

Empirical Trials and Incidental Findings on the Path to Genomic Medicine

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Disclosures

Research Grants:	NHGRI, NIA
Research Collaborations:	Pathway, 23andMe
Speaking (compensated):	None
Advisory (compensated):	Lilly
Equity:	None

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R01 HG002213 (Green)

R01 AG021136 (Tschanz)

R01 HG005092 (Green)

P50 HG003170 (Church)

K24 AG027841 (Green)

R01 AG031171 (Qiu)

R01 HG006615 (Holm)

R21 HG00603 (Wang)

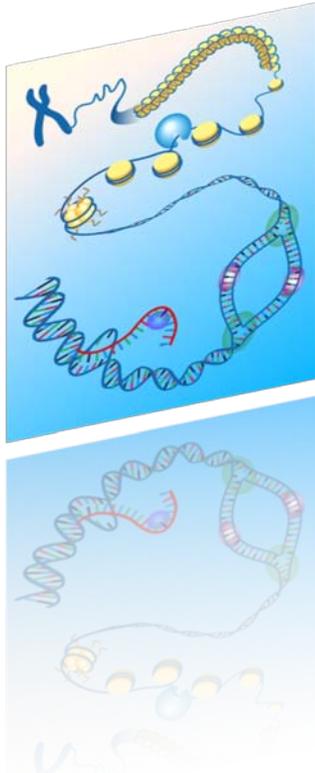
R01 CA154517 (Petersen/Koenig/Wolf)

The Path to Genomic Medicine

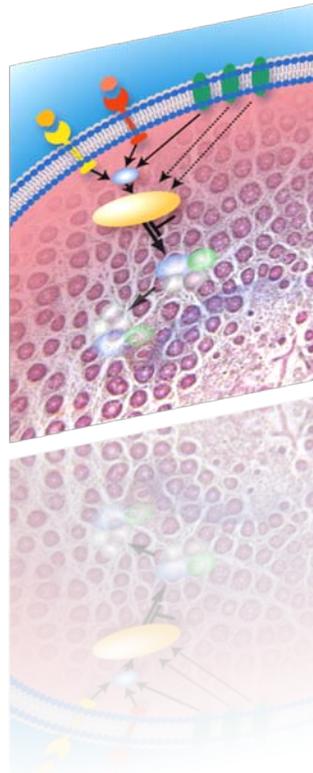
Understanding
the Structure of
Genomes



Understanding
the Biology of
Genomes



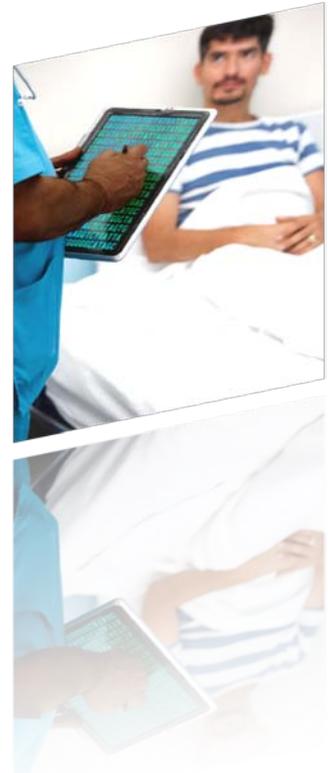
Understanding
the Biology of
Disease



Advancing
the Science of
Medicine

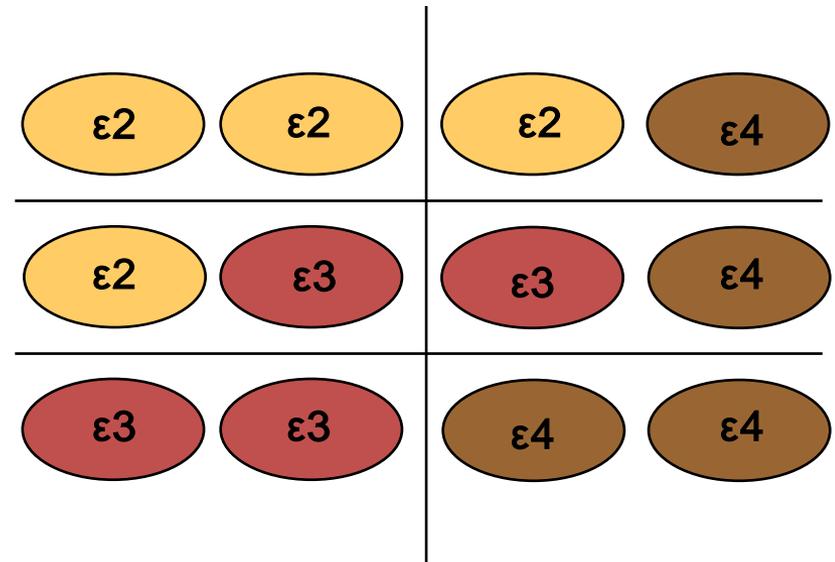
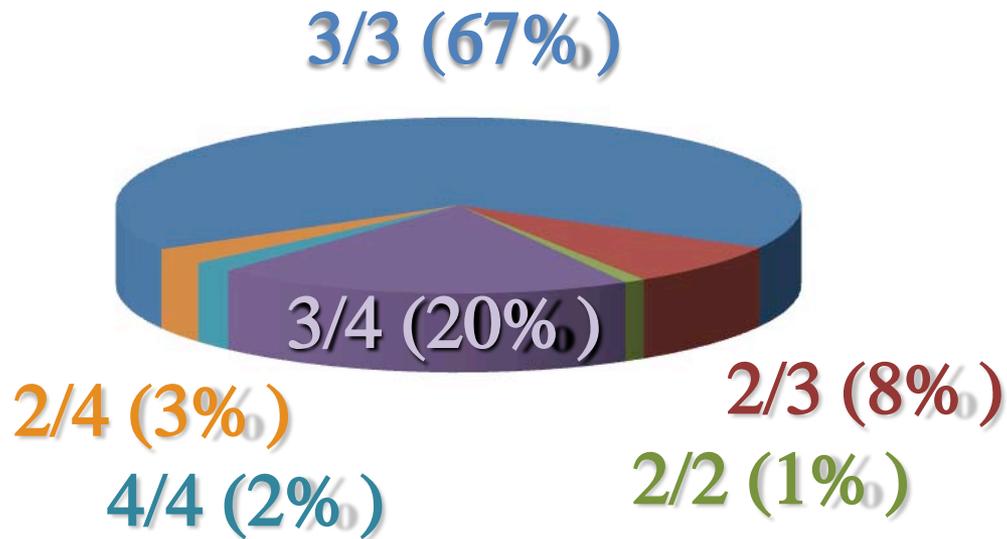


Improving the
Effectiveness
of Healthcare



G2P
GENOMES to People

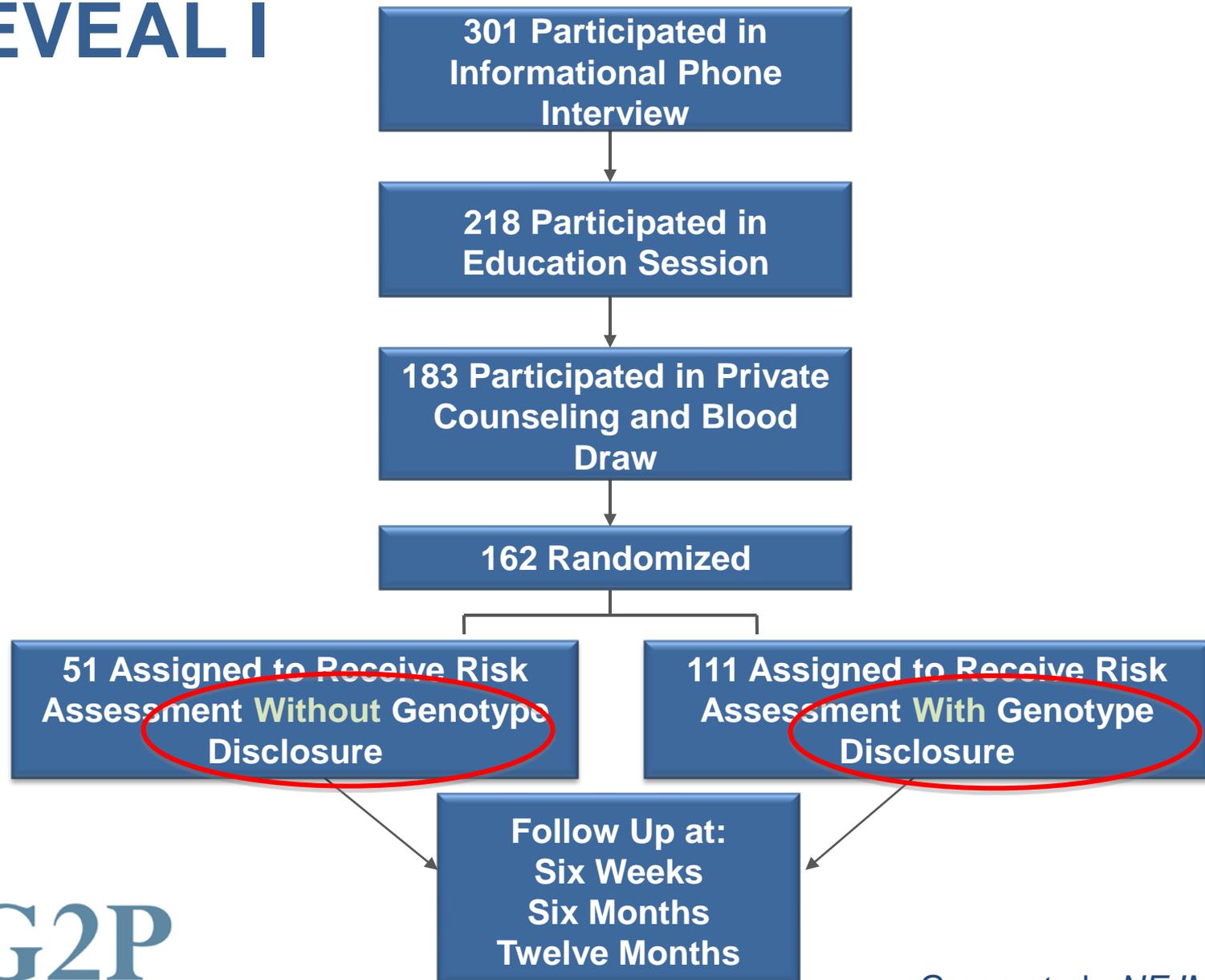
APOE Genotypes in the General Population



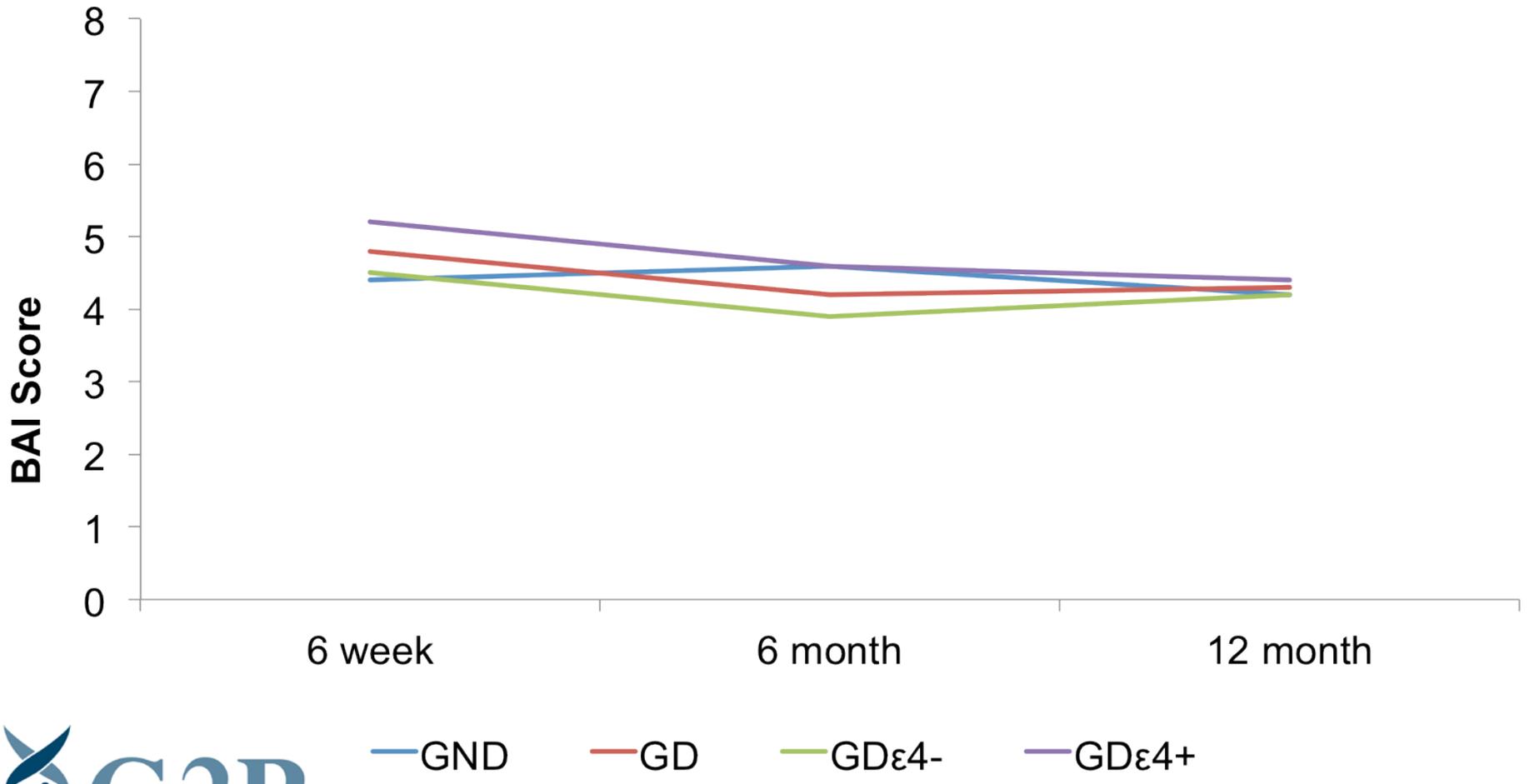
The REVEAL Study NHGRI-funded (2000-2013)



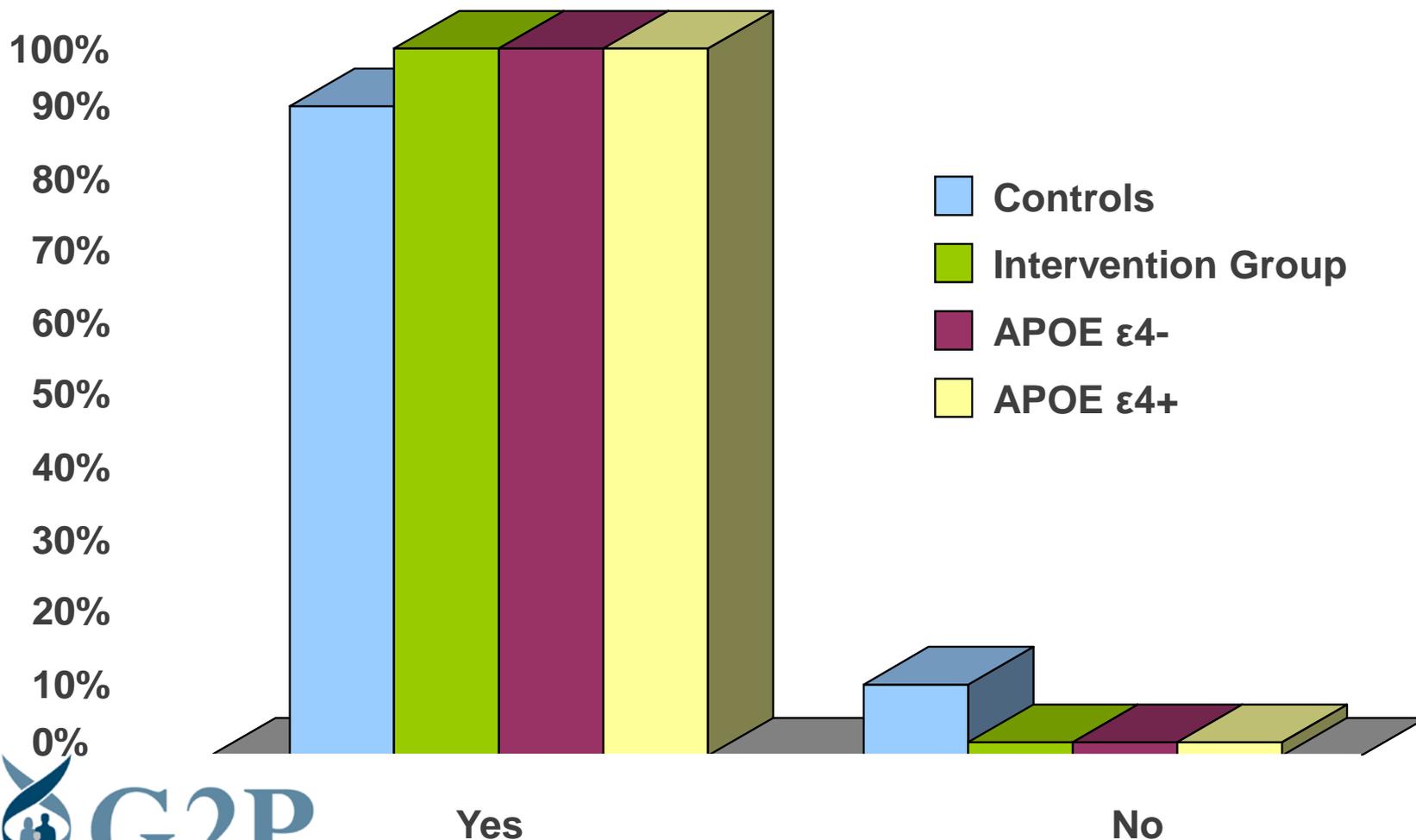
REVEAL I



Mean Anxiety Scale Scores After Disclosure

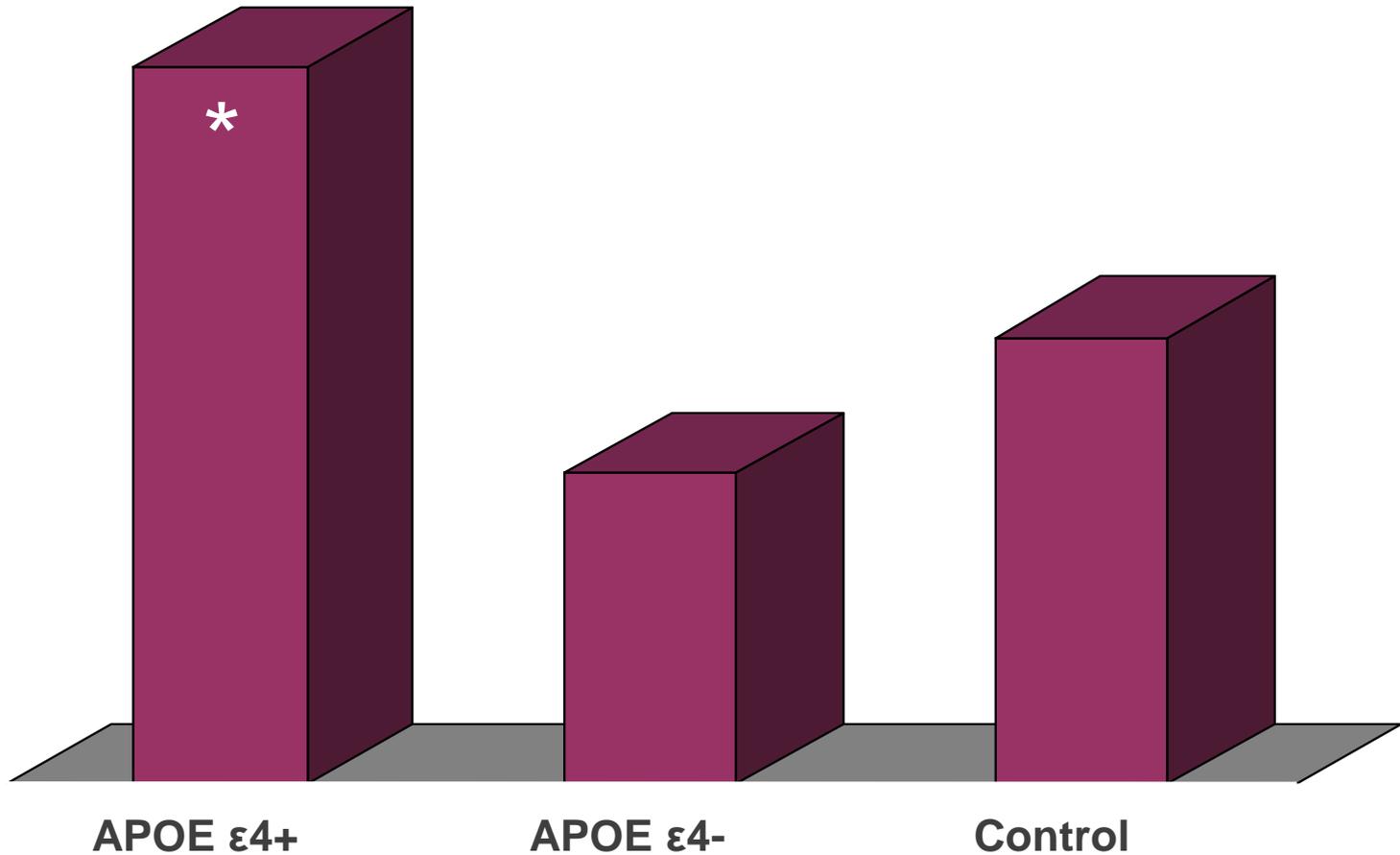


Would Do Risk Assessment Again...

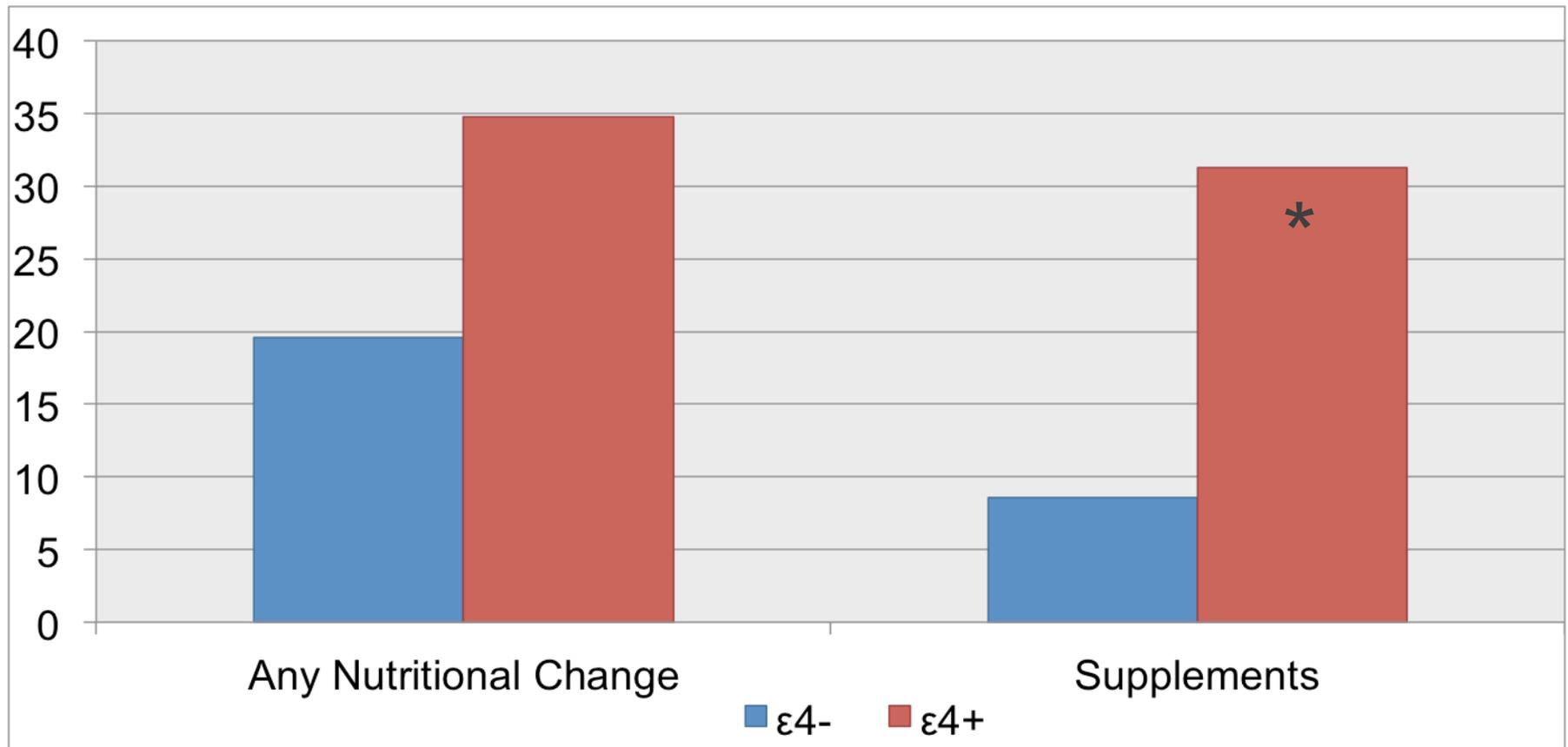


Willingness to Pay for AD Genetic Testing (reported after having obtained it)

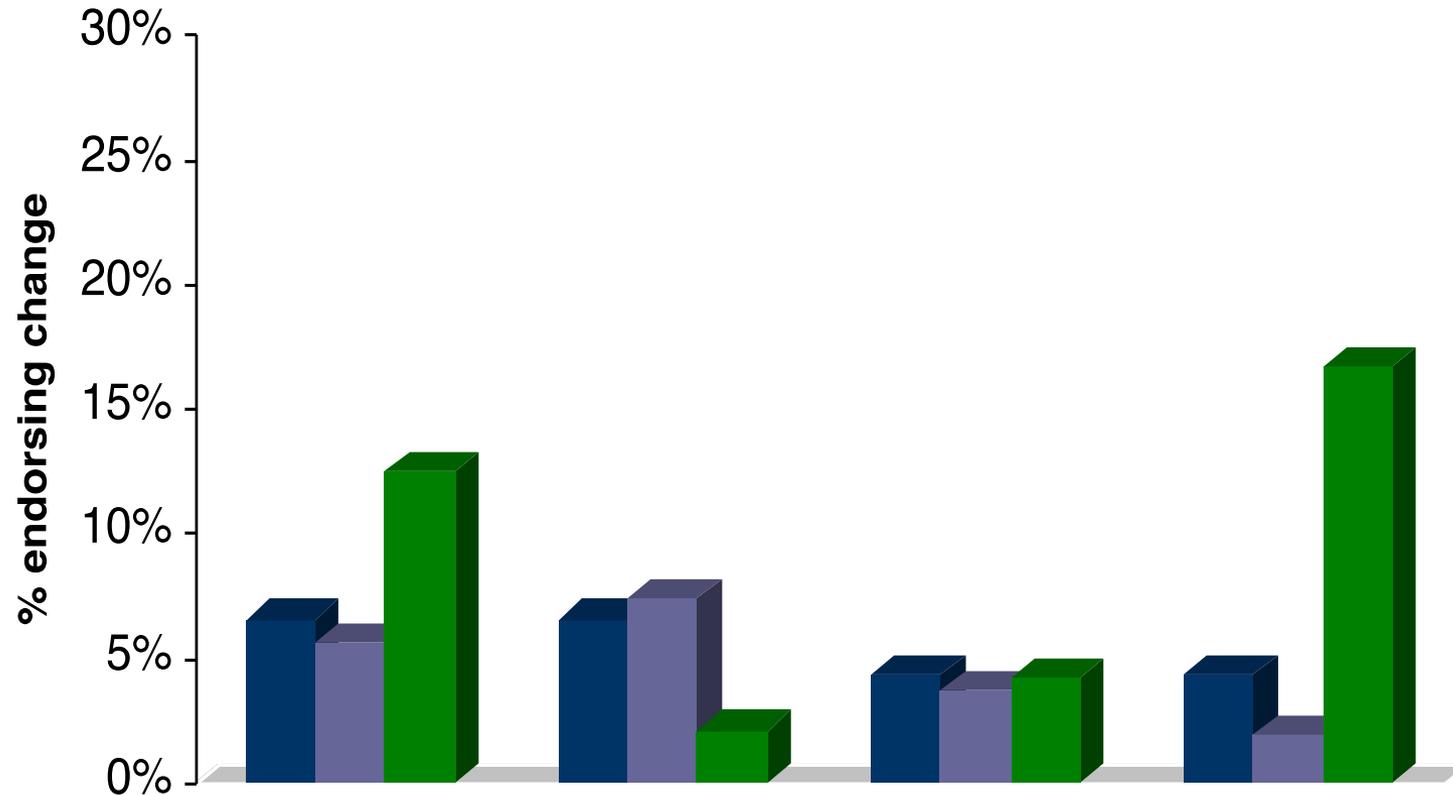
Health Behavior Changes at 1 Year (Vitamins, Exercise, Medications)

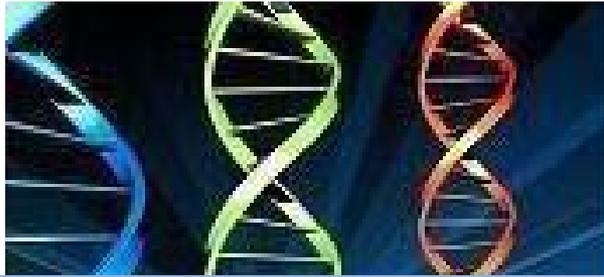


Health Behavior Changes at 6 Weeks (Nutrition and Supplements)

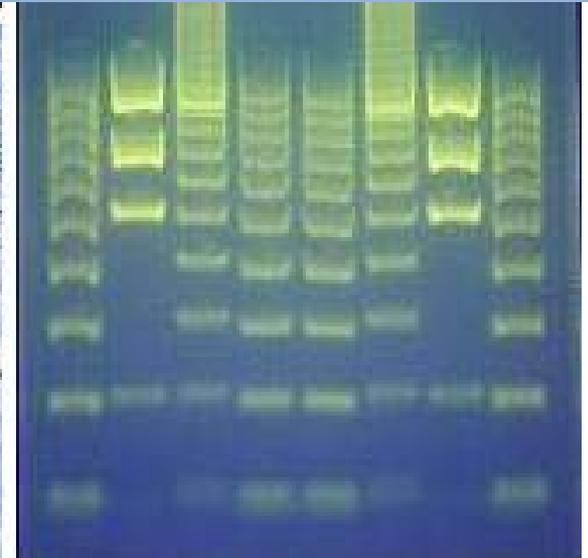


Insurance Changes 1 Year After APOE Disclosure

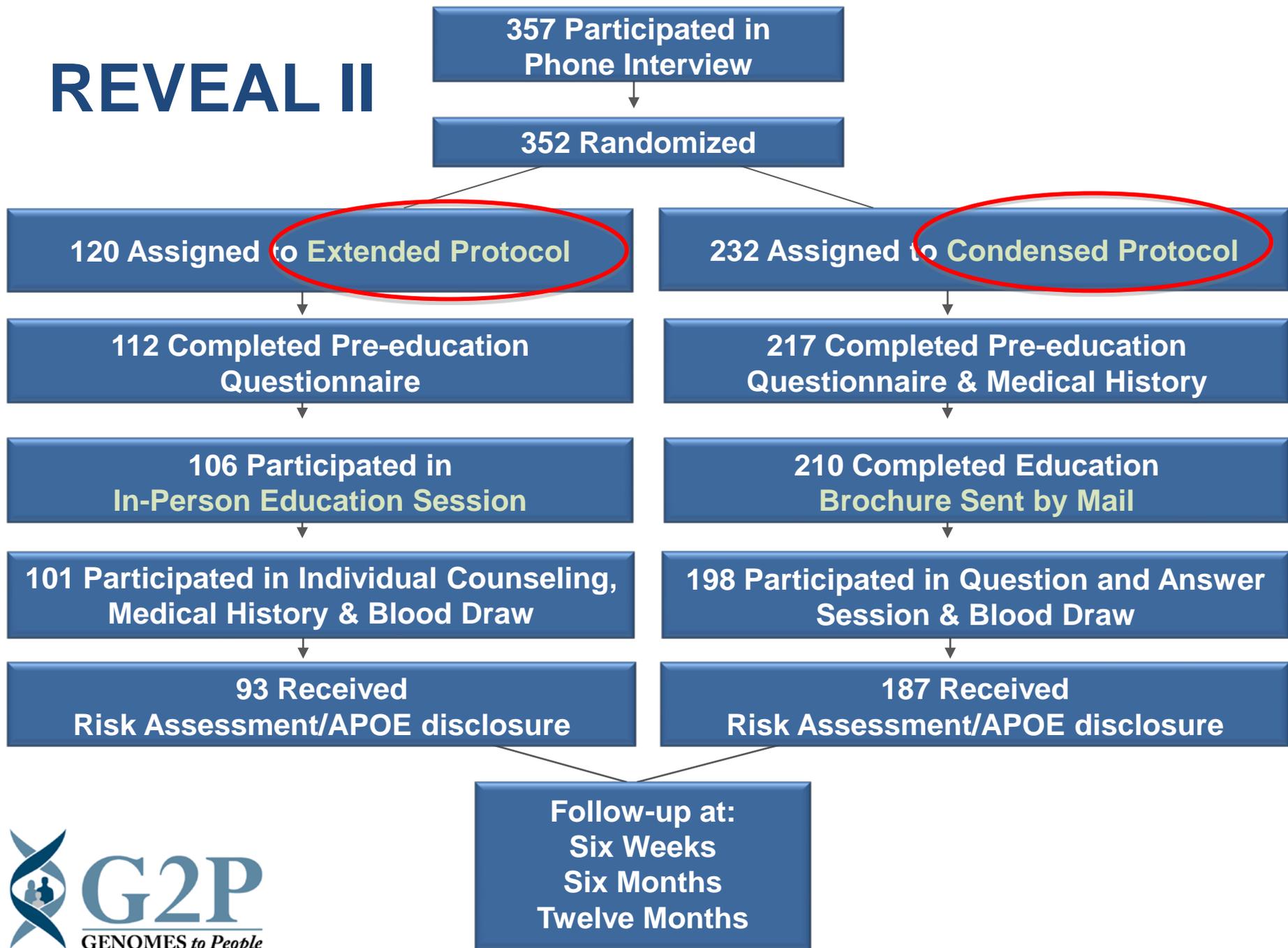




Dosing the Disclosure: Education and Counseling

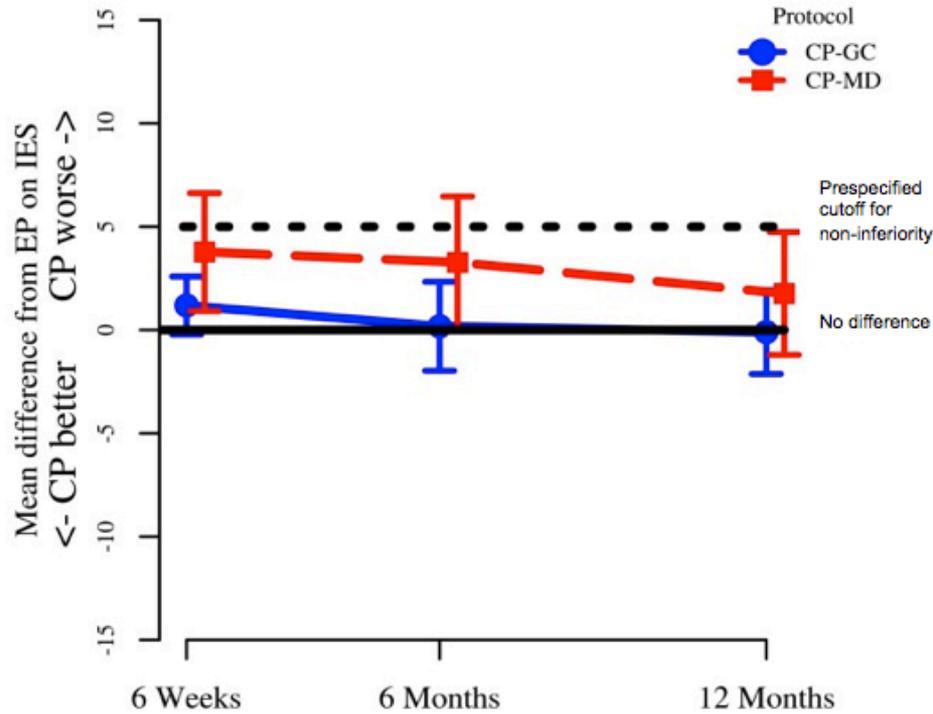


REVEAL II

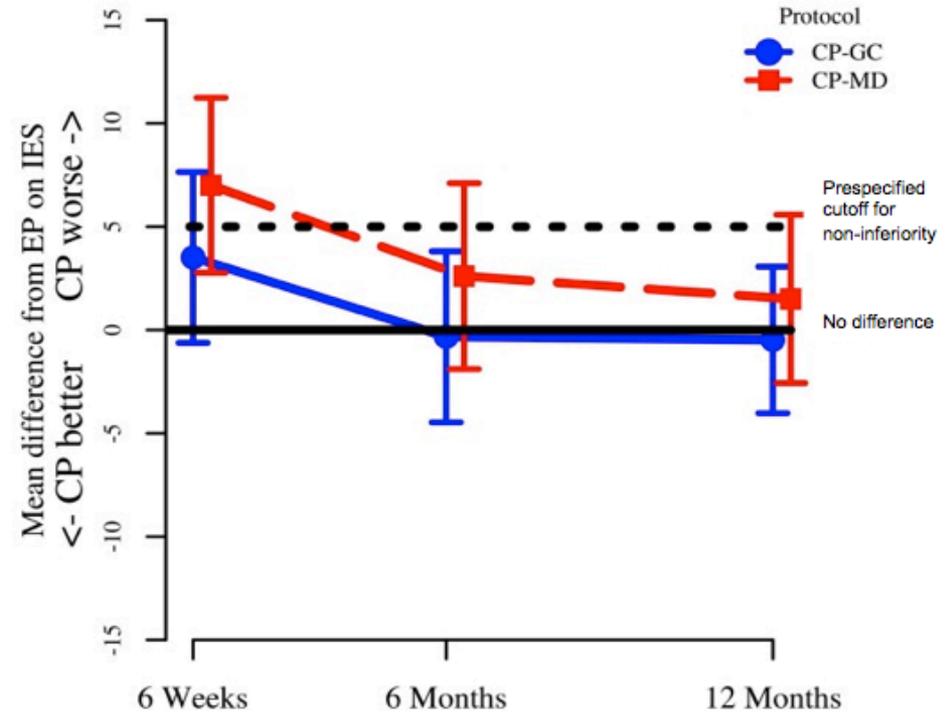


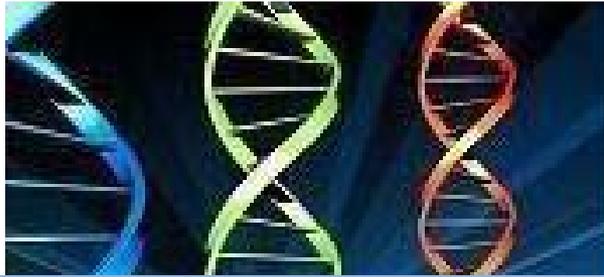
Condensed vs Extended Disclosure

Test-Related Distress among $\epsilon 4-$

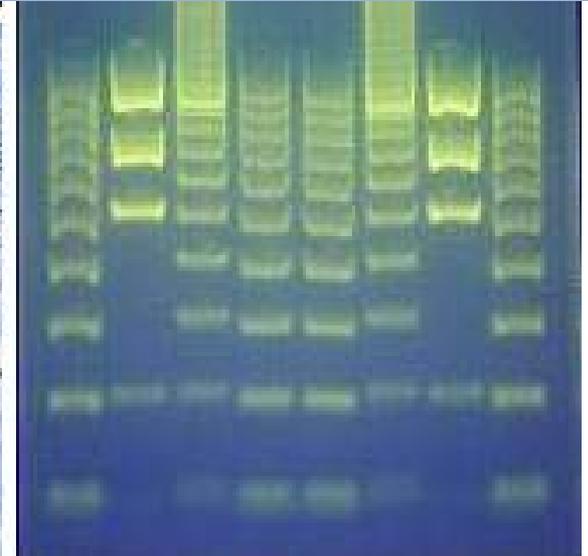
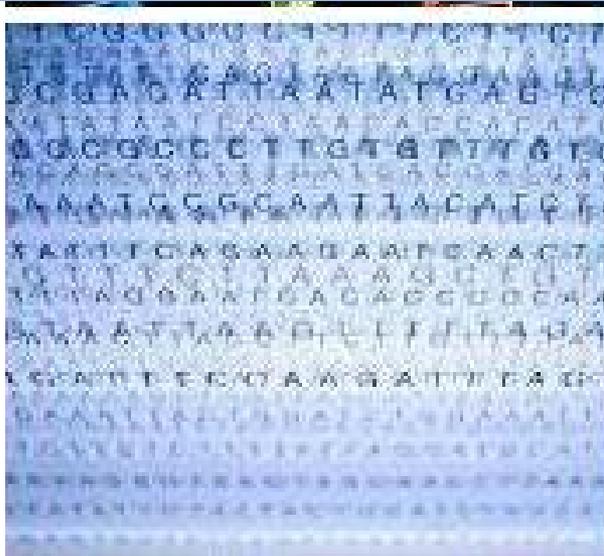


Test-Related Distress among $\epsilon 4+$

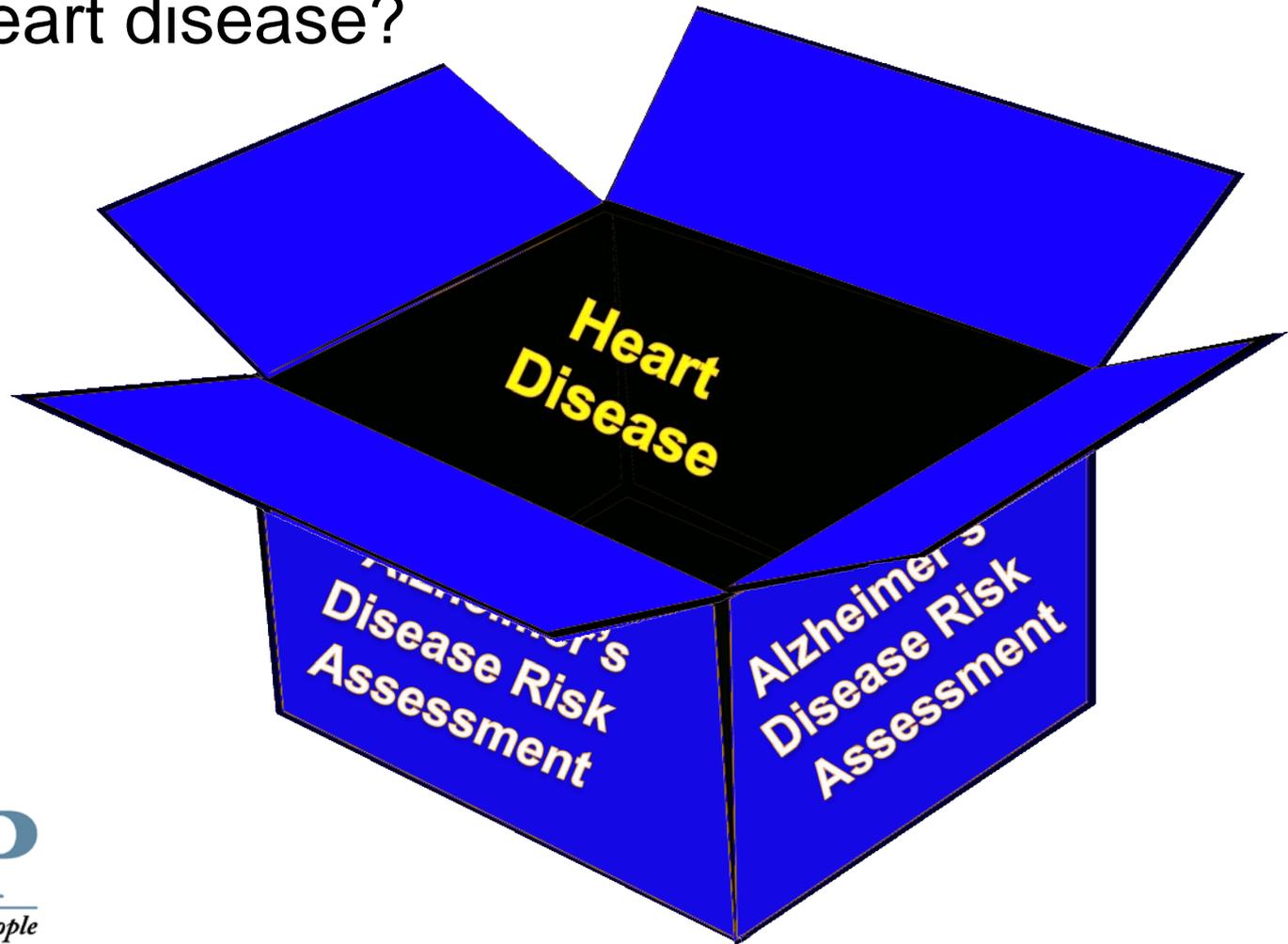




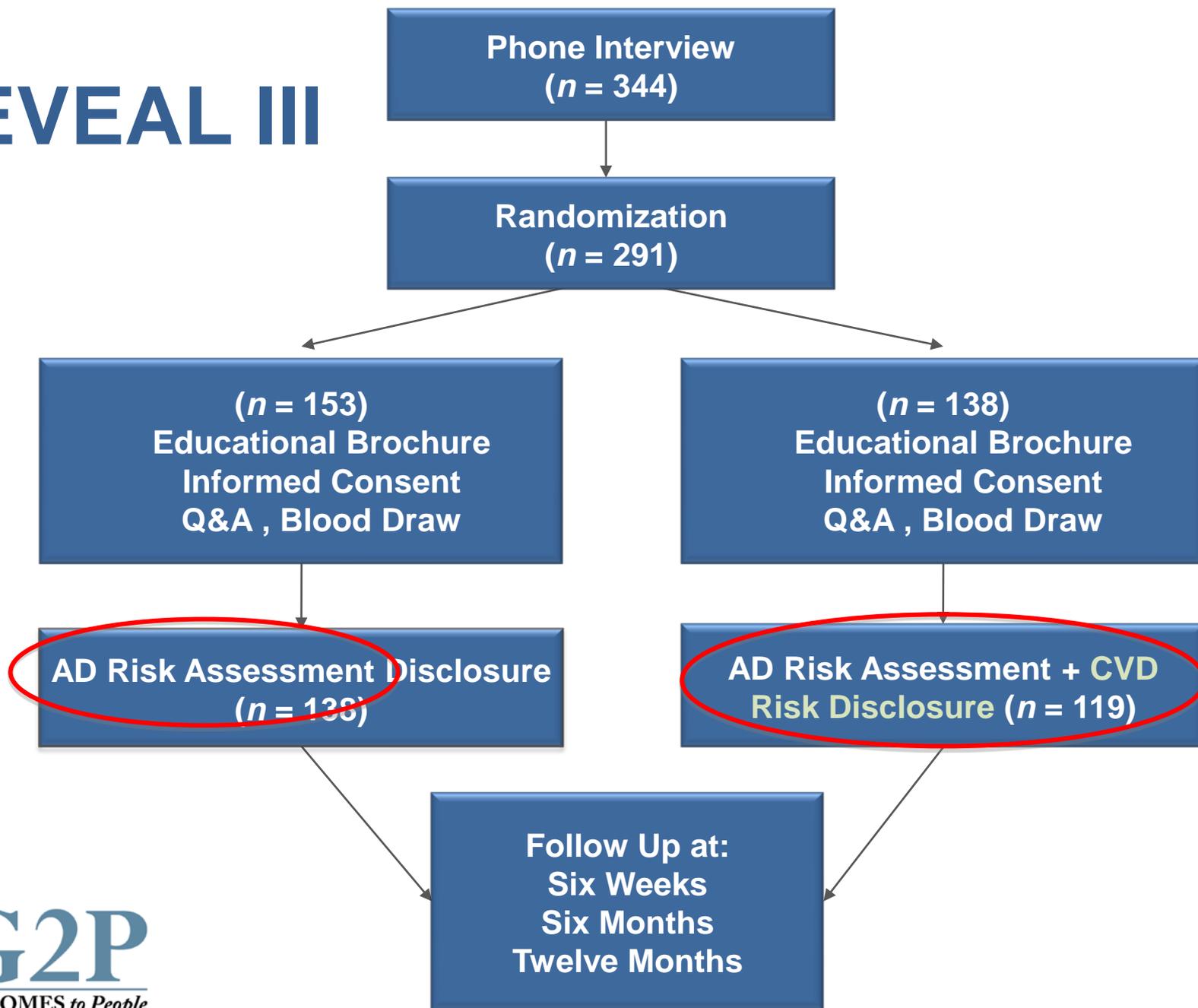
Diluting the Disclosure: Adding an Incidental Result



During a genetic risk assessment for Alzheimer's disease...what happens when one learns that *APOE* is also associated with heart disease?



REVEAL III

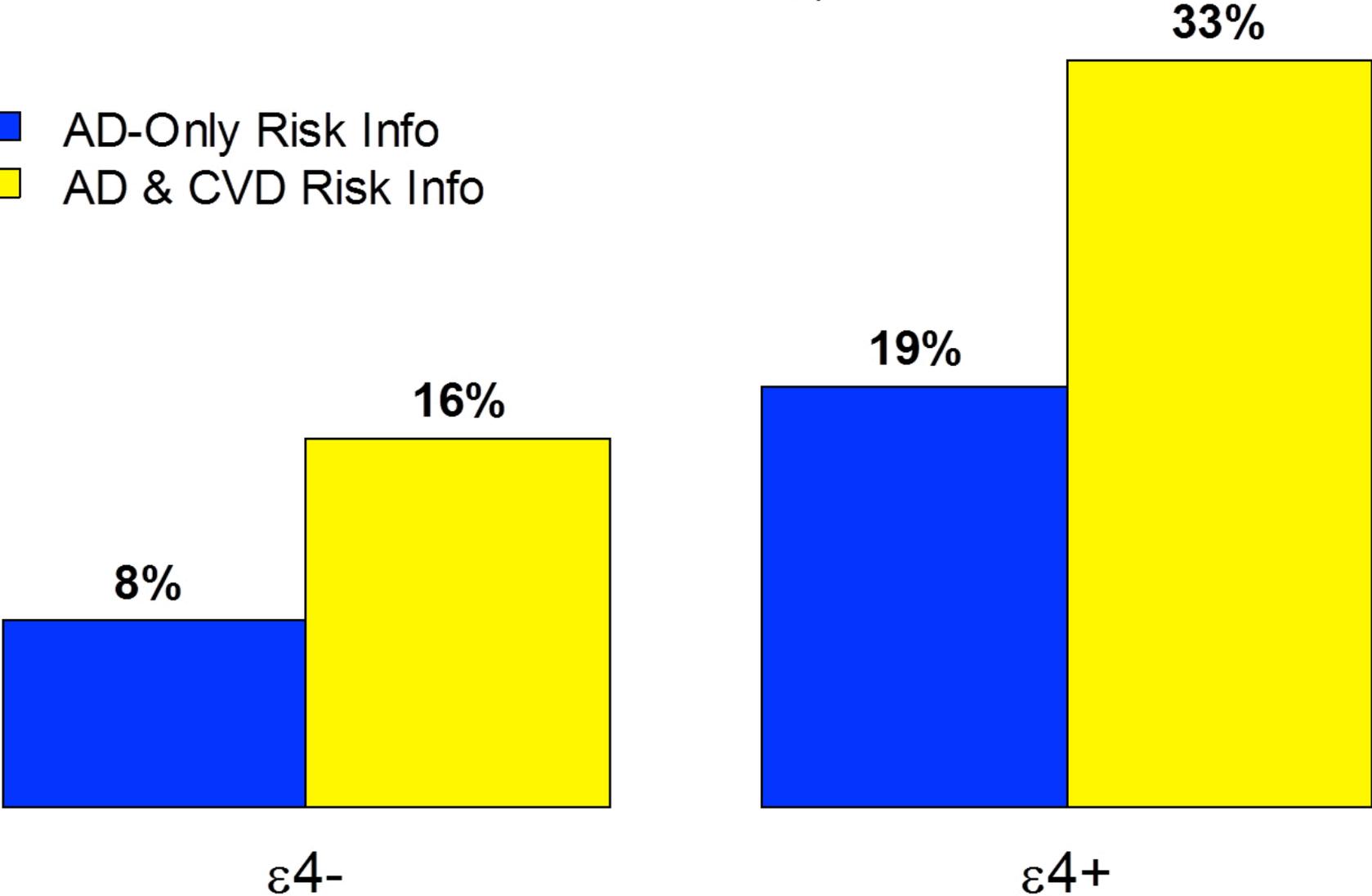


Exercise

$\epsilon 4$ status: OR=2.5, p=0.010

AD+CVD Info: OR=2.2, p=0.039

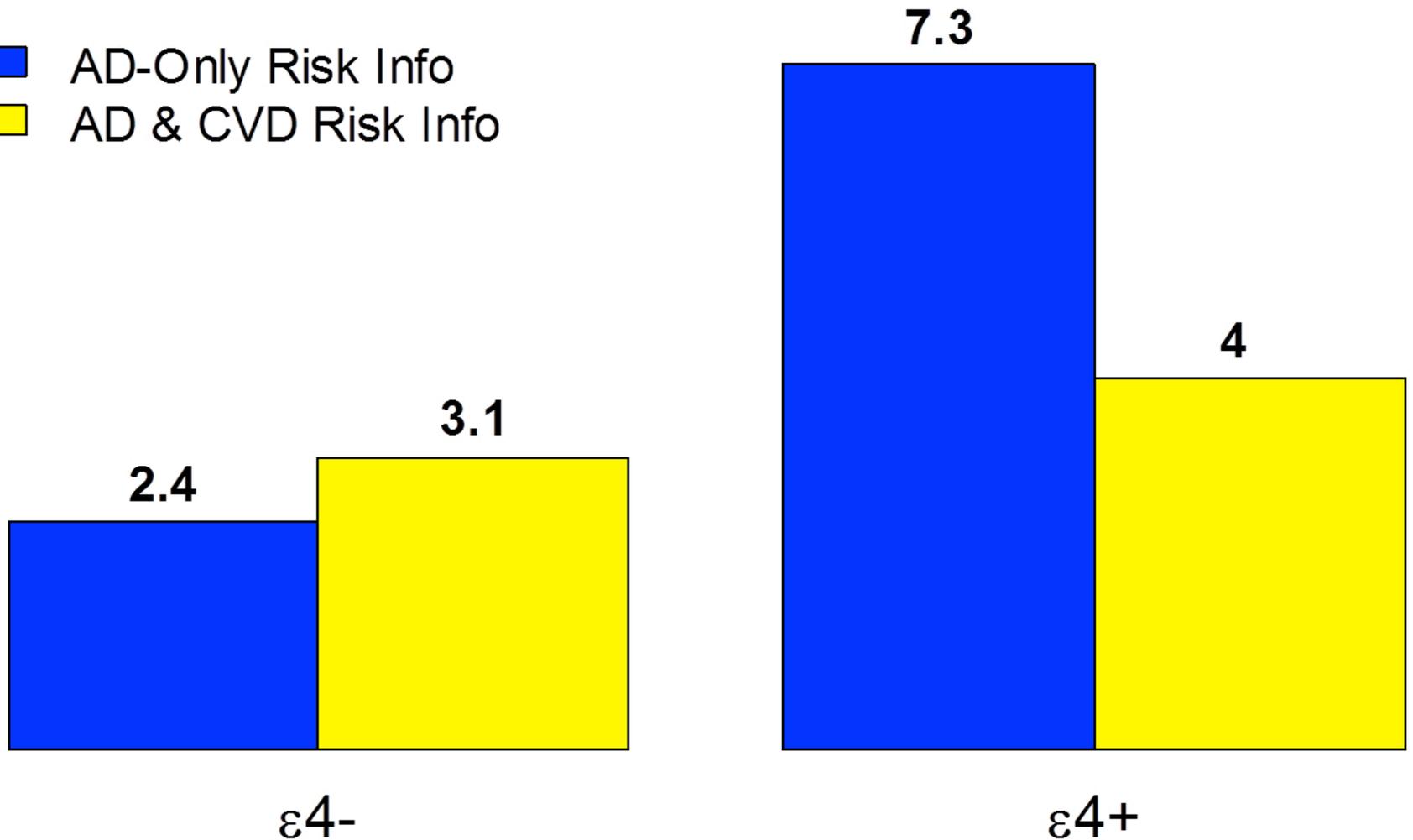
- AD-Only Risk Info
- AD & CVD Risk Info



Test-Related Distress

Interaction: $\beta=-4.1$, $p=0.03$

- AD-Only Risk Info
- AD & CVD Risk Info

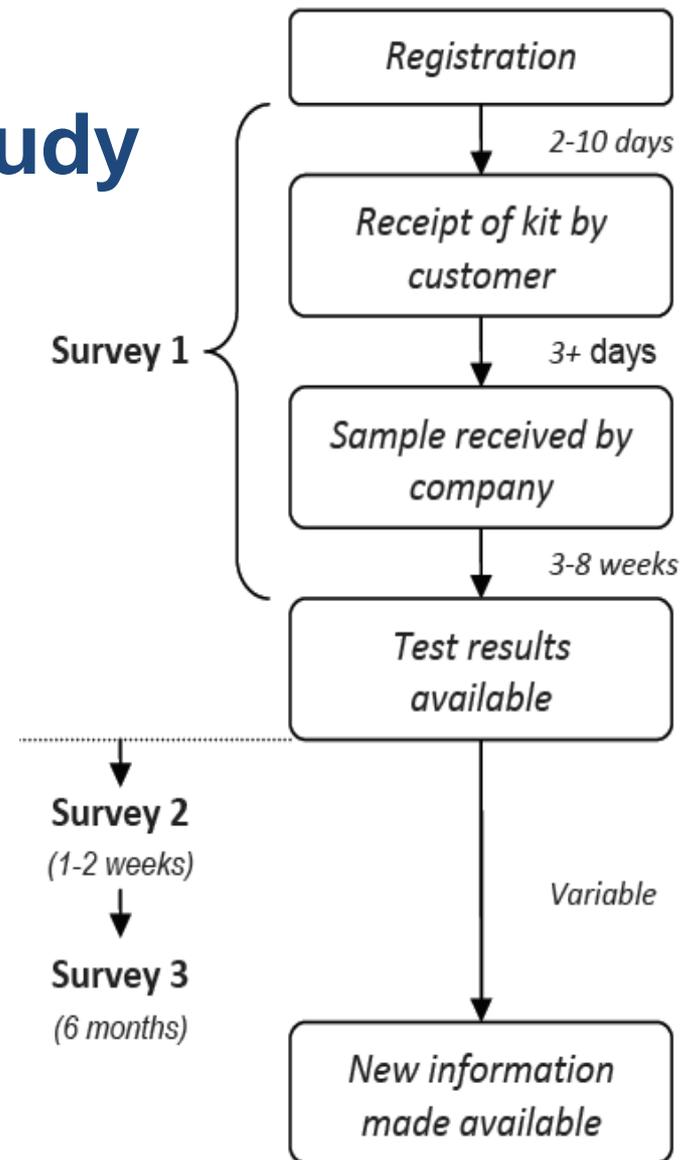


Impact of Personal Genomics Testing Study (PGen Study)

(Green-Roberts, PIs)



NHGRI R01 HG005092

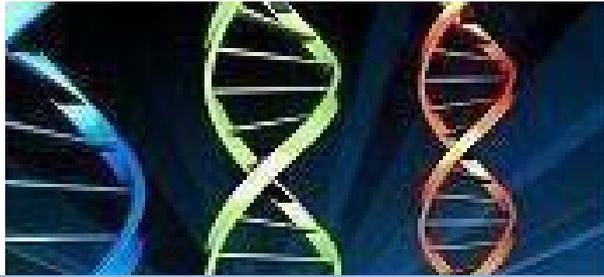


Healthcare Utilization After DTC Testing

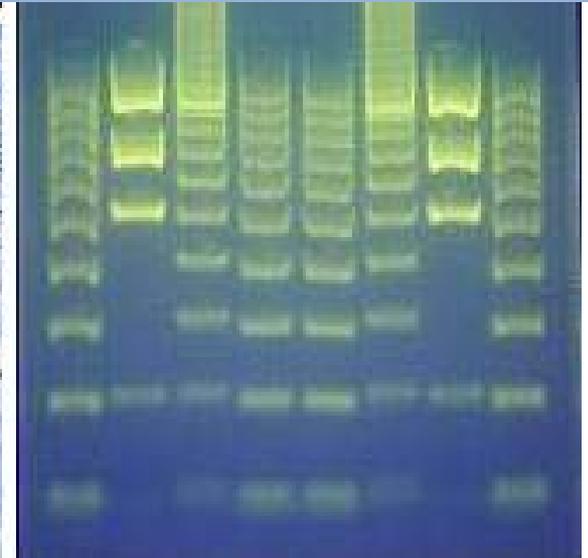
Self-report at 6 months	Number (%) of N = 986
Discussed results w/ PCP	256 (27.7%)
Discussed results w/genetics specialist	25 (2.7%)
Results prompted me to make appt w/ medical professional	Already made appt: 105 (10.8%) Plan to make appt: 100 (10.3%)
Had tests, exams, or procedures due to genetic info	104 (10.7%)
Genetic info will influence how I manage my health in future	Somewhat or Strongly Agree: 567 (59.2%)

Predictors of having Tests, Exams, or Procedures due to DTC Results

Predictor	Odds ratio (p-value) *
Speaking w/doctor about tests, exams, or procedures due to genetic results	41.1 (p<.001)
Perception of 'many' or 'all' results showing above average risk	9.0 (p=.032)
Better self-reported general health	2.4 (p<.001)
Higher baseline anxiety	2.4 (p=.002)
Pre-test intention to discuss results w/PCP	1.8 (p=.008)
Pre-test intention to discuss results w/other medical professional	1.8 (p=.010)



Using Whole Genome Sequencing In the Practice of Medicine



The MedSeq Project (U01 HG006500)

A Center for Sequencing Exploratory Research

Teams from:

Brigham and Women's Hospital/Harvard Medical School

Baylor College of Medicine

Duke University School of Medicine

Exploring the integration of whole genome sequencing into the practice of clinical medicine.



Exploring WGS in 2 Contexts

Patients with Disease

10 cardiologists &
100 of their patients with
familial hypertrophic
cardiomyopathy

Healthy Patients

10 primary care physicians &
100 of their generally healthy
adult patients

General Genomic Medicine

Recruit and enroll 10 primary care physicians and 100 of their healthy middle-aged patients

Randomize physicians and patients

Disease-Specific Genomic Medicine

Recruit and enroll 10 cardiologists and 100 of their patients presenting with familial hypertrophic cardiomyopathy (HCM)

Randomize physicians and patients

Collect data on physician and patient preferences, motivations, risk perceptions, intentions

Standard of Care & Family History

Patients treated according to current standard of care guidelines and risk assessment based on family history

Standard of Care, Family History & WGS

Physician receives clinically meaningful information derived from WGS, with a specific cardiovascular focus

Standard of Care, HCM Genetic Testing & Family History

Patients treated according to current standard of care guidelines, genetic information by disease-specific testing and family history

Standard of Care, HCM Genetic Testing, Family History & WGS

Physician receives disease-specific interrogation of HCM-associated variants and non-HCM clinically meaningful risk variant interpretation derived from WGS

Genetics Resource Center

Optional source for physician to seek guidance in interpretation.

Collect data on physician experience and clinical flow: Disclosure preferences, use of GRC, decision-making

Physician disclosure to patients

Decides on further work-up or treatment plan

Collect physician, patient, health and economic outcome variables

Baseline (prior to disclosure), 6 weeks, and 6 months post-disclosure

Medical Record Review

MedSeq General Genome Report

LABORATORY FOR MOLECULAR MEDICINE
65 LANDSDOWNE ST, CAMBRIDGE, MA02139
PHONE: (617) 768-8500 / FAX: (617) 768-8513
<http://pcpgm.partners.org/lmm>



CENTER FOR PERSONALIZED
GENETIC MEDICINE

A teaching affiliate of:



SAMPLE – DO NOT USE FOR CLINICAL CARE

Name: John Doe

DOB: 01/23/45

Sex: Male

Race: Caucasian

Accession ID: 0123456789

Specimen: Blood, Peripheral

Received: 01/23/45

Family #: F12345

Referring physician: John Smith, M.D.

Referring facility: DoubleHelixHospital

GENERAL GENOME REPORT

RESULT SUMMARY

Sequencing of this individual's genome was performed and covered 98.2% of all positions at 8X or higher, resulting in over 3.6 million variants compared to a reference genome. These data were analyzed to identify previously reported variants of potential clinical relevance as well as novel variants that could reasonably be assumed to cause disease (see methodology below). All results are summarized on page 1 with further details provided on subsequent pages.

A. MONOGENIC DISEASE RISK: 2 VARIANTS IDENTIFIED

This test identified 2 genetic variant(s) that may be responsible for existing disease or the development of disease in this individual's lifetime.

Disease (Inheritance)	Phenotype	Gene Variant	Classification
A1. Episodic ataxia type II (Autosomal Dominant)	Poor coordination and balance	CACNA1A p.Arg2156GlyfsX32	Pathogenic
A2. Hypertrophic cardiomyopathy (Autosomal Dominant)	Progressive heart failure	MYBPC3 p.Thr146AsnfsX7	Pathogenic



MedSeq General Genome Report

B. CARRIER RISK: 3 VARIANTS IDENTIFIED

This test identified carrier status for 3 autosomal recessive disorder(s).

Disease	Phenotype	Gene Variant	Classification	Carrier Phenotype*
B1. Cystic fibrosis	Chronic lung and digestive disease	CFTR c.1585-1G>A	Pathogenic	Infertility (moderate evidence)
B2. Myotoniacongenita	Muscle disease	CLCN1 p.Arg894X	Pathogenic	Latent myotonia (case report only)
B3. Usher syndrome type II	Hearing loss and retinitis pigmentosa	USH2A p.Gly204ArgfsX12	Pathogenic	None reported

As a carrier for recessive genetic variants, this individual is at higher risk for having a child with **one or more of these highly penetrant disorders**. To determine the risk for this individual's children to be affected, the partner of this individual would also need to be tested for these variants. Other biologically related family members may also be carriers of these variants. ***Carriers for some recessive disorders may be at risk for certain mild phenotypes. Please see variant descriptions for more information.**

C. PHARMACOGENOMIC ASSOCIATIONS

This test identified the following variant(s) associated with drug use and dosing. Additional pharmacogenomic results may be requested, but will require confirmation of the result.

Drug	Risk and Dosing Information
C1. Warfarin	Increased dose requirement
C2. Clopidogrel	Increased risk of bleeding, Decreased risk of cardiovascular events
C3. Digoxin	Chance of increased metabolism and decreased serum concentration of digoxin
C4. Hydrochlorothiazide	Increased effect on blood pressure
C5. Metformin	Increased effect on glucose tolerance

A young girl with red hair, wearing a light blue dress, is crying and shouting while being sprayed with water from a sprinkler. She is in the foreground, looking towards the left. In the background, another child is visible near a house, also being sprayed with water. The scene is outdoors on a lawn.

The Problem of Incidental Findings

What are Expert Choices for Return of Secondary (Incidental) Findings in Clinical Sequencing

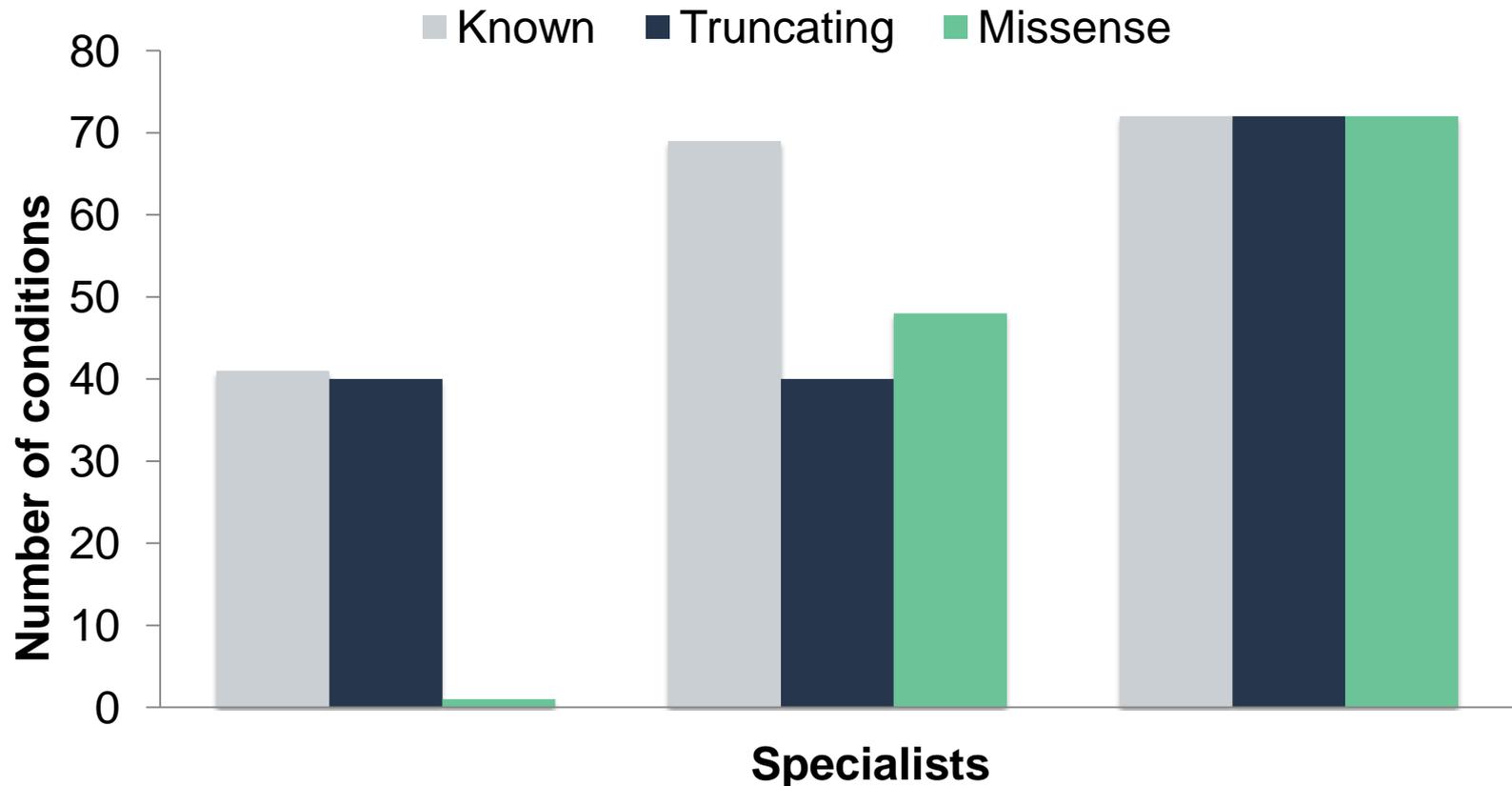
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SPECIAL ARTICLE | **Genetics
in Medicine**

Exploring concordance and discordance for return of incidental findings from clinical sequencing

Robert C. Green, MD, MPH^{1,2}, Jonathan S. Berg, MD, PhD³, Gerard T. Berry, MD^{4,5}, Leslie G. Biesecker, MD⁶, David P. Dimmock, MD⁷, James P. Evans, MD, PhD³, Wayne W. Grody, MD, PhD⁸⁻¹⁰, Madhuri R. Hegde, PhD¹¹, Sarah Kalia, ScM¹, Bruce R. Korf, MD, PhD¹², Ian Krantz, MD¹³, Amy L. McGuire, JD, PhD¹⁴, David T. Miller, MD, PhD^{4,15}, Michael F. Murray, MD^{1,2}, Robert L. Nussbaum, MD¹⁶, Sharon E. Plon, MD, PhD^{17,18}, Heidi L. Rehm, PhD^{2,19} and Howard J. Jacob, PhD^{7,20}

Concordance Patterns for Incidental Return – Adult Patient

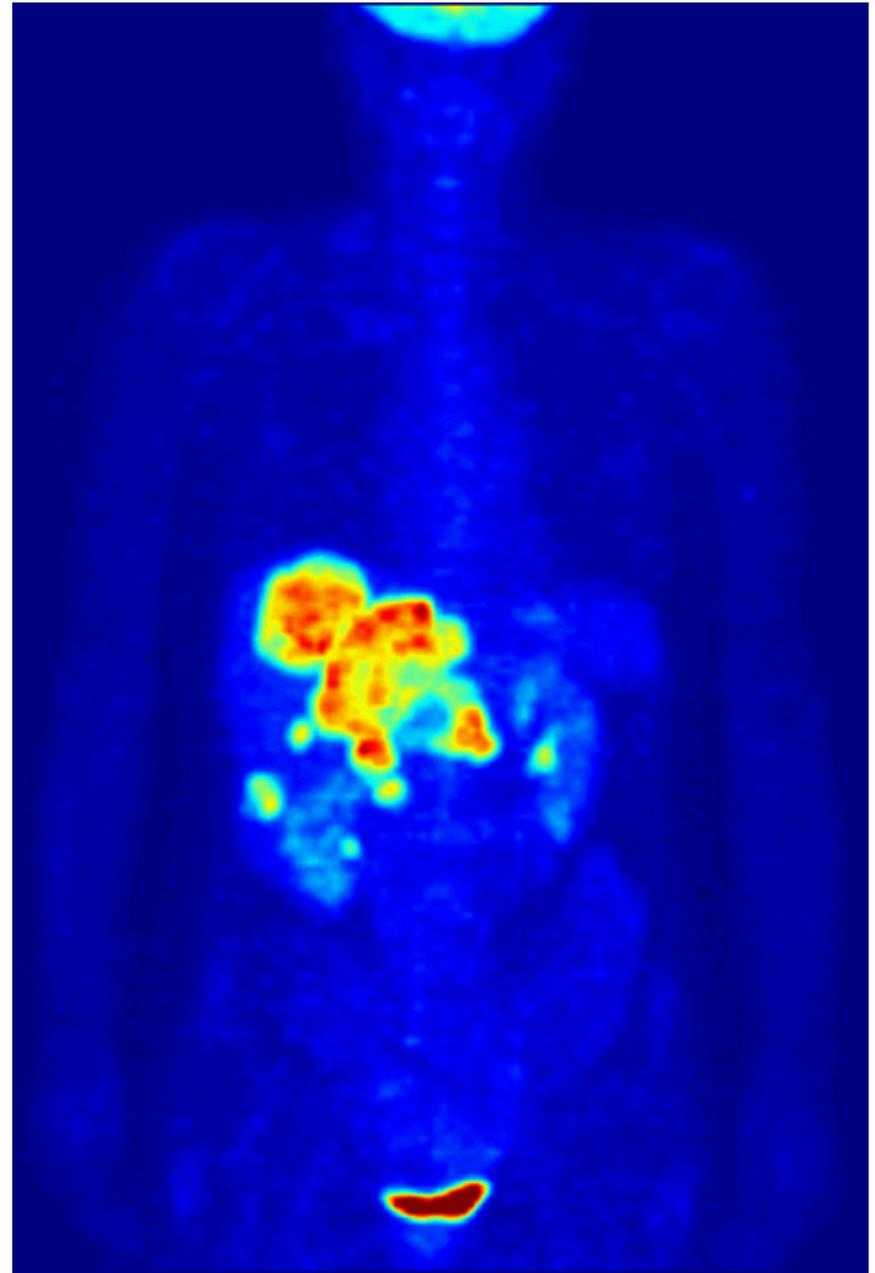


* out of a total of 72 conditions/genes (excluding repeat expansion, chromosomal, and deletion conditions)

Incidental Findings:

What is the
right analogy?

How can reports be
generated and
scaled?



American College of Medical Genetics and Genomics

ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

Robert C. Green, MD, MPH^{1,2}, Jonathan S. Berg, MD, PhD³, Wayne W. Grody, MD, PhD⁴⁻⁶, Sarah S. Kalia, ScM, CGC¹, Bruce R. Korf, MD, PhD⁷, Christa L. Martin, PhD, FACMG⁸, Amy McGuire, JD, PhD⁹, Robert L. Nussbaum, MD¹⁰, Julianne M. O'Daniel, MS, CGC¹¹, Kelly E. Ormond, MS, CGC¹², Heidi L. Rehm, PhD, FACMG^{2,13}, Michael S. Watson, MS, PhD, FACMG¹⁴, Marc S. Williams, MD, FACMG¹⁵, Leslie G. Biesecker, MD¹⁶



Green, et al. *Genetics in Medicine*, in press

Principles: creating a list...

- Generate a specific list.
- Generate a minimum list of variants/conditions that laboratories should seek and report to ordering clinician.
- Known or Expected Pathogenic only.
- Revise the list at least annually.

Principles: creating a minimum list...

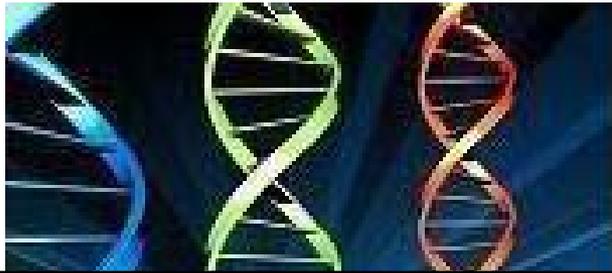
- High penetrance.
- Long asymptomatic period.
- Highly efficacious treatment available.
- Not part of newborn screening.

ACMG Recommendations

Divergence from Current Genetics Practice

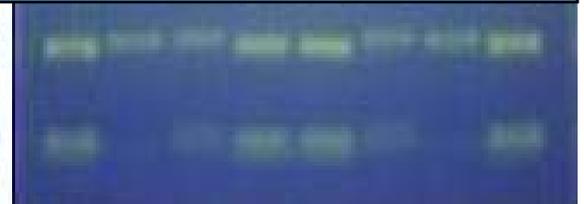
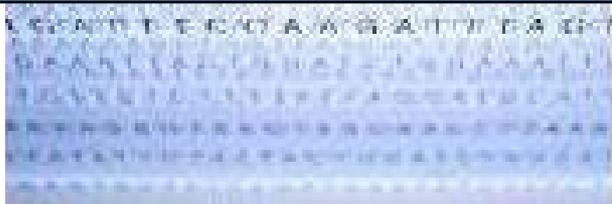
- Systematically include positive findings in the report returned to clinicians for exome and genome sequencing.
- Return same findings regardless of the age of the patient.

**Convergence with Current
Medical Practice!**



“...even though evidence is insufficient, the clinician must still provide advice, patients must make choices, and policymakers must establish policies”

US Preventive Services Task Force, 2009



Thank You !!!



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Twitter: [genomes2people](https://twitter.com/genomes2people)

