

Return of Individual Research Results: Insights from Research in Translational Genomics

Robert C. Green, MD, MPH

Professor of Neurology, Genetics and Epidemiology
Boston University Schools of Medicine and Public Health

Associate Director

Partners Center for Personalized Genetic Medicine
Division of Genetic, Department of Medicine
Brigham and Women's Hospital and Harvard Medical School

Financial Disclosures

Research Grants:	NIH Myriad, Elan, Lilly, Medivation
Speaking (compensated):	none
Advisory (compensated):	Bellus Health
Advisory (uncompensated):	23andMe, Navigenics, Myriad
Equity:	none

Financial Disclosure: Current NIH Grant Funding

R01 HG002213 (Green)

R01 MH080295 (Stern)

R01 HG005092 (Green)

P30 AG13846 (Kowall)

K24 AG027841 (Green)

U01 AG24904 (Weiner)

R01 HG00603 (Wang)

U01 AG15477 (Breitner)

RC1 HG005491 (Holm)

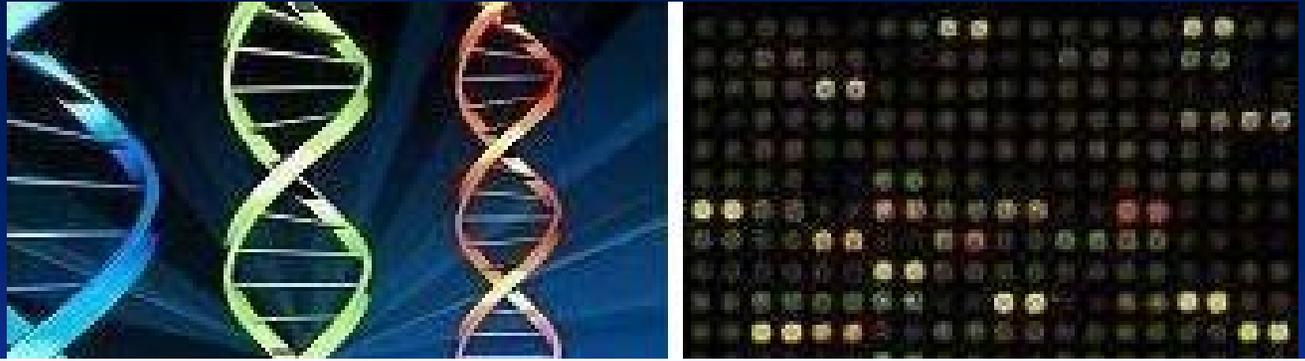
R01 AG21136 (Tschanz)

P50 HG003170 (Church)

U01 AG10483 (Aisen)

R01 HG003178 (Wolf)

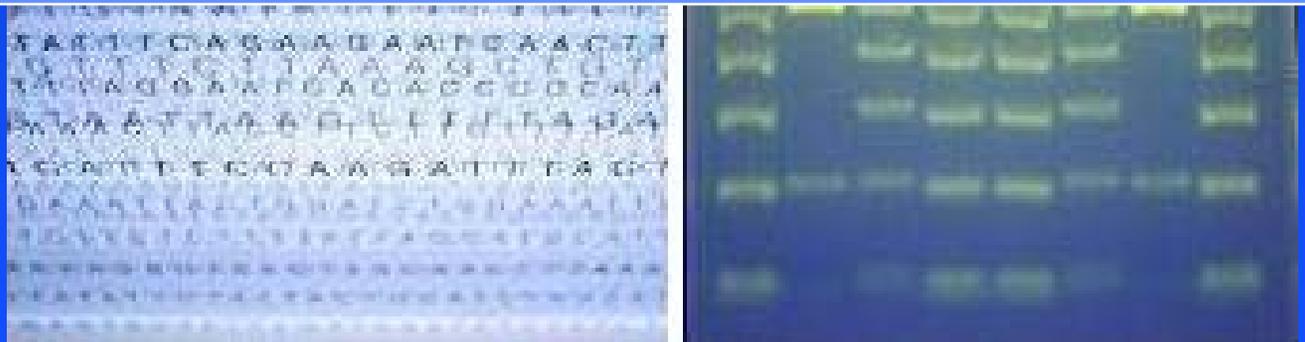
R01 AG027161 (Sager)



Genetics in Medicine

What are the benefits & risks of utilizing genetic information?

Genetics in Public Health



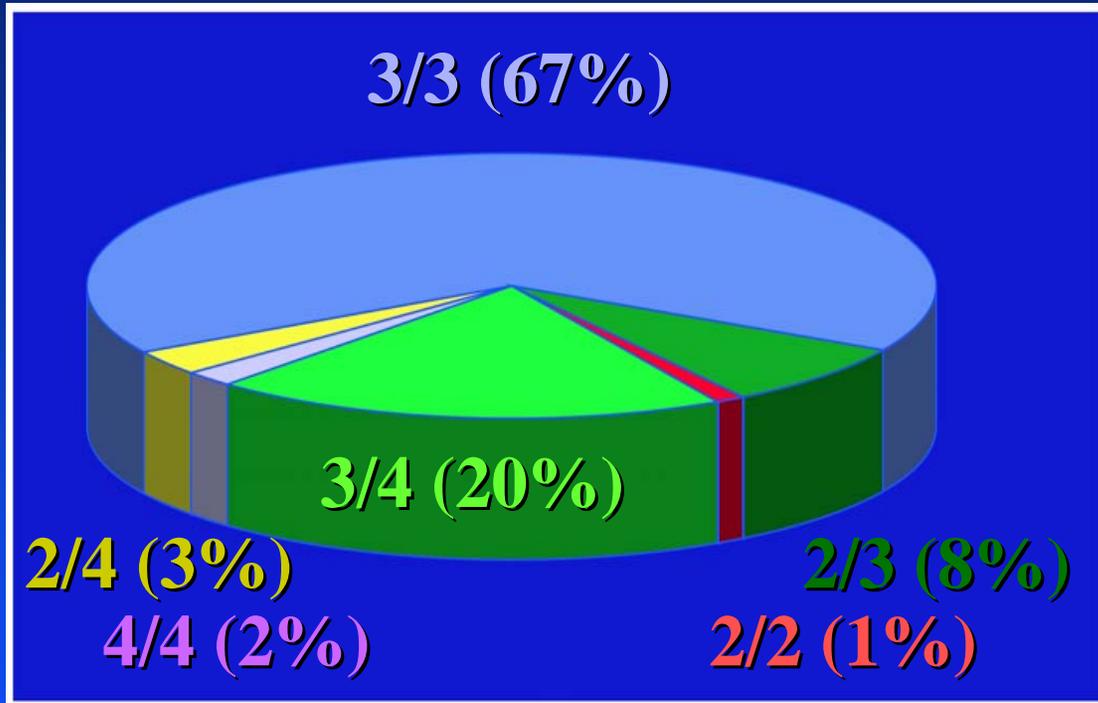
Good ethics (and good policy) start with good data....

The REVEAL Study

Empirically measure the benefits, risks and behavioral/health outcomes of genetic susceptibility testing...

All genetic testing is susceptibility testing...

APOE Genotypes in the General Population



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



APOE and Alzheimer's Disease

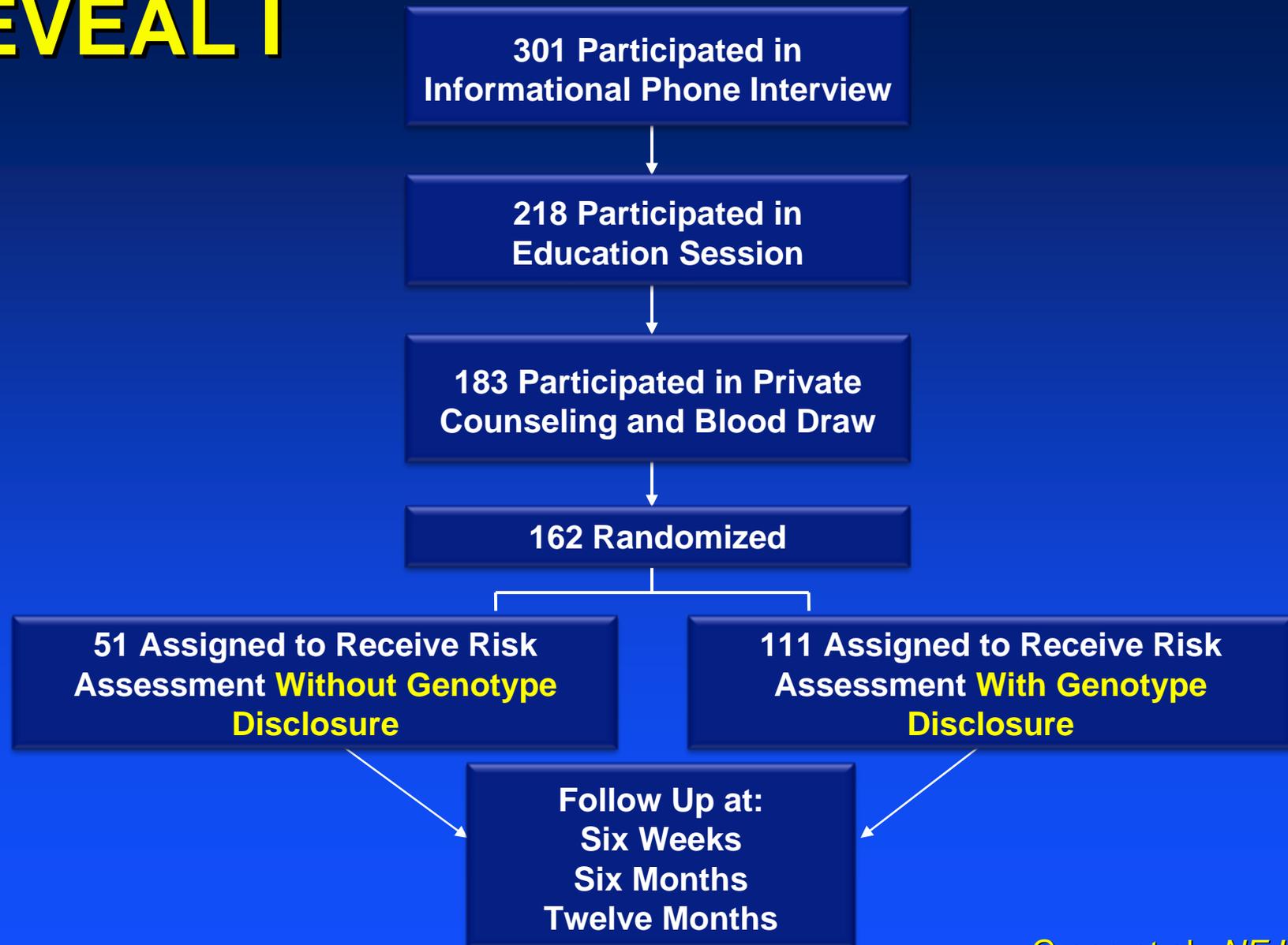
A Unique Model for Exploring Clinical and Personal Utility

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

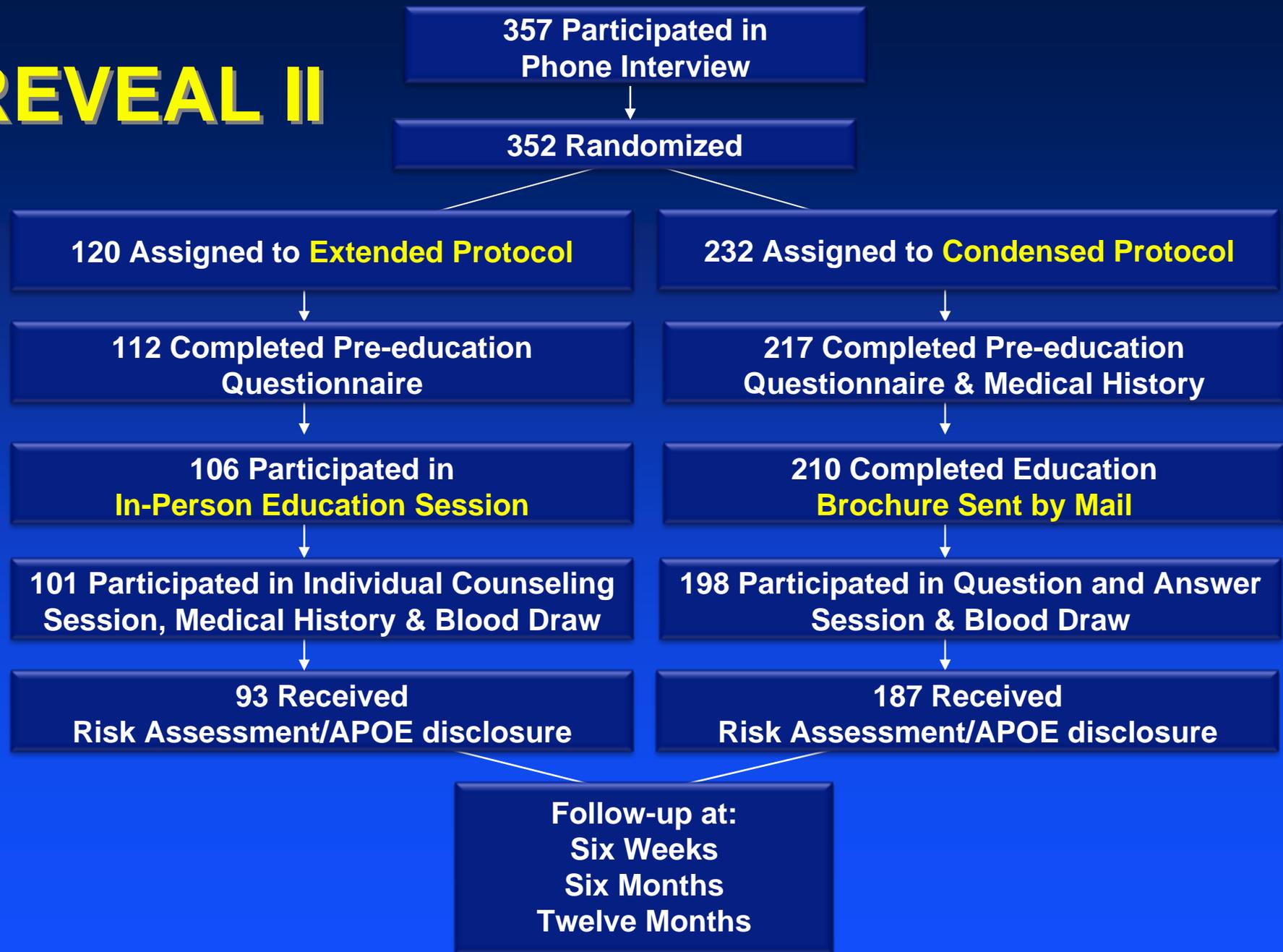
Questions about Genetic Risk Disclosure

- How should genetic risk information be communicated?
- Who will request it and why?
- Will it cause anxiety, depression or distress?
- How will it be understood and remembered?
- How do baseline perceptions change after disclosure?
- How will it influence health behaviors and health outcomes?
- Is there 'false reassurance' with negative results?
- How will risk information influence insurance purchasing?
- Who will people tell about their genetic results?
- What happens with unexpected (incidental) information?
- How can we combine genotypic & phenotypic information?

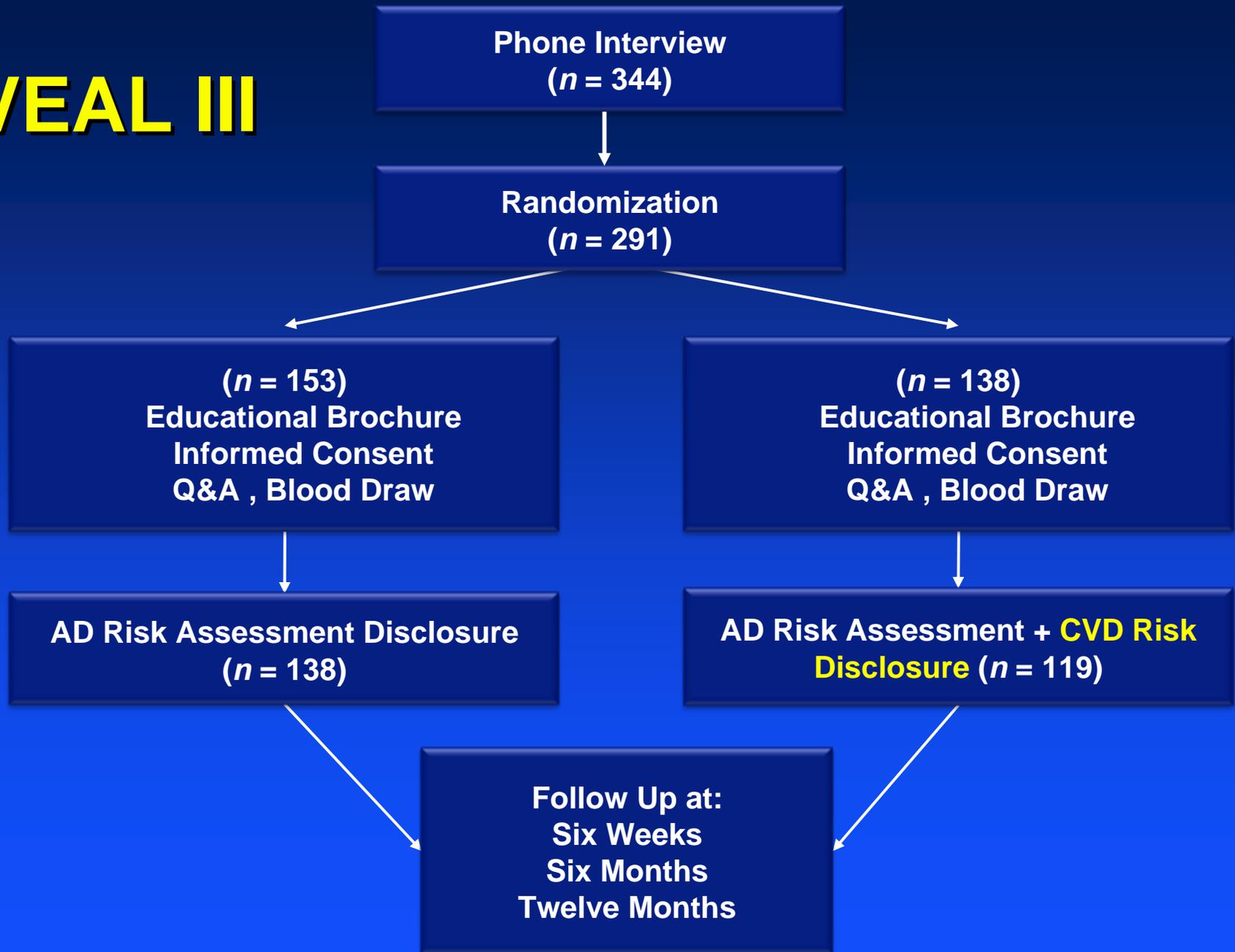
REVEAL I



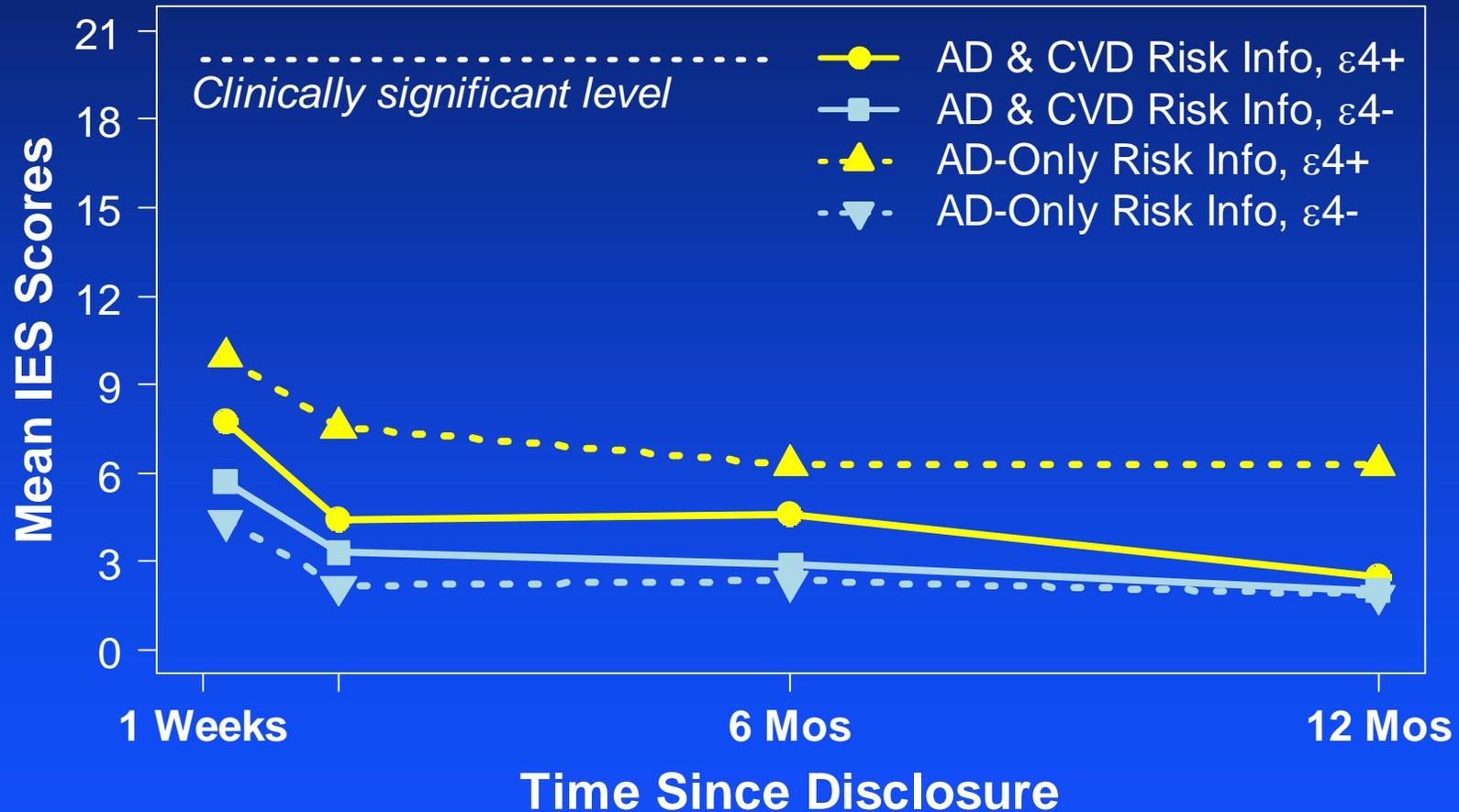
REVEAL II



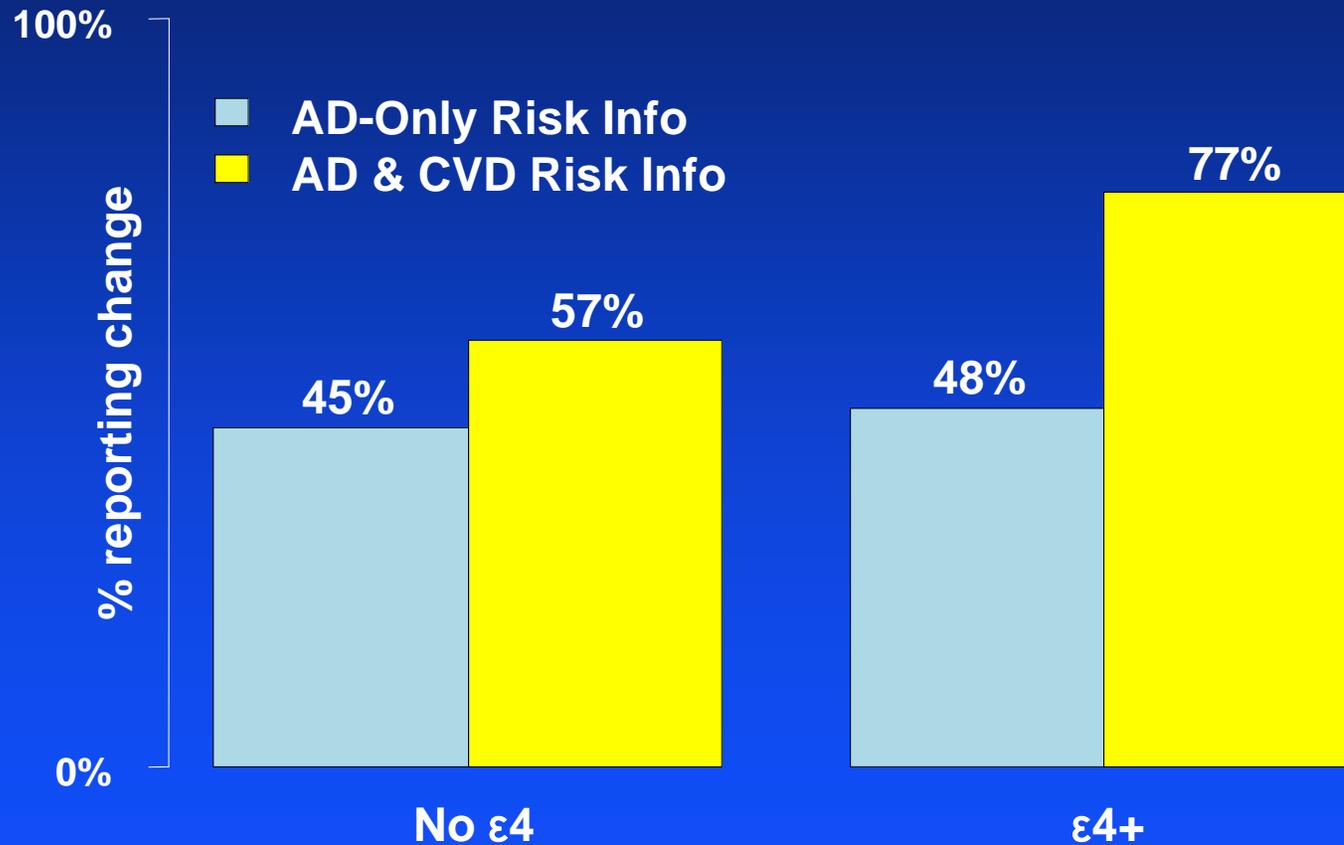
REVEAL III



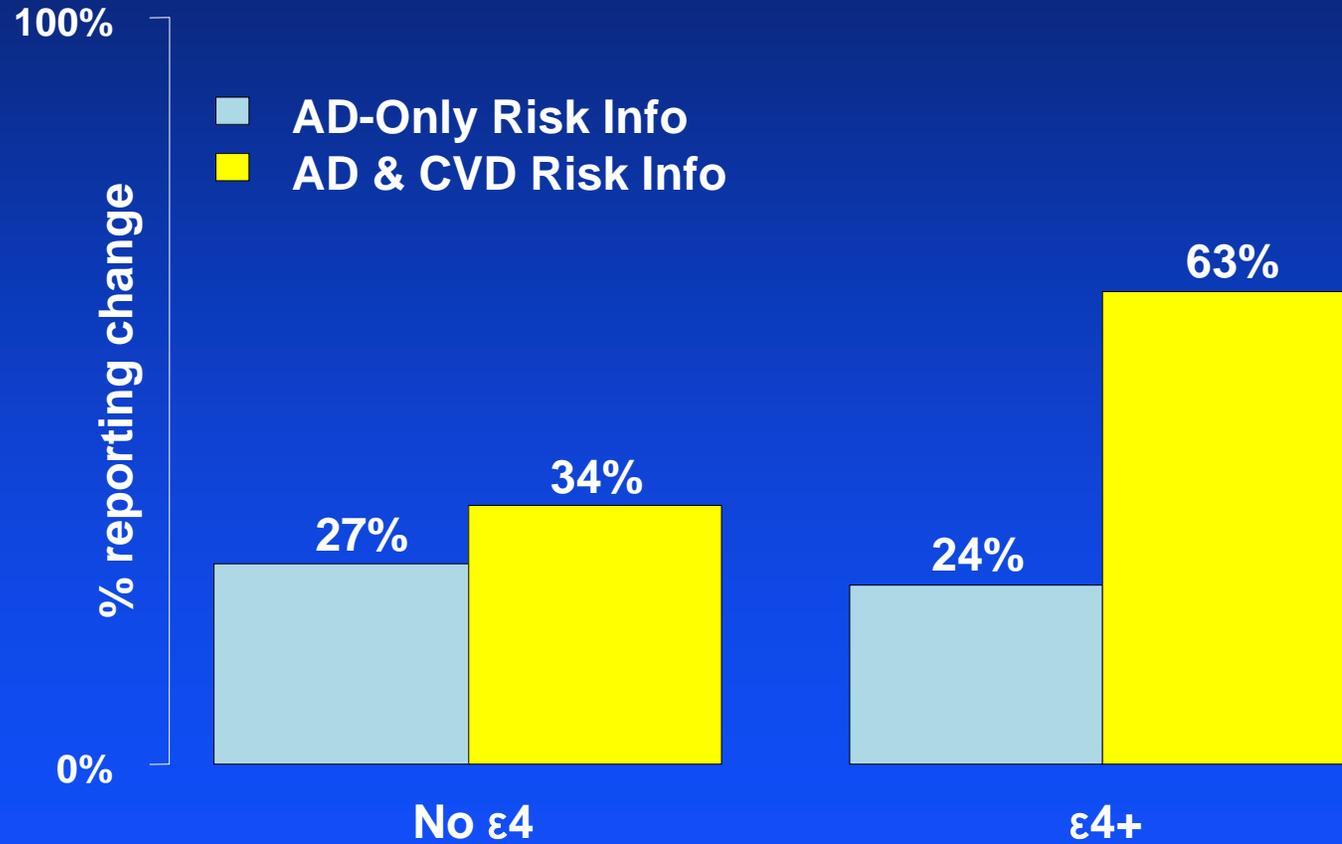
Psychological Impact of Incidental Finding



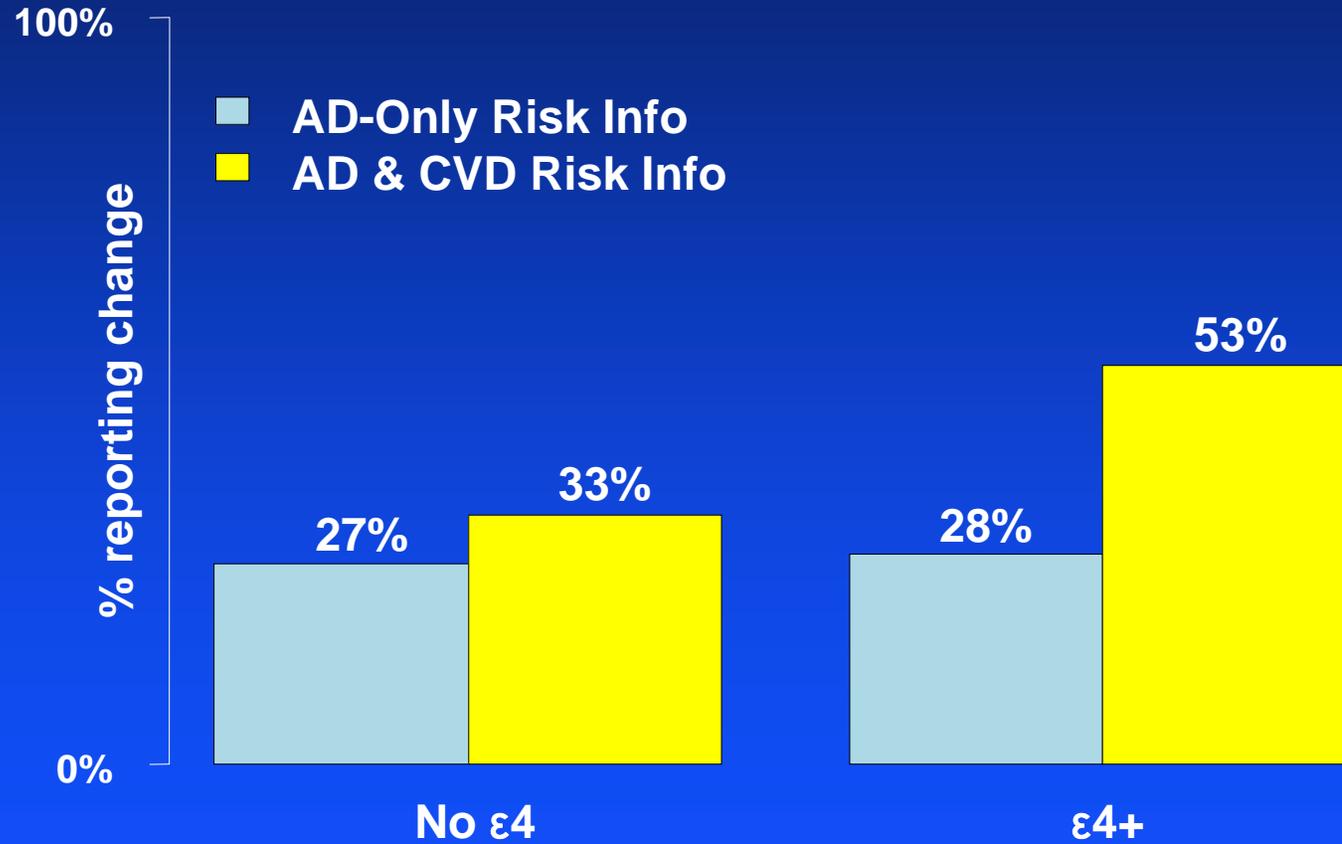
Any Behavior Change



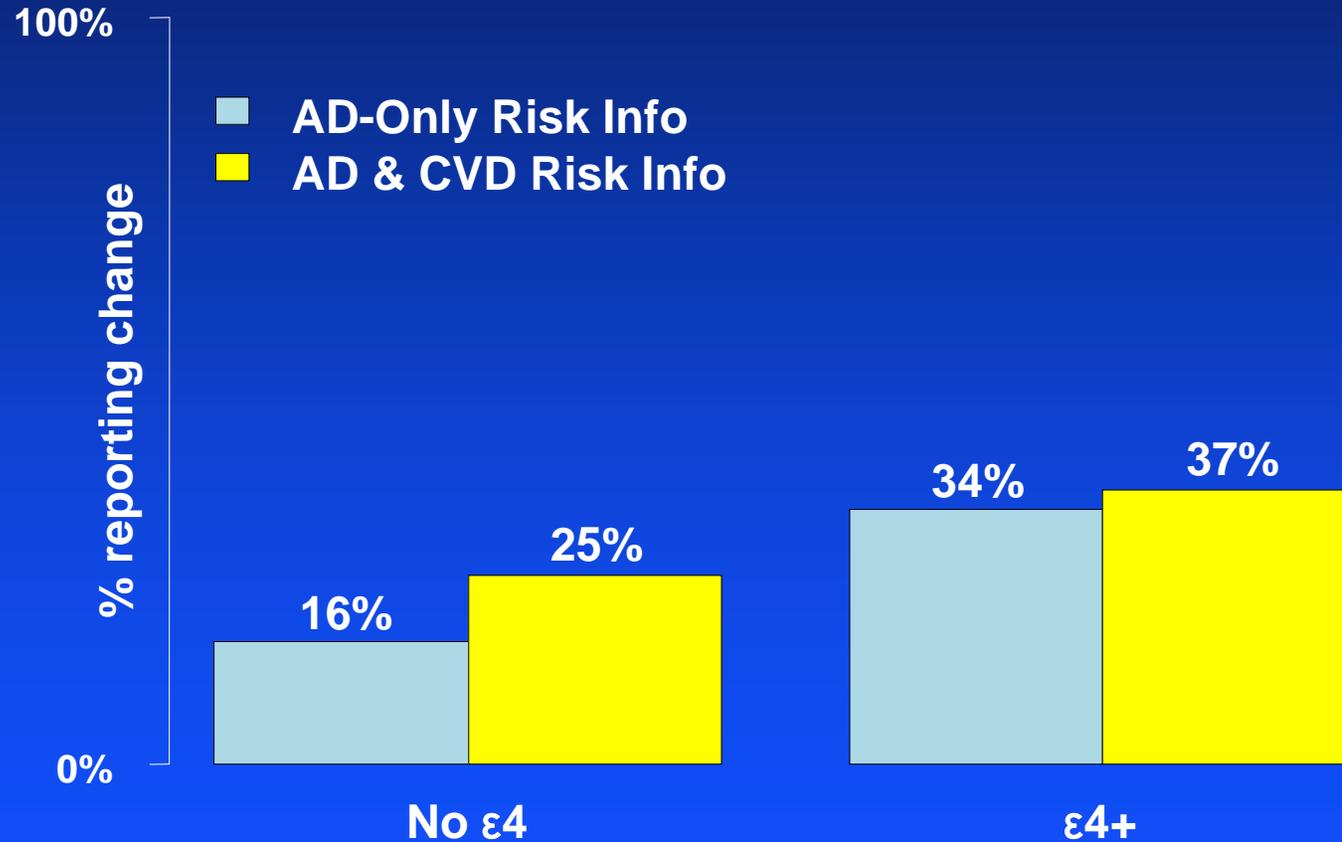
Exercise Change



Diet Change



Mental Exercise Change



Incidental findings in REVEAL...

- Participants were pleased and satisfied, even when they received information that they did not expect
- Participants understood the information
- Participants reported acting on both medically “actionable” and medically “non-actionable” information.

Case Studies in Incidental Genetic Findings

In a Cytogenetics Laboratory Rotation, Trainees Prepare and Examine Their Own Karyotypes and One is Abnormal

What should be done if...

- trainee is a 16 year old high school student vs. a medical student vs. a post-doctoral (PhD) researcher vs. a genetics (MD) fellow?
- the abnormality is a non-descript balanced translocation vs. a Philadelphia chromosome $t(9;22)$ vs. sex chromosome opposite of assigned gender?
- the trainee is 1 month pregnant?
- laboratory lacks IRB approval to use samples in this manner?

A Clinical Genetics Laboratory Uses Stored Samples Sent for Condition A to Perform Novel Test Development and Finds Variants

What should the laboratory do if...

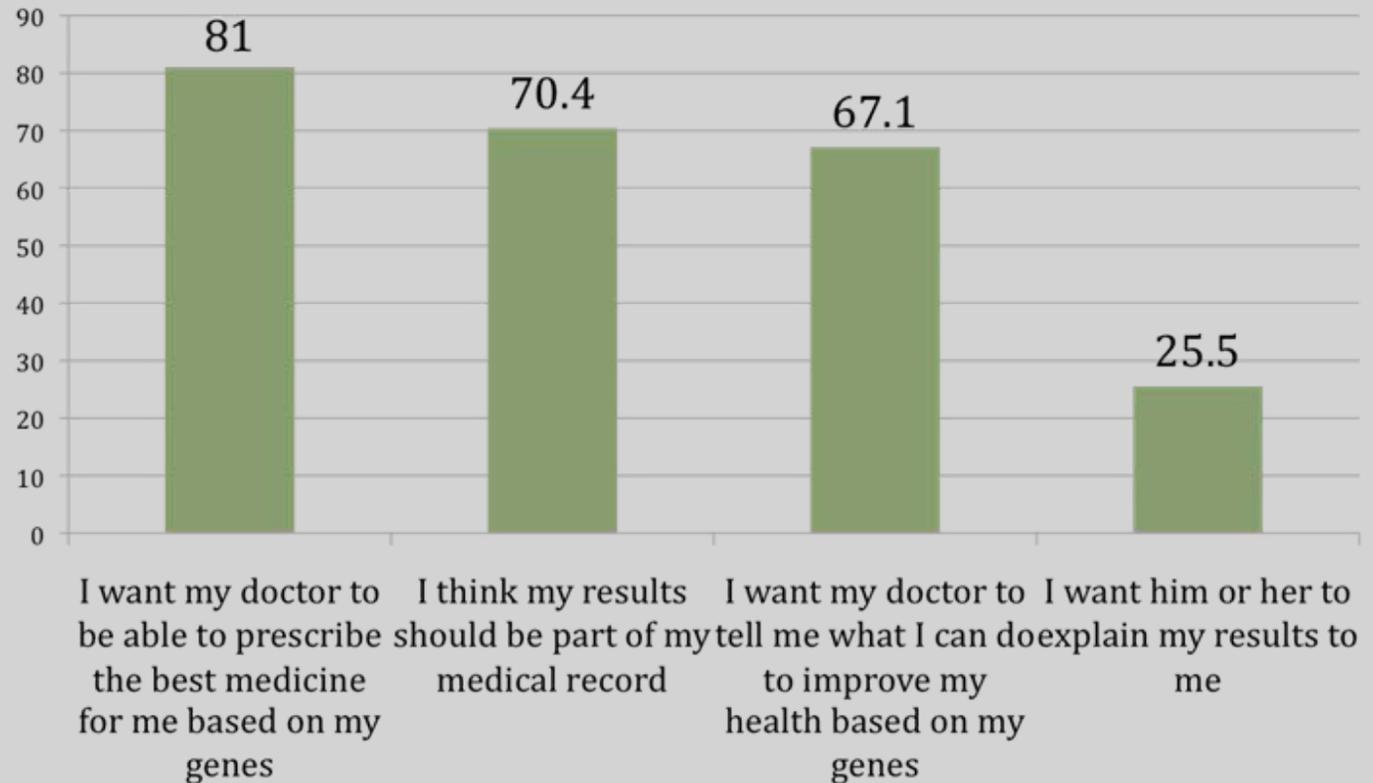
- discovered variant is for the same indication as the original test (Condition A) vs. an entirely separate indication (Condition B)?
- discovered variant is well-recognized pathogenic variant vs. previously undescribed variant that is likely pathogenic?
- discovered variant is for clearly treatable disease vs. surveillance (unknown health impact) vs. carrier state vs. clearly untreatable.
- laboratory lacks IRB approval to use samples in this manner?

Who should help subjects/patients understand genetic information?

Sharing Genomic Information with Physicians

94% of respondents reported they were *very likely or likely* to share their genetic profile information with their health care providers

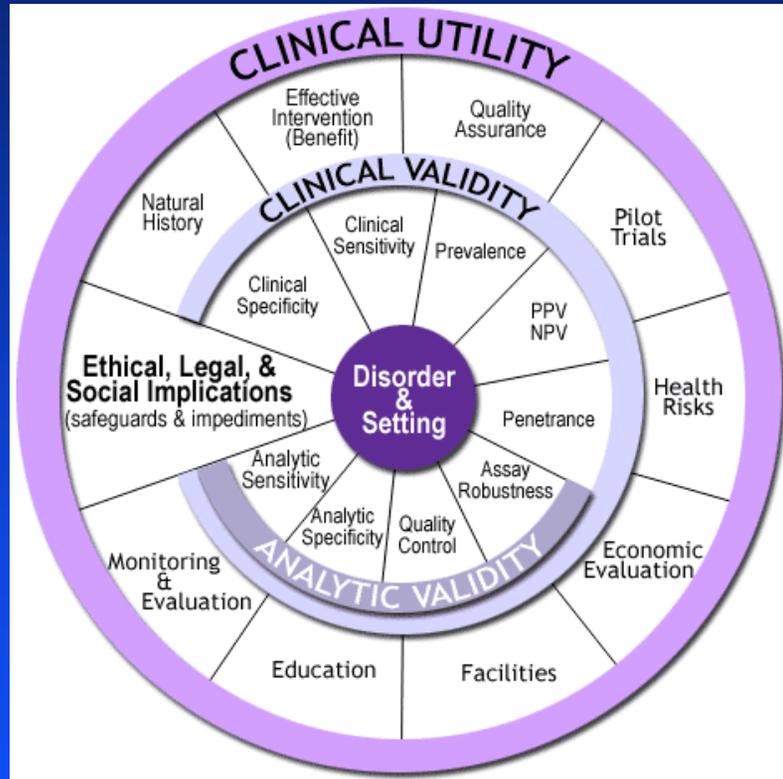
% indicating reason for sharing genomic information



How important is actionability?

The ACCE Model for Genetic Testing

Do “Benefits” = Clinical Utility?



- Alytic Validity
- Clinical Validity
- Clinical Utility
- ELSI

What about ‘personal utility’?

How Not
to Be a Jerk
as Teacher

Tech Makeovers
for Your Home
and Office

The Coolest New
Hybrid You've
Never Heard Of

TESTED & RATED
39
NEW PRODUCTS
BY JAMES MOSELEY

WIRED



SERGEY'S

SEARCH

CAN GOOGLE COFOUNDER
LOOK FOR PARKINSON'S CURE? HE GETS THE SCIENCE

By Thomas H. Davenport

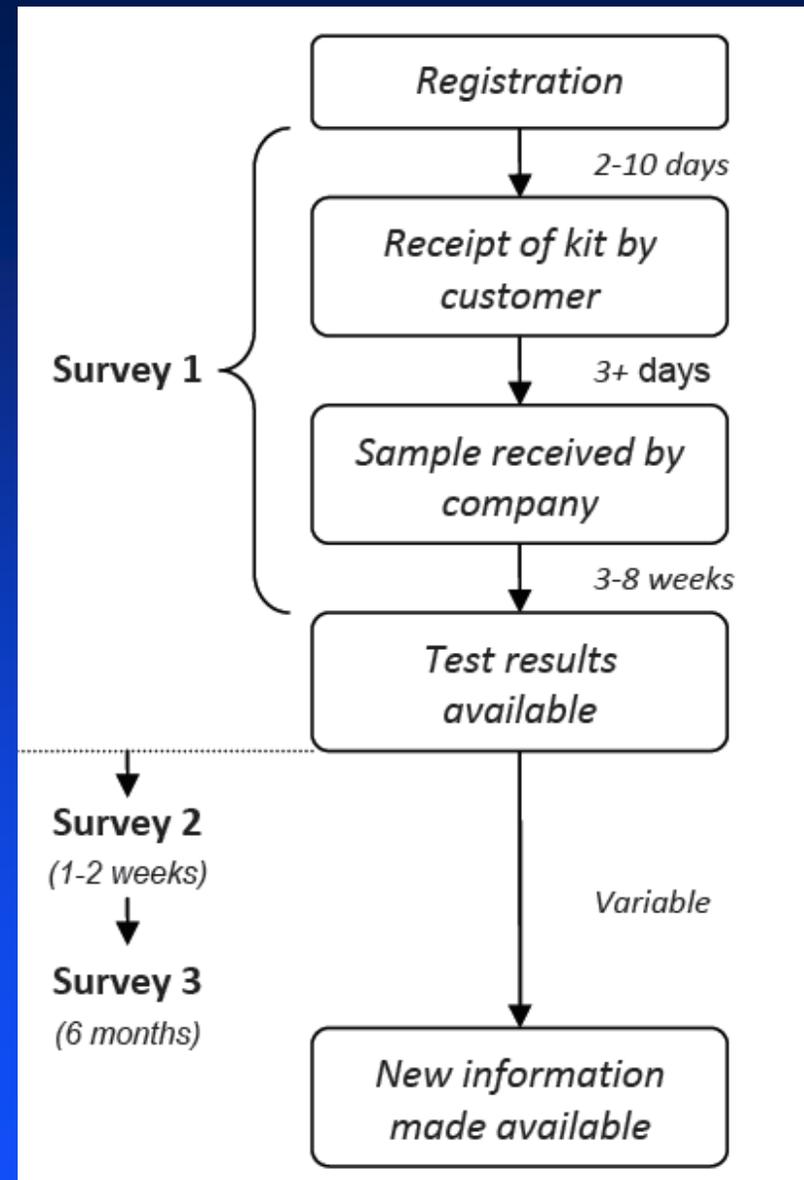
New Research Studies in Translational Genomics and Health Outcomes

Direct-to-Consumer Genetic Testing

Natural experiments in the impact of genetic risk disclosure!

Survey Protocol for Green and Roberts DTC Genetic Testing Study

NIH funding has begun
October, 2010

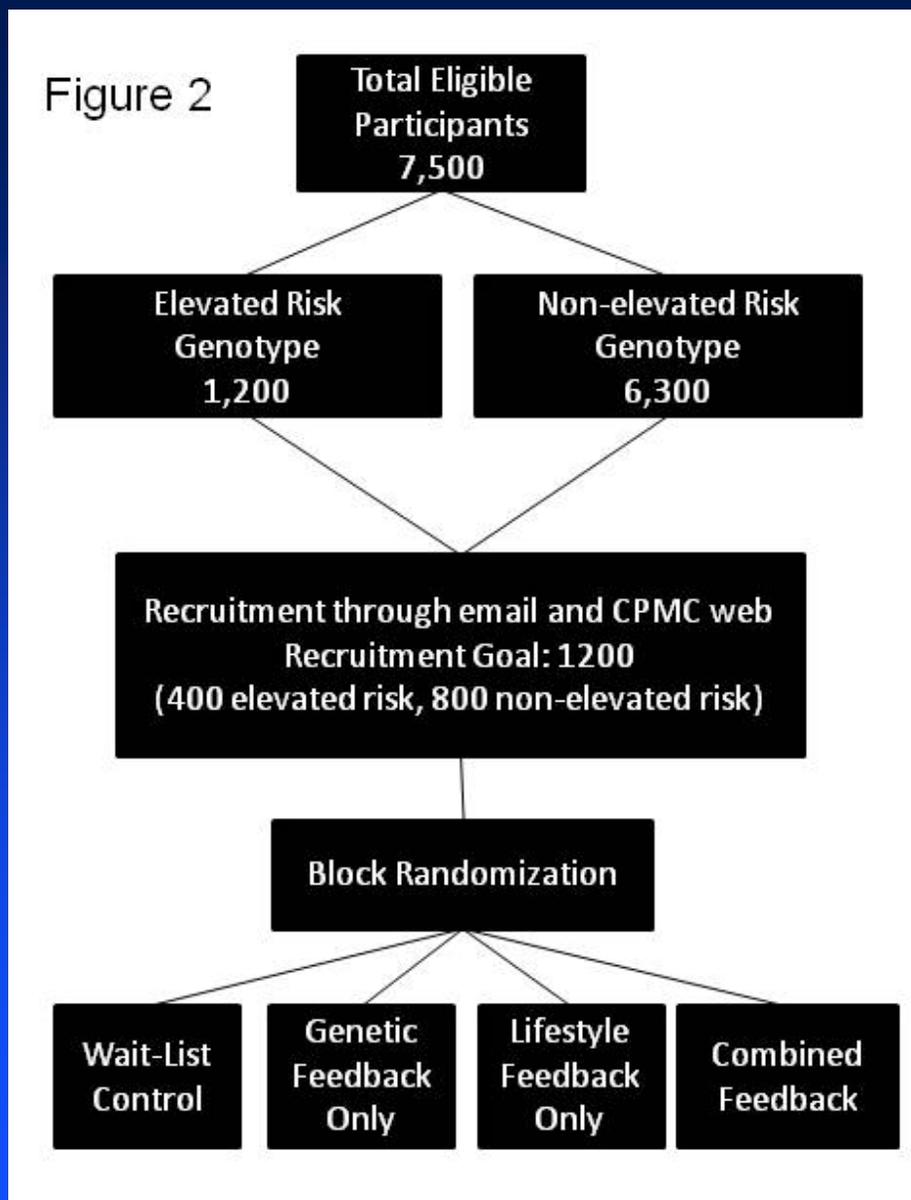


Collaboration in Other Funded Trials in Genetic Disclosure and Health Outcomes

- Obesity risk disclosure (Wang, PI)
- Diabetes risk disclosure (Grant, PI)
- Children's Hospital "Gene Partnership" (Holm, PI)
- CEGS/Personal Genome Project (Church, PI)
- Coriell Personalized Medicine Initiative (Christman, PI)
- Collaborative on Exploratory Clinical Sequencing

Communicating Genetic Risk for Obesity (Wang, PI)

**NHGRI
R21 HG00603**

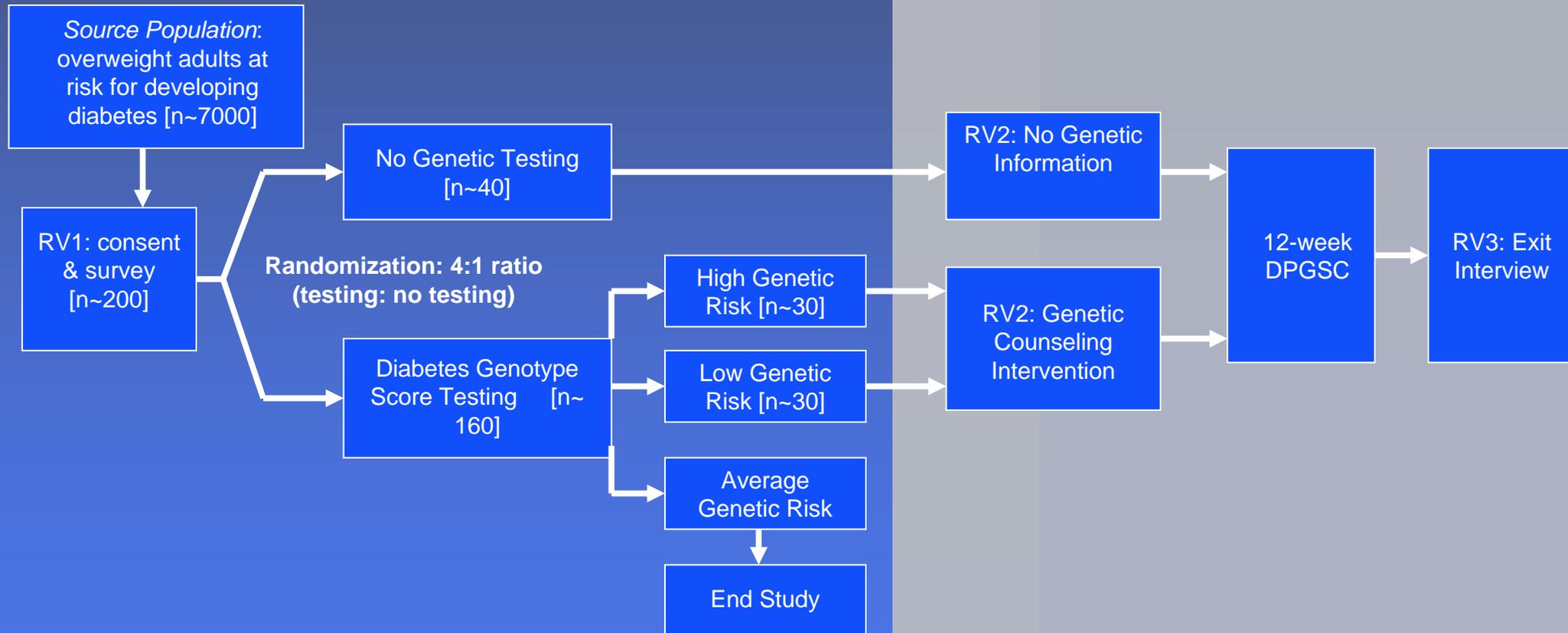




NIDDK R21 DK084527 (Grant, PI) Study Design

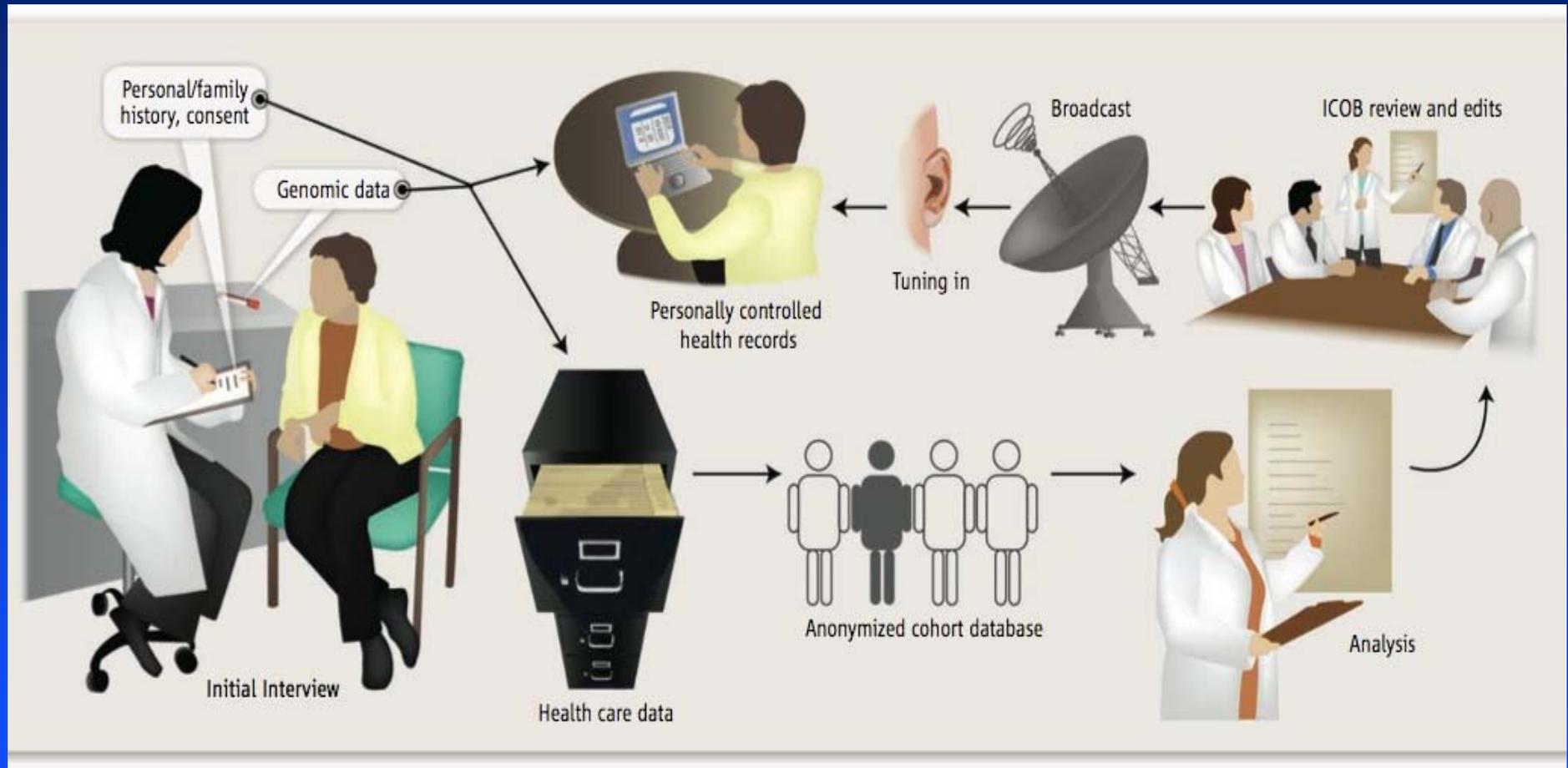
Phase 1

Phase 2



Slide courtesy of Richard Grant

Children's Hospital Gene Partnership NHGRI RC1 HG005491 (Holm, PI)



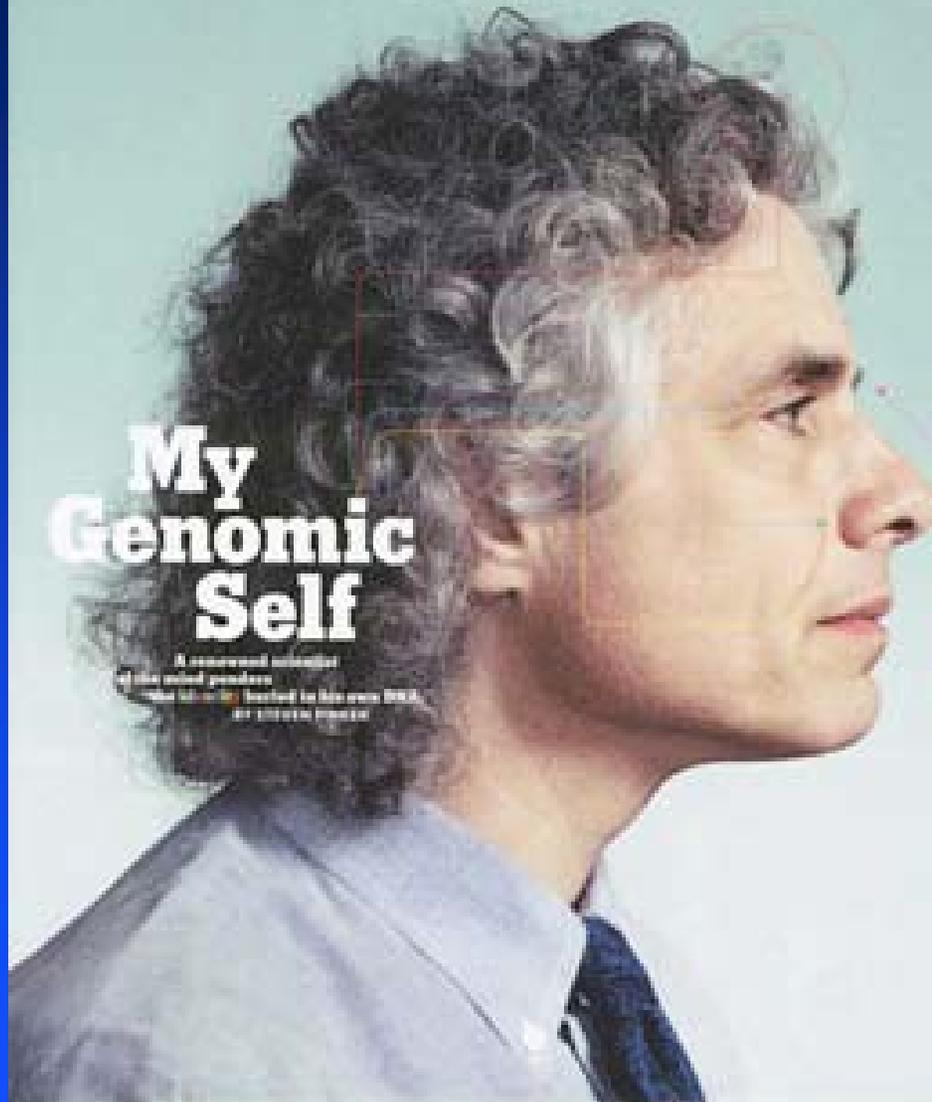
Kohane et al, 2007
Slide courtesy of Ingrid Holm, MD, MPH

Special Double: 1. Barack Obama's Vision, 2. Obama's Vision: How Obama Became Obama? 3. Bill Clinton's Last Year: How Obama Became Obama?

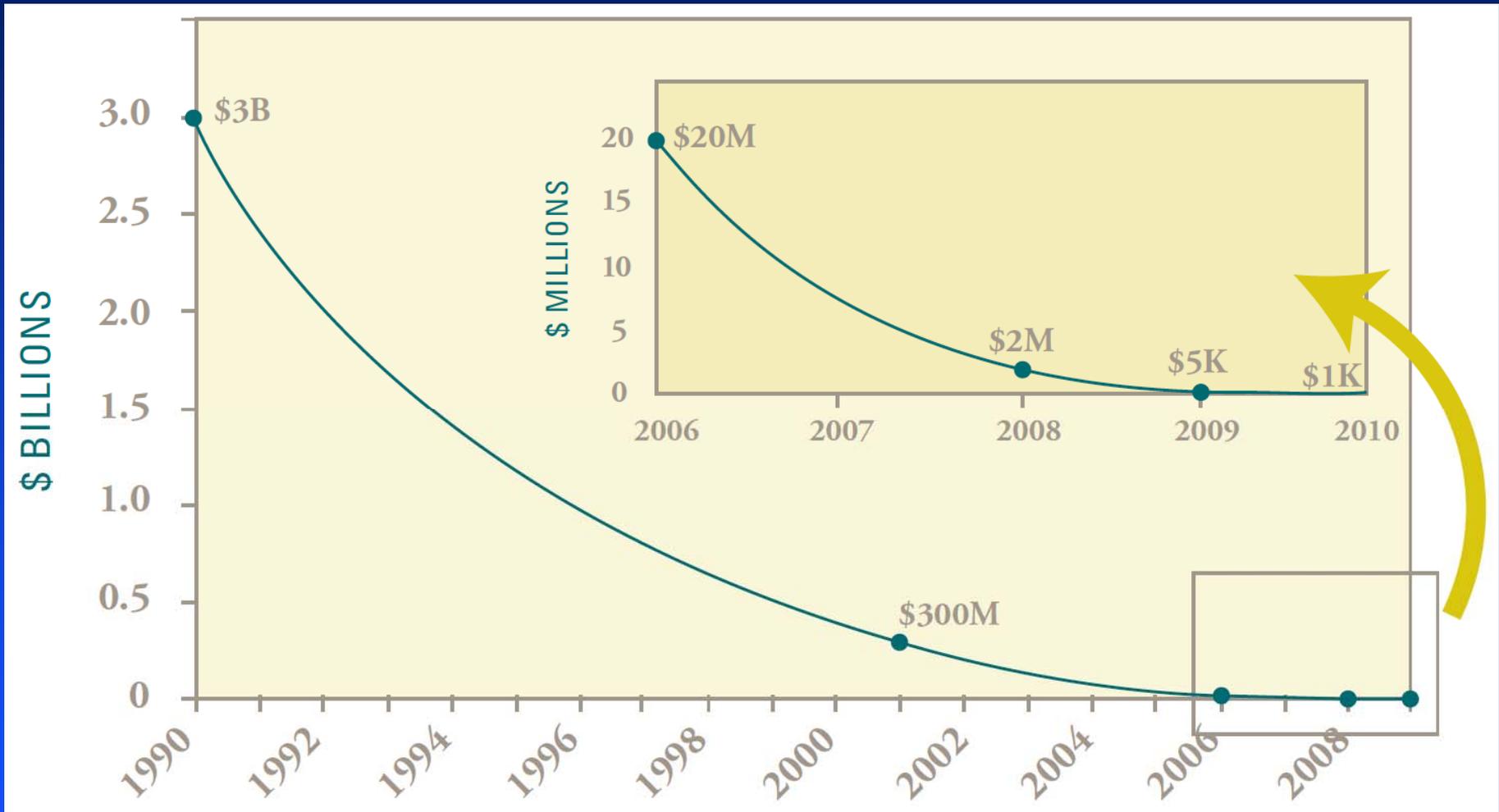
The New York Times Magazine

My Genomic Self

A personal portrait
of the world's greatest
geneticist, who has
looked to his own DNA
for answers



The Shrinking Cost of Whole Genome Sequencing



Source: The Case for Personalized Medicine, Ernst & Young, May, 2009

Issues in the Integration of Whole Genome Sequencing and Medicine

- Validation of population-based associations
- Interpretation of novel variants
- Communication of risk information, including incidental findings
- Measurement of behavioral, health and economic indices

Incidental Findings in Genetics will Not Come One at a Time

