Building an Evidence Base for the Future of Genomics

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Brigham and Women's Hospital and Broad Institute

G2P GENOMES *to People*

PARTNERS HEALTHCARE | PERSONALIZED MEDICINE

BWH

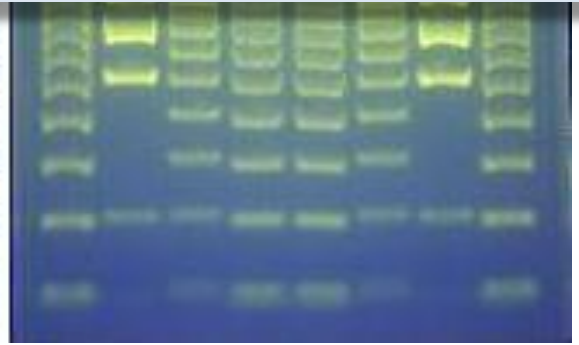
Disclosures

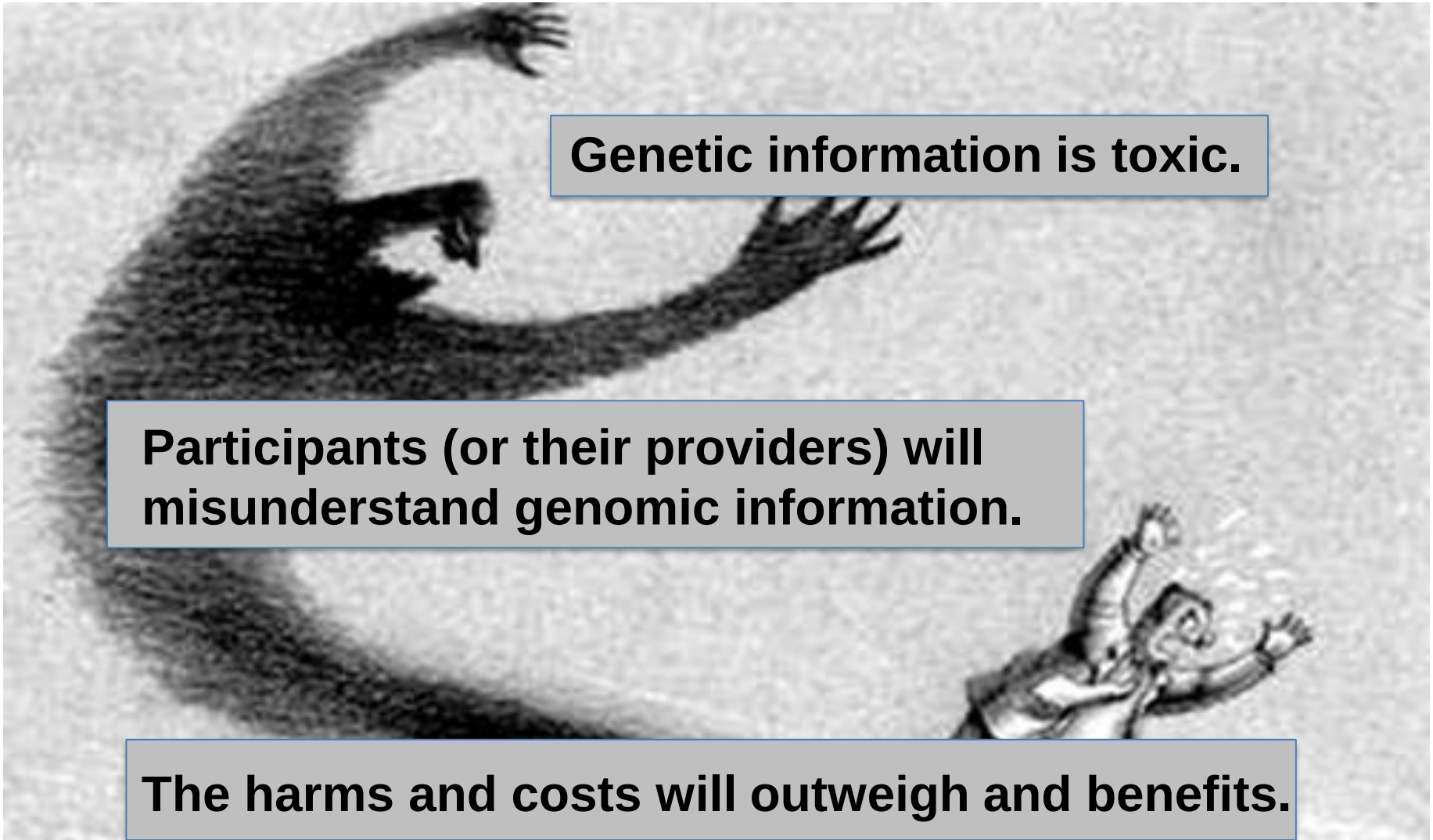
Research: US National Institutes of Health
NHGRI – NICHD - NIA
US Department of Defense
Broad Institute of MIT & Harvard

Advisory: AIA, Applied Therapeutics, Helix, Ohana Biosciences, OptraHealth, Prudential, Veritas

Co-Founder: Genome Medical - a technology and services company providing genetics expertise to patients, providers, employers and care systems (www.genomemedical.com)

What are the barriers to genomic medicine?




Genetic information is toxic.
Participants (or their providers) will misunderstand genomic information.
The harms and costs will outweigh and benefits.

The REVEAL Study

The PGen (DTC) Study

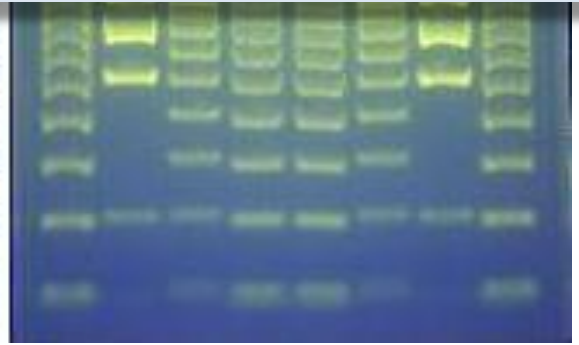
The MedSeq Project

The BabySeq Project

The PeopleSeq Consortium

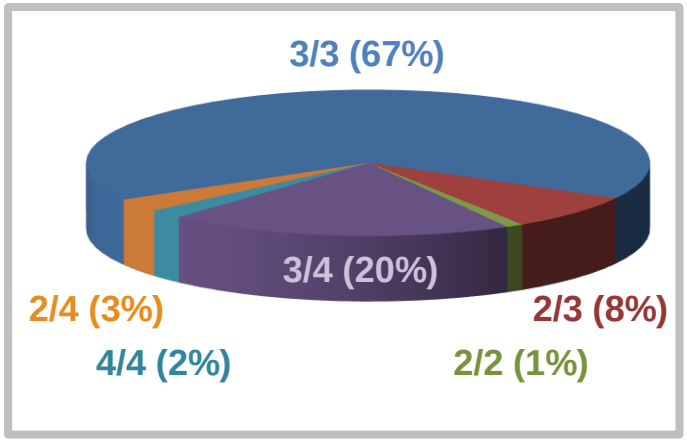
The MilSeq Project

Is genomic information toxic?



REVEAL Study of APOE Disclosure

NIH HG02213 / AG047866 (2000-2019)



Roberts et al, *Genet Med*, 2004
Cupples et al, *Genet Med*, 2004
LaRusse et al, *Genet Med*, 2004
Zick et al, *Hlth Aff*, 2005
Eckert et al, *Genet Med*, 2006

Chao et al, *Alz Dement*, 2008
Christensen et al, *Genet Med*, 2008
Fanshawe et al, *Genet Test*, 2008
Cassidy et al, *Alz Dement*, 2008
Chung et al, *Alz Dement*, 2009

Green et al, *NEJM*, 2009
Green et al, *Alz Dement*, 2011
Roberts et al, *Genet Med*, 2012
Christensen et al, *Ann Int Med*, 2016
Christensen et al, *Genet Med*, 2017

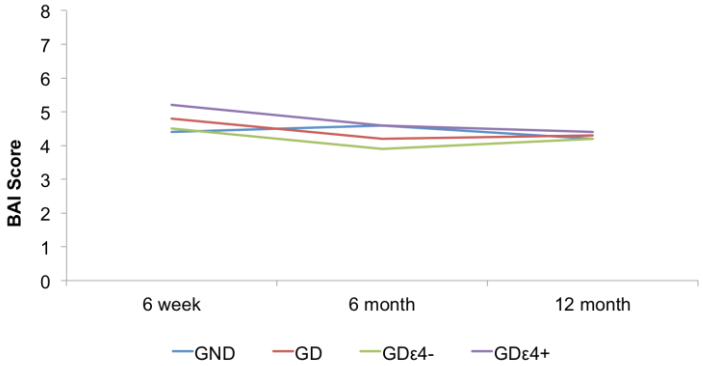
The REVEAL Study: Disclosing APOE Genotype

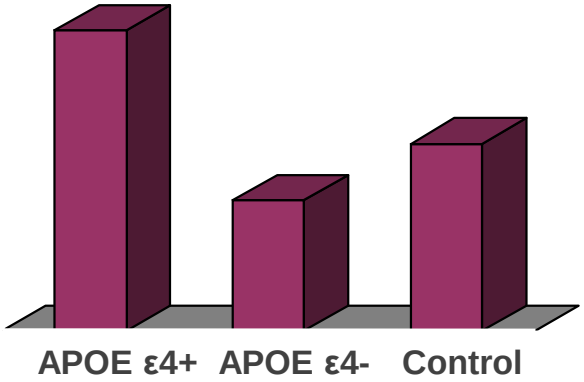
The NEW ENGLAND JOURNAL of MEDICINE

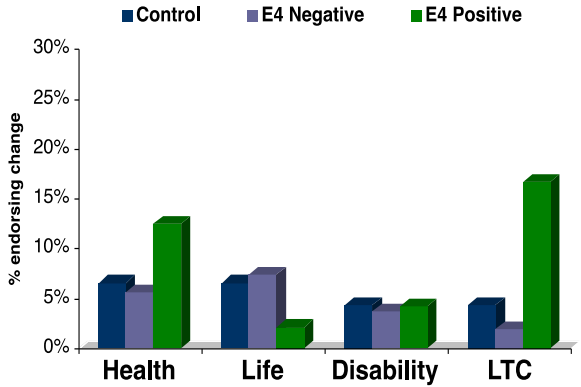
ORIGINAL ARTICLE

Disclosure of *APOE* Genotype for Risk of Alzheimer's Disease

Robert C. Green, M.D., M.P.H., J. Scott Roberts, Ph.D., L. Adrienne Cupples, Ph.D., Norman R. Relkin, M.D., Ph.D., Peter J. Whitehouse, M.D., Ph.D., Tamsen Brown, M.S., Susan LaRusse Eckert, M.S., Melissa Butson, Sc.M., A. Dessa Sadovnick, Ph.D., Kimberly A. Quaid, Ph.D., Clara Chen, M.H.S., Robert Cook-Deegan, M.D., and Lindsay A. Farrer, Ph.D., for the REVEAL Study Group*

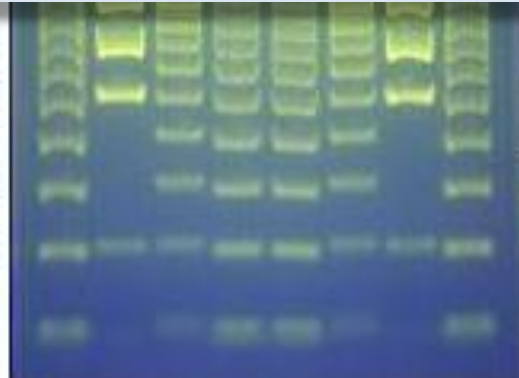






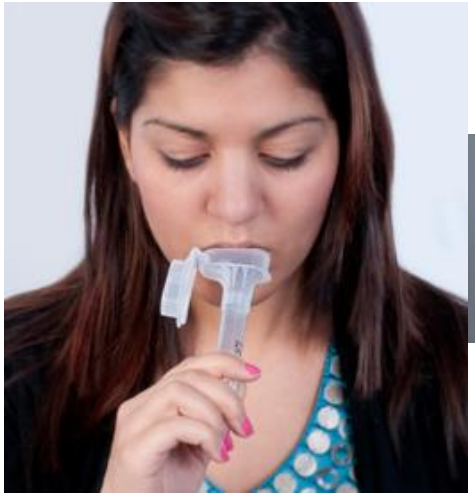
Zick et al, *Health Affairs*, 2005; Chao et al, *Alzheimer's & Dementia*, 2008; Green et al, *New Engl J Med*, 2009; Taylor et al, *Health Affairs*, 2010

Is genomic information misunderstood?



Impact of Personal Genomics (PGen) Study

NIH HG005092 (2010-2014)

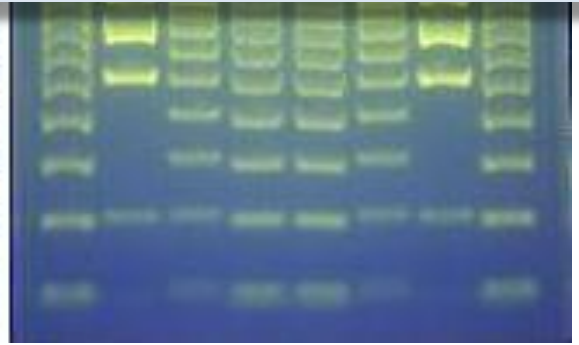


Green and Farahany, *Nature*, 2014
Ostergren et al, *Publ Hlth Genomics*, 2015
Carere et al, *BMC Med Genetics*, 2015
Van der Wouden et al, *Ann Int Med*, 2016

Krieger et al, *Nature Biotech*, 2016
Carere et al, *Genet Med*, 2016
Gray et al, *J Clin Onc*, 2017
Roberts et al, *Publ Hlth Genomics*, 2017

Landry et al, *J Comm Genet* 2017
Koeller et al, *J Genet Couns*, 2017
Nielsen et al, *BMC Med Genomics*, 2017
Gollust et al, *Milbank Quart*, 2017

How are we using exome and genome sequencing in the current practice of medicine?



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Elizabeth G. Phimister, Ph.D., *Editor*

Diagnostic Clinical Genome and Exome Sequencing

Leslie G. Biesecker, M.D., and Robert C. Green, M.D., M.P.H.

SEQUENCING OF THE GENOME OR EXOME FOR CLINICAL APPLICATIONS, hereafter referred to as clinical genome and exome sequencing (CGES), has now entered medical practice.[1] Several thousand CGES tests have already been ordered for patients, with the goal of establishing diagnoses for rare, clinically unrecognizable, or puzzling disorders that are suspected to be genetic in origin. We anticipate increases in the use of CGES, the key attribute of which — its breadth — distinguishes it from other forms of laboratory testing. The interrogation of variation in about 20,000 genes simultaneously can be a powerful and effective diagnostic method.[2]

In the clinical realm, WES/WGS is currently used most for:

- undiagnosed disease

and

- treatment of cancer

Biesecker and Green, *NEJM,* 2014

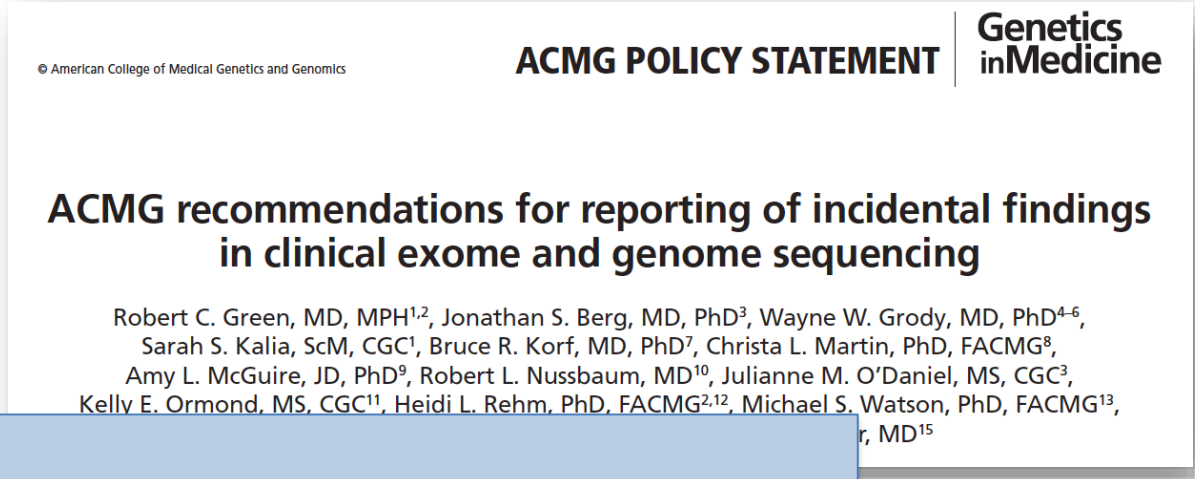
The problem and opportunity of incidental and unanticipated findings with clinical sequencing

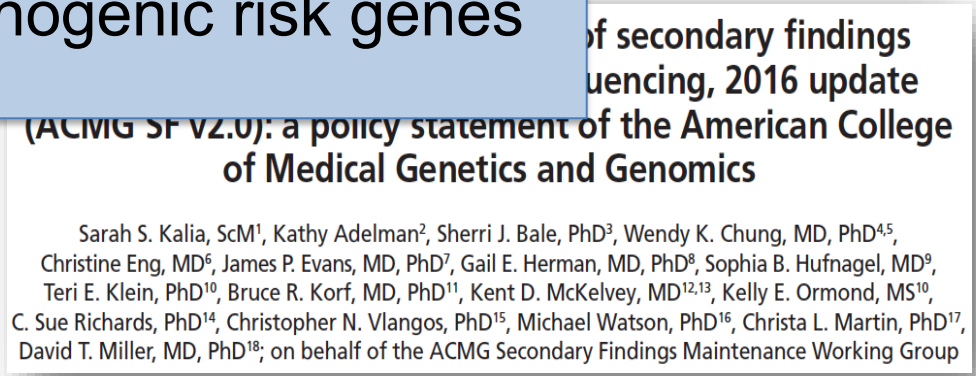
Inherited Cancer Disorders
Hereditary Breast and Ovarian Cancer
Li-Fraumeni Syndrome
Peutz-Jeghers Syndrome
Lynch Syndrome
Familial adenomatous polyposis
Von Hippel Lindau syndrome
Retinoblastoma
WT1-related Wilms tumor
Neurofibromatosis type 2
Tuberous Sclerosis Complex
Multiple Endocrine
Multiple Endocrine
Familial Medullary
PTEN Hamartoma
Polyposis/Juvenile
Hereditary Paraga

Cardiac Disorders
EDS - vascular type
Hypertrophic cardiomyopathy
Dilated cardiomyopathy
Catecholaminergic polymorphic ventricular tachycardia
Arrhythmogenic right ventricular cardiomyopathy
Romano-Ward Long QT Syndromes, Brugada Syndrome
Marfan Syndrome, Loeys-Dietz, Familial Thoracic Aortic Aneurysms

Other:Wilson Disease, OTC, Malignant hyperthermia susceptibility, Familial hypercholesterolemia

The “ACMG 59” monogenic risk genes

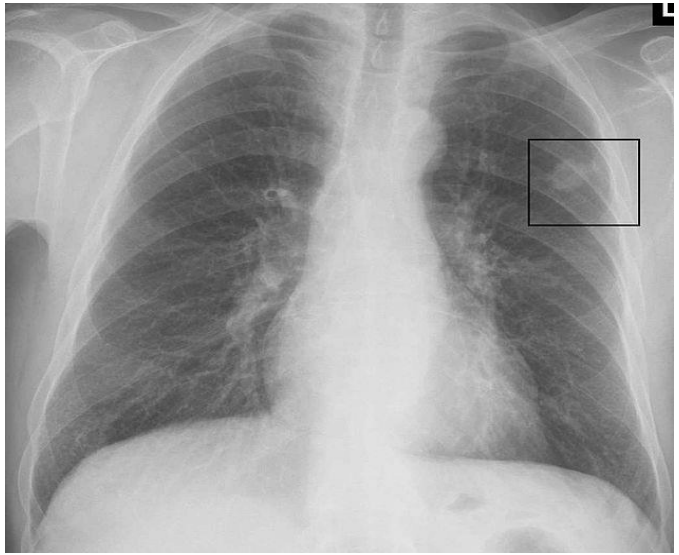


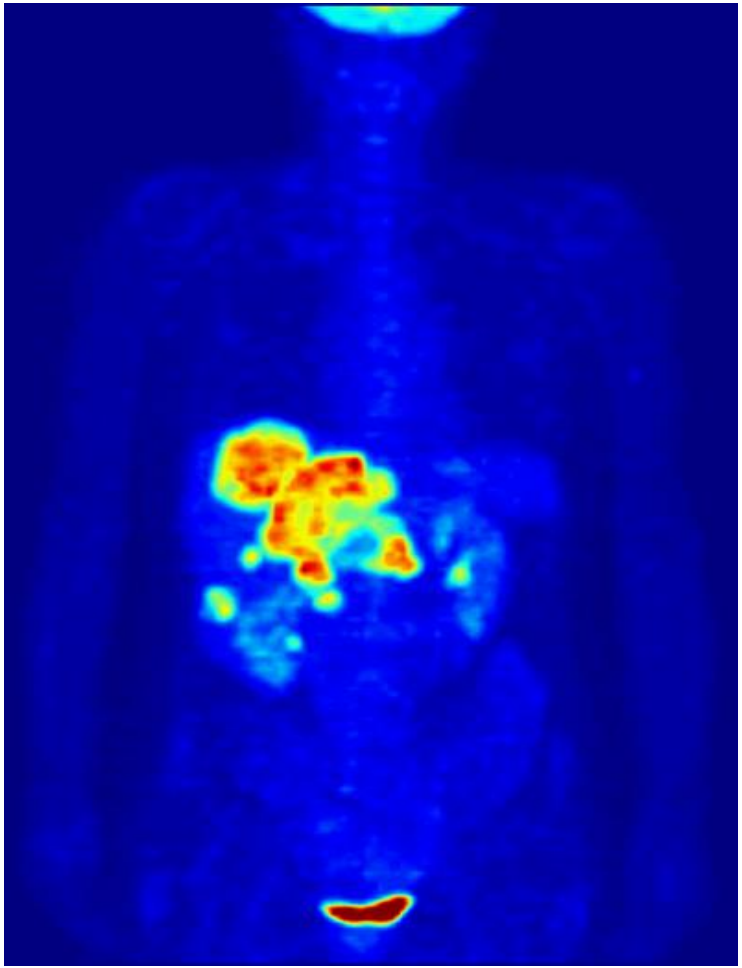


Green et al, *Genet Med*, 2013
Kalia et al, *Genet Med*, 2016

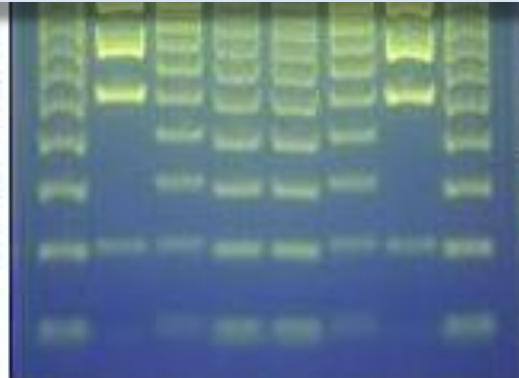
Genome Screening

What is the right analogy?





How will large scale research projects manage unanticipated genomic findings?



Major US Biobank/Sequencing Research Studies

Study	Recruitment	Sponsor	Focus	Current Return
Geisinger MyCode	200,000+	Industry	Enriched & Healthy	Indication plus 80 monogenic to EHR
Million Veteran	600,000 / 1 million	US Govt	Enriched & Healthy	None except possible pilot
PMI / AllofUs	100,000 / 1 million	US Govt	Enriched & Healthy	Considering return of ACMG59, PGx, all data “available”

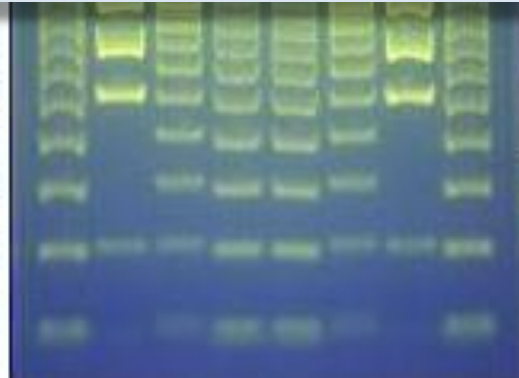
AoU RP Actual and Projected Enrollments: As of 6/26/18

Month	May	June	July	August	Sept.	Oct.	Nov.	Dec. 2017	Jan. 2018	Feb.	March	April	May	June 26th
Projected Full Enrollment	10	370	1,334	2,857	5,135	9,056	13,634	21,550	31,245	38,955	47,380	58,330	68,520	80,020
Total Enrollment	11	486	1,571	3,153	5,229	8,375	12,165	15,642	20,975	26,717	35,790	42,997	67,367	78,186
Full Participant	0	232	835	2,020	3,282	5,107	7,460	10,044	13,319	16,341	20,680	25,528	32,351	37,924
Registered	1	191	525	840	1,557	2,526	3,639	4,389	5,727	7,437	10,407	12,351	24,445	28,039
Member	7	63	211	293	390	742	1,066	1,209	1,929	2,939	4,703	5,118	10,571	12,223
FP		63% FP	63% FP	71% FP	64% FP	56% FP	55% FP	47% FP	43% FP	42% FP	44% FP	44% FP	47% FP	47% FP

Enrolled Participants (N)

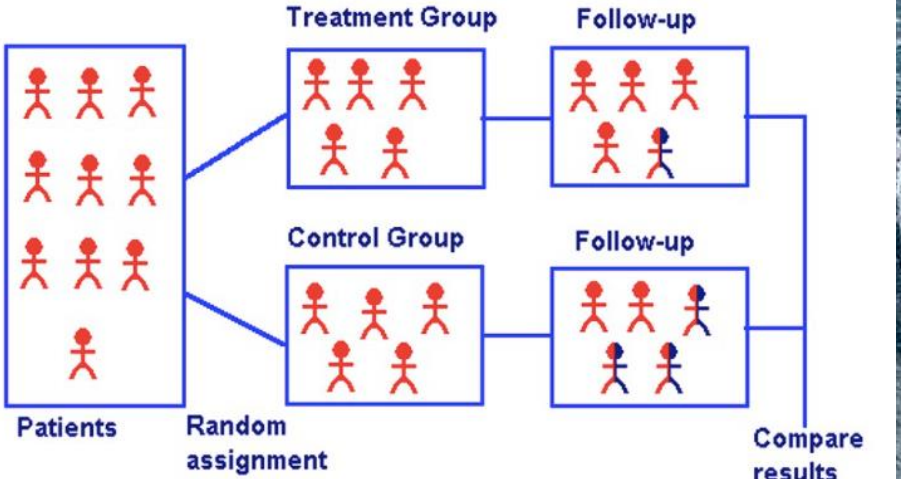
90,000
80,000
70,000
60,000
50,000
40,000
30,000
20,000
10,000
0

What are the medical, behavioral and economic outcomes associated with unanticipated findings from sequencing?

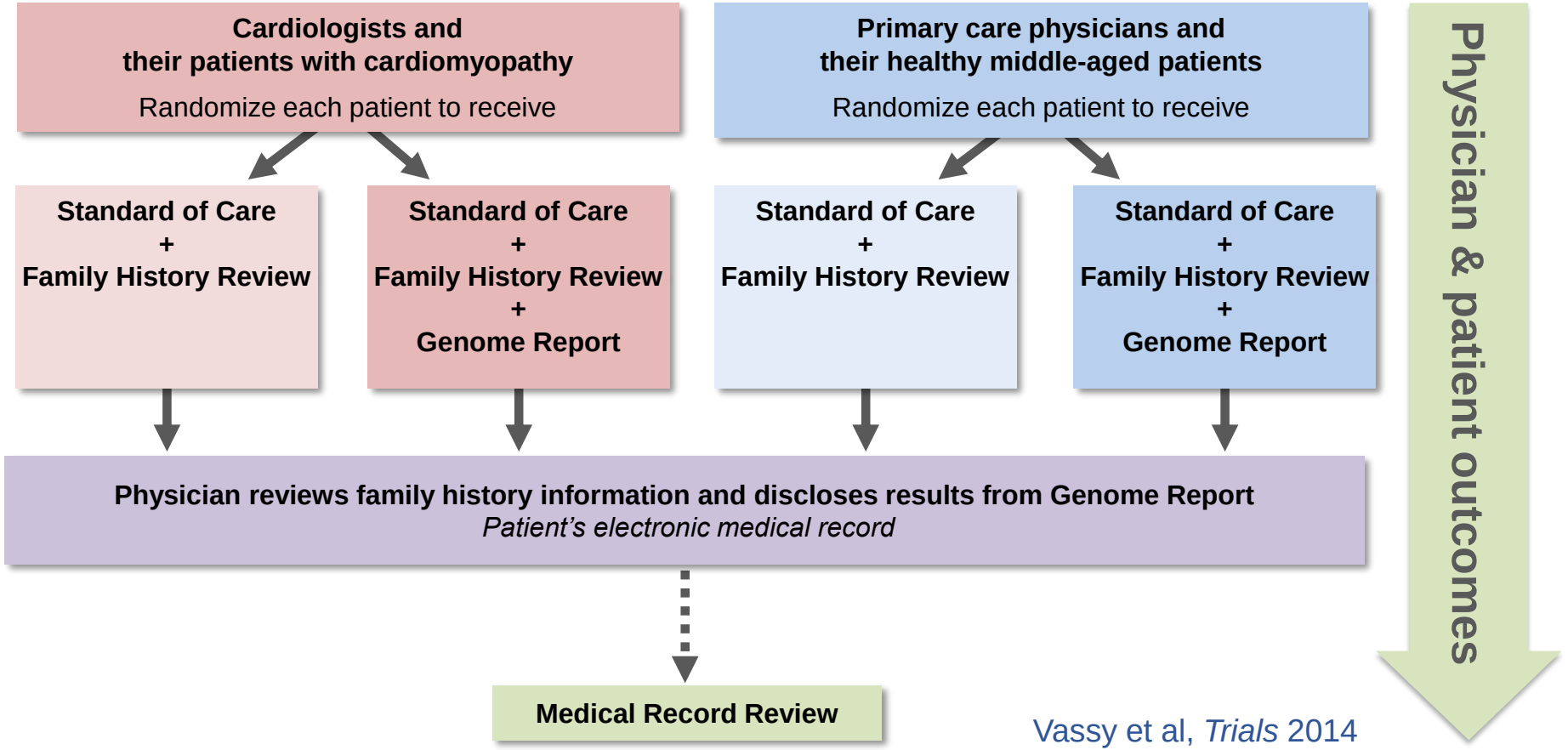


The MedSeq Pilot Project

NIH HG006500

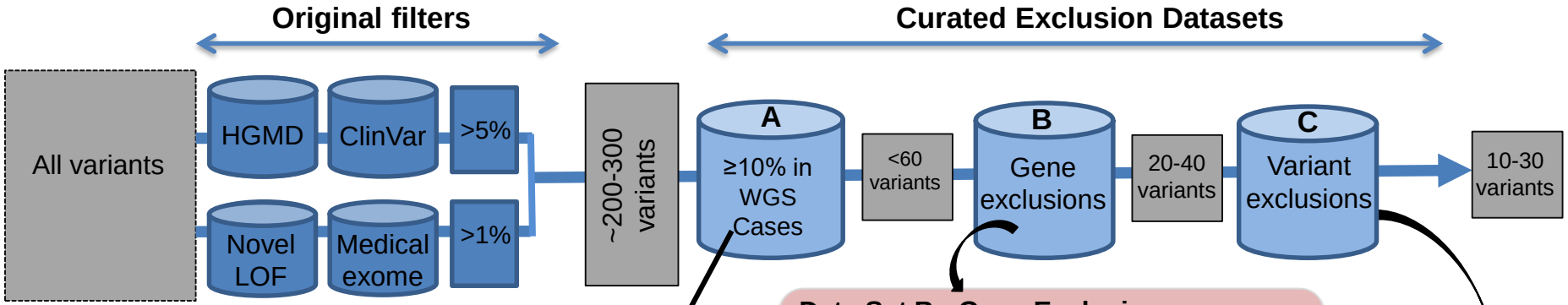


The MedSeq Project



Vassy et al, *Trials* 2014

Genome / Exome Filtering Approach



Data Set A ≥ 10% MAF WGS Cases

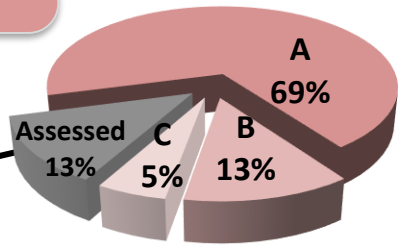
- Excludes common technical FPs
- Common indels wrong nomenclature
- Exceptions FV, HFE, SERPINA1

Data Set B - Gene Exclusions

- Evidence for gene-disease association = none, limited, or disputed
- Non medically relevant phenotype

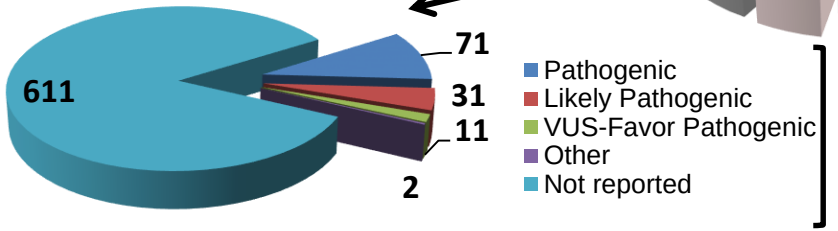
Data Set C - Variant Exclusions

- Benign interpretation
- LOF but LOF not disease mechanism
- GWAS or PGx association only



Not reported variants: 82%

- VUS, Likely Benign, Benign
- False positive variants



Reported variants: 18%

McLaughlin et al, *BMC Med Genetics*, 2014

Understandable reporting

- Monogenic risk variants
- Polygenic risk variants
- Carrier variants
- Pharmacogenomic variants
- Blood groups

- Additional Pages…
  - Structured variant data
  - Variant evidence
  - Disease/inheritance
  - Supporting references

Vassy et al, *Trials*, 2014
McLaughlin et al, *BMC Med Genetics*, 2014

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65 LANDSDOWNE ST, CAMBRIDGE, MA02139
PHONE: (617) 768-8500 / FAX: (617) 768-8513
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**

GENERAL GENOME REPORT

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.

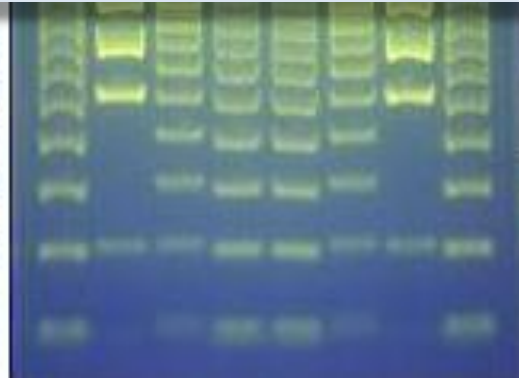
Drug	Risk and Dosing Information
C1. Warfarin	Decreased dose requirement.
C2. Clopidogrel	Typical risk of bleeding and cardiovascular events.
C3. Digoxin	Increased serum concentration of digoxin.
C4. Metformin	Typical glycemic response to metformin.
C5. Simvastatin	Lower risk of simvastatin-related myopathy.

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

MedSeq Project
Medical Outcomes



Reported findings from MedSeq Project analysis of variants in ~4600 genes

	Mendelian Disease Risk SFs	Carrier Status SFs	Diagnostic Findings in the Cardiology Cohort
# of patients	21/100 (21%)	92/100 (92%)	24/50 (48%)
Mean reported variants per patient	.21	2.3	0.54
Range of reported variants per patient	0-1	0-7	0-2

McLaughlin et al, *BMC Med Genetics*, 2014
Vassy et al, *Ann Int Med*, 2017

Unanticipated monogenic disease risk variants

Gene	Disease	Classification	Phenotype?
RDH5	Fundus albipunctatus (x2)	P	
PPOX	Variegate porphyria	P	
LHX4	Combined pituitary hormone deficiency	P	
HFE	Hereditary hemochromatosis (x2)	P	
COL2A1	Spondyloepiphyseal dysplasia congenita	LP	
ANK2	Ankyrin-B related cardiac arrhythmia	LP	
KCNQ1	Romano-Ward syndrome	LP	
F5	Factor V Leiden thrombophilia	Risk alle	
ARSE	Chondrodysplasia punctata	VUS: FP	
TNNT2	Hypertrophic cardiomyopathy	VUS: FP	
PDE11A	Primary pigmented micronodular adrenocortical disease	VUS: FP	

"White spots" in fundi, difficulty with dark adaptation

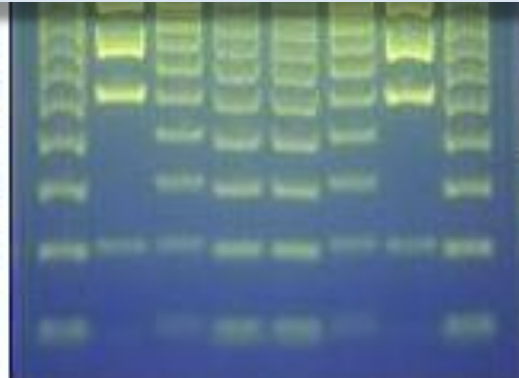
"Odd rashes," family history of photosensitivity

Normal ferritin, elevated transferrin saturation

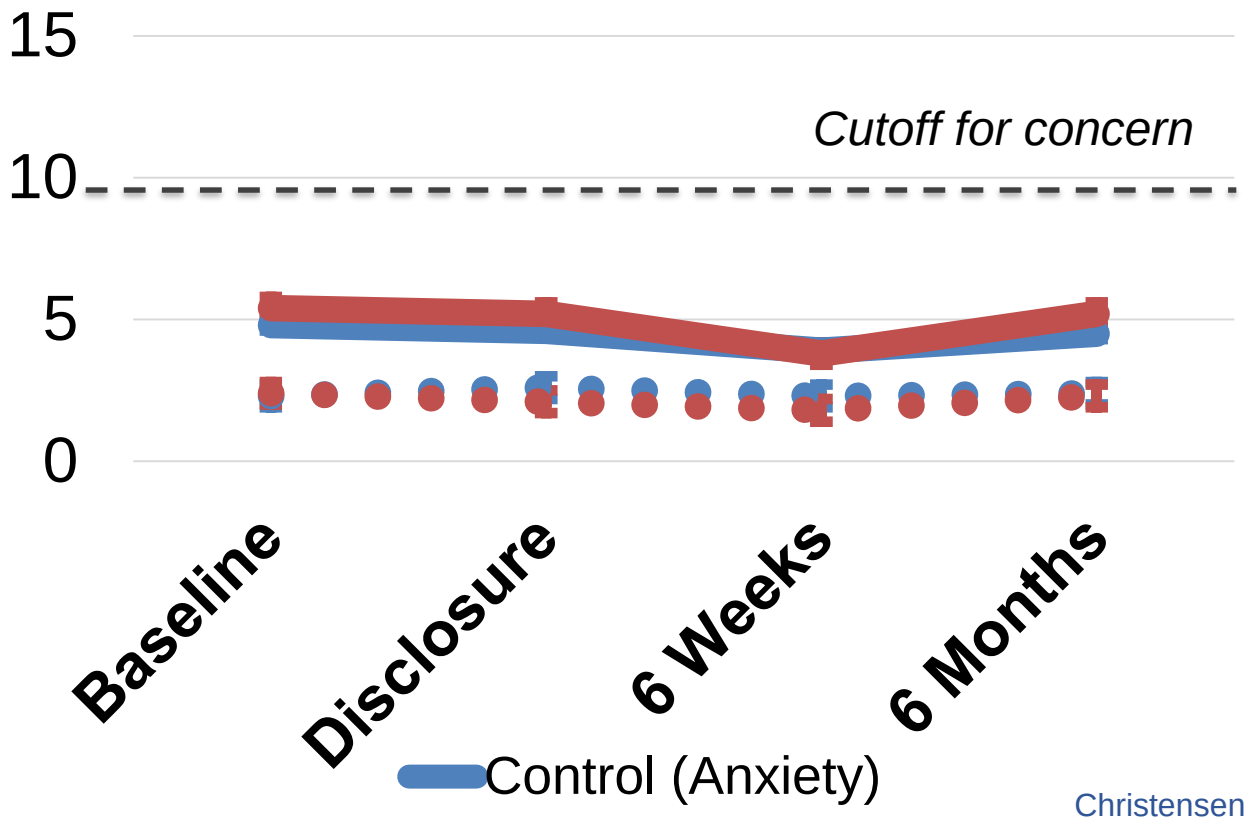
Negative ECG and stress test

Vassy et al, *Ann Int Med*, 2017

MedSeq Project
Behavioral Outcomes

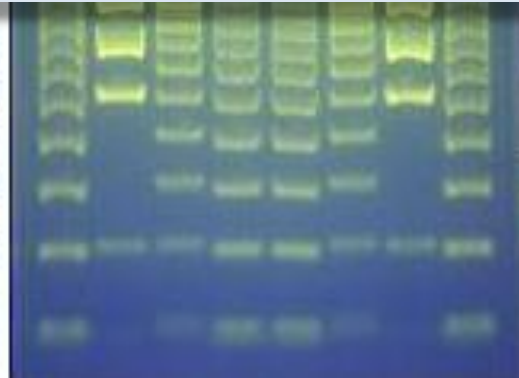


Anxiety and Depression in Whole Genome Sequencing

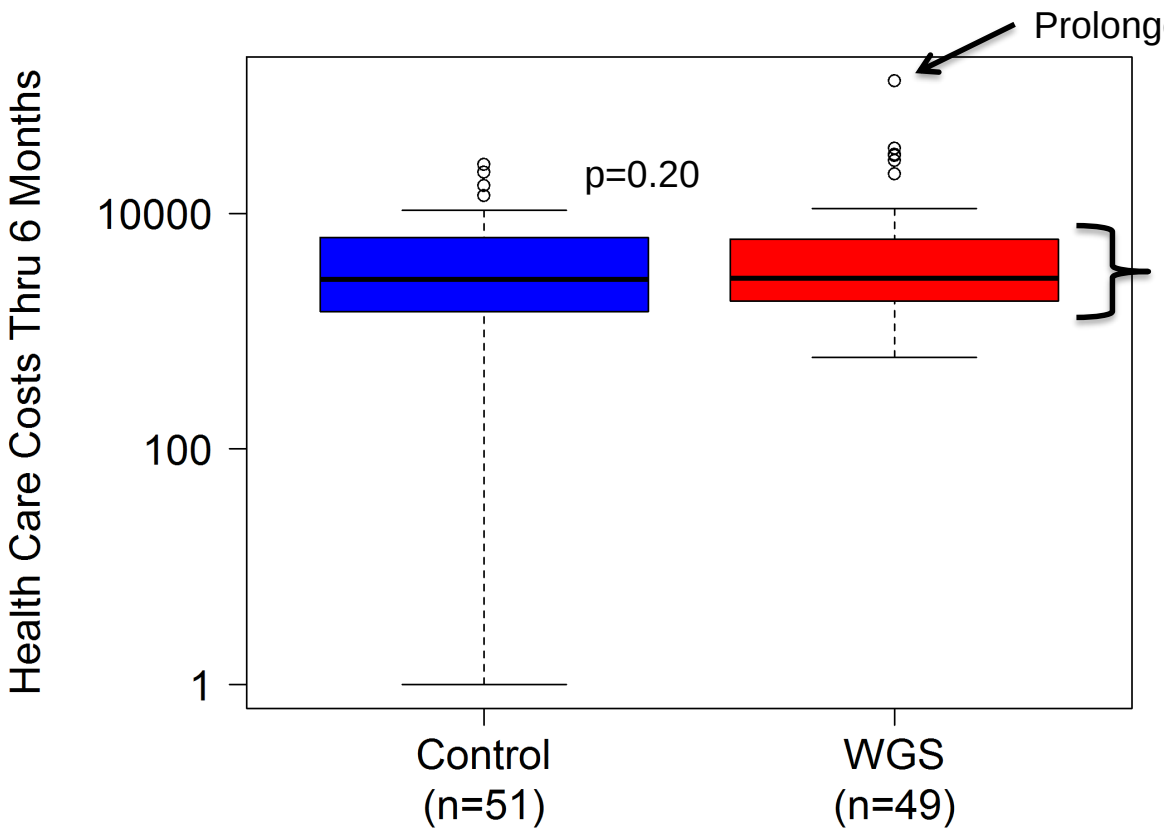


Christensen et al, in preparation

MedSeq Project
Economic Outcomes



Medical Costs After Sequencing



New diagnostic findings

Median:

$2,756 vs $2,819

Mean:

$4,841 vs $8,750

Vassy et al, *Ann Int Med*, 2017
Christensen et al, *Genet Med*, 2018

BabySeq™

NIH NSIGHT Consortium - HD077671 (2013-2018)

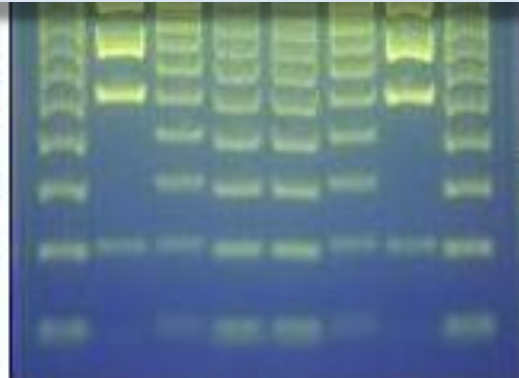
"…whether you like it or not, a complete sequencing of newborns is not far away"

Francis Collins, 2012

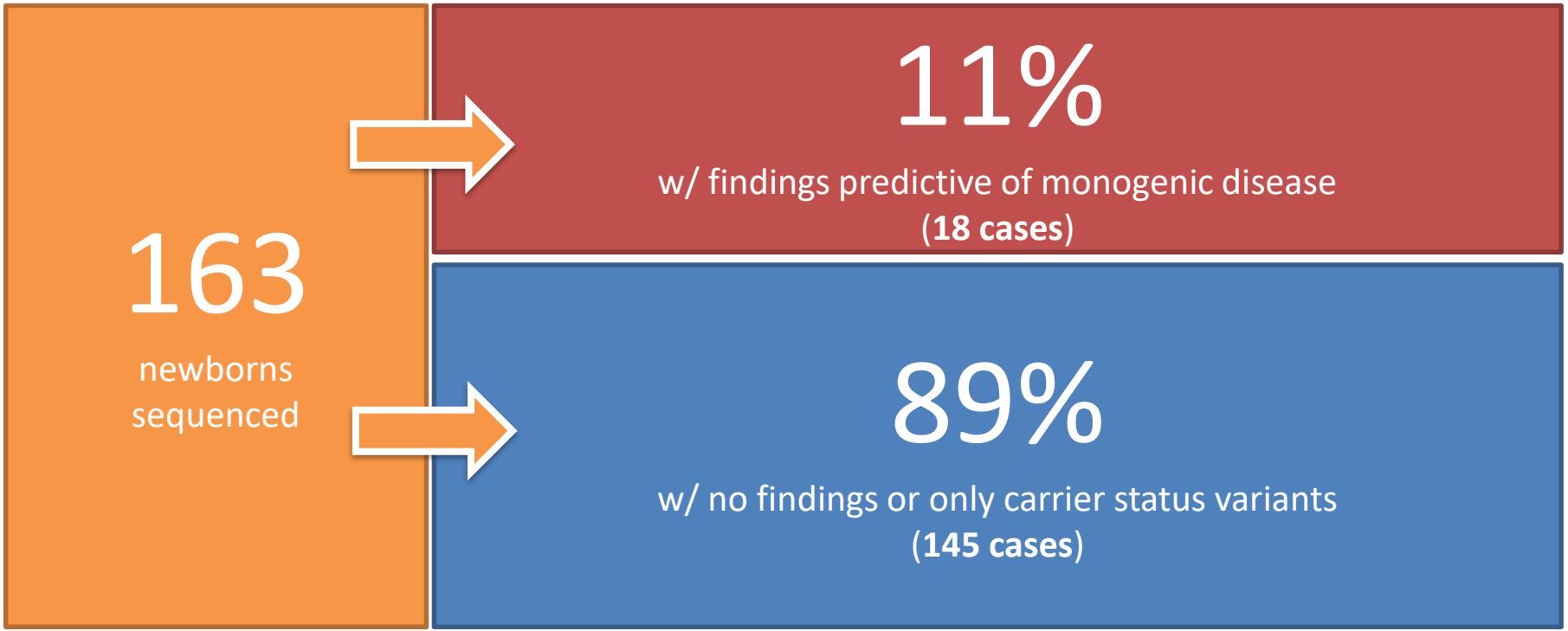
PARTNERS HEALTHCARE | PERSONALIZED MEDICINE

BCM Baylor College of Medicine

BabySeq Project
Preliminary Medical Outcomes

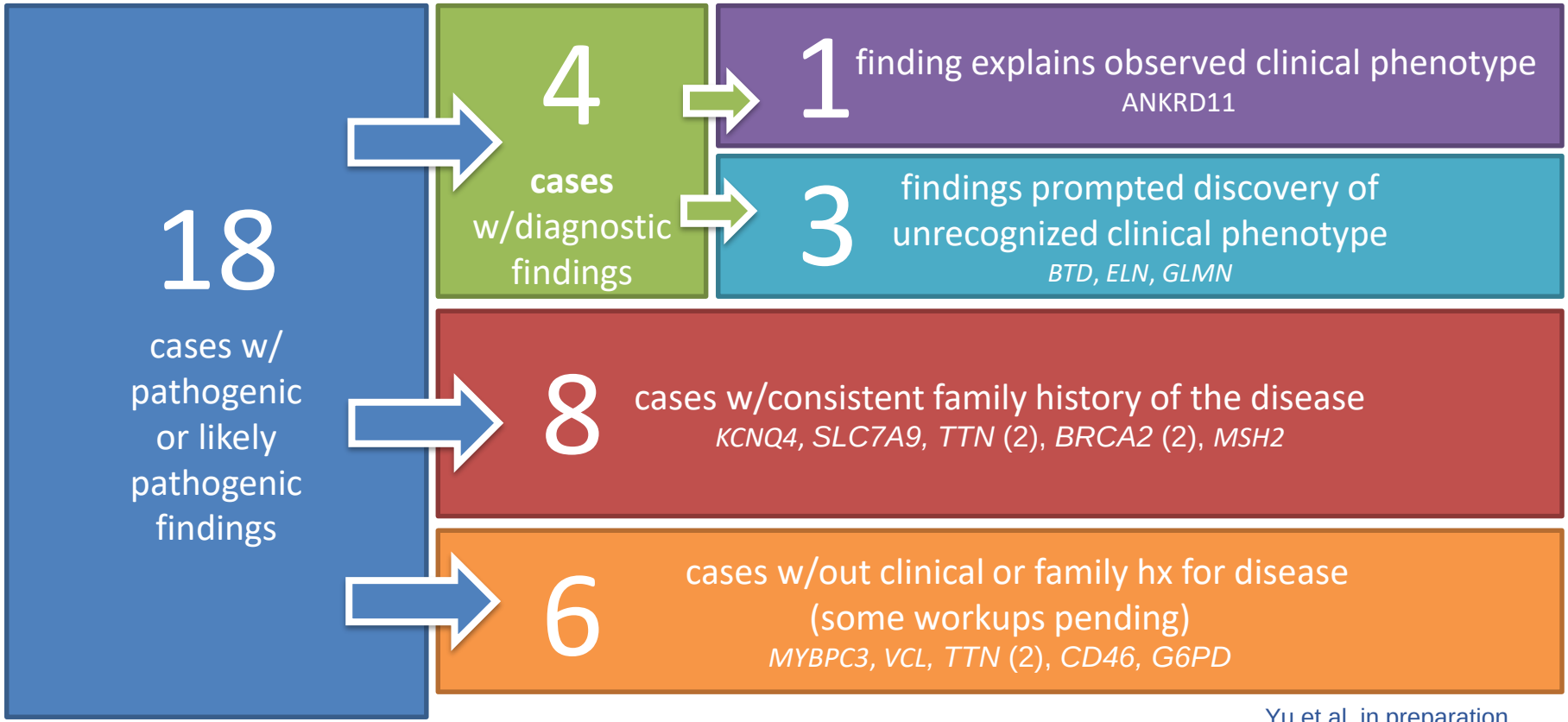


BabySeq Unanticipated Monogenic Disease Risks



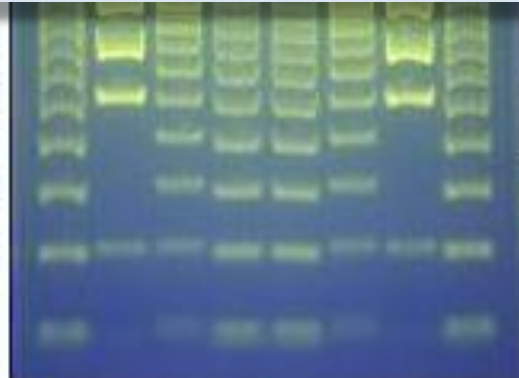
Yu et al, in preparation

BabySeq Unanticipated Monogenic Disease Risks and Findings

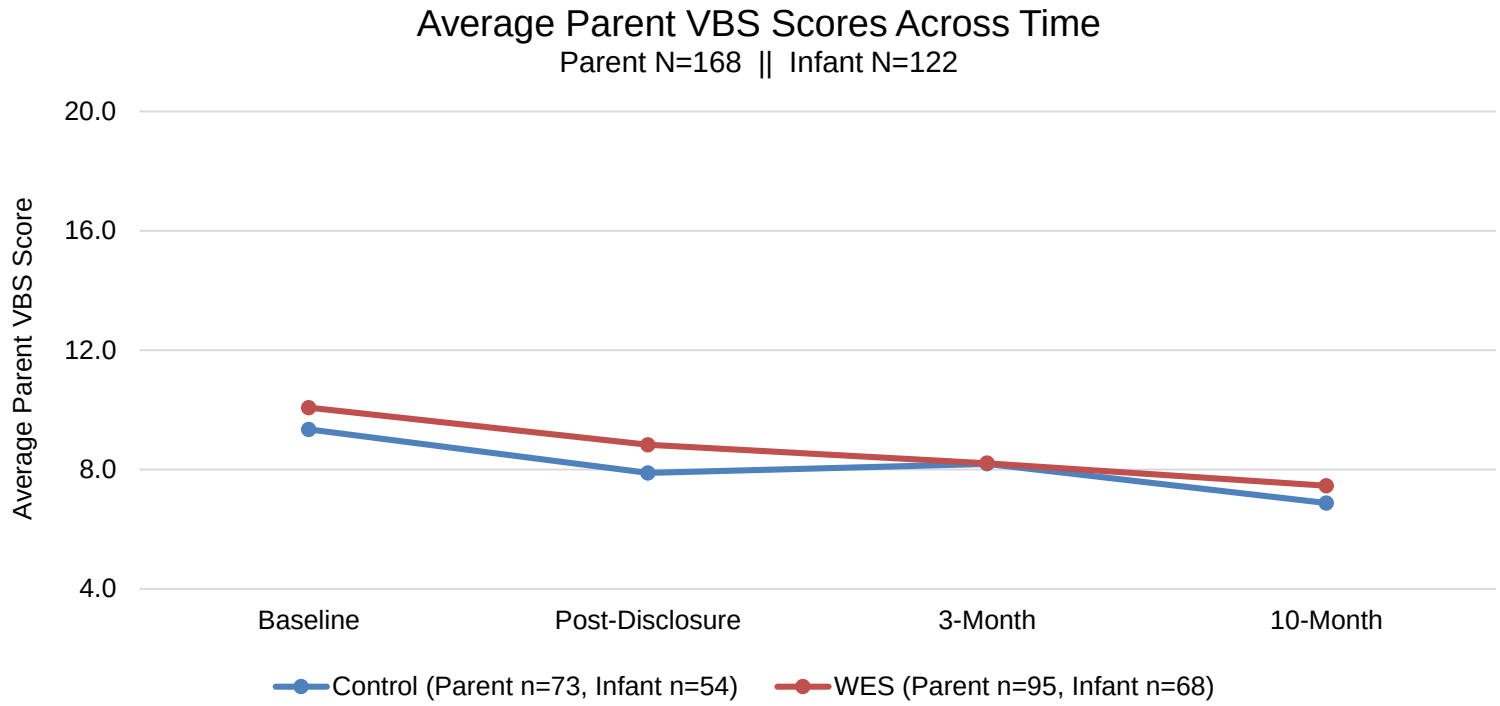


Yu et al, in preparation

BabySeq Project
Preliminary Behavioral Outcomes

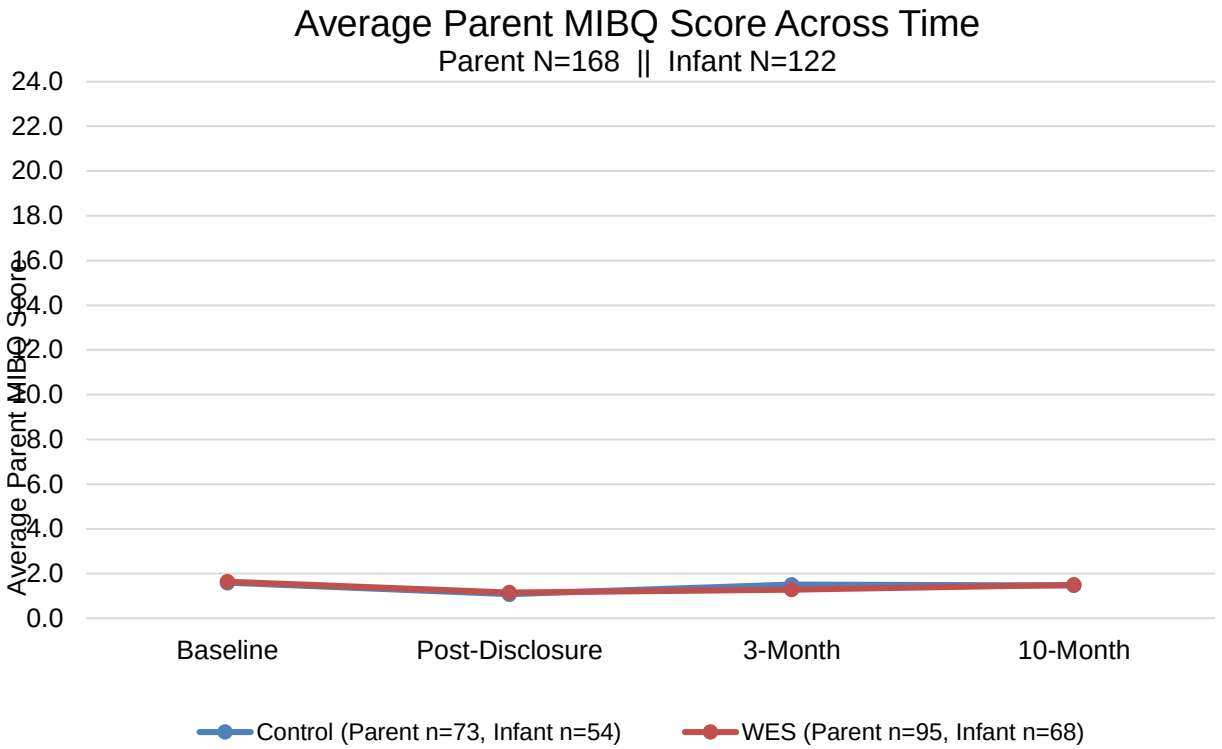


Preliminary data from BabySeq show no difference between randomization arms on Vulnerable Baby Scale



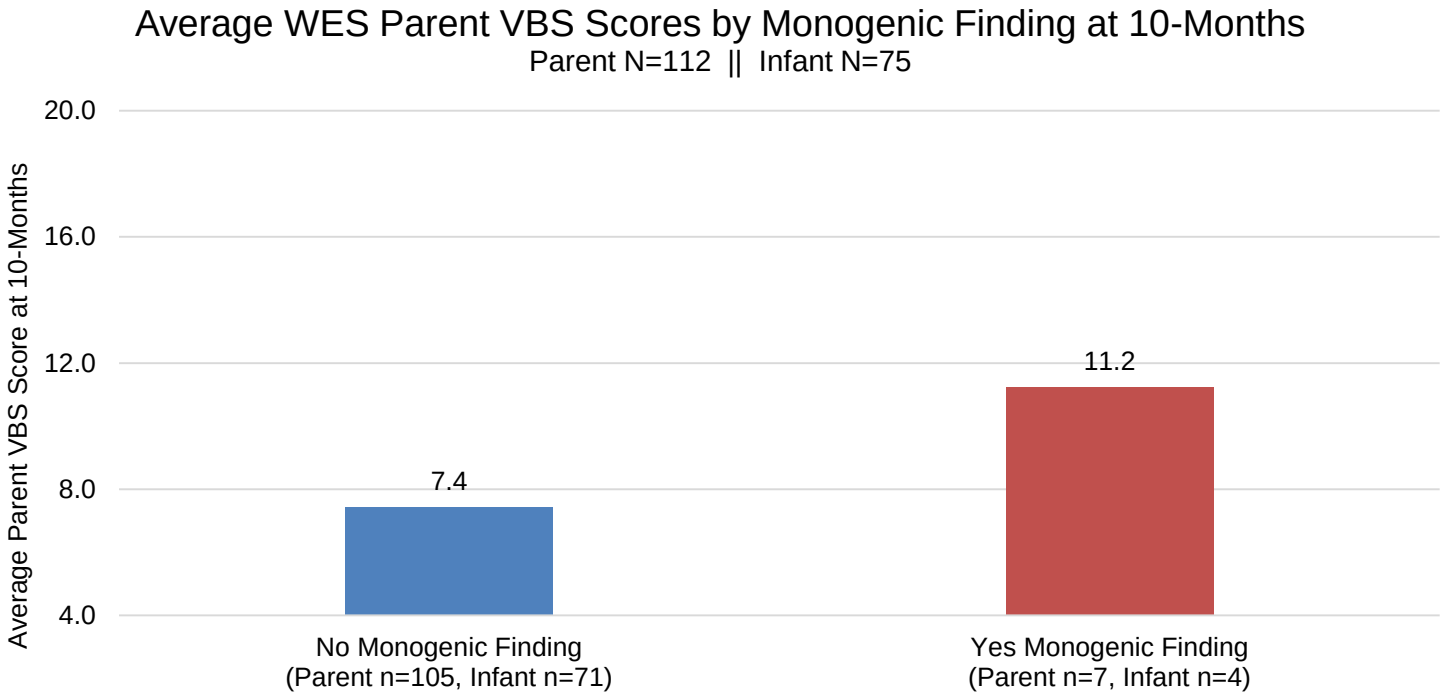
Pereira et al, in preparation

Preliminary results from BabySeq show no difference between randomization arms on Mother Infant Bonding Questionnaire



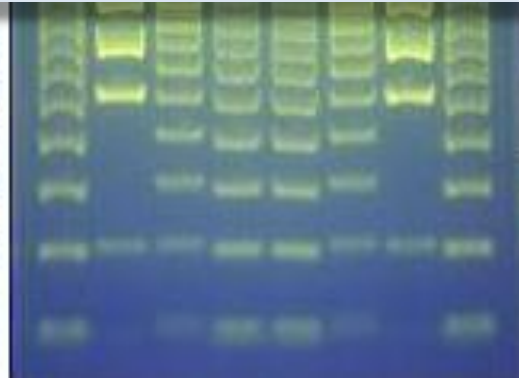
Pereira et al, in preparation

Preliminary results from BabySeq show a difference only at 10 months on the Vulnerable Baby Scale in parents whose baby had a monogenic disease risk finding

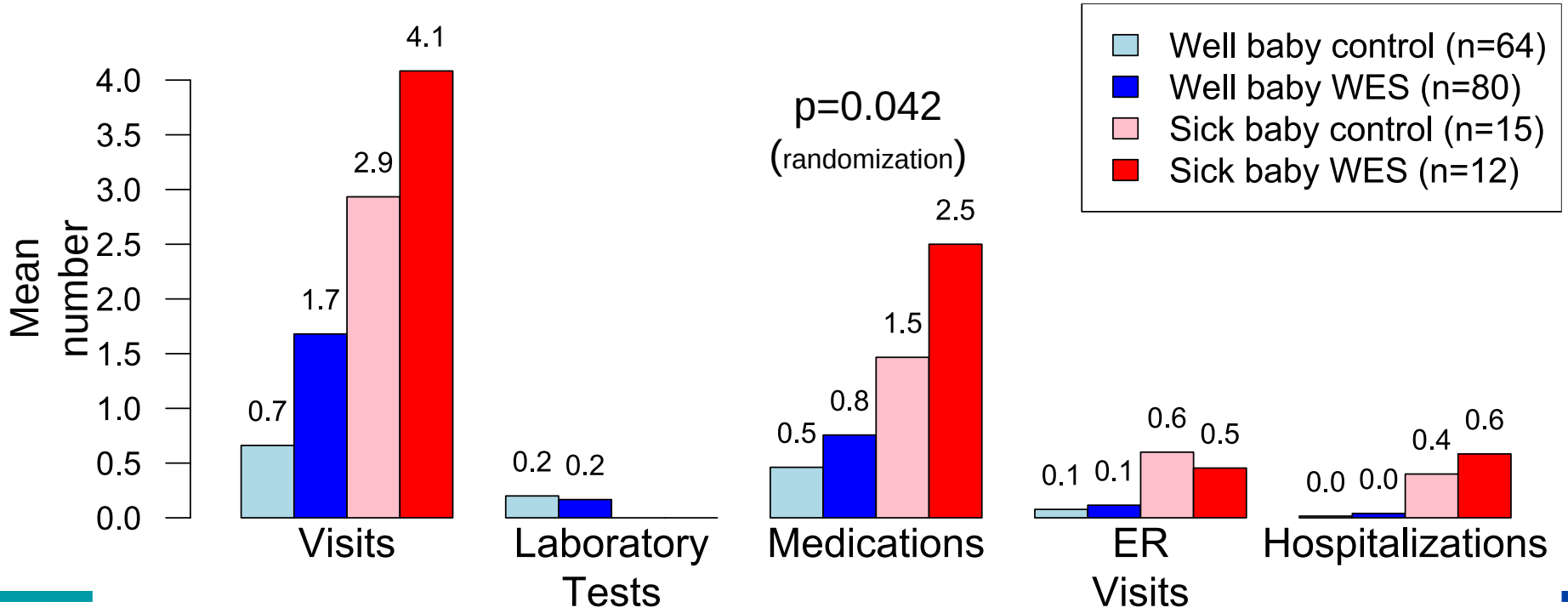


Pereira et al, in preparation

BabySeq Project
Preliminary Economic Outcomes



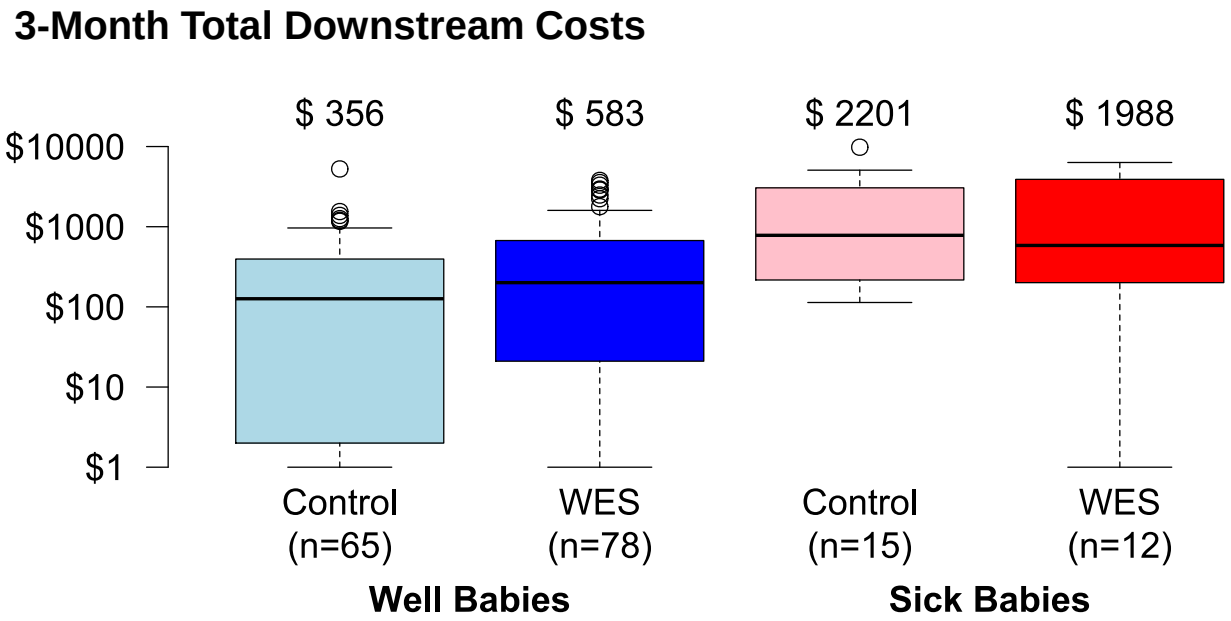
Babies in the WES arm appear to be receiving more services in the 3 months post-disclosure



BabySeq™

Christensen et al, in preparation

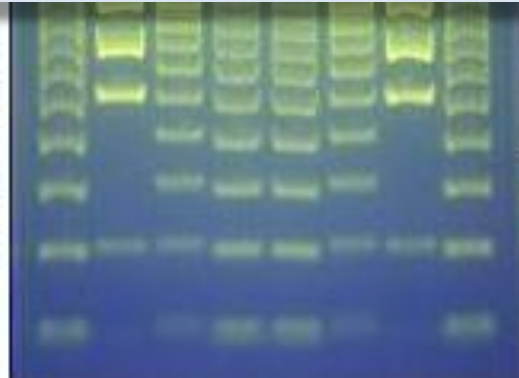
Overall expenditures are trending higher when babies receive sequencing



Christensen et al, in preparation

But wait, there's more!

The Challenge of Penetrance



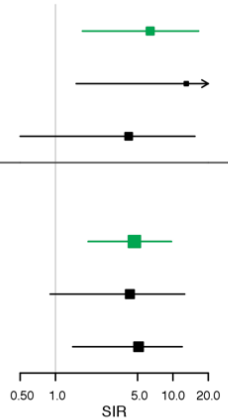
HUMAN GENETICS

Aggregate penetrance of genomic variants for actionable disorders in European and African Americans

Framingham Heart Study (N=462) and Jackson Heart Study (N=3218)

Pradeep Natarajan,[1,2,3]* Nina B. Gold,[2,4]* Alexander G. Bick,[2,3,5]* Heather McLaughlin,[2,6,7] Peter Kraft,[8] Heidi L. Rehm,[2,6,7] Gina M. Peloso,[2,3] James G. Wilson,[9] Adolfo Correa,[10] Jonathan G. Seidman,[2,5] Christine E. Seidman,[2,5,11,12] Sekar Kathiresan,[1,2,3†] Robert C. Green[2,3,7,11†‡]

Genes	Observed	Expected	SIR	P
Framingham Heart Study				
All ACMG Genes	4/5 (80.0%)	0.62/5 (12.4%)	6.4 (1.7-16.5)	<0.001
Cancer	2/2 (100%)	0.47/2 (23.5%)	13.0 (1.5-47.0)	0.006
Cardiovascular	2/3 (66.7%)	0.46/3 (15.3%)	4.2 (0.5-15.4)	0.06
Jackson Heart Study				
All ACMG Genes	7/26 (26.9%)	1.4/26 (5.4%)	4.7 (1.9-9.7)	<0.001
Cancer	3/12 (25.0%)	0.7/12 (5.8%)	4.3 (0.9-12.6)	0.03
Cardiovascular	4/14 (28.6%)	0.8/14 (5.7%)	5.1 (1.4-12.0)	0.004



Natarajan et al, *Science Trans Med*, 2016.

The Power of Small Data

Population screening

Newborn sequencing

- Robust monogenic risk identified in 11-18% of 3 separate populations screened with the full Mendeliome.
- Consistent reassurance that psychological distress rare among individuals/families electing risk information.
- Previously undiscovered medical abnormalities, and medical benefits in multiple domains identified in one-quarter of those with positive monogenic findings.
- Downstream medical costs are increased, but modestly.
- Penetrance of Mendeliome may be higher than anticipated over long time frame and with directed (non-EHR) phenotyping.
- In combination with polygenic risks, reproductive risks, pharmacogenomic risks and novel uses such as blood typing, the genome can provide tremendous (aggregate) value today.

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cser Clinical Sequencing Exploratory Research

MEDSEQ

BWH

Baylor College of Medicine

DukeMedicine

Geisinger

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Thank you !

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