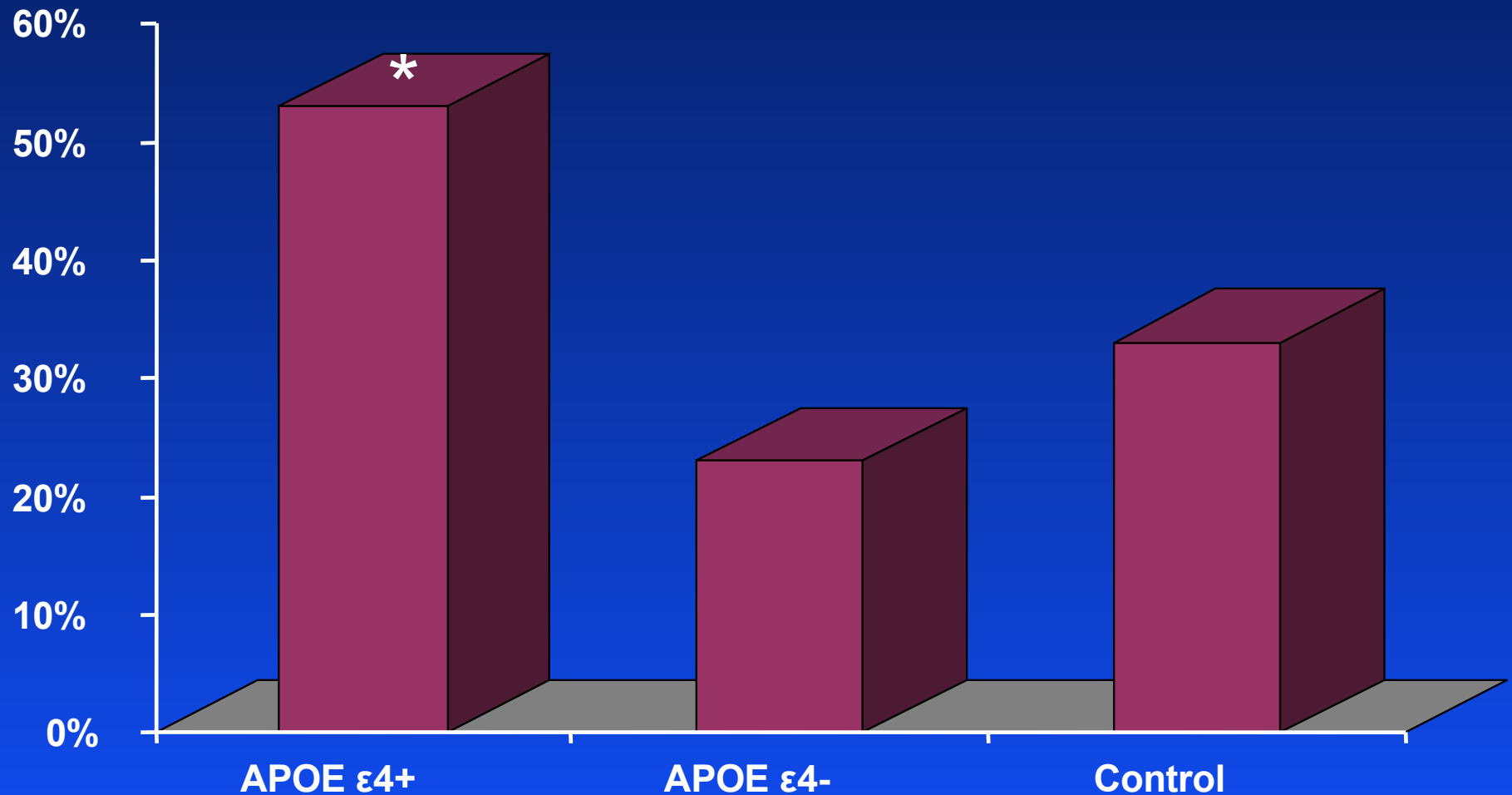


# REVEAL Questions

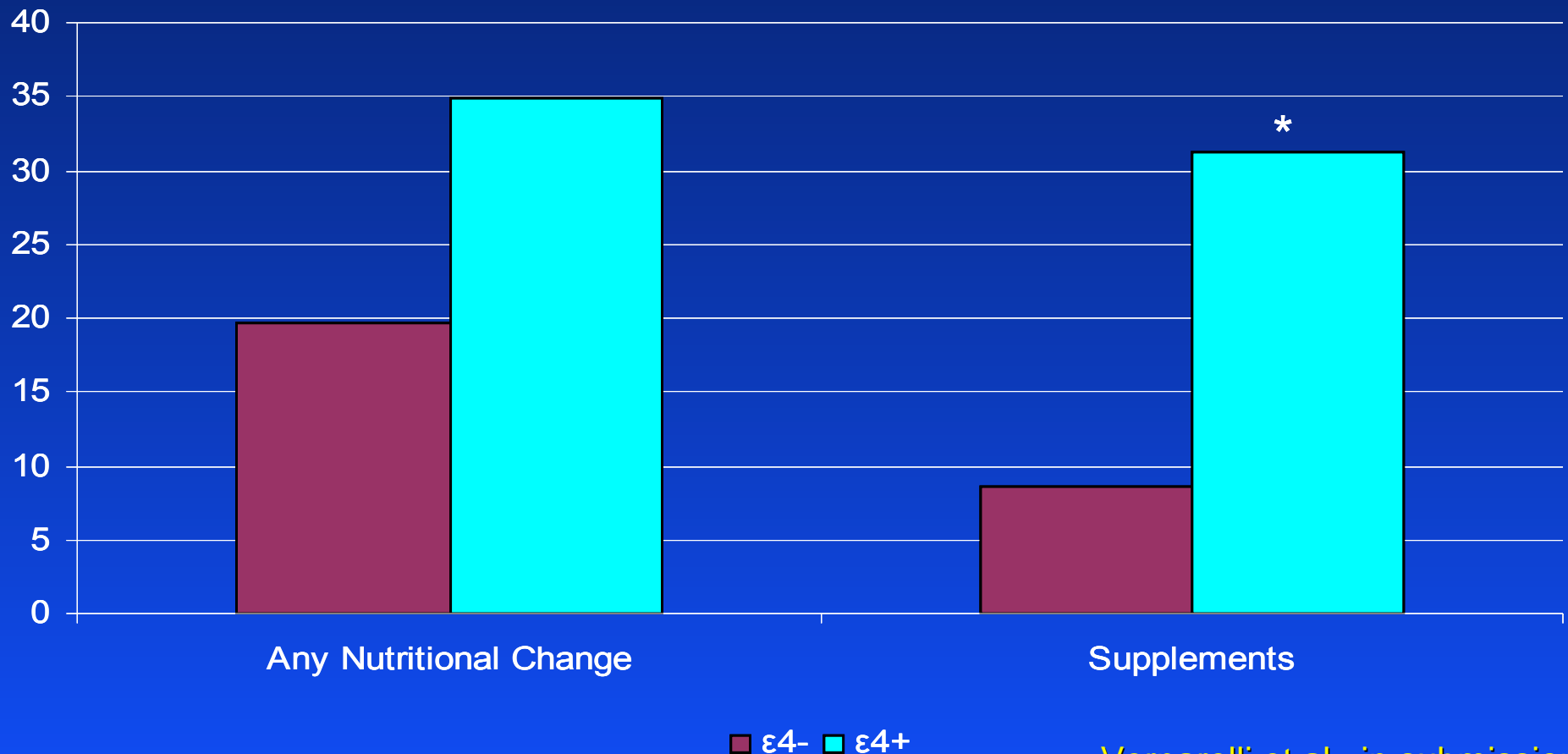
---

Does the information change their behavior  
(health behavior)?

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



# Health Behavior Changes at 6 Weeks (Nutrition and Supplements)



Vernarelli et al., in submission

# REVEAL Questions

---

How should we address ethnicity?

## Risk of Dementia Among White and African American Relatives of Patients With Alzheimer

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

**Context** Evidence exists that the attributable to specific genetic factors vary considerably among ethnic groups, providing an opportunity to evaluate lifetime risk of dementia among African American probands with a family history of Alzheimer disease.  
**Objective** To compare lifetime risk of dementia among African American probands with a family history of Alzheimer disease and their white relatives.  
**Design and Setting** Risk analysis using medical records between May 1990 and May 1999 in the Multi-Institutional Research in Alzheimer's Genetic Epidemiology Study Group.  
**Participants** A total of 17 639 first-degree relatives of 2339 white AD probands, and 2211 first-degree relatives of 255 African American AD probands.  
**Main Outcome Measures** Cumulative incidence of dementia.

Li  
fo

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

po  
to  
or  
(A  
sh  
tic  
tia  
in  
lib  
AF

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

While AD in other US ethnicities and 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.<sup>1-10</sup>

...the probability of having an APOE ε4 allele appears to be higher in white families. These data provide estimates of the risk of dementia among 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, MD, MPH, 715 Locust St, Philadelphia, PA 19106 (rcgreen@wharton.upenn.edu).

*Alzheimer Disease and Associated Disorders*  
Vol. 17, No. 1, pp. 19-26  
© 2003 Lippincott Williams & Wilkins, Inc., Philadelphia

# 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\*

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

†Yvonne G. Hipps, PhD  
‡Department of Health, Behavior, and Society  
§Yvonne G. Hipps, PhD  
¶Department of Health, Behavior, and Society  
‡Department of Health, Behavior, and Society  
§Department of Health, Behavior, and Society  
¶Department of Health, Behavior, and Society

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

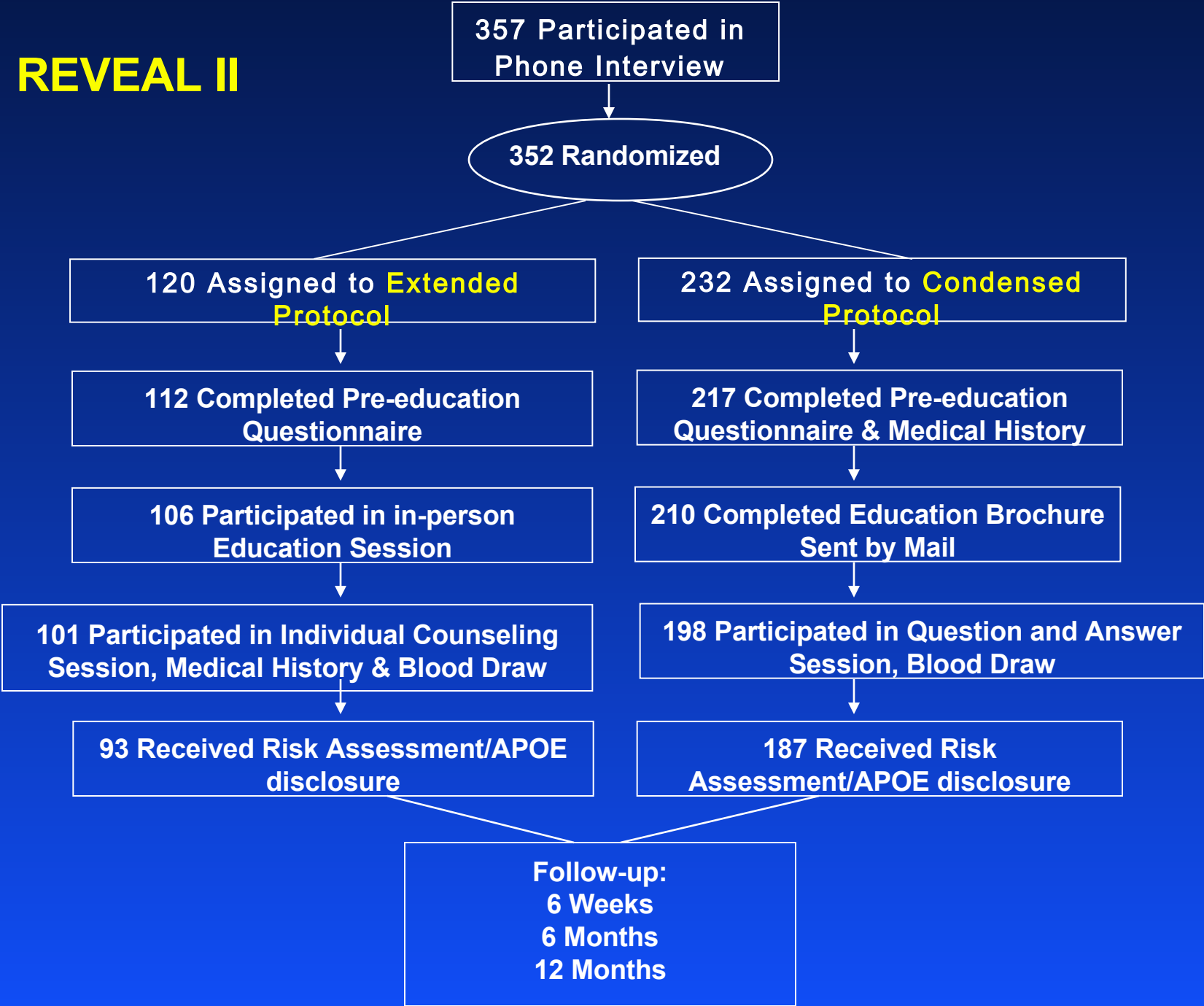
YVONNE G. HIPPS,<sup>1</sup> J. SCOTT ROBERTS,<sup>2</sup> LINDSAY A. FARRER,<sup>3</sup> and ROBERT C. GREEN<sup>3</sup>

# REVEAL Questions

---

Are preparatory genetic counseling protocols  
necessary for safe disclosure?

# REVEAL II



# 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 Study Collaborators

---

## Boston University

Robert C. Green, MD, MPH (PI)  
Susan Hiraki, MS, CGC  
Lindsay A. Farrer, PhD  
Robert Stern, PhD  
L. Adrienne Cupples, PhD  
Tamsen Brown, CGC  
Clara Chen, MHS  
Anil Nair, MD  
Winston Chung  
Michael Cassidy  
Holly Gooding

## University of Michigan

Scott Roberts, PhD (Co-PI)  
Erin Linnenbringer, MS, CGC  
Kurt Christensen, MPH  
Wendy Uhlmann, MD, CGC

## Howard University

Thomas Obisesan, MD, MPH  
Grace-Ann Fasaye, ScM, CGC  
Charmaine Royal, PhD  
Tiffiney Greer, CGC

## Case Western

Melissa Barber, ScM  
Peter Whitehouse, MD

## Cornell

Normal Relkin, MD, PhD  
Elana Cox, MS  
Lisa Ravdin, PhD

## External Advisory Board

Robert Cook-Deegan, PhD

## Consultants

George Annas, JD, MPH  
Barbara Biesecker, MS  
Deepak Bhatt, MD  
Deborah Blacker, MD, ScD  
Gail Geller, PhD  
Eric Juengst, PhD  
Jason Karlawish, MD  
Theresa Marteau, PhD  
Ronald Petersen, PhD, MD  
Kimberly Quaid, PhD  
Deborah Roter, DrPH  
Eric Topel, MD

# The REVEAL Study

---

Thank you!

Questions?