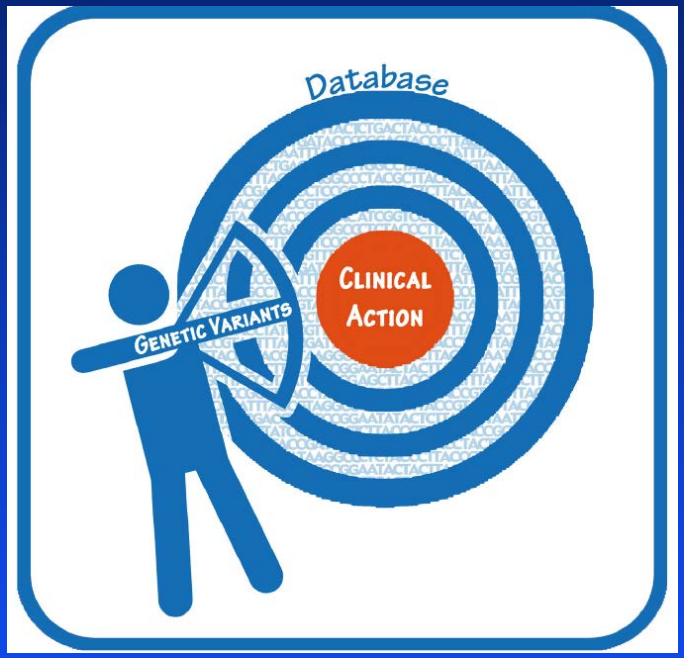
Contrasting Clinician and Patient Perspectives on Variant Disclosure



Robert C. Green, MD, MPH, Director *G2P* - Translational Genomics & Health Outcomes
Associate Director, Partners Center for Personalized Genetic Medicine
Division of Genetics, Department of Medicine
Brigham and Women's Hospital and Harvard Medical School

Disclosures

Research Grants:	NIH
Speaking (compensated):	none
Advisory (compensated):	none
Advisory (uncompensated):	none
Research collaboration:	Pathway Genomics, 23andMe
Equity:	none

Key Collaborators at BWH / HMS

Heidi Rehm, Mike Murray, Scott Weiss, Sandy Aronson

Zak Kohane, Ingrid Holm, David Margulies

Kricket Seidman

George Church

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Contrasting Clinician and Patient Perspectives on Variant Disclosure

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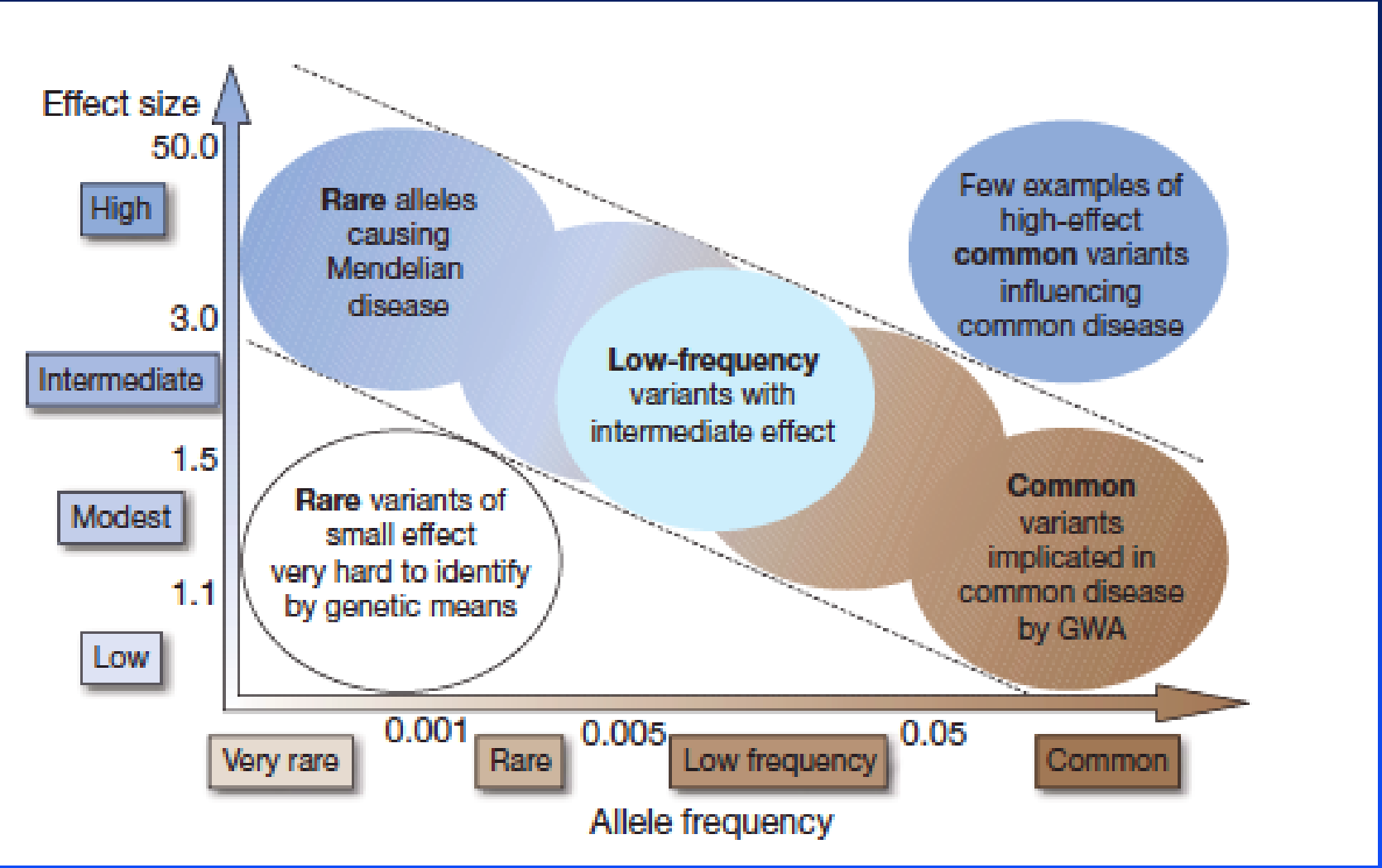
Incidental Findings in Genomic Medicine
What to look for? What to disclose?

Various Variants…



McCarthy et al., *Nat Rev Gen*, 2008

Manolio et al., *Nature*, 2009

What do Patients/Consumers Want Disclosed?

It varies…..

Personal Genome Project

"PGP"

1) Open access data
2) Examination to assure informed consent
4) Genome sequence and epigenome
5) Multi-traits
6) Cells available
7) IRB approval for 100,000 volunteers

16,000 volunteers
74 countries
2,418 scored 100% on entrance exam
1,056 medical records online
500 genomes in the pipeline

DTC Testing: A Consumer Driven Experiment in Incidental Findings

Invention of the Year

TIME

1. The Retail DNA Test

By Anita Hamilton

ARTICLE TOOLS

Print

Email

Sphere

AddThis

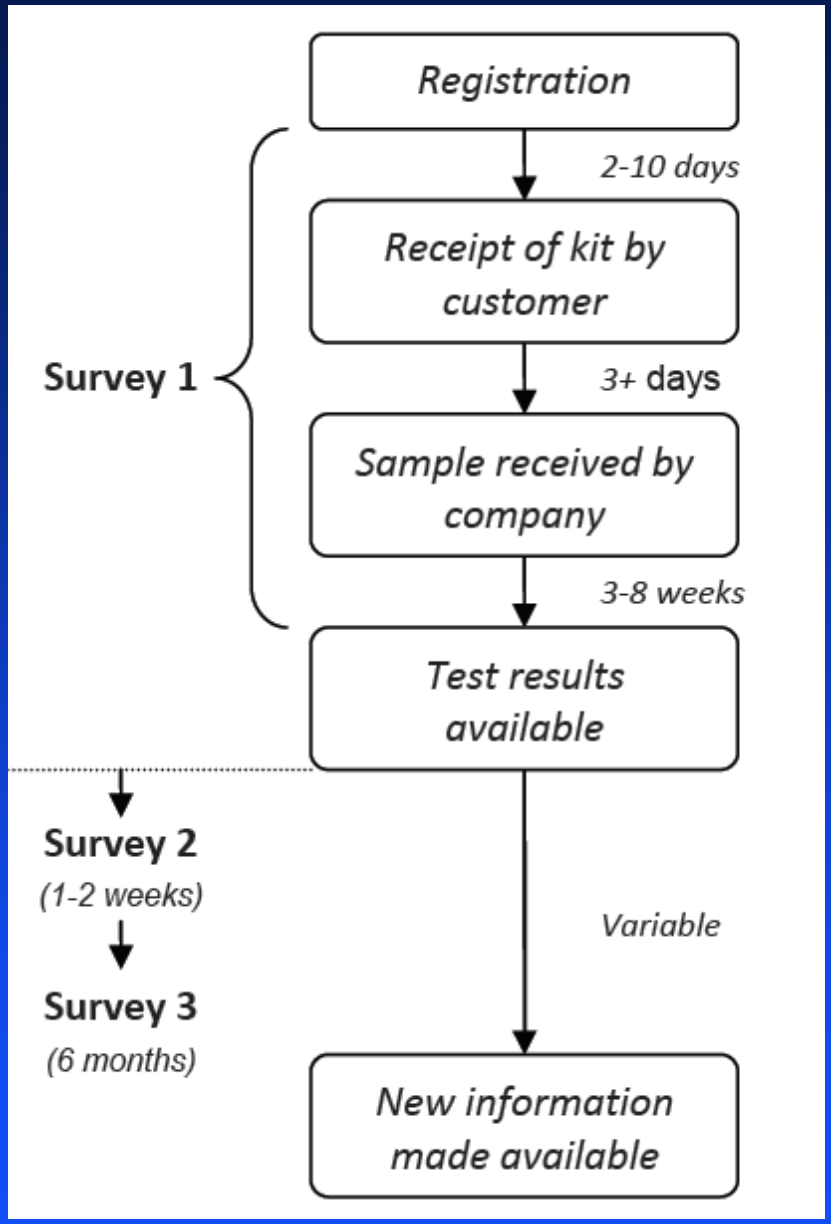
RSS

Yahoo! Buzz

Before meeting with Anne Wojcicki, co-founder of a consumer gene-testing service called 23andMe, I know just three things about her: she's pregnant, she's married to Google's Sergey Brin,

Impact of Personal Genomics Testing Study

"P-Gen"



R01 HG005092 (Green-Roberts)

Can we even define “Clinical Actionability”?

Probably not…..

Many Shades of “Actionable”

Narrow definition of clinical utility
* The information may help participants to treat or avoid disease

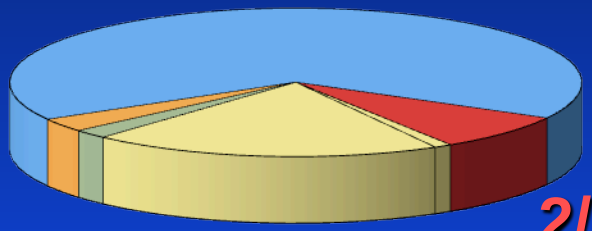
Broader definition of clinical utility
* The information may motivate participants to change their behavior
* Participants could learn more about the condition or gene
* Participants could monitor research and progress
* Participants could participate in other related research
* The information could be useful to participants in the future

Personal utility
* The knowledge could empower participants
* The information could give participants a feeling of control
* The information could benefit the participant's family
* The information could make participants feel respected by the researchers
* The information could make participants feel more involved in the study
* The information could help participants plan or live more fully

Other reasons
* Results belong to the participant
* Participants want to know what the researchers learn about them
* Results are compensation for participating

Personal Communication, David Kaufman, 2011

The REVEAL Study
NGHRI funded 2000-2013

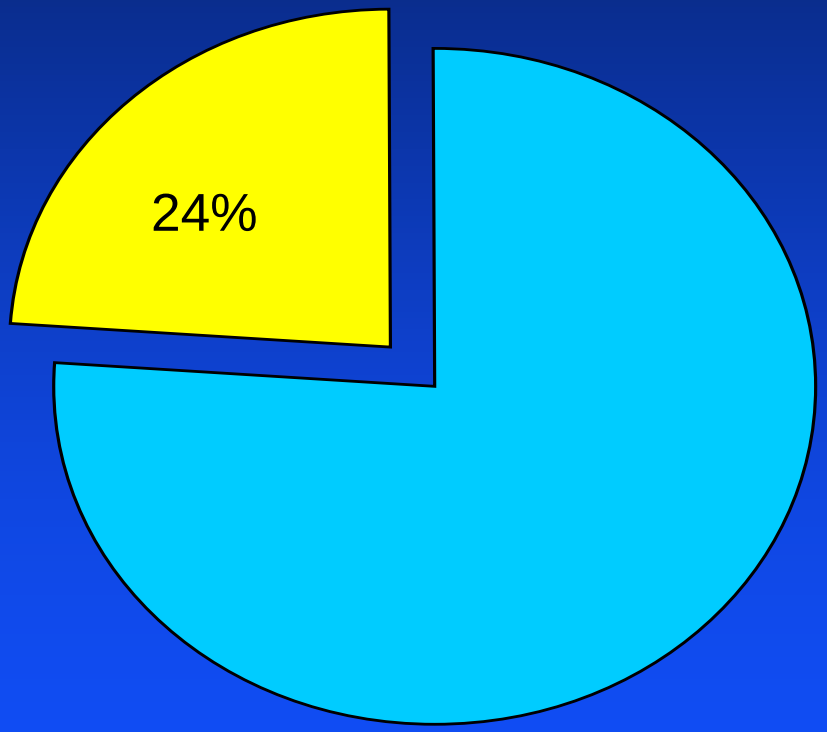


There are six possible combinations of the APOE forms. These combinations are called genotype.

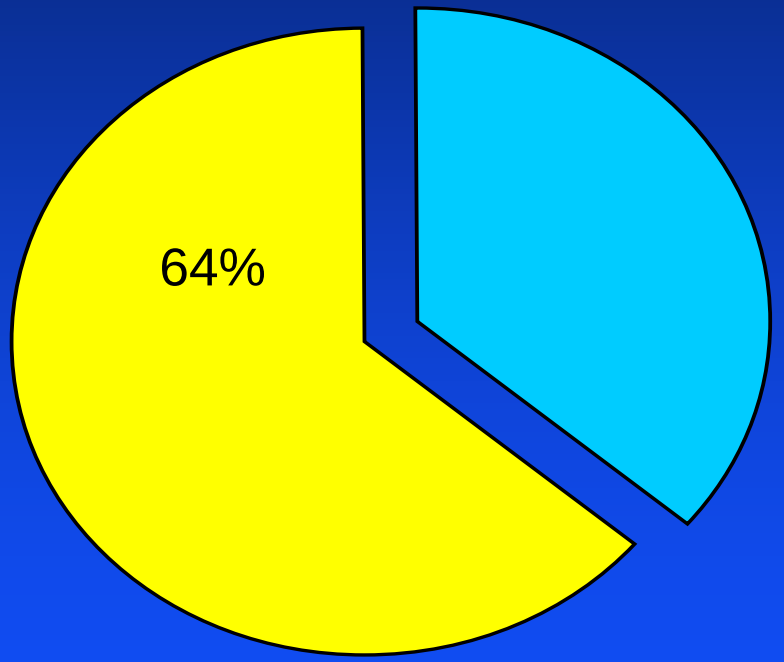
ε2	ε2	ε2	ε4
ε2	ε3	ε3	ε4
ε3	ε3	ε4	ε4

REVEAL Study: Persons Agreeing to Participate

Systematically Ascertained

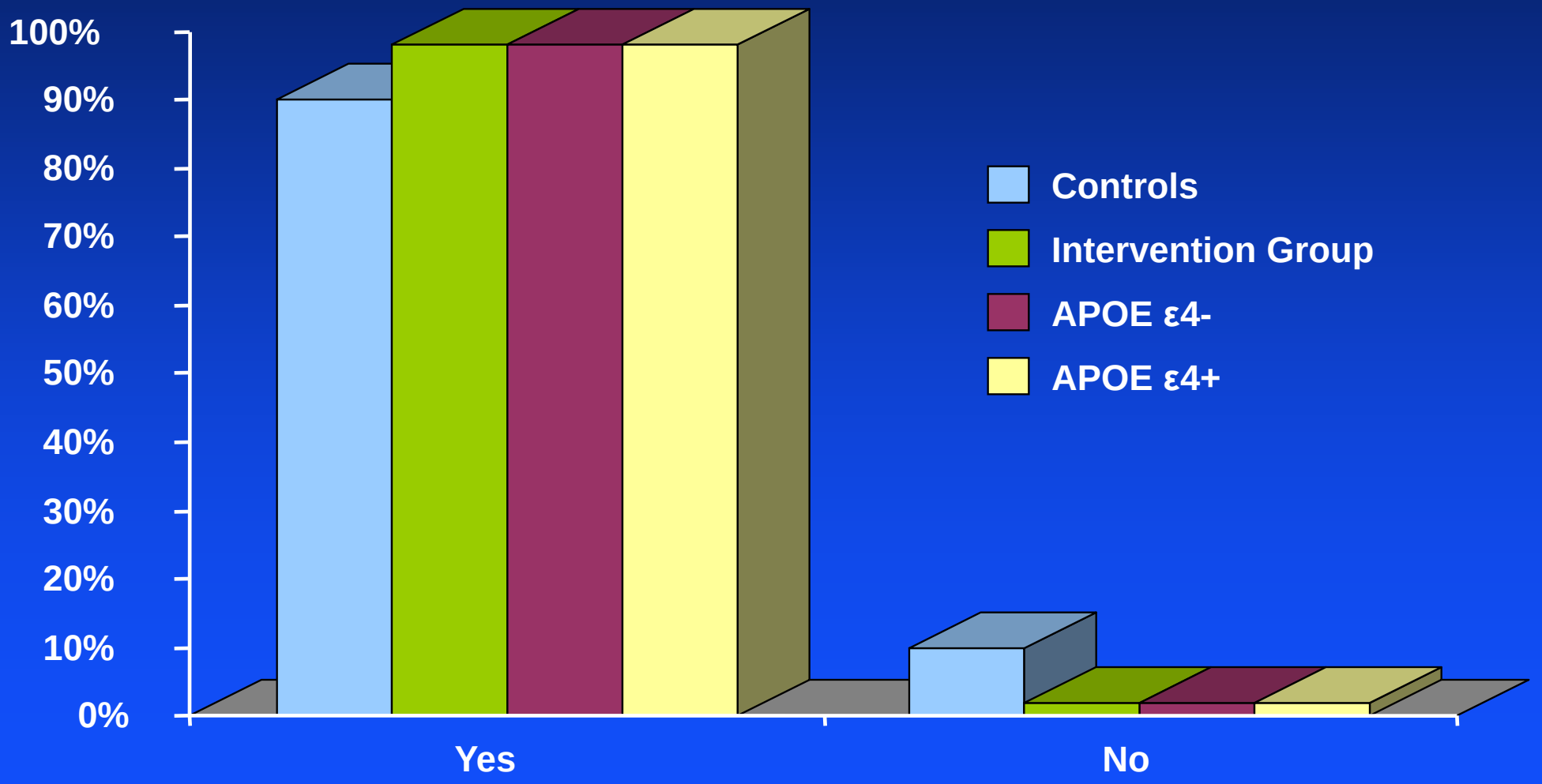


Self Referred



Roberts et al. *Genetics in Medicine*, 2004

REVEAL Study: Would Do Risk Assessment Again…



Green et al., *New Engl J Med*, 2009

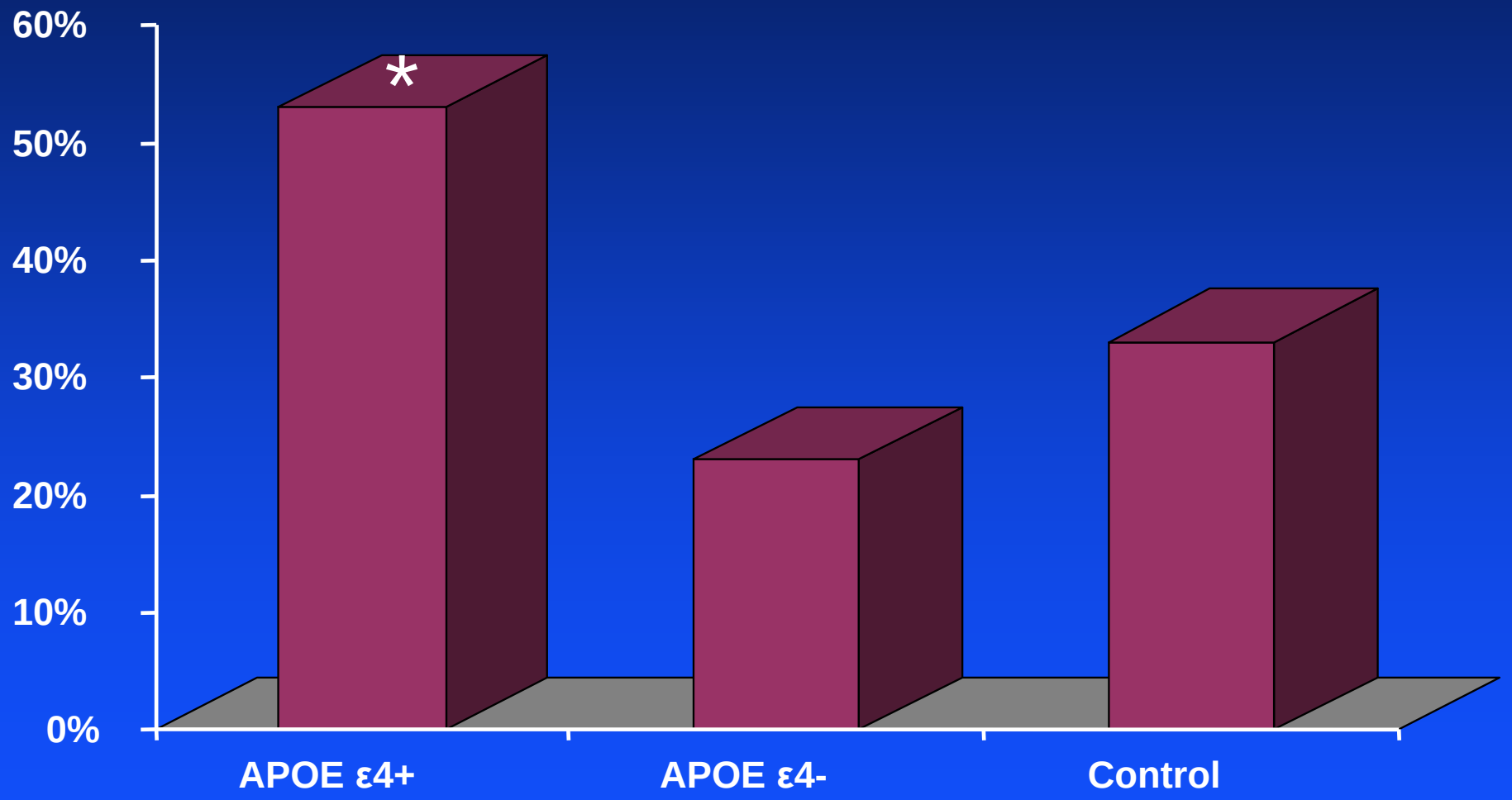
The REVEAL Study: Willingness to Pay

TABLE 3. AMOUNT WILLING TO PAY FOR ALZHEIMER'S DISEASE RISK ASSESSMENT

Variable	*Willing to pay >$100 for testing* (n=106)	*Willing to pay ≤$100 for testing* (n=150)	*Adjusted (multivariable)*[a] *Odds ratio (95% CI)*	*p-value*
Mean age	56.9±10.4	58.5±10.5	1.011 (0.980, 1.043)	0.4864
Sex (% female)	68 (64.2%)	112 (74.7%)	0.702 (0.361, 1.363)	0.2956
Race (% African American)	13 (12.3%)	35 (23.3%)	0.959 (0.424, 2.170)	0.9203
Mean education, in years	16.6±2.4	15.8±2.5	1.076 (0.949, 1.219)	0.2533
Income (% ≥$50K)	89 (88.1%)	90 (64.8%)	2.969 (1.367, 6.450)	0.0060
APOE status (% ε4 positive)	47 (44.3%)	56 (37.3%)	1.119 (0.619, 2.024)	0.7091
Baseline Self-Perceived Risk	53.0±22.3	49.1±22.6	1.004 (0.990, 1.018)	0.5567
Increased desire to know future AD status	91 (86.7%)	98 (65.3%)	3.224 (1.516, 6.856)	0.0024
Increased concern about developing AD someday	75 (71.4%)	89 (59.3%)	1.324 (0.681, 2.575)	0.4079

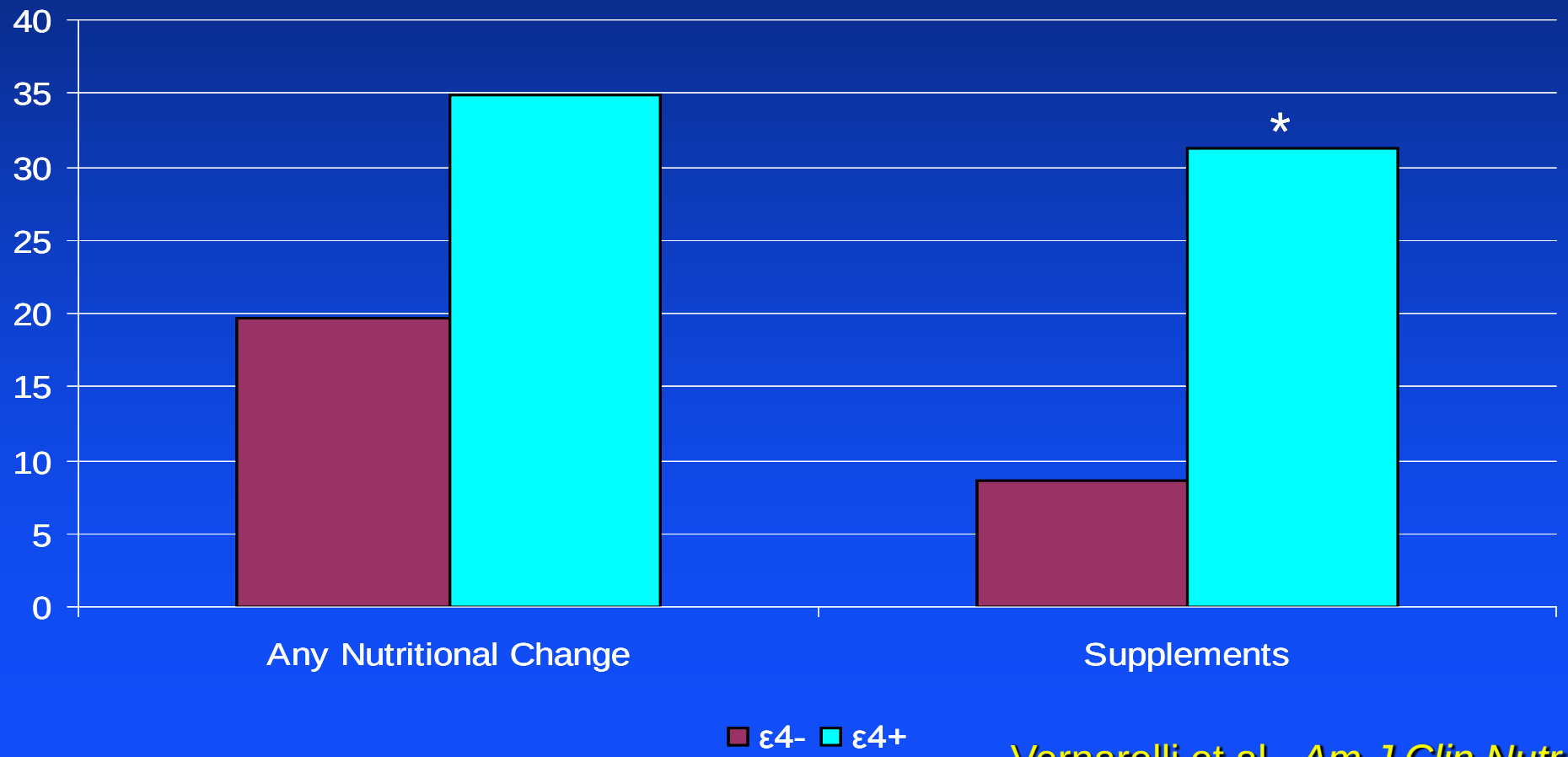
Kopits, et al. *Genetic Testing Molec Biomarkers*, 2011

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



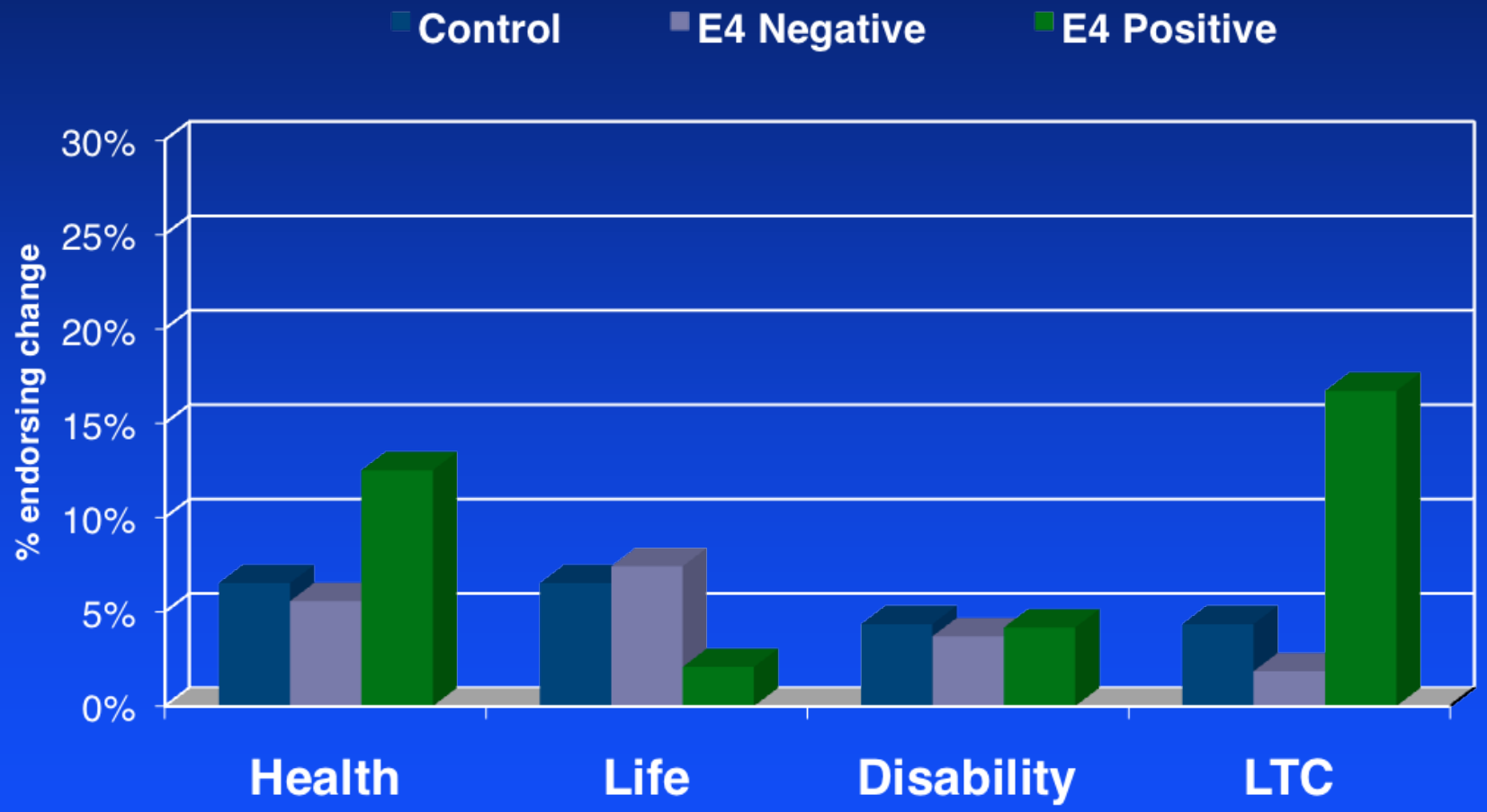
Chao, et al. *Alz Dis Assoc Dis*, 2008

REVEAL Study: Nutritional Changes and Supplement Use at 6 Weeks



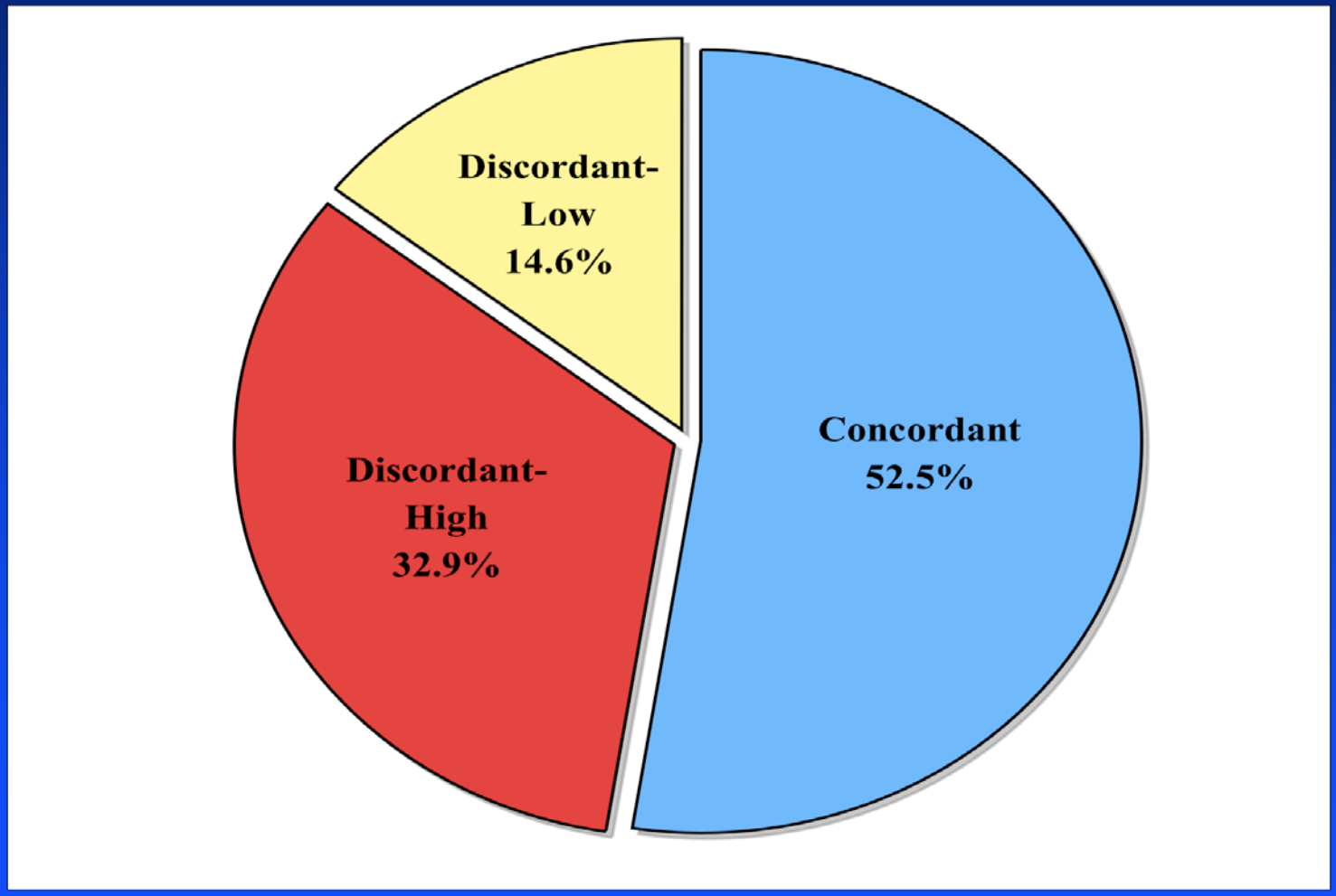
Vernarelli et al., *Am J Clin Nutr*, 2010

REVEAL Study: Insurance Changes 1 Year After APOE Disclosure



Zick et al., *Health Affairs*, 2005

The REVEAL Study:
"I know what you told me, but this is what I think…"



Linnenbringer et al., *Genetics in Medicine*, 2010

REVEAL Study: "Pros" of Disclosure

Table 3 Ratings of individual pros and individual cons at baseline and at 12 months ordered by magnitude of change (1 = not at all important, 5 = extremely important)

	Mean at baseline	Mean at 12 months	Δ	*P*
Pros				
To seek information on preventative measures	4.26	3.75	−0.51	<0.001
The need to make arrangements for my long-term care	3.67	3.31	−0.36	<0.001
To know more about my risk in case better treatments become available	4.26	3.91	−0.35	<0.001
The desire to contribute to research on AD	4.11	3.86	−0.25	<0.001
The desire to start doing things sooner than I had planned to	3.37	3.18	−0.19	0.018
To give information about my children's possible risk of AD	3.01	2.82	−0.19	0.020
The need to arrange my personal affairs	3.69	3.56	−0.13	0.097
To confirm the feeling that I might already be developing AD	2.32	2.19	−0.13	0.099
To put my mind at ease if I found out I was not at risk for AD	3.53	3.45	−0.08	0.346
The need to prepare my family for my possible illness	3.43	3.38	−0.05	0.513
Curiosity	3.17	3.26	.09	0.256

Christensen, et al. *Genetics in Medicine*, 2011

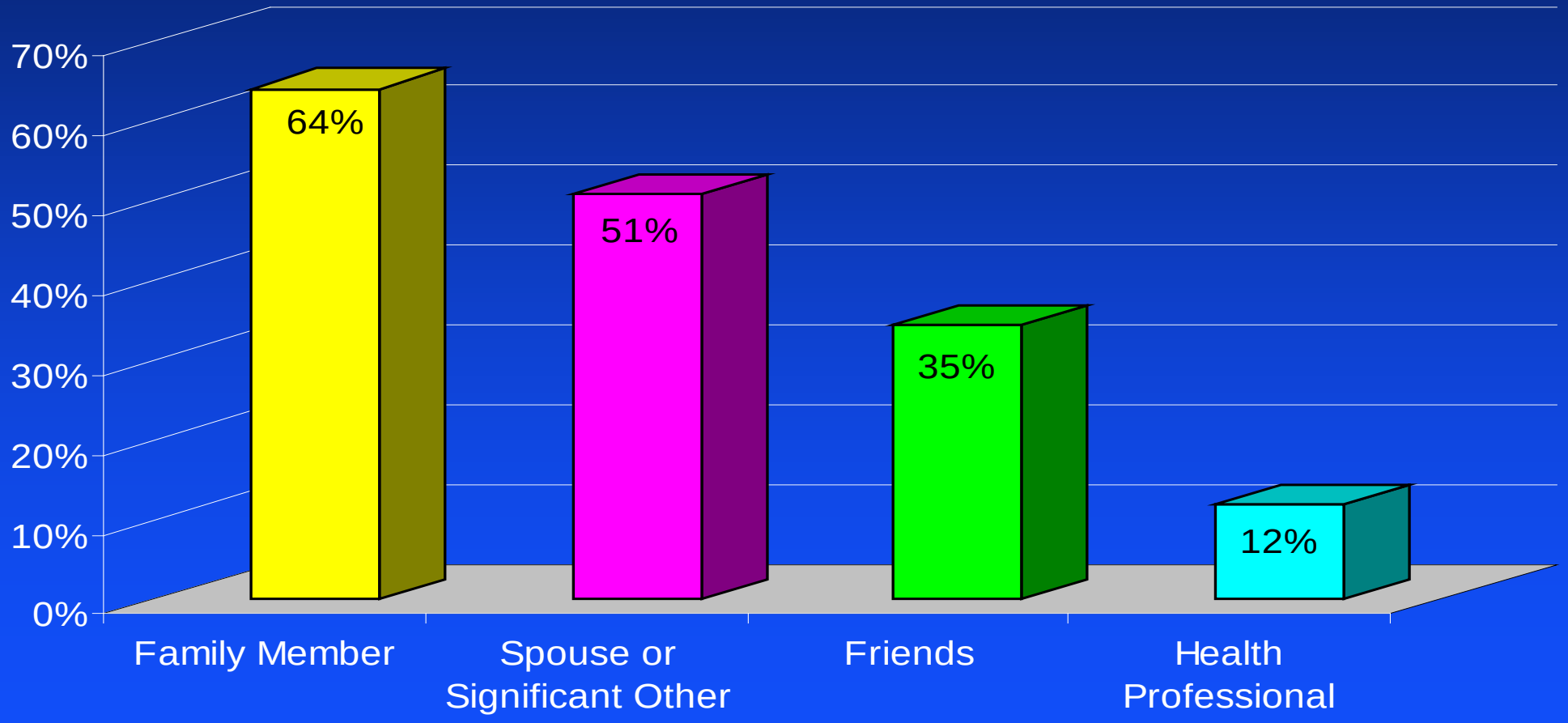
REVEAL Study: "Cons" of Disclosure

Table 3 Ratings of individual pros and individual cons at baseline and at 12 months ordered by magnitude of change (1 = not at all important, 5 = extremely important)

Cons				
There is no way to cure or prevent AD	1.93	2.18	.25	0.007
The test does not give me a definite answer about whether I might get AD or not	2.13	2.30	.17	0.017
It could make me worry about my children's risk of getting AD	1.81	1.79	−0.02	0.727
My family does not think it is a good idea for me	1.25	1.20	−0.05	0.350
It would be too upsetting to find out I'm at risk for AD	1.96	1.88	−0.08	0.289
The test results might upset my loved ones	2.10	1.97	−0.13	0.075
The test procedure would be too burdensome	1.37	1.24	−0.13	0.011
Discrimination fears				
The results could affect my employment	1.60	1.85	0.25	0.001
The results could affect my health insurance	2.37	2.48	0.11	0.184
The results could change how people look at or act toward me	1.78	1.88	0.10	0.153

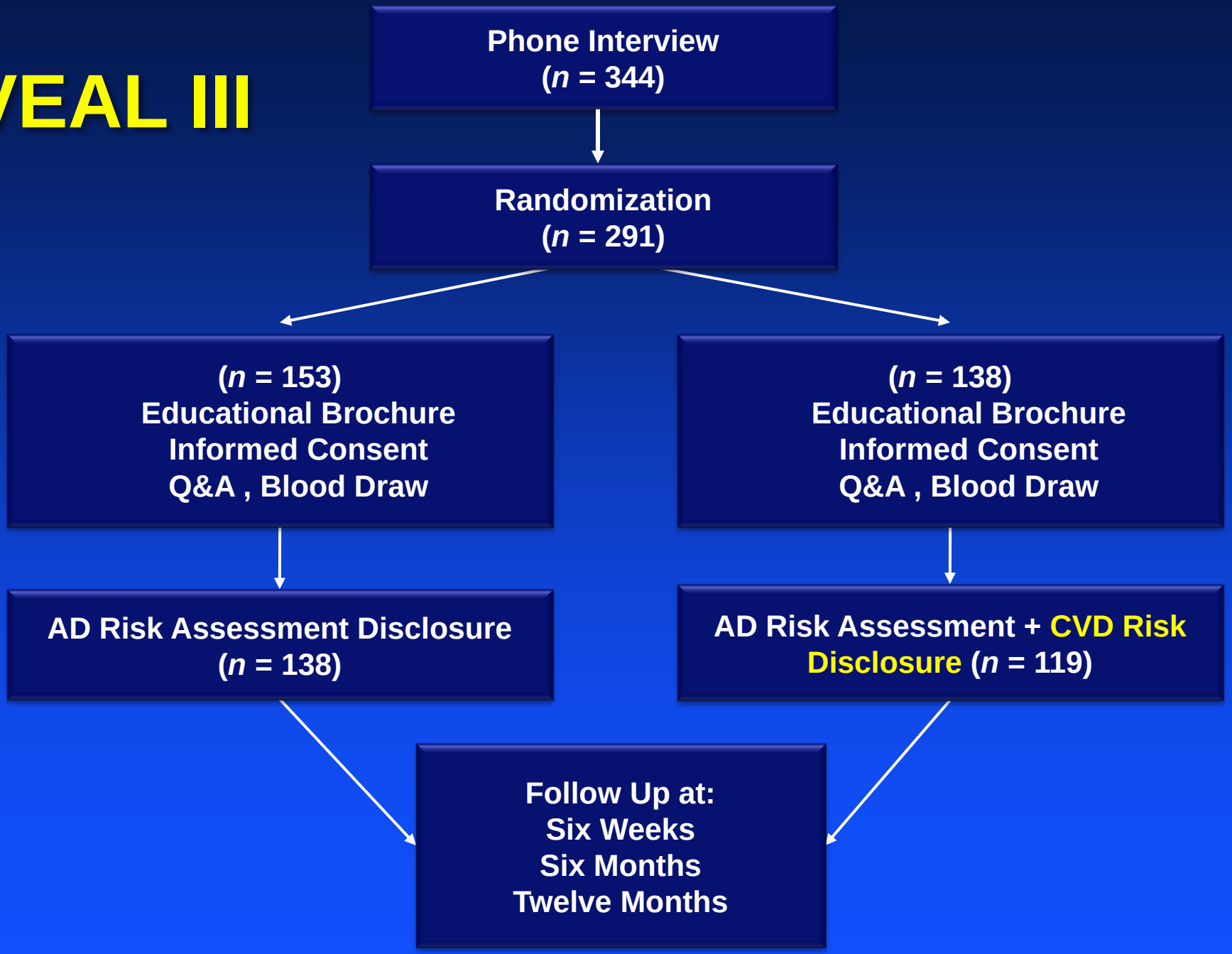
Christensen, et al. *Genetics in Medicine*, 2011

REVEAL Study: Telling Others Your Results

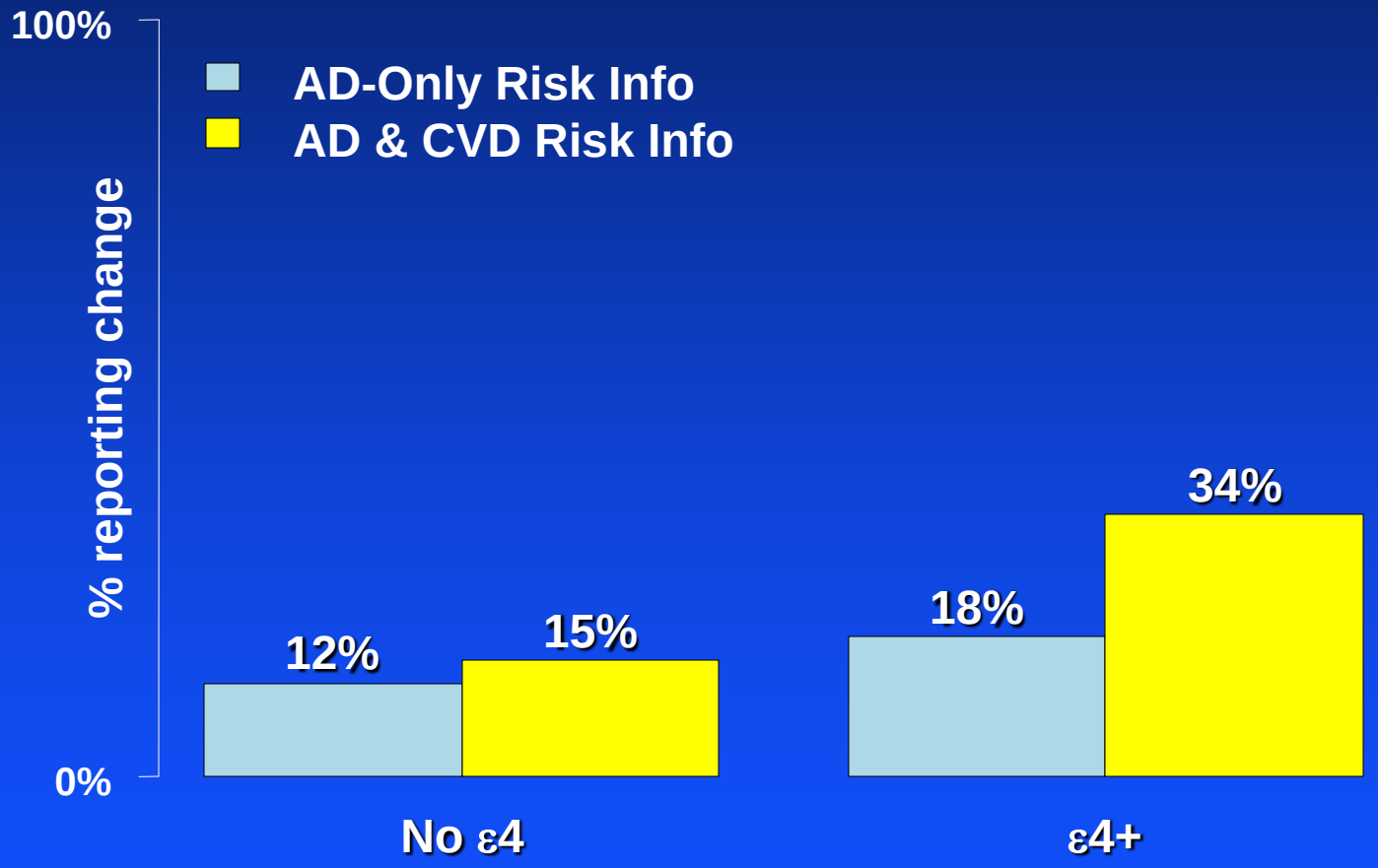


Ashida et al., *J Health Communication*, 2009.

REVEAL III

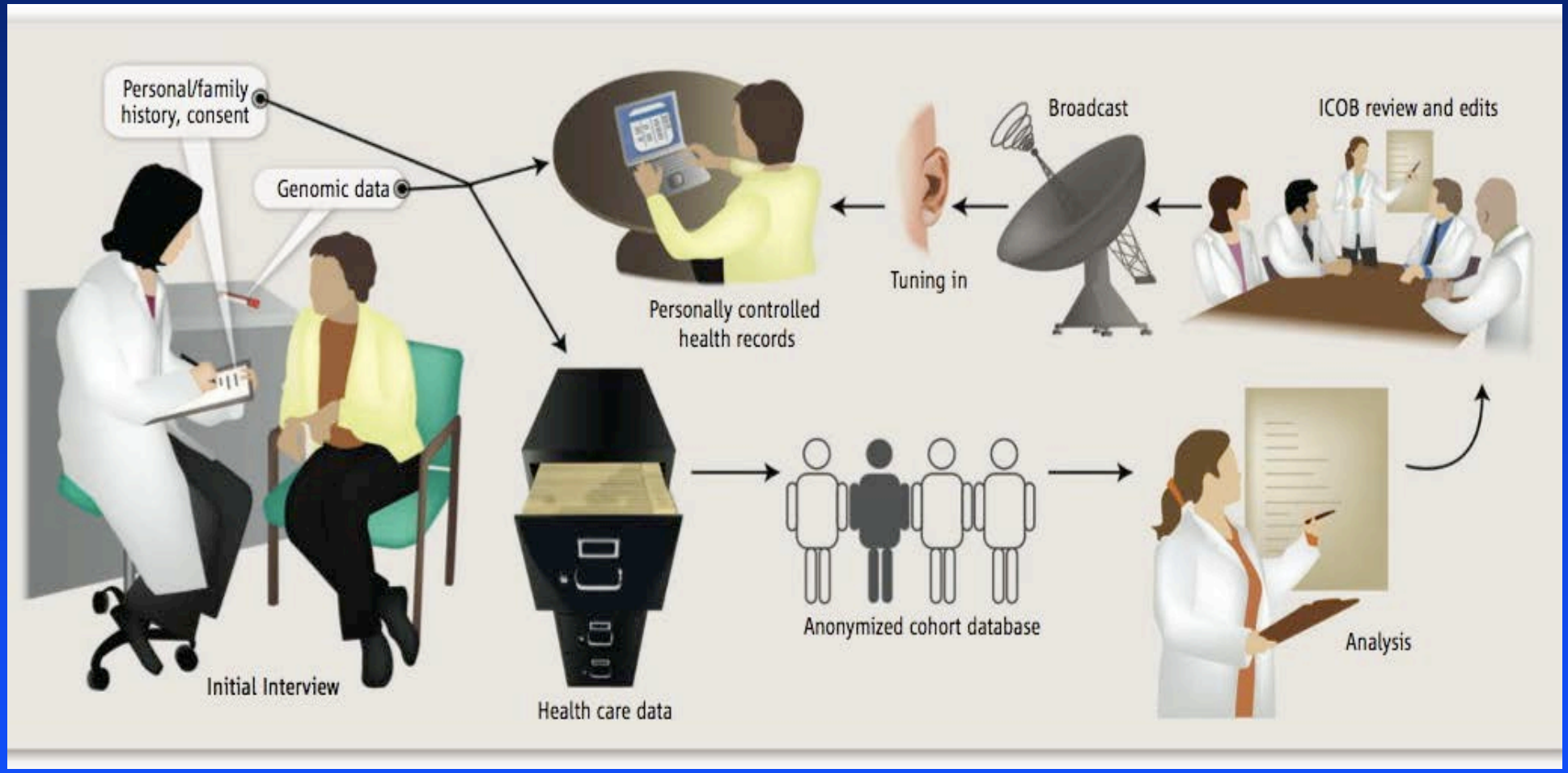

Phone Interview
(n = 344)
Randomization
(n = 291)
(n = 153)
Educational Brochure
Informed Consent
Q&A , Blood Draw
(n = 138)
Educational Brochure
Informed Consent
Q&A , Blood Draw
AD Risk Assessment Disclosure
(n = 138)
AD Risk Assessment + CVD Risk Disclosure (n = 119)
Follow Up at:
Six Weeks
Six Months
Twelve Months

REVEAL Study: Rational Response to Incidental Findings - Exercise Change (6 weeks)



Green et al., *presented at ACMG, 2011*

Return of Incidental Genetic Findings Children's Hospital "Gene Partnership"



Kohane et al, Science, 2007
RC1 HG005491 (Holm), R01 HG006615 (Holm)

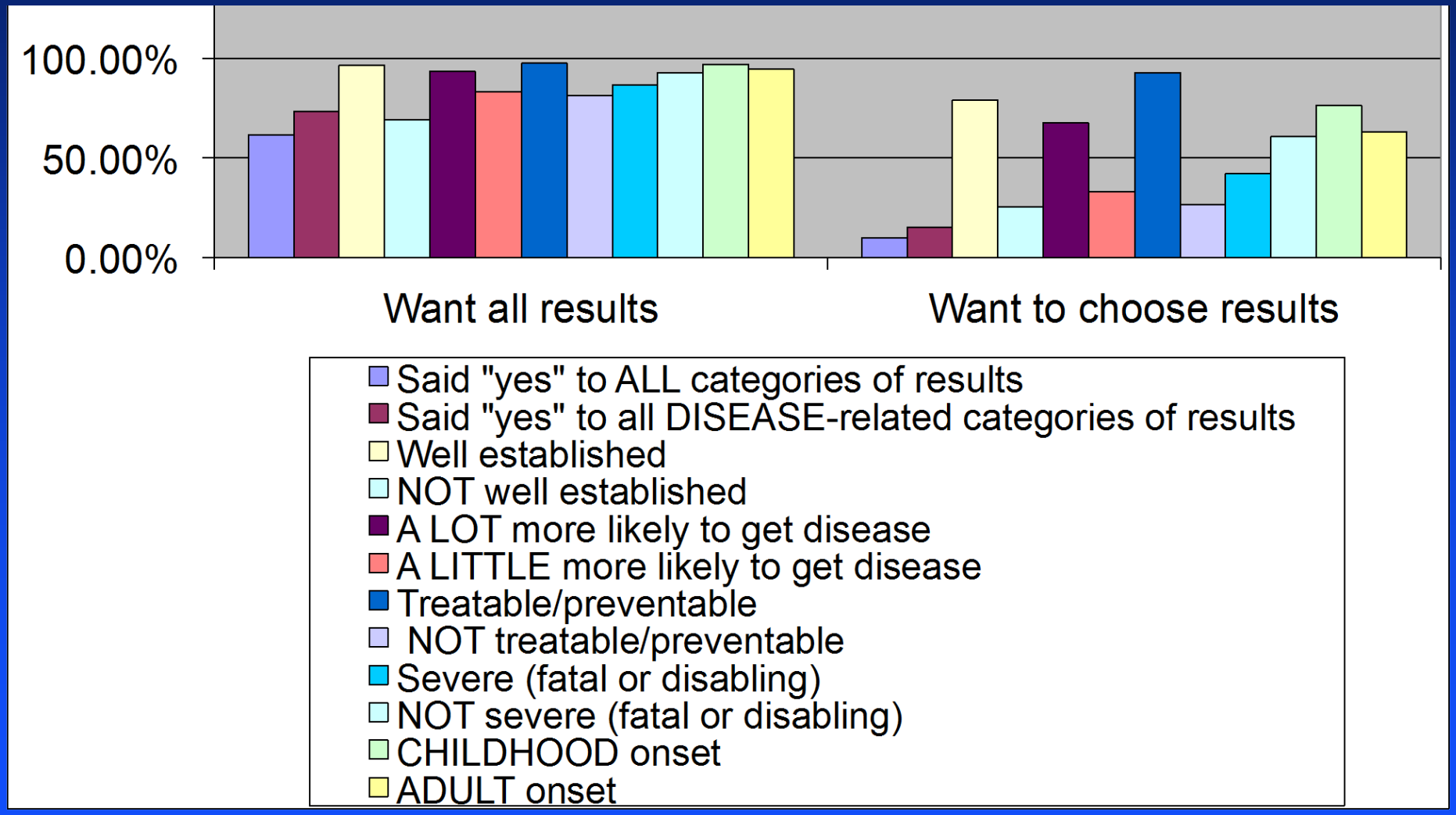
Preference Setting
Survey of 1126 Parents in a DNA Biobank

	Parents' results	Childs' results
Want ALL research results.	78.6%	84.0%
Want to CHOOSE research results to receive	21.4%	16.1%

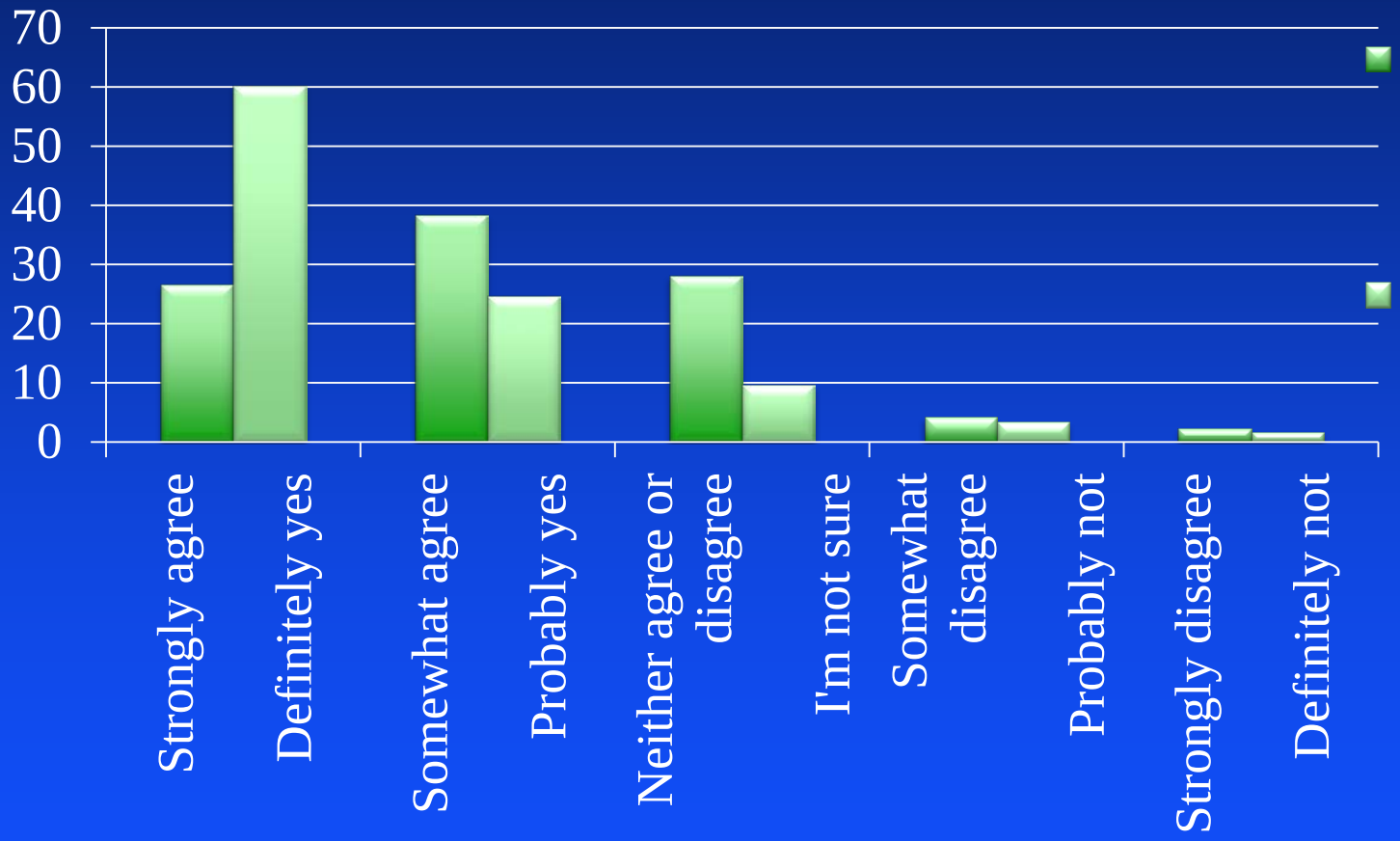
	Parent enrolling self	Parent enrolling child
MORE LIKELY	61.3%	68.8%
NO DIFFERENCE	35.0%	27.6%
LESS LIKELY	3.7%	3.6%

RC1 HG005492 (Holm)

Preference Setting
Survey of 1126 Parents in a DNA Biobank



Survey of 1126 Parents in a DNA Biobank
The "Diagnostic Misconception"



- Participating in a DNA research bank could help me directly.
- Would you want to receive your genetic research results from participating in a DNA research bank?

Green et al, ASHG, 2011
RC1 HG005492 (Holm)

What do Clinicians Want Disclosed?

It varies…..

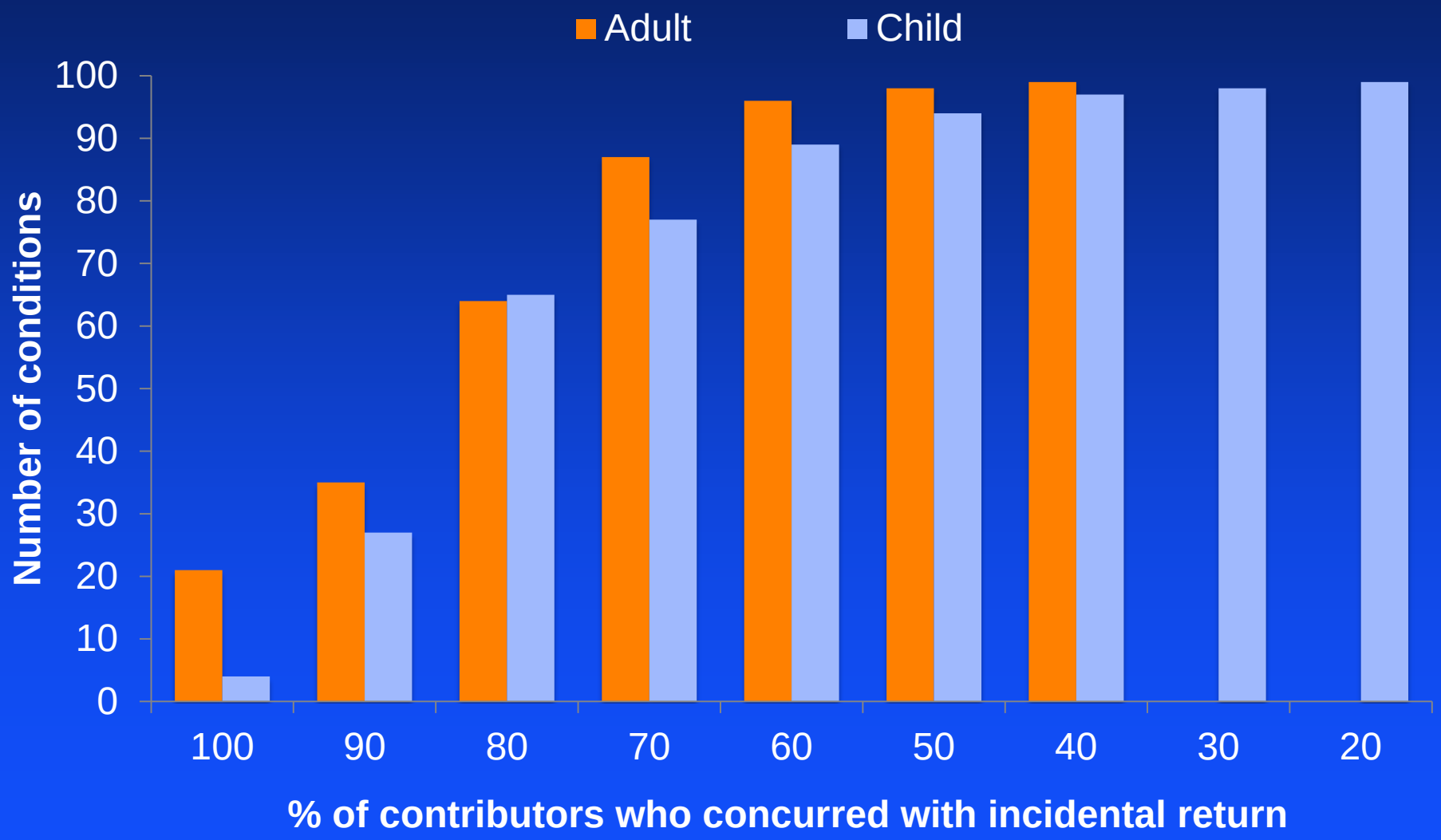
What do Clinicians Want Disclosed?

- Robert C. Green, MD, MPH
- Jonathan S. Berg, MD, PhD
- Leslie Biesecker, MD
- David Dimmock, MD
- James P. Evans, MD, PhD
- Wayne W. Grody, MD, PhD
- Madhuri Hegde, PhD
- Bruce R. Korf, MD, PhD
- Ian Krantz, PhD
- David Miller, MD, PhD
- Mike Murray, MD
- Robert Nussbaum, MD, PhD
- Sharon Plon, MD
- Heidi L. Rehm, PhD, FACMG
- Howard J. Jacob, PhD

...top 88 conditions from GeneTests, based on frequency ordered, adding breast/ovarian cancer, chromosomal abnormalities, CNVs and repeat expansions.... which variants discovered in the course of clinical whole genome sequencing should be returned to the referring physician…

Green et al., *in submission*

Concordance for Incidental Return of a Known Pathogenic Mutation (max = 99 conditions)



Green et al., *in submission*

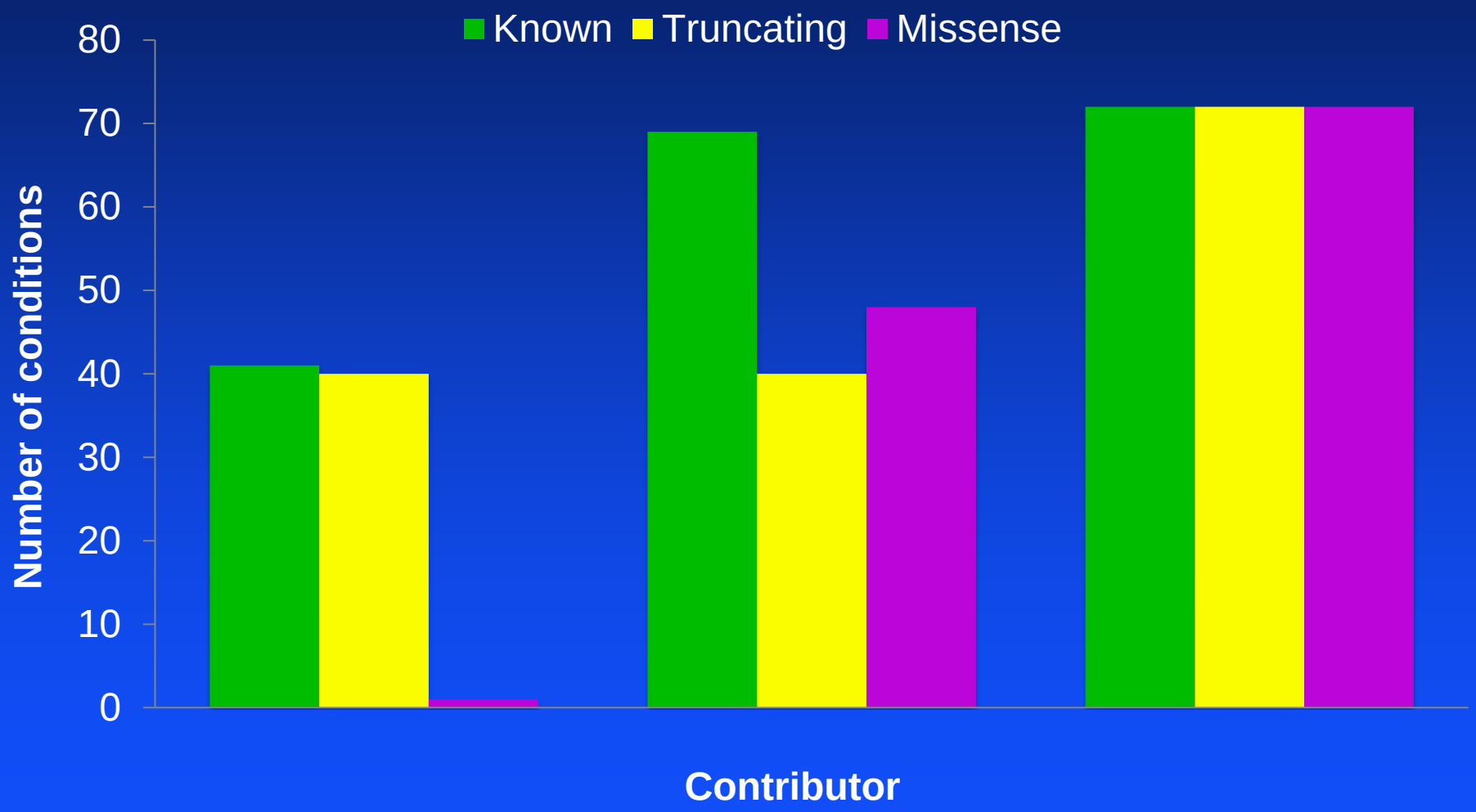
Conditions/genes selected by all contributors for incidental return in adults

- Hereditary Breast and Ovarian Cancer
- Li-Fraumeni Syndrome
- Lynch Syndrome
- APC-Associated Polyposis
- MUTYH Polyposis
- Von Hippel-Lindau*
- MEN 1
- MEN 2
- PTEN Hamartoma Tumor Syndrome*
- Retinoblastoma*
- Gaucher Disease
- Phenylketonuria
- Galactosemia
- Homocystinuria
- Tyrosinemia Type 1
- Pompe Disease
- Wilson Disease
- GSD Type 1a
- Fabry Disease
- Familial Hypercholesterolemia
- Romano-Ward (Long QT)*

* Asterisk indicates condition/gene selected by all contributors for incidental return in **children**

Green et al., *in submission*

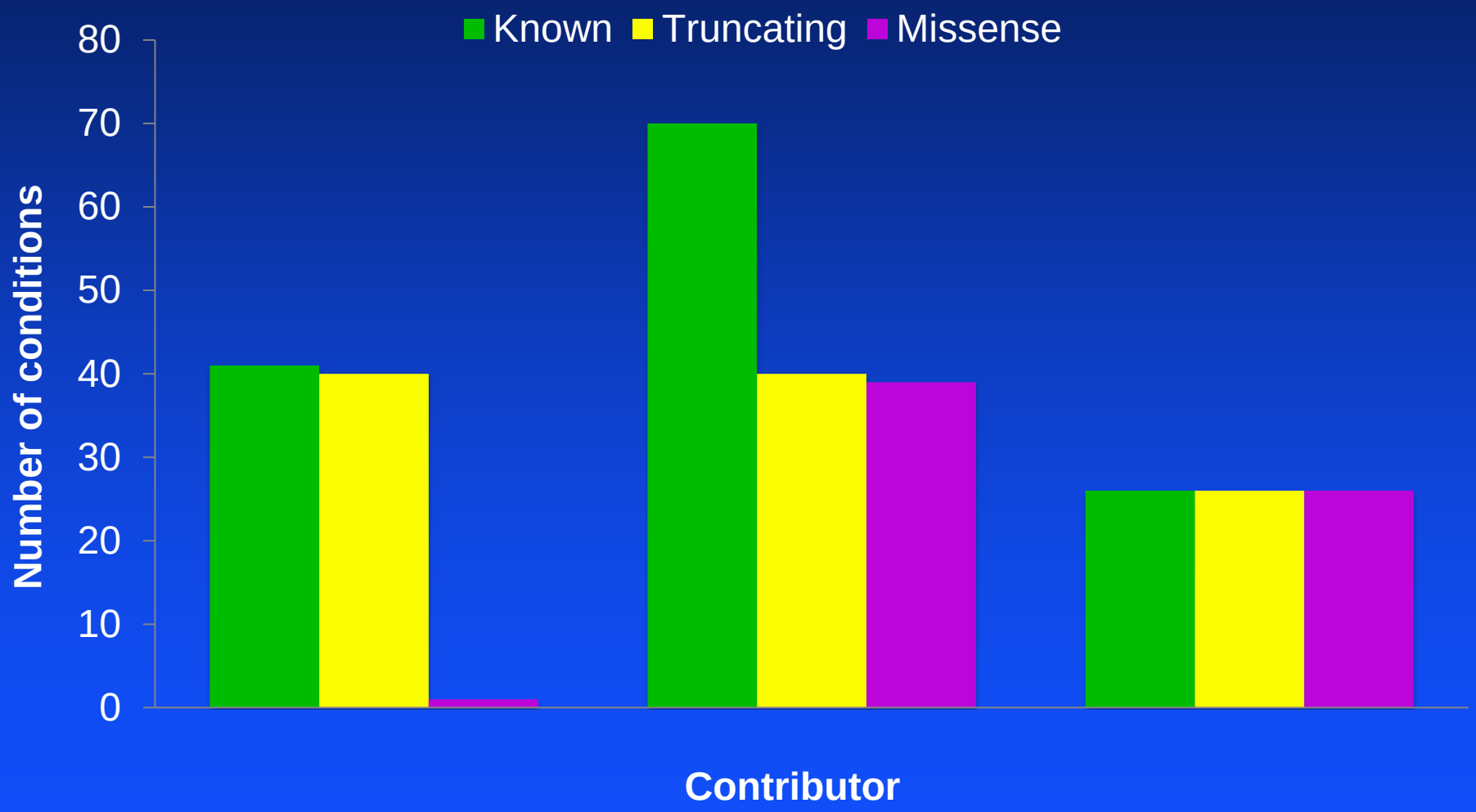
Concordance Patterns for Incidental Return – Adult Patient



* out of a total of 72 conditions/genes (excluding repeat expansion, chromosomal, and deletion conditions)

Green et al., *in submission*

Concordance Patterns for Incidental Return – Patient < 18



* out of a total of 72 conditions/genes (excluding repeat expansion, chromosomal, and deletion conditions)

Green et al., *in submission*