Newborn Sequencing and the Challenge of Incidental Findings

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Division of Genetics, Department of Medicine
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VE RI TAS BWH

Disclosures

Research Grants:	NIH
Research Collaborations:	Pathway, 23andMe
Speaking (compensated):	None
Advisory (compensated):	None
Equity:	None

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Current NIH Grant Funding

U01 HG006500 (Green)

R01 HG002213 (Green)

R01 HG005092 (Green)

K24 AG027841 (Green)

R21 HG00603 (Wang)

R01 HG06379 (Kullo)

U01 AG024904 (Weiner)

R01 AG031171 (Qiu)

R01 HG006615 (Holm)

P60 AR047782 (Kats/Karlson)

P50 HG003170 (Church)

R01 CA154517 (Petersen/Koenig/Wolf)

R01 HG007063 (Phillips)

T32 GM007748 (Morton)

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G2P or “Genomes to People” are Research Studies in Translational Genomics and Health Outcomes

Genomes to Patients
Genomes to Physicians
Genomes in Public Health

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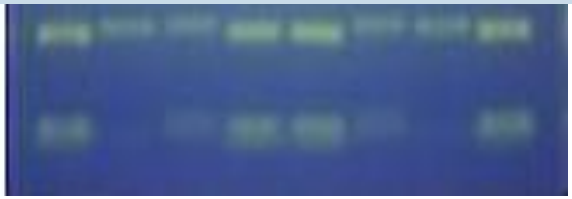
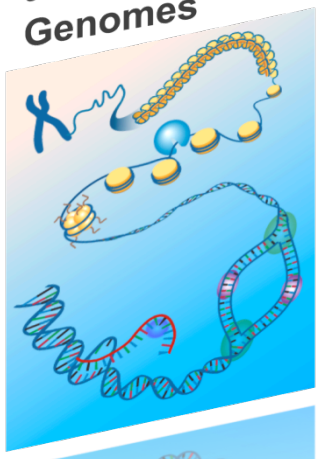


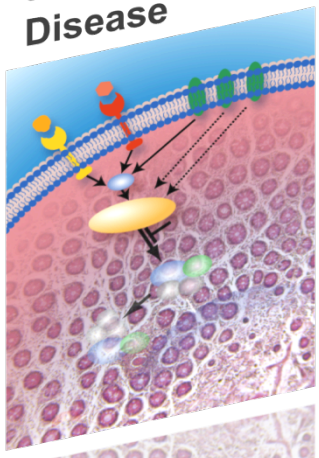
The Path to Genomic Medicine

Understanding the Structure of Genomes

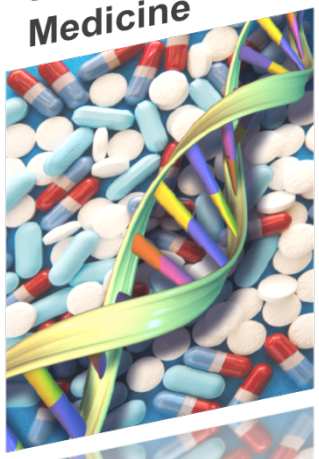
Understanding the Biology of Genomes



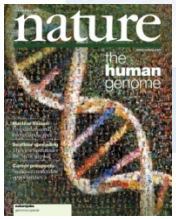
Understanding the Biology of Disease



Advancing the Science of Medicine

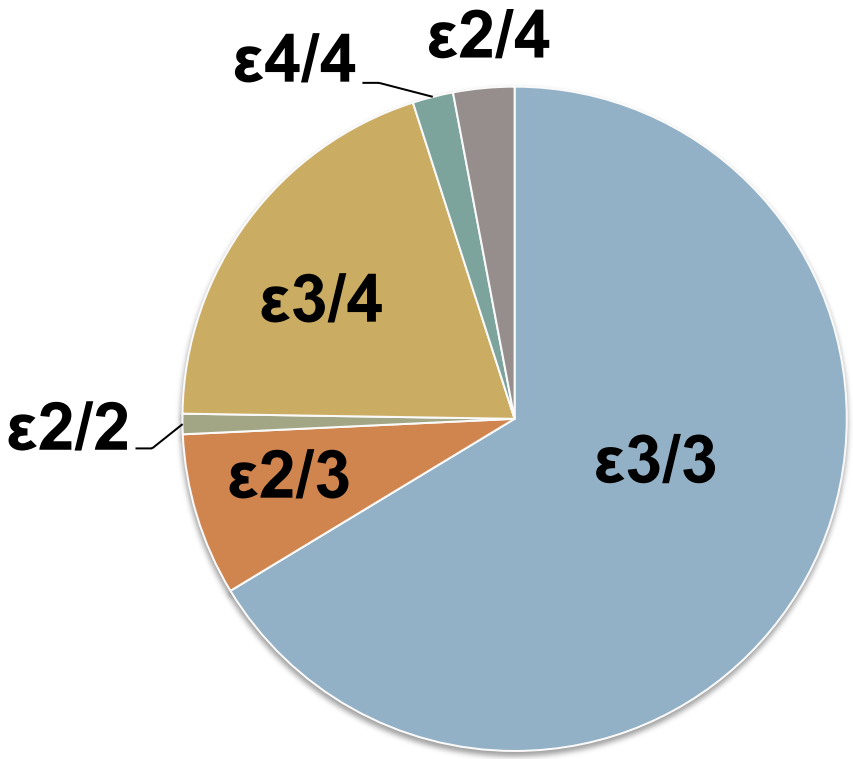


Improving the Effectiveness of Healthcare



The REVEAL Study
NHGRI-funded (2000-2014)

APOE Genotypes in the General Population



ε2	ε2	ε2	ε4
ε2	ε3	ε3	ε4
ε3	ε3	ε4	ε4

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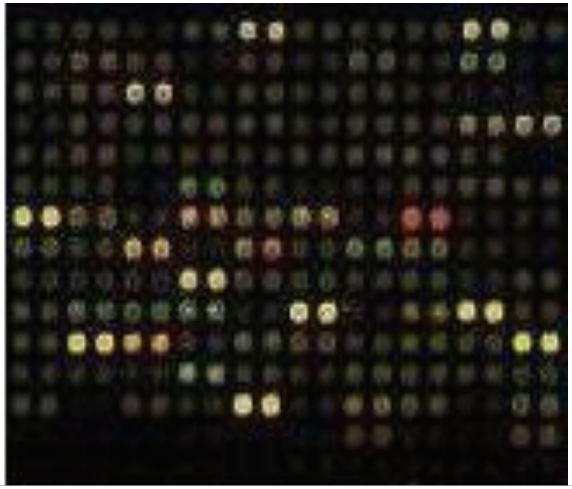
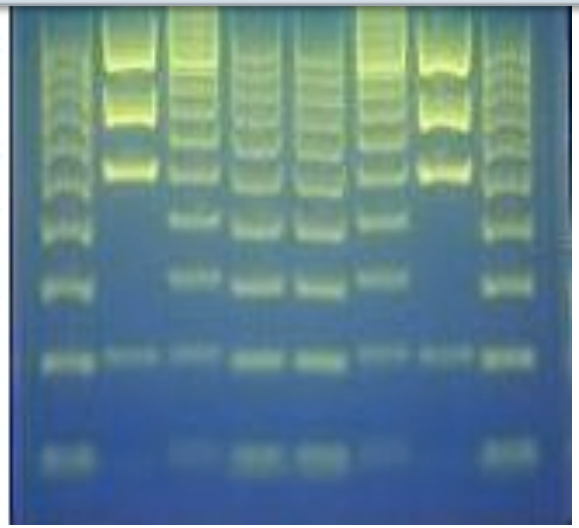


The Danger of Disclosure
Is Genetic Information Harmful?



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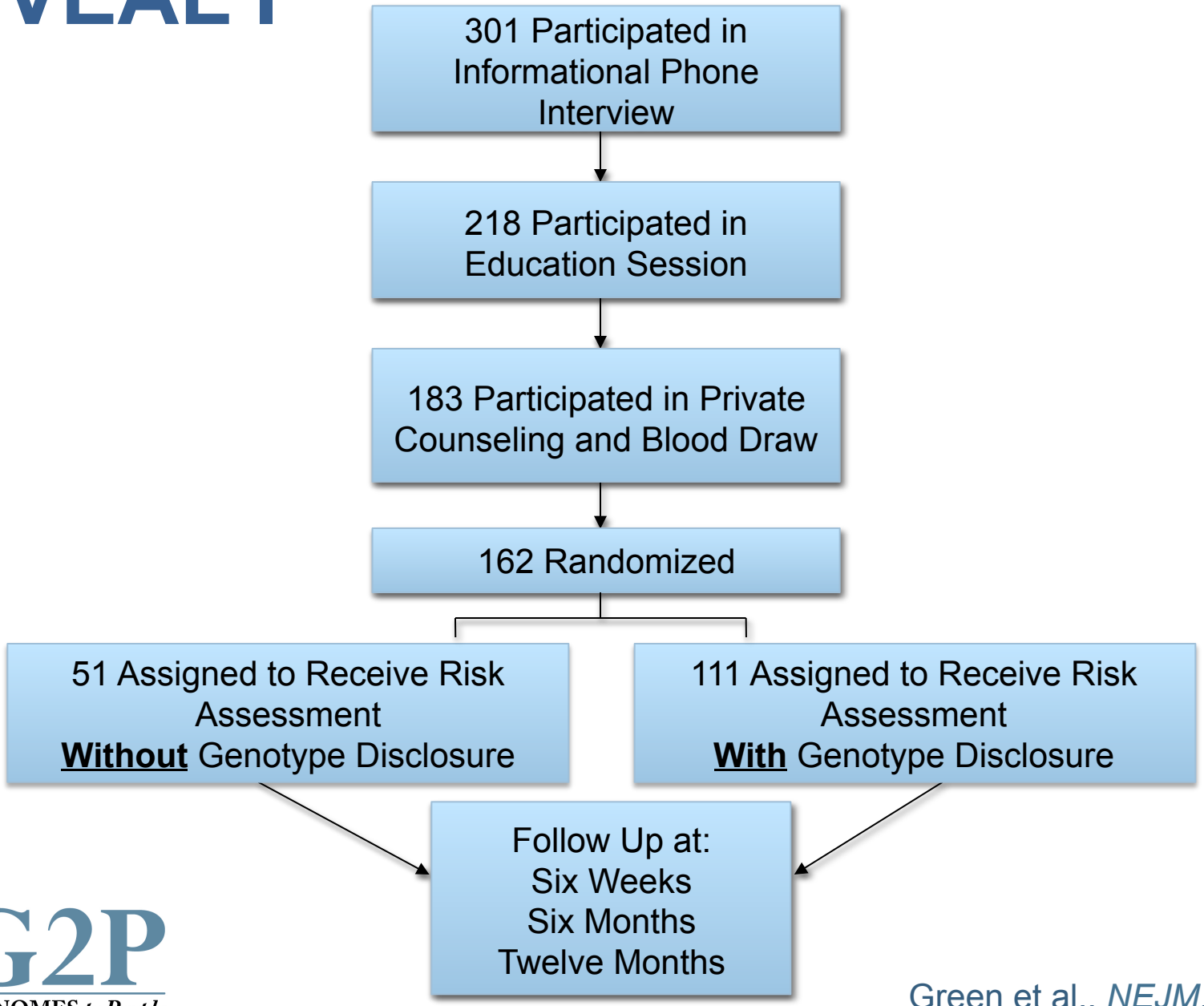
REVEAL I



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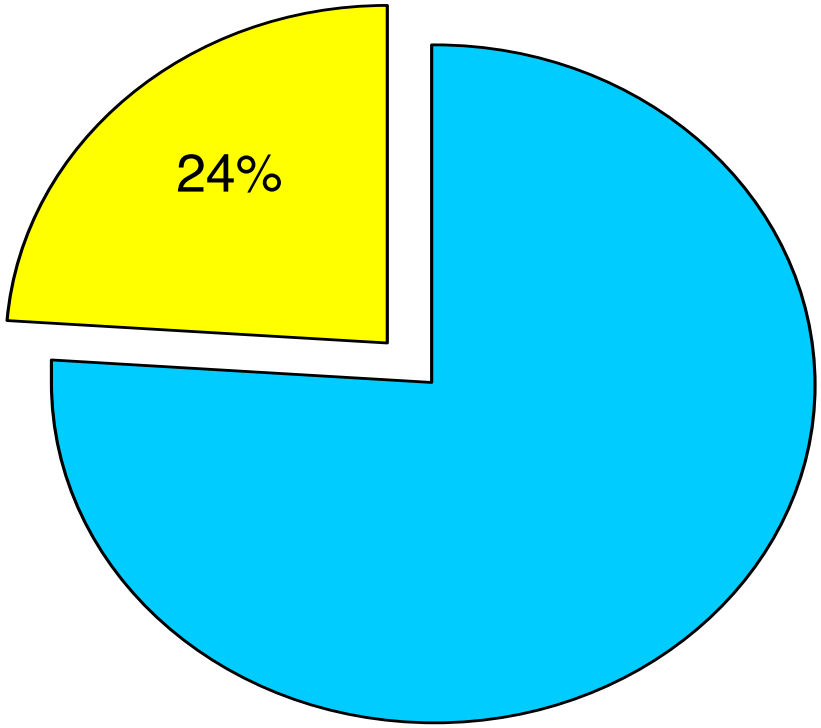
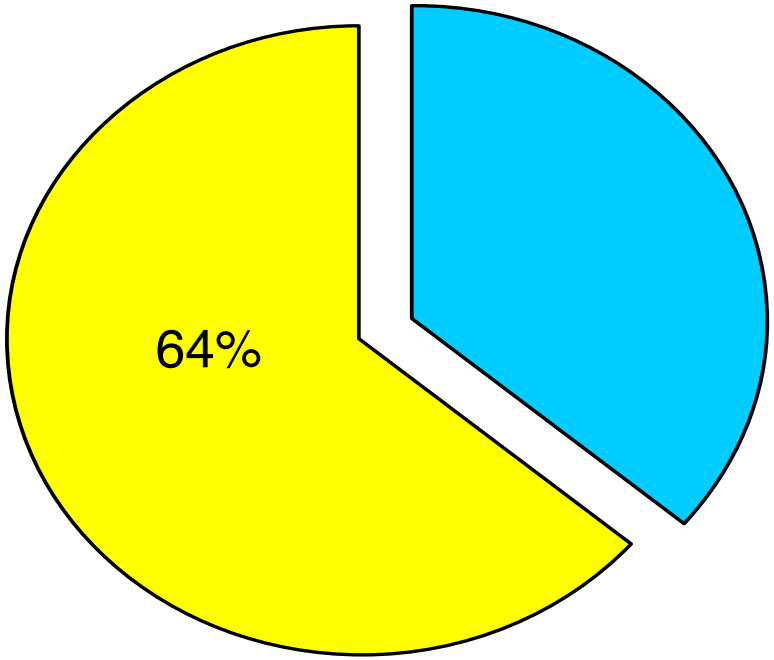
Green et al., *NEJM*, 2009

Persons Agreeing to Participate in the REVEAL Study





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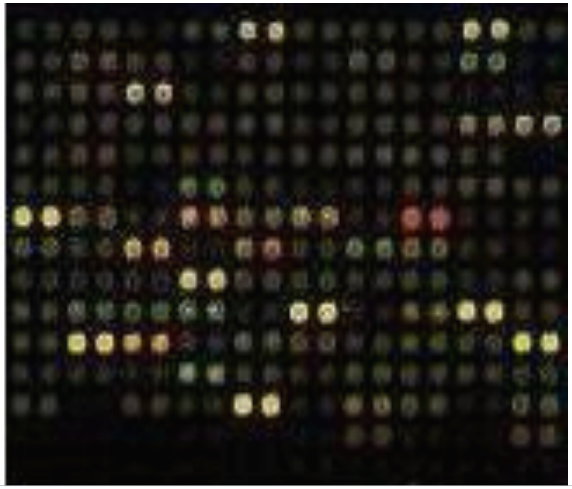
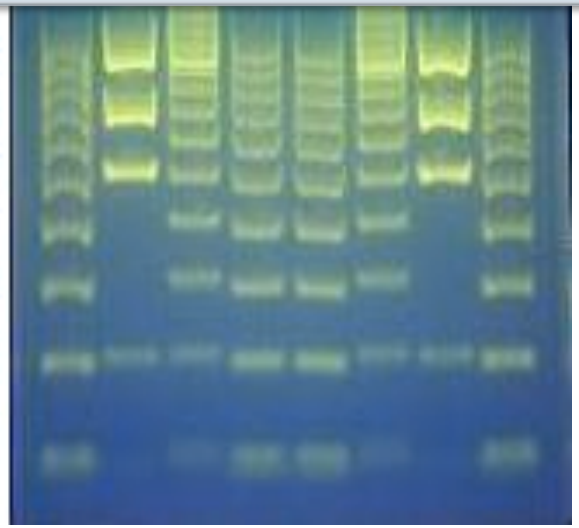
Roberts, et al. *Genetics in Medicine*, 2004



Diluting the Disclosure: Adding an Incidental Result



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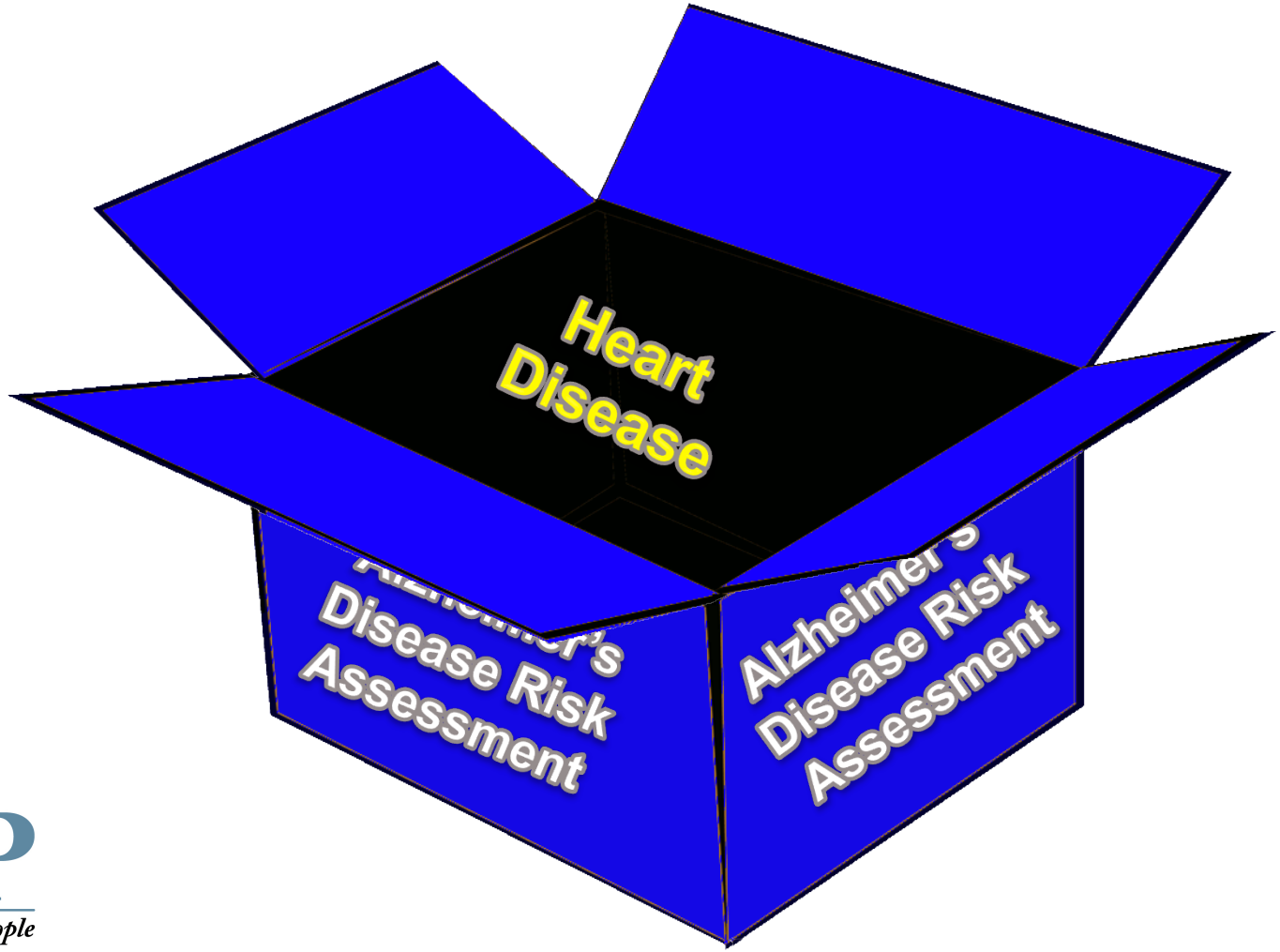
During genetic risk assessment for Alzheimer's disease…what happens when one learns a surprise finding?



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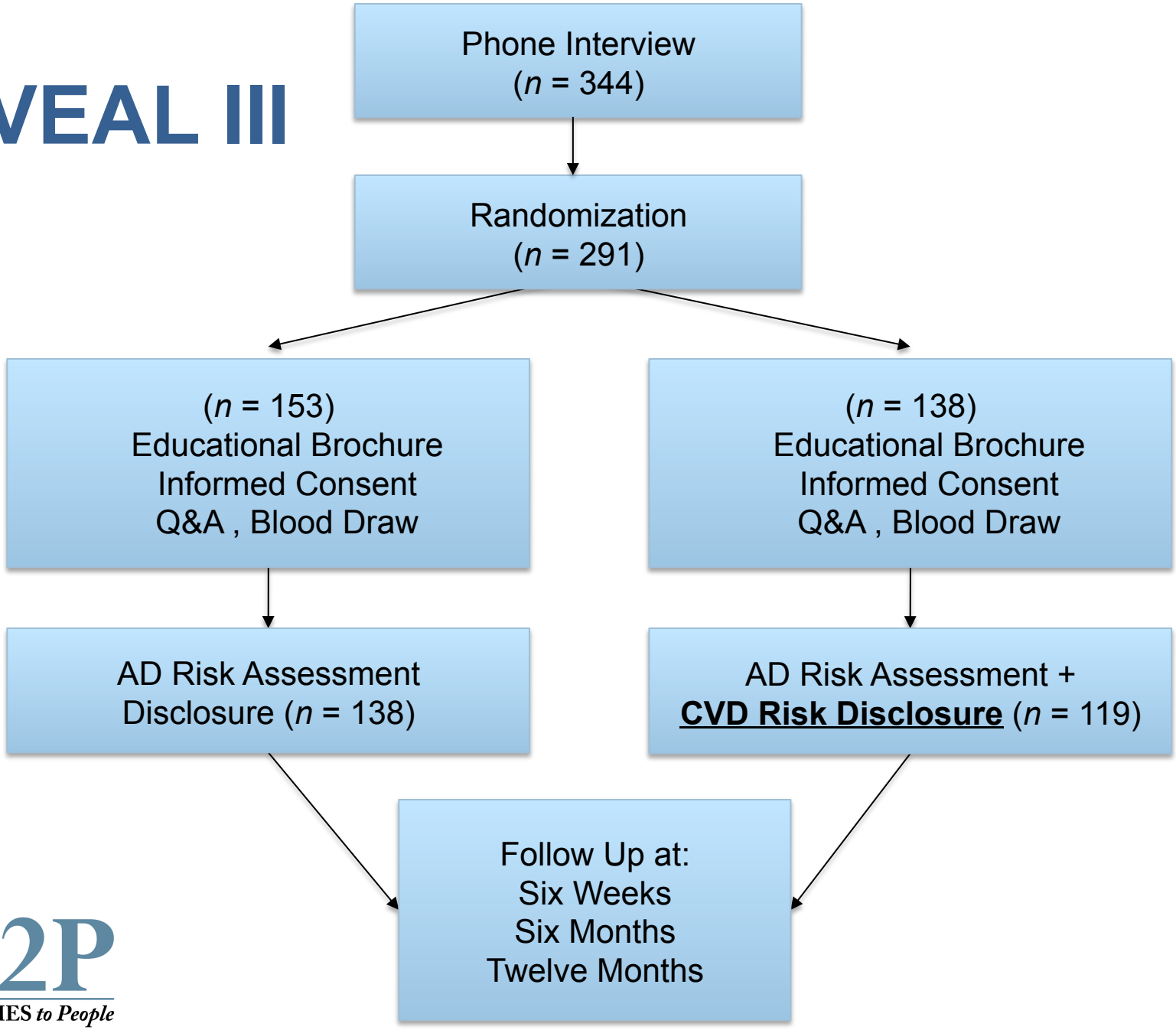
REVEAL III



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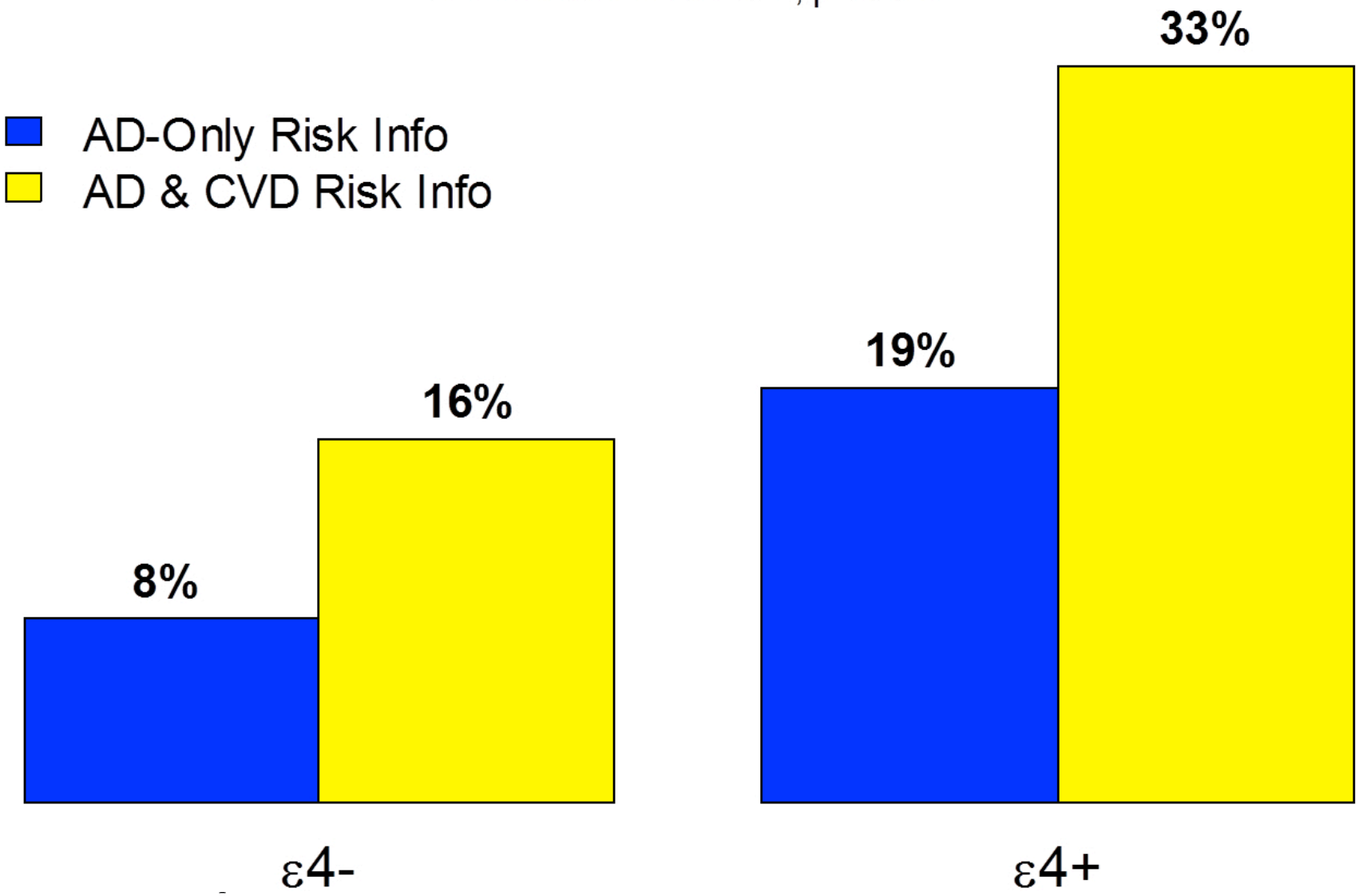
Exercise

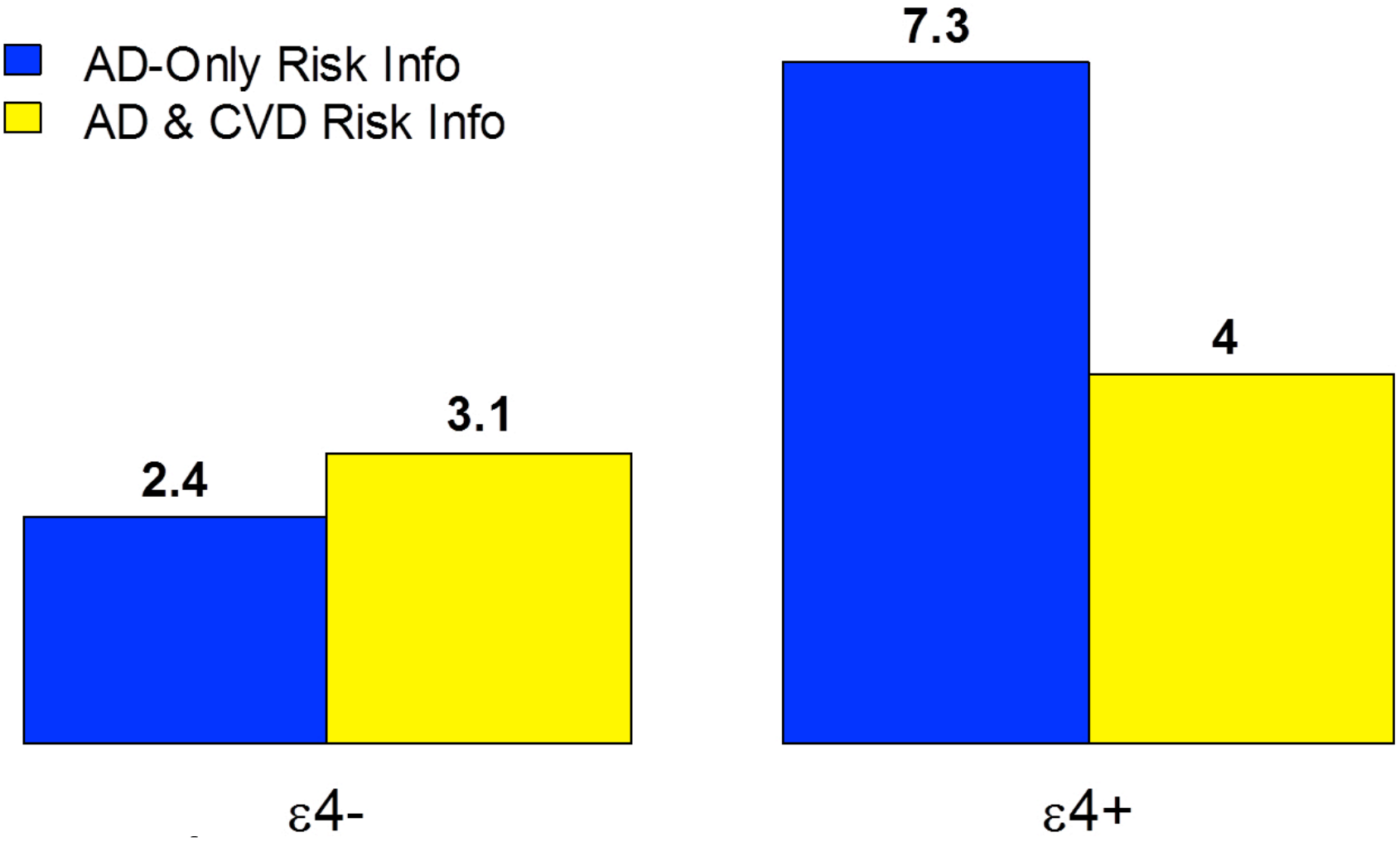
ε4 status: OR=2.5, p=0.010

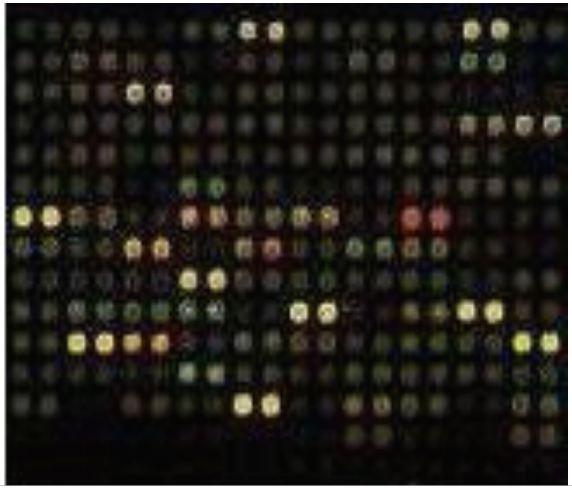
AD+CVD Info: OR=2.2, p=0.039



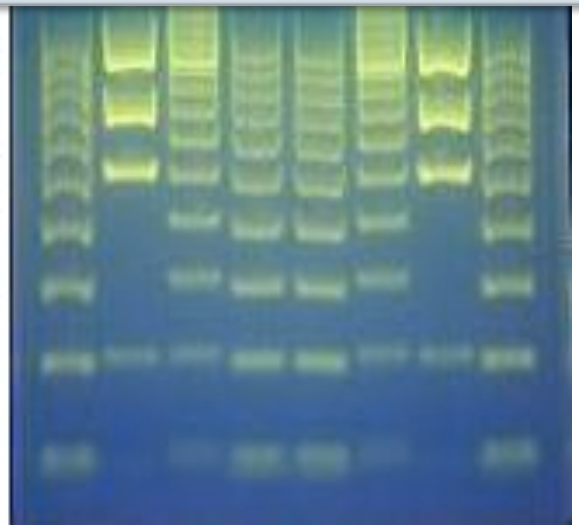
Test-Related Distress

Interaction: β=-4.1, p=0.03





Direct-to-Consumer Genetic Testing
A Naturalistic Experiment in Incidental Findings



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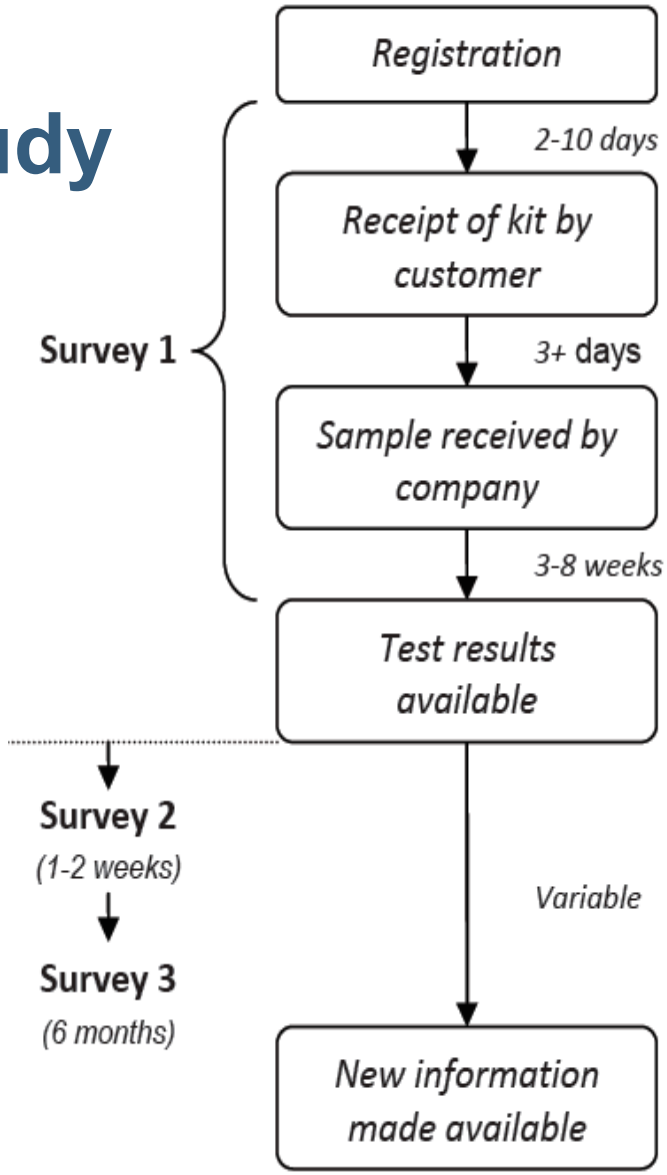
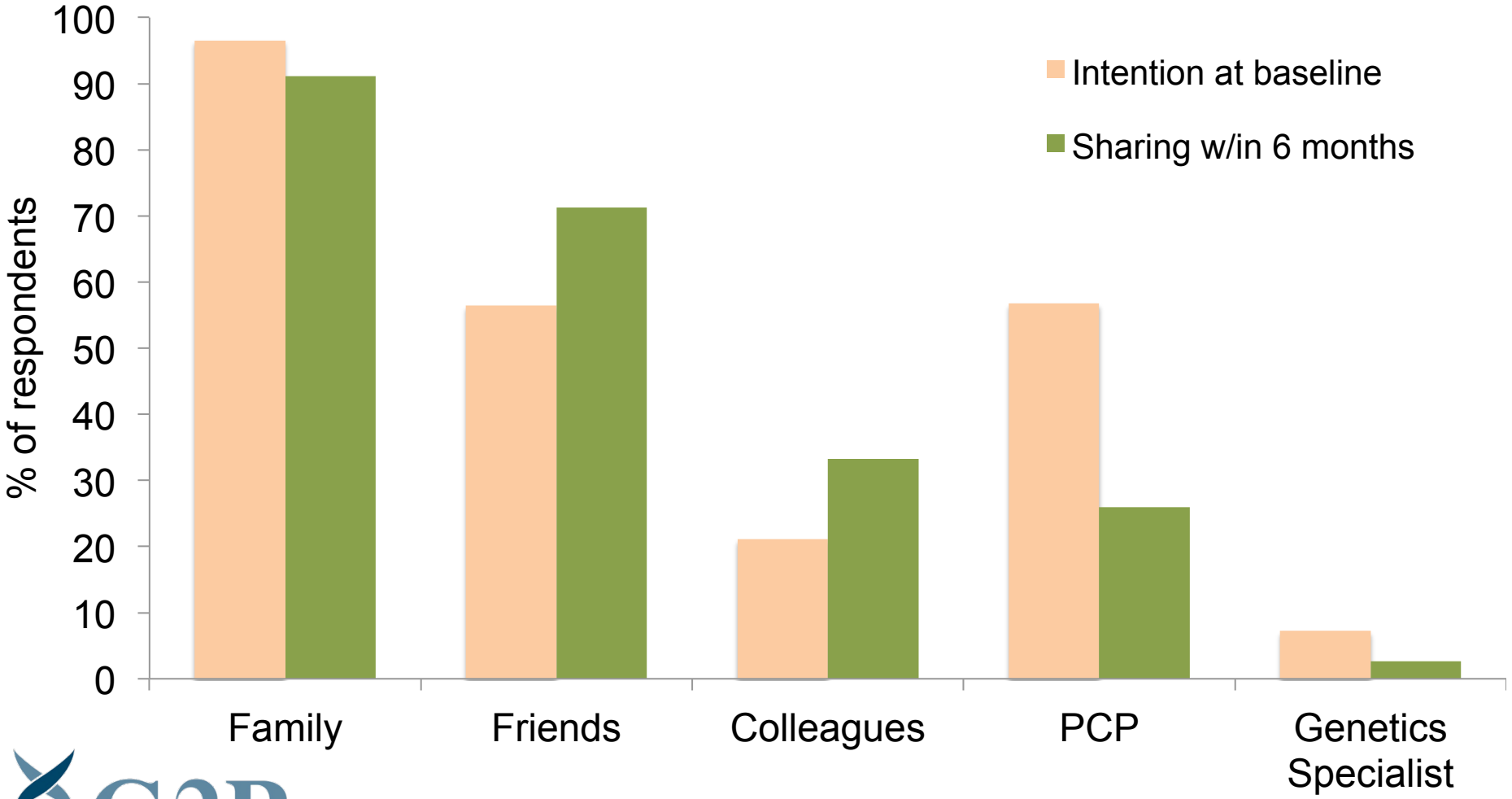
Impact of Personal Genomics (PGen) Study

(Green-Roberts, PIs)



NHGRI R01 HG005092

Plans to Share Results and Reported Sharing after 6 months



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PGen Healthcare Utilization within 6 months

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%)

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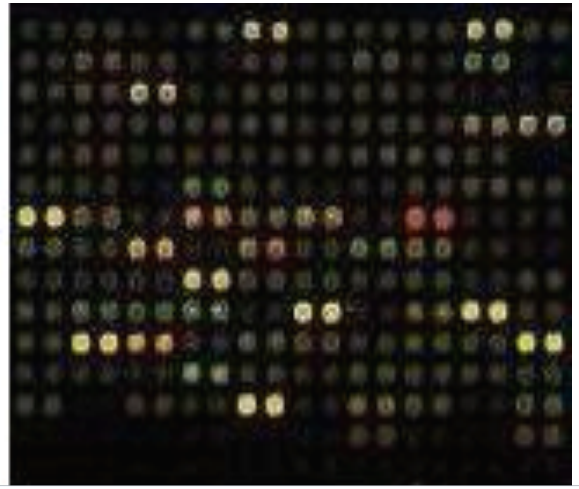
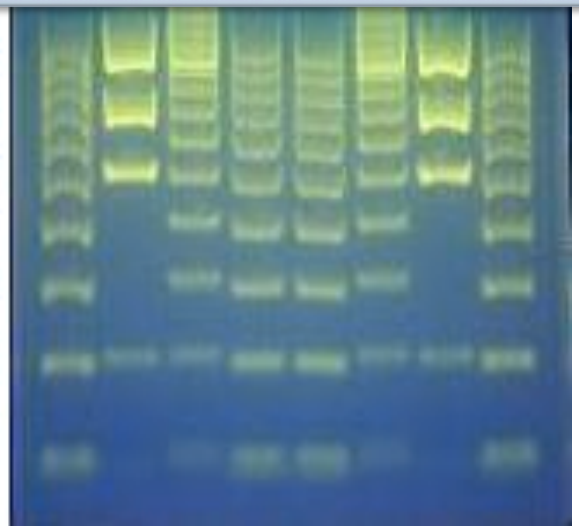


Using Whole Genome Sequencing In the Practice of Medicine



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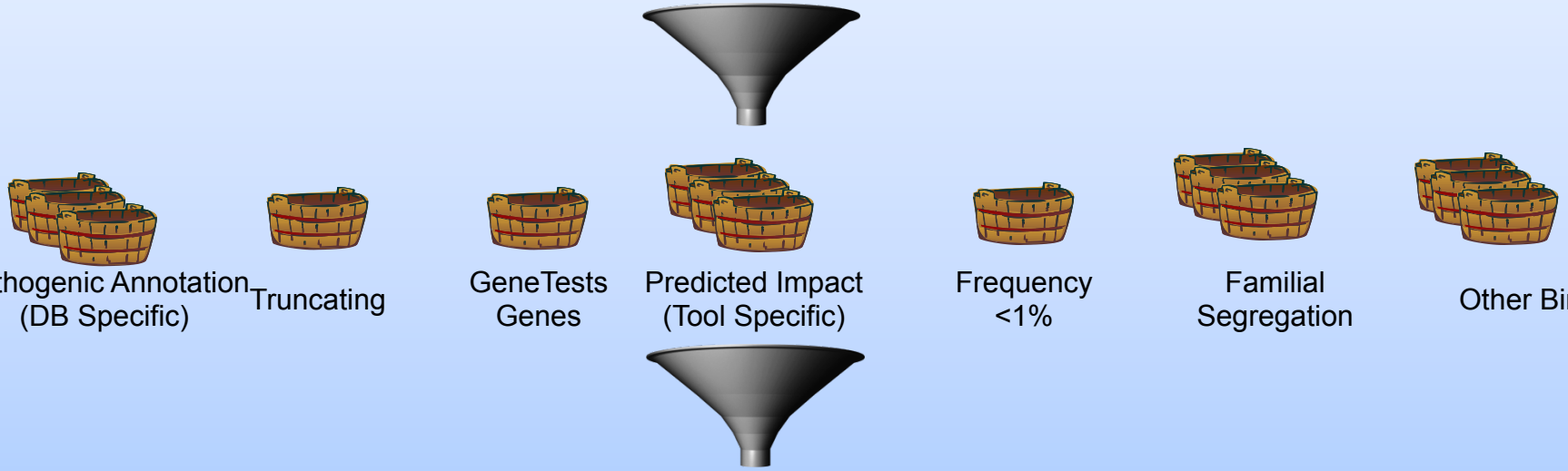
Interpretation of Sequences in Affected Patients

2 – 5 Million Variants



10-50 Variants to Be Manually Assessed

0-2 Causative Variants

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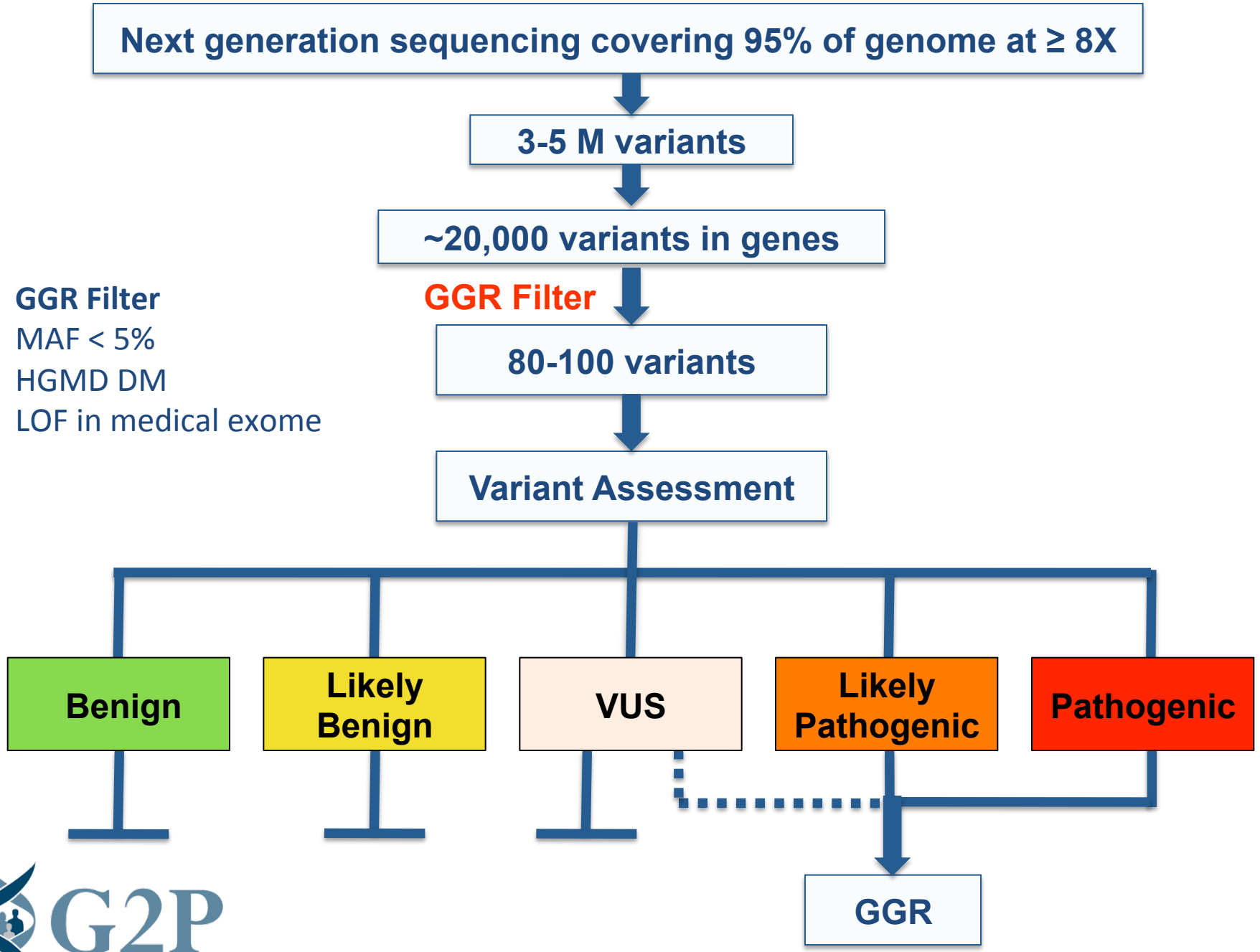
Slide courtesy of Sandy Aronson



GGR Filter
MAF < 5%
HGMD DM
LOF in medical exome

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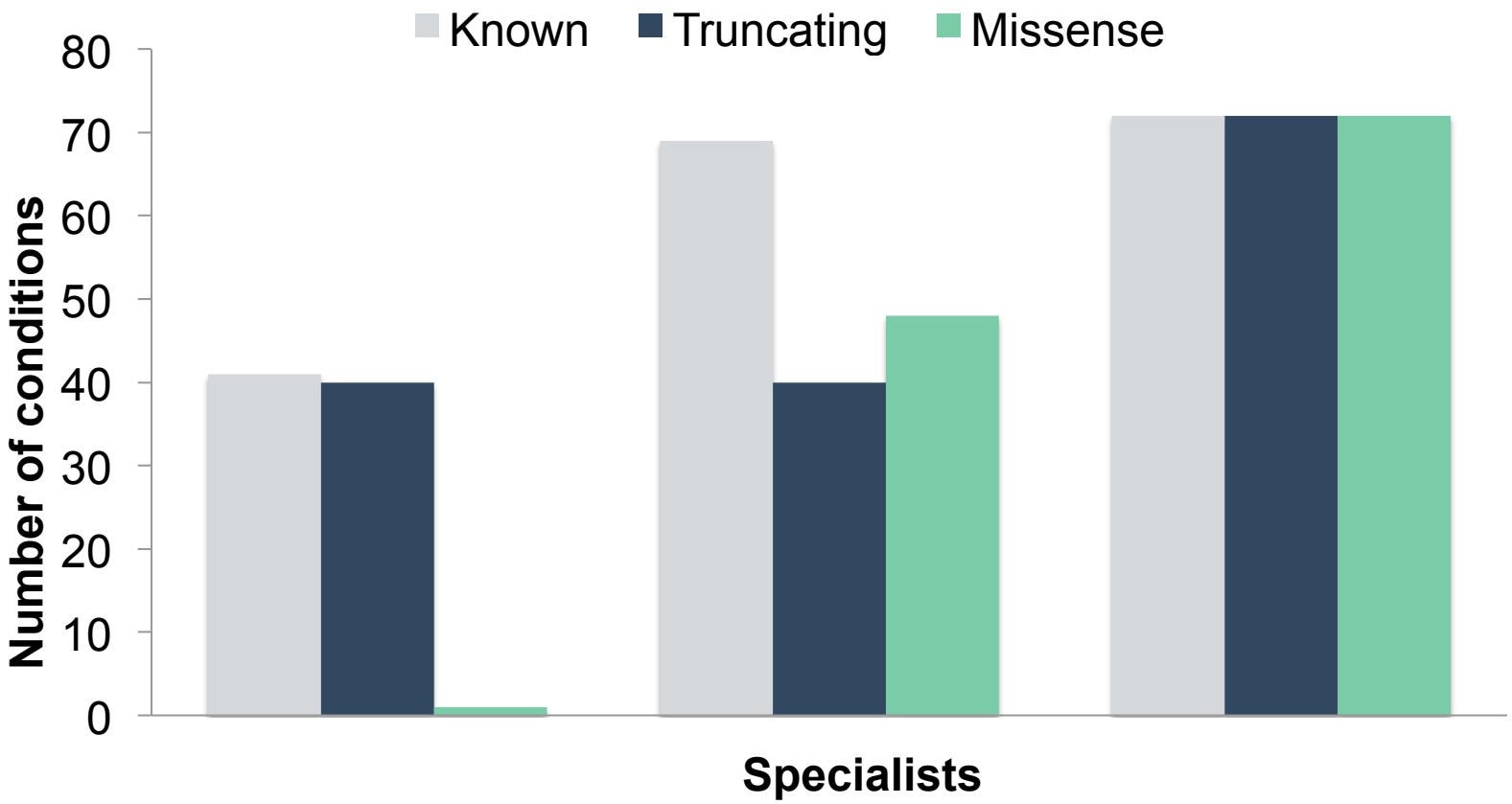
Slide courtesy of Heidi Rehm

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. Genetics in Medicine, 2012

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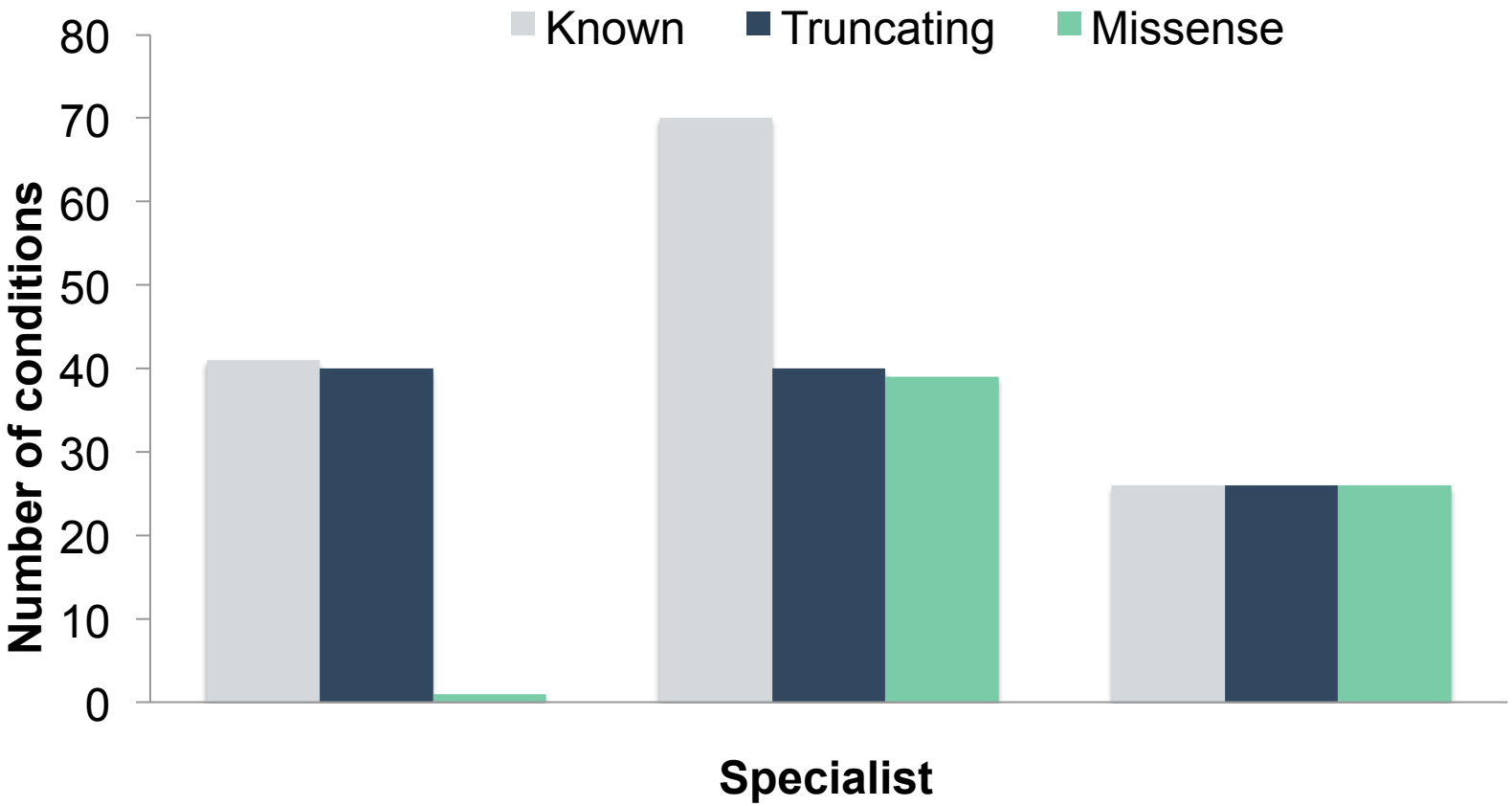
Concordance Patterns for Incidental Return – Patient < 18



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Green et al. Genetics in Medicine, 2012

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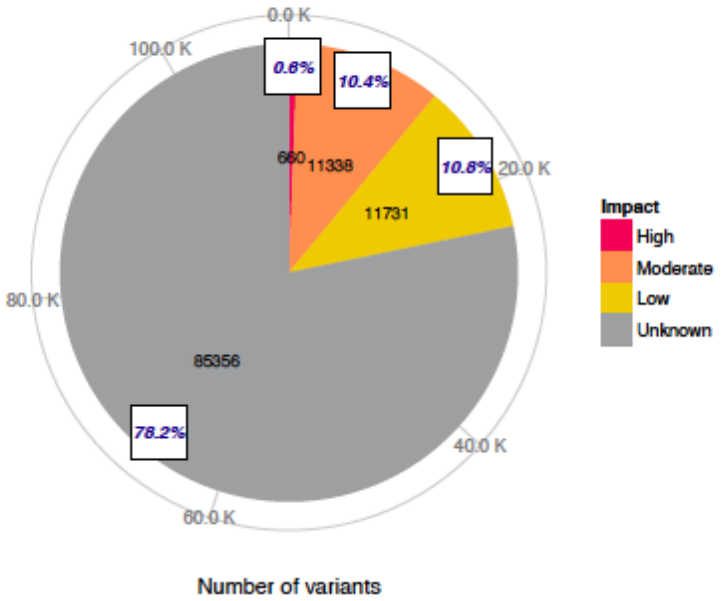
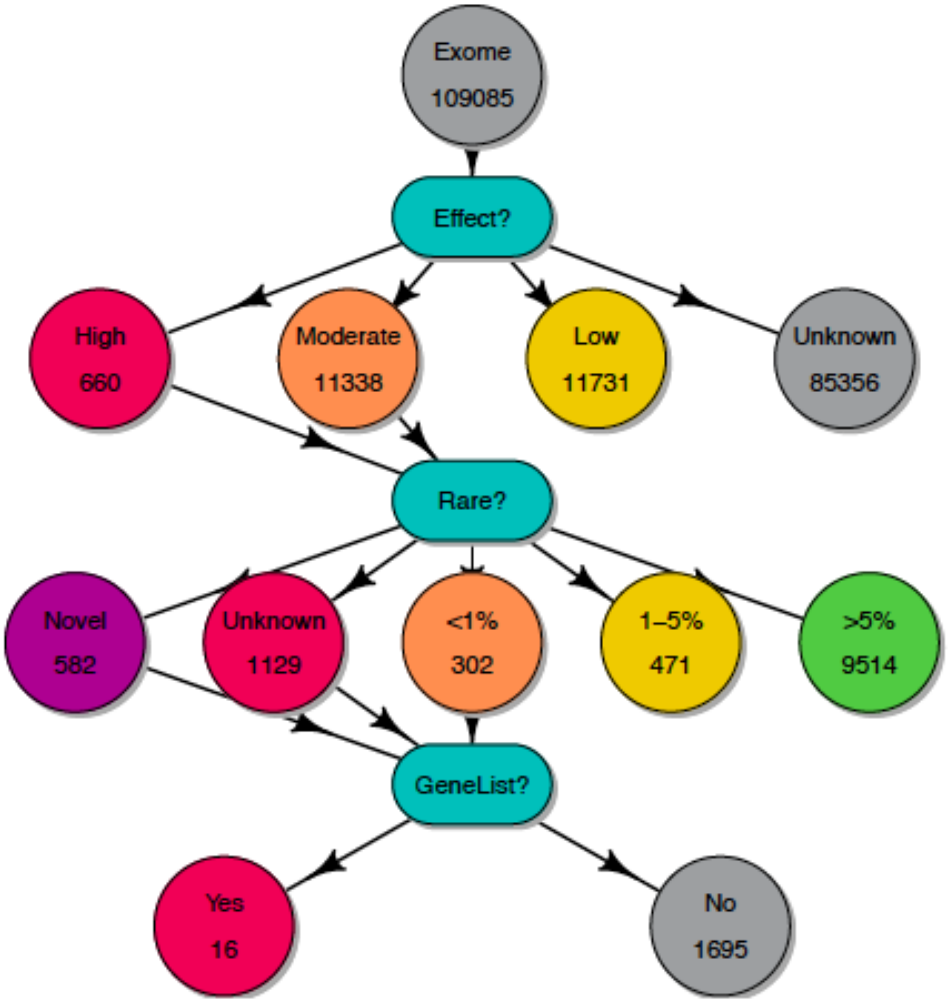
Robert Green's Sequence

Filtering your variants

Characterizing your variant





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Robert Green's Sequence

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The MedSeq Project

U01 HG006500

Clinical Sequencing Exploratory Research

Teams from:

Brigham and Women's Hospital/Harvard Medical School

Boston Children's Hospital

Baylor College of Medicine

Duke University School of Medicine

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

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MEDSEQ™

Exploring WGS in 2 Contexts

Patients with Disease	Healthy Patients
10 cardiologists & **100** of their patients with familial hypertrophic or dilated cardiomyopathy	**10** primary care physicians & **100** of their generally healthy adult patients

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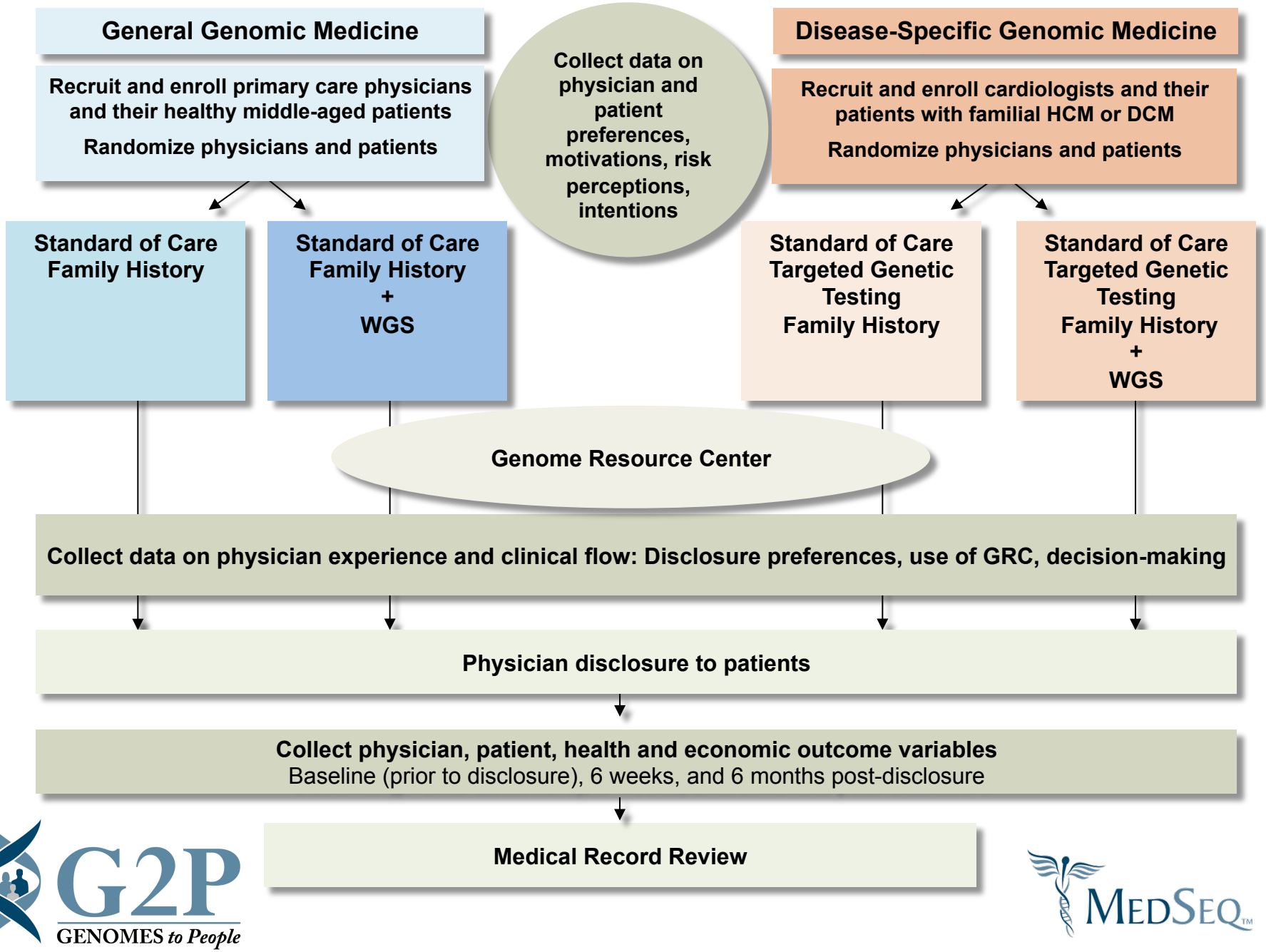
MEDSEQ™


General Genomic Medicine
Recruit and enroll primary care physicians and their healthy middle-aged patients
Randomize physicians and patients
Collect data on physician and patient preferences, motivations, risk perceptions, intentions
Disease-Specific Genomic Medicine
Recruit and enroll cardiologists and their patients with familial HCM or DCM
Randomize physicians and patients
Standard of Care Family History
Standard of Care Family History + WGS
Standard of Care Targeted Genetic Testing Family History
Standard of Care Targeted Genetic Testing Family History + WGS
Genome Resource Center
Collect data on physician experience and clinical flow: Disclosure preferences, use of GRC, decision-making
Physician disclosure to patients
Collect physician, patient, health and economic outcome variables
Baseline (prior to disclosure), 6 weeks, and 6 months post-disclosure
Medical Record Review
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MedSeq Project "Genome Report"

- 1 Page Summary!
- Additional Pages…
  - Structured variant data
  - Variant interpretation
  - Disease/inheritance
  - Supporting references

Heidi Rehm

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http://pcpgm.partners.org/lmm

PARTNERS HEALTHCARE

CENTER FOR PERSONALIZED GENETIC MEDICINE

A teaching affiliate of: HARVARD MEDICAL SCHOOL

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: Double Helix Hospital

SAMPLE GENERAL GENOME REPORT SAMPLE

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.

RESULT SUMMARY

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

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. Myotonia congenita	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 variants associated with drug use and dosing. Additional pharmacogenomic results may be requested, but will require additional molecular confirmation prior to disclosure.

Drug	Risk and Dosing Information
C1. Warfarin	Decreased dose requirement.
C2. Clopidogrel	Typical risk of bleeding and cardiovascular events.
C3. Digoxin	Increased serum concentration of digoxin.
C4. Metformin	Typical glycemic response to metformin.
C5. Simvastatin	Lower risk of simvastatin-related myopathy.

D. BLOOD GROUPS

This test identified the ABO Rh blood type as O positive. Additional blood group information is available at the end of the report.

It should be noted that the disease risk section of this report is limited only to variants with evidence for causing highly penetrant disease, or contributing to highly penetrant disease in a recessive manner. Not all variants identified have been analyzed, and not all regions of the genome have been adequately sequenced. These results should be interpreted in the

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Disease	Phenotype	Gene Variant	Classification	Carrier Phenotype*
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B2. Myotonia congenita	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.

Drug	Risk and Dosing Information
C1. Warfarin	Decreased dose requirement.
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C3. Digoxin	Increased serum concentration of digoxin.
C4. Metformin	Typical glycemic response to metformin.
C5. Simvastatin	Lower risk of simvastatin-related myopathy.

D. BLOOD GROUPS

This test identified the ABO Rh blood type as O positive. Additional blood group information is available at the end of the report.

It should be noted that the disease risk section of this report is limited only to variants with evidence for causing highly penetrant disease, or contributing to highly penetrant disease in a recessive manner. Not all variants identified have been analyzed, and not all regions of the genome have been adequately sequenced. These results should be interpreted in the

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65 Landsdowne St., Cambridge, MA 02139
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http://pcpgm.partners.org/lmm

PARTNERS HEALTHCARE

CENTER FOR PERSONALIZED GENETIC MEDICINE

A teaching affiliate of:
HARVARD MEDICAL SCHOOL

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: Double Helix Hospital

SAMPLE GENERAL GENOME REPORT SAMPLE

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.

RESULT SUMMARY

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

B. CARRIER RISK: 3 VARIANTS IDENTIFIED

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

C. PHARMACOGENOMIC ASSOCIATIONS

This test identified the following variants associated with drug use and dosing. Additional pharmacogenomic results may be requested, but will require additional molecular confirmation prior to disclosure.

Drug	Risk and Dosing Information
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DETAILED VARIANT INFORMATION

A. MONOGENIC DISEASE RISK

Disease (Inheritance)	Gene (Transcript)	Variant (Classification)	Variant Frequency	Disease Prevalence	References (PMID)
A1. Episodic ataxia type II (Autosomal Dominant)	CACNA1A (NM_023035)	c.6466delA p.Arg2156GlyfsX32 Heterozygous (Pathogenic)	Not previously reported	<1/100,000	8898206 11370629 9600739 11564488

VARIANT INTERPRETATION: The Arg2156GlyfsX32 variant in CACNA1A has not been reported previously. This frameshift variant is predicted to lead to a truncated or absent protein, resulting in a loss-of-function. Loss-of-function mutations in the CACNA1A gene have been associated with episodic ataxia type II, with at least 20 different mutations having been reported including segregation with disease in a large family and a de novo occurrence (Ophoff 1996, Scoggan 2001, Yue 1998, Jouvenceau 1991).

DISEASE INFORMATION: Episodic ataxia type II is characterized by paroxysmal attacks of ataxia, vertigo, and nausea typically lasting minutes to days in duration. Attacks can be associated with dysarthria, diplopia, tinnitus, dystonia, hemiplegia, and headache. About 50% of affected individuals have migraine headaches. Penetrance is reported to be 80-90%. Adapted from GeneReviews abstract: http://www.ncbi.nlm.nih.gov/books/NBK1501/

FAMILIAL RISK: In most cases, an individual inherits a CACNA1A variant from a parent. The de novo (new) mutation rate is unknown. The chance of this patient's siblings having the variant is dependent on the parents' status, but may be as high as 50% if one parent carries this variant. The patient has a 50% chance of passing on this variant to any of his children. Due to incomplete penetrance, a family member may have this variant and be clinically unaffected. Adapted from GeneReviews abstract: http://www.ncbi.nlm.nih.gov/books/NBK1501/

to progressive heart failure to sudden cardiac death. Common symptoms include shortness of breath, chest pain, palpitations, orthostasis, presyncope, and syncope. Adapted from GeneReviews abstract: http://www.ncbi.nlm.nih.gov/books/NBK1768/.

FAMILIAL RISK: An individual may inherit a MYBPC3 variant from a parent. The de novo (new) mutation rate is unknown. The chance of this patient's siblings having the variant is dependent on the parents' status, but may be as high as 50% if one parent carries this variant. The patient has a 50% chance of passing on this variant to any of his children. Adapted from GeneReviews abstract: http://www.ncbi.nlm.nih.gov/books/NBK1768/.

B. CARRIER RISK

Disease (Inheritance)	Gene (Transcript)	Variant (Classification)	Variant Frequency	Disease Prevalence (Carrier Freq.)	References (PMID)	Carrier Phenotype
B1. Cystic Fibrosis (Autosomal Recessive)	CFTR (NM_000492)	c.1585-1G>A p.? Heterozygous (Pathogenic)	0.1% (12/8600) European American	1/3200 Caucasian (1/25)	2236053 20021716 21679131	Infertility

VARIANT INTERPRETATION: The 1585-1G>A variant in CFTR occurs in the invariant region (+/- 1,2) of the splice consensus sequence and is predicted to cause altered splicing leading to an abnormal or absent protein. The 1585-1G>A variant has been found to be causative for cystic fibrosis in both a homozygous and compound heterozygous state (Kerem 1990, Gallati 2009). In addition, heterozygosity for this variant has also been reported in individuals with azoospermia and oligospermia, indicating that carrier status for this variant may pose an increased risk for male infertility (Gallati 2009, Tomaiuolo 2011).

DISEASE INFORMATION: CFTR-related disorders include cystic fibrosis (CF) and congenital absence of the vas deferens (CAVD). Cystic fibrosis affects epithelia of the respiratory tract, exocrine pancreas, intestine, male genital tract, hepatobiliary system, and exocrine sweat glands, resulting in complex multisystem disease. More than 95% of males with CF are infertile as a result of azoospermia caused by absent, atrophic, or fibrotic Wolffian duct structures. Adapted from GeneReviews abstract: http://www.ncbi.nlm.nih.gov/books/NBK1250/

FAMILIAL RISK: A carrier of cystic fibrosis has a 50% chance of passing on the CFTR variant to any of his/her children. The risk of this patient's child having cystic fibrosis is dependent on the CFTR carrier status of the patient's partner. This patient likely inherited the CFTR variant from one of his parents. Other biologically related family members may also be carriers of this variant. Adapted from GeneReviews abstract: http://www.ncbi.nlm.nih.gov/books/NBK1250/

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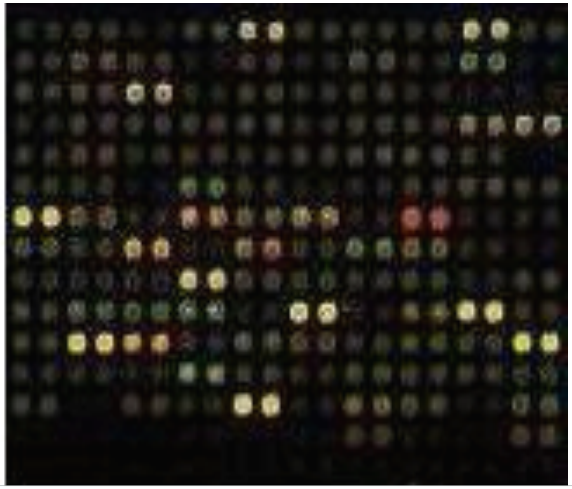
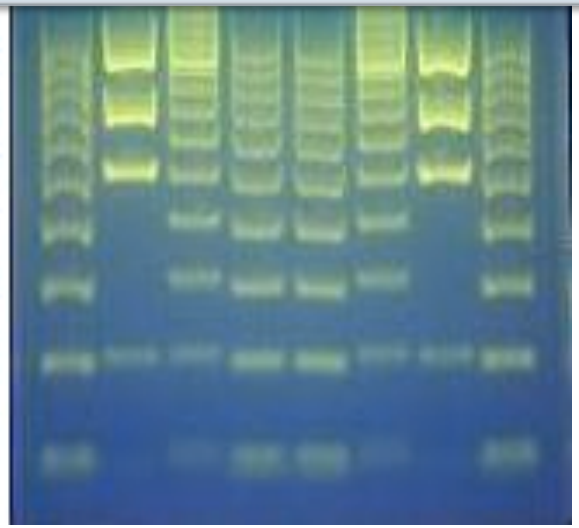


Parents Want Predictive Information About their Children



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Survey of Parents in a DNA Biobank
N = 1126

	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%

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Green et al, 2011
RC1 HG005492 (Holm)

Newborn Genomic Screening

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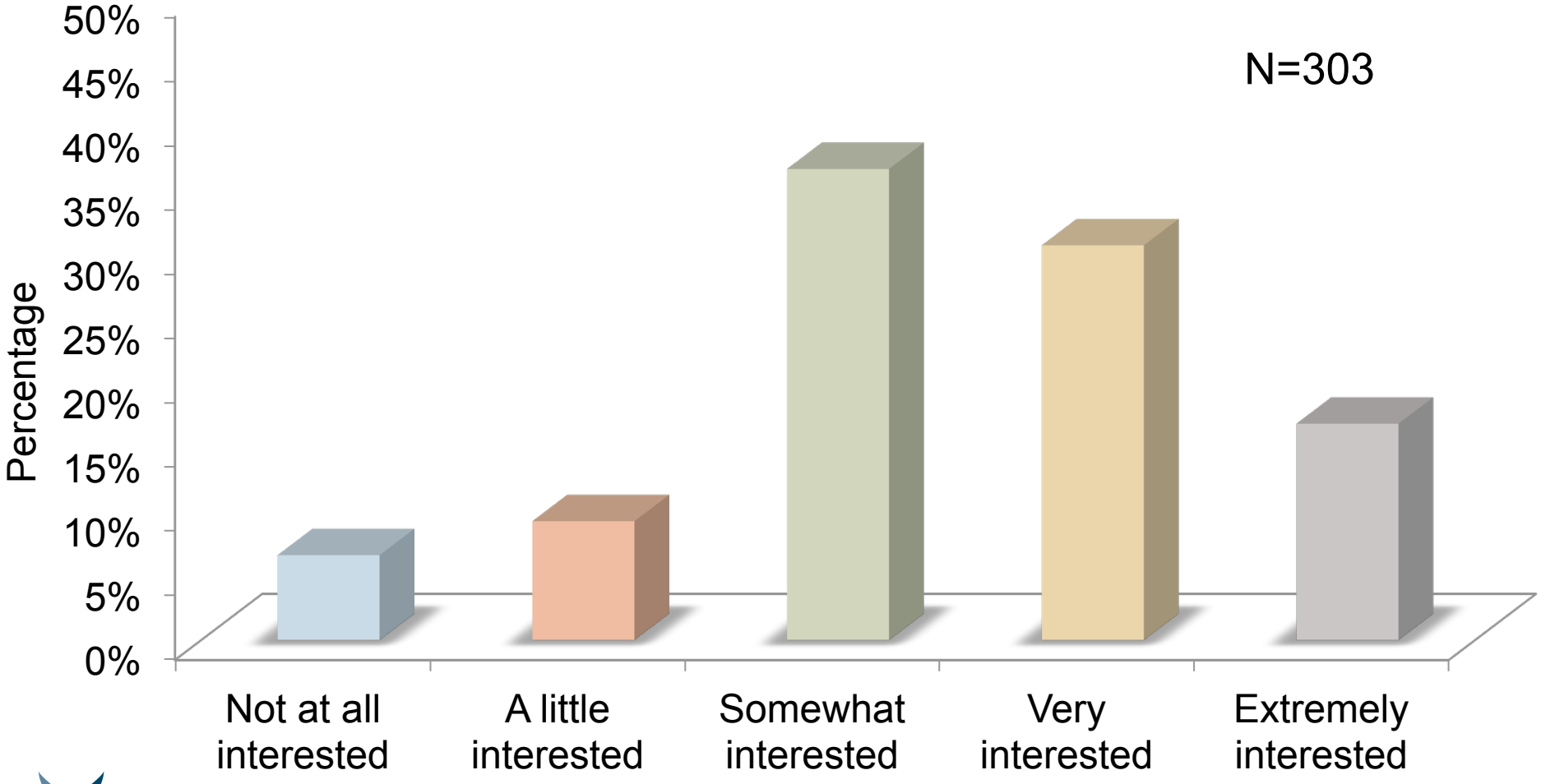
How interested would you be in genome screening for your baby?



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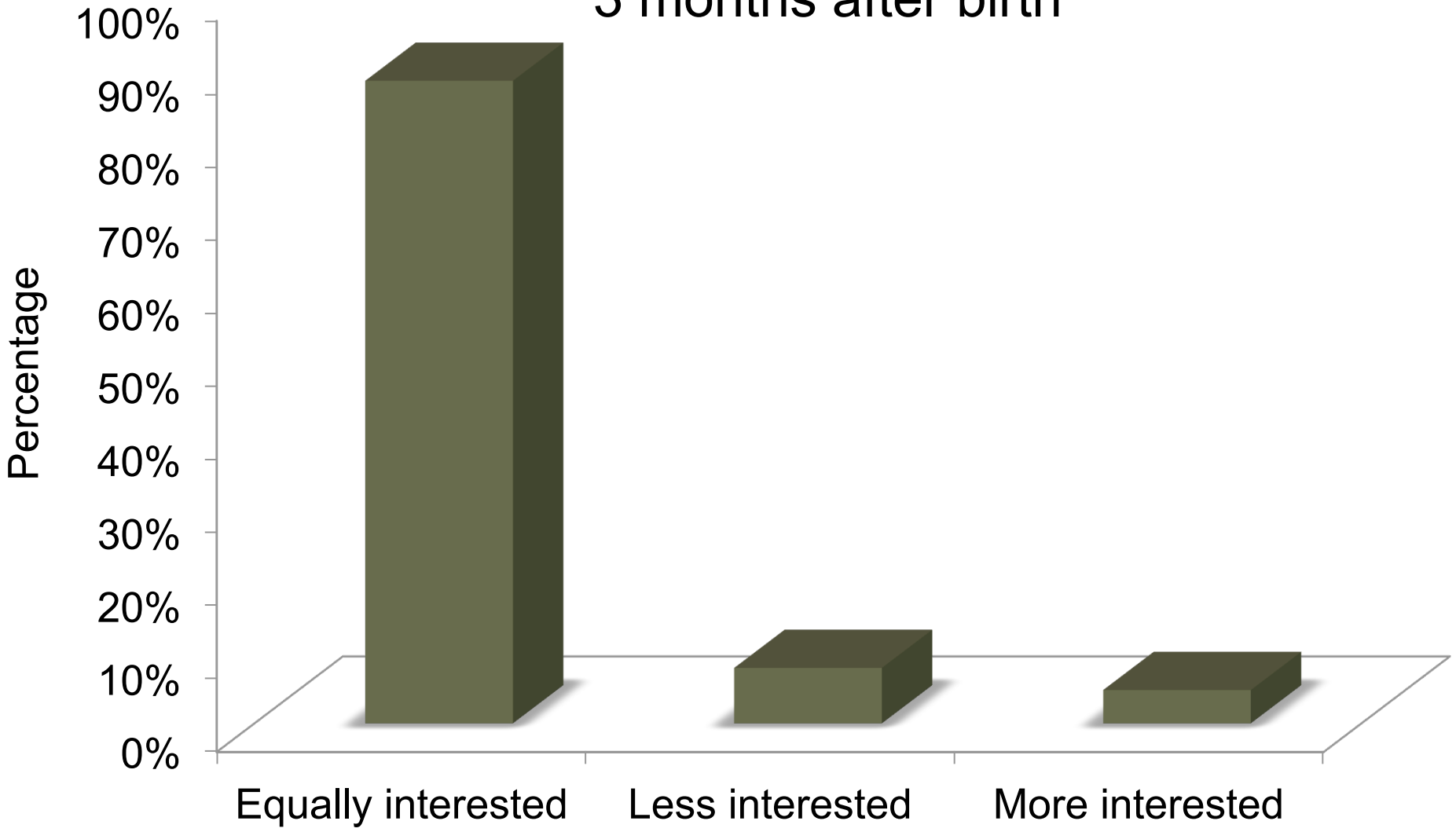
Parent Interest in Newborn Genome Screening: 3 months after birth



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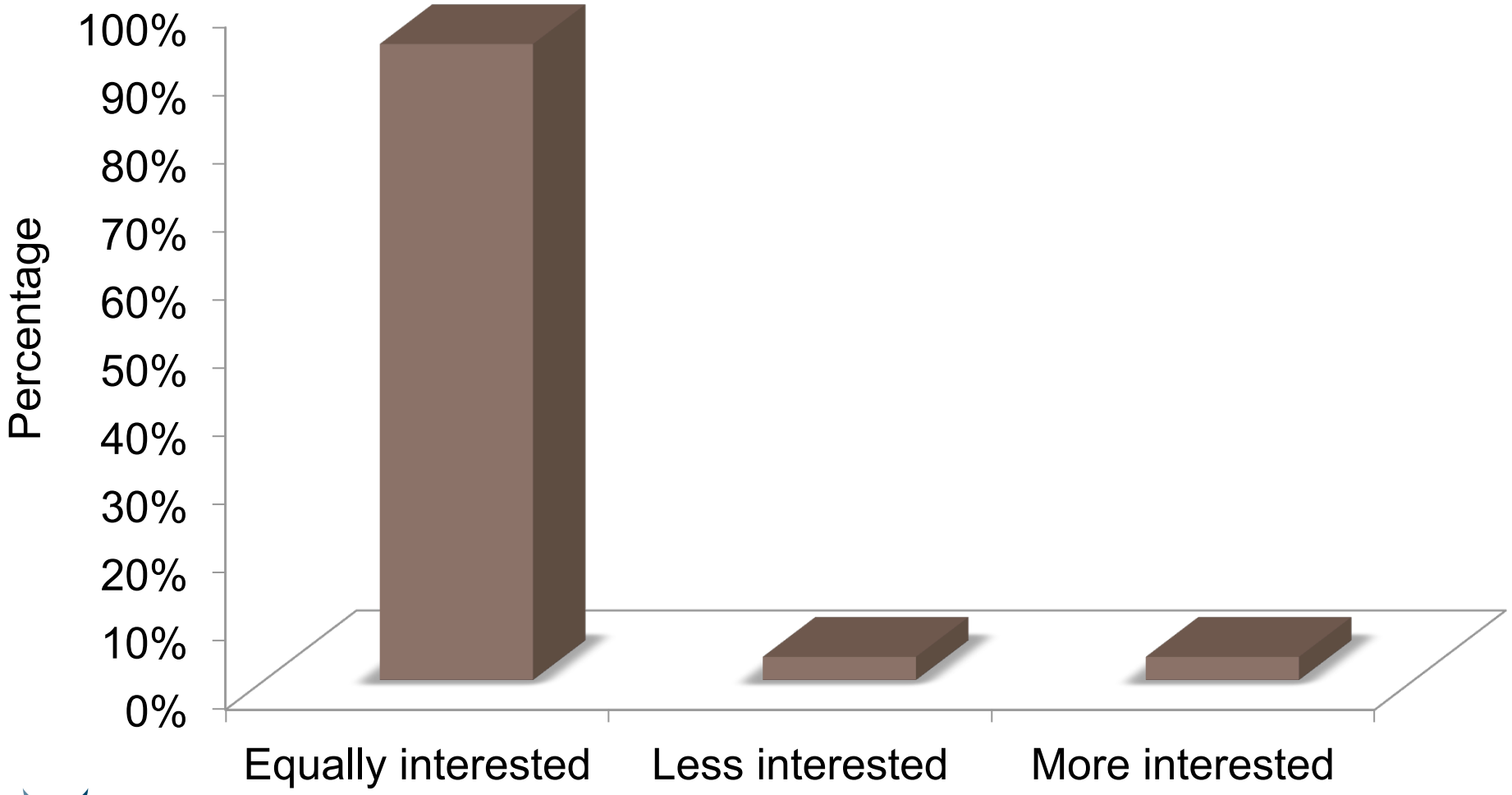
Parent Interest in Newborn Genome Screening: after Mock Results at 3 months



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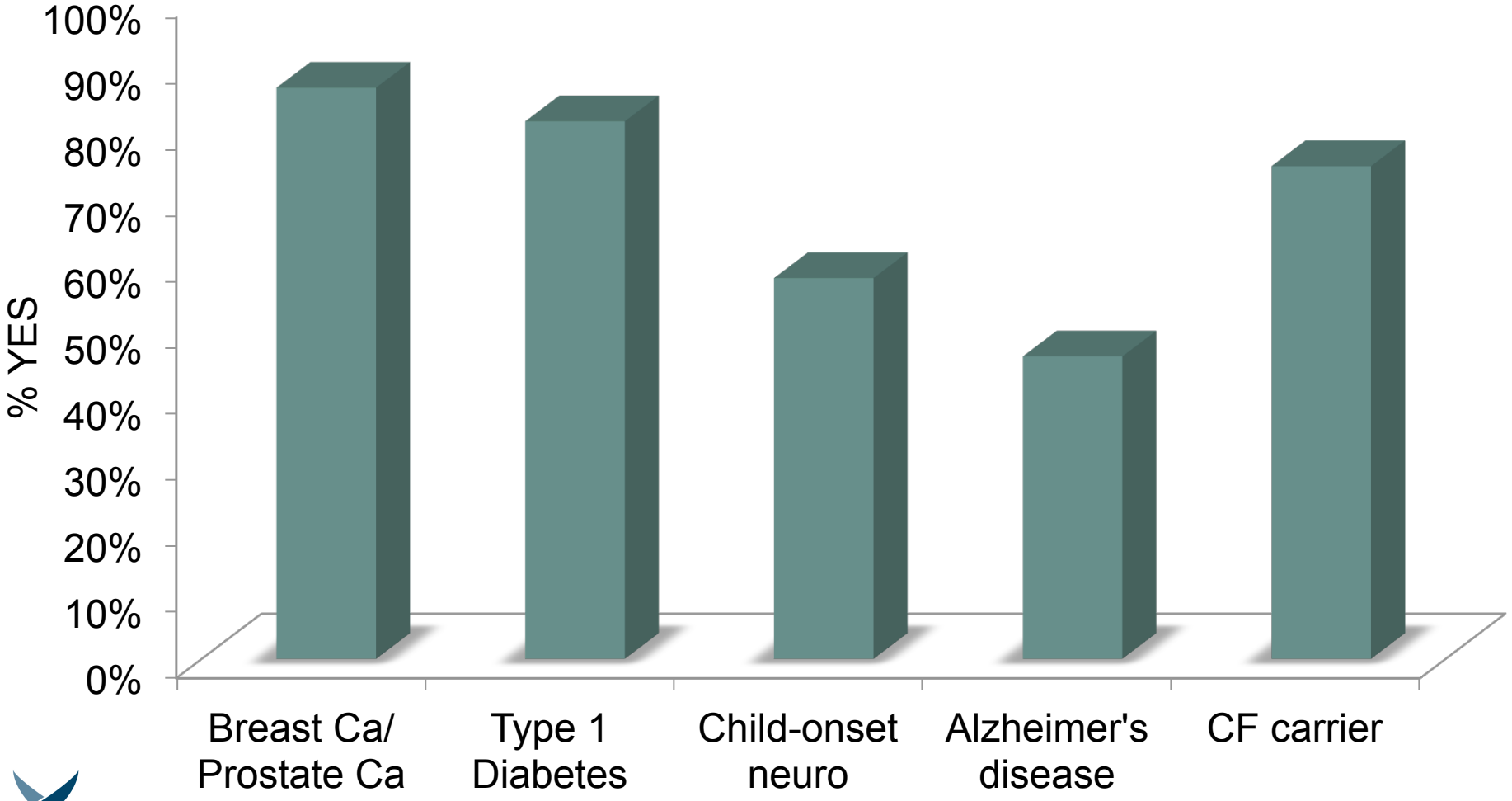
Would you want to know if your baby had a gene mutation related to these conditions?



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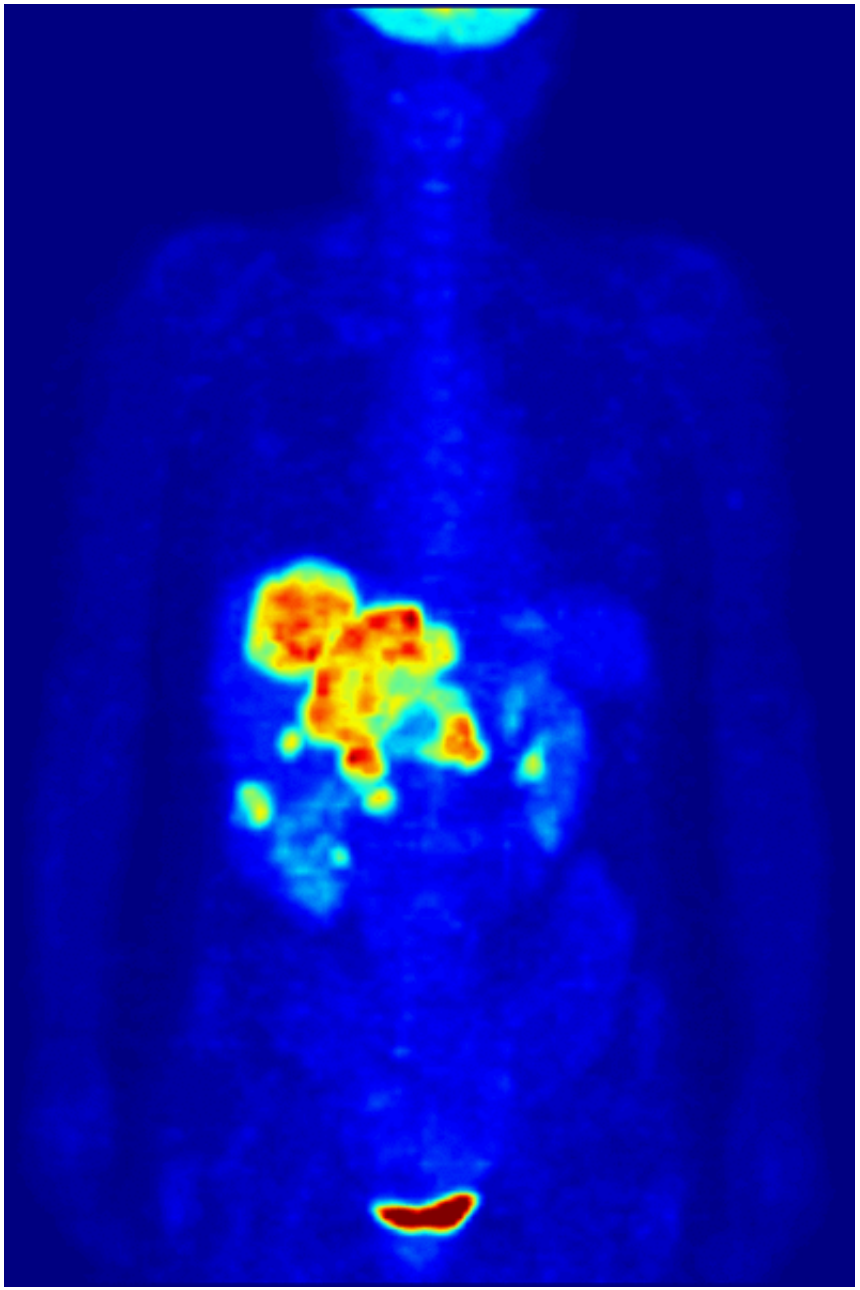
The Problem of
Incidental Findings
in
Clinical Sequencing

Incidental Findings:

What is the
right analogy?

How can reports be
generated and
scaled?



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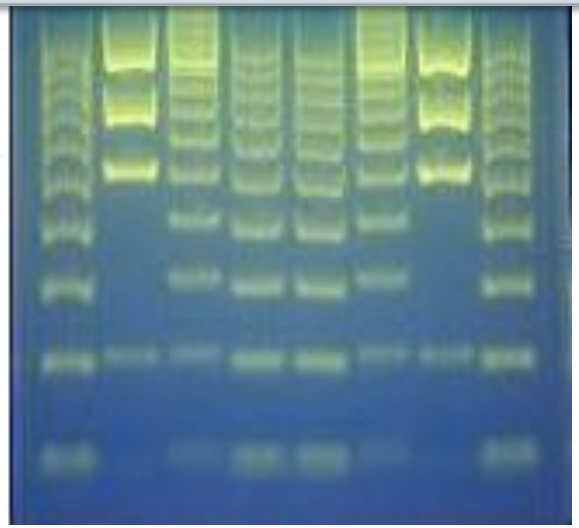
Population Screening
vs
Opportunistic Screening



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Setting Professional Standards for Incidental Findings in Clinical Sequencing

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ACMG POLICY STATEMENT | Genetics inMedicine

ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing

Robert C. Green, MD, MPH[1,2], Jonathan S. Berg, MD, PhD[3], Wayne W. Grody, MD, PhD[4–6], Sarah S. Kalia, ScM, CGC[1], Bruce R. Korf, MD, PhD[7], Christa L. Martin, PhD, FACMG[8], Amy McGuire, JD, PhD[9], Robert L. Nussbaum, MD[10], Julianne M. O'Daniel, MS, CGC[11], Kelly E. Ormond, MS, CGC[12], Heidi L. Rehm, PhD, FACMG[2,13], Michael S. Watson, MS, PhD, FACMG[14], Marc S. Williams, MD, FACMG[15] and Leslie G. Biesecker, MD[16]

[Q1]

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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.

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Principles: creating a minimum list…

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

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ACMG List of IFs

Inherited Cancer Disorders

Hereditary Breast and Ovarian Cancer
Li-Fraumeni Syndrome
Peutz-Jeghers Syndrome
Lynch Syndrome
Familial adenomatous polyposis
MYH-Associated Polyposis; Adenomas, multiple colorectal, FAP type 2; Colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas
Von Hippel Lindau syndrome
Multiple Endocrine Neoplasia Type 1
Multiple Endocrine Neoplasia Type 2
Familial Medullary Thyroid Cancer (FMTC)
PTEN Hamartoma Tumor Syndrome
Retinoblastoma
Hereditary Paraganglioma-Pheochromocytoma Syndrome
WT1-related Wilms tumor
Neurofibromatosis type 2
Tuberous Sclerosis Complex

Cardiac Disorders

EDS - vascular type
Marfan Syndrome, Loeys-Dietz Syndromes, and Familial Thoracic Aortic Aneurysms and Dissections
Hypertrophic cardiomyopathy,
Dilated cardiomyopathy
Catecholaminergic polymorphic ventricular tachycardia
Arrhythmogenic right ventricular cardiomyopathy
Romano-Ward Long QT Syndromes Types 1, 2, and 3, Brugada Syndrome
Familial hypercholesterolemia

Other: Malignant hyperthermia susceptibility

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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!

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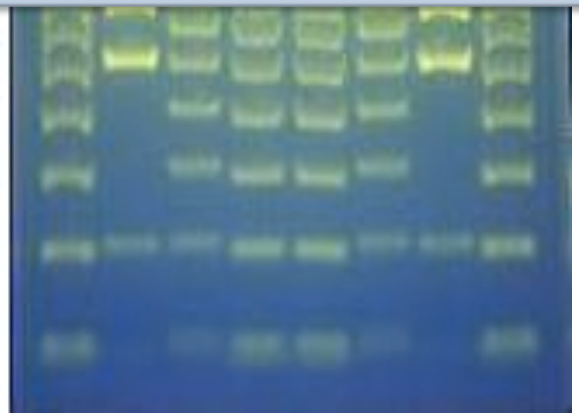
Population Screening
vs
Opportunistic Screening
vs
Resource to be Periodically Interrogated



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Genomics & Epigenomics as a Reference

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"…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

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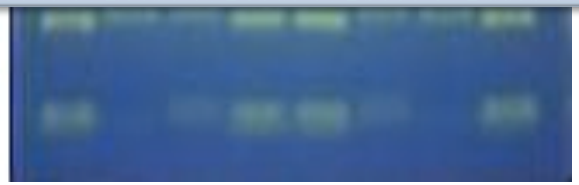

chapter in Ginsburg and Willard (eds)
Genomic and Personalized Medicine, 2nd Edition, 2013, in press

CHAPTER

Clinical Genome Sequencing

Robert C. Green, Heidi L. Rehm, and Isaac S. Kohane

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Thank You !!!

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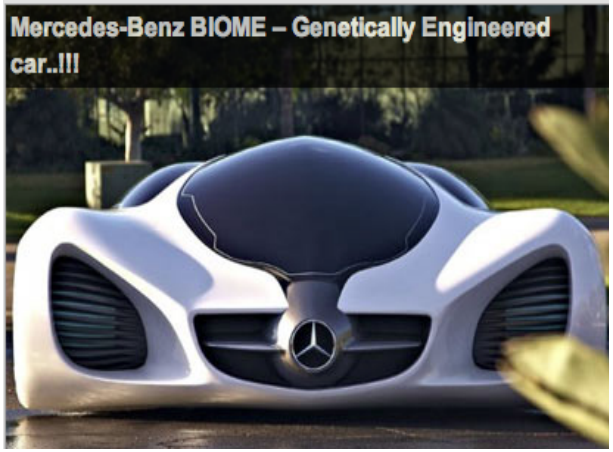

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