The BabySeq Project: Sequencing Healthy Newborns and the Path to Preventive Genomics

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"…whether you like it or not, a complete sequencing of newborns is not far away"
Francis Collins, 2012

Mass General Brigham

Support and Disclosures

Research: National Institutes of Health
NHGRI, NIA, NICHD, NHLBI, NCATS
Department of Defense
Broad Institute of MIT & Harvard
Snite Foundation
Franca Sozzani Fund for Preventive Genomics

Advisory: AIA, Grail, SavvySherpa, Verily

Co-Founder: Genome Medical

What is the evidence required to implement genomics in day-to-day medical care?

Mass General Brigham

REVEAL

PGen

MedSeq

BabySeq

MilSeq

PeopleSeq

PopSeq

AllofUs Research Program

MGB Biobank / eMERGE III/IV

Verily Project Baseline

BabySeq Project team

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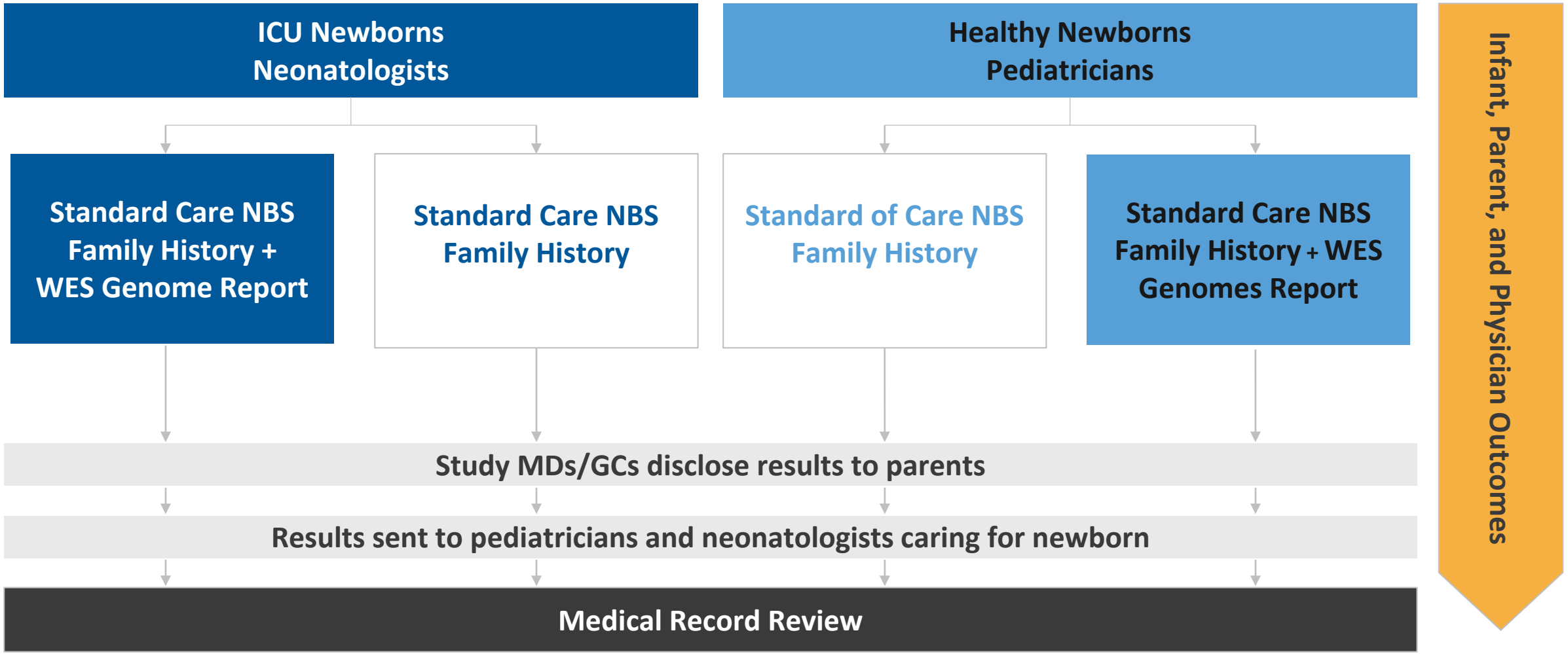
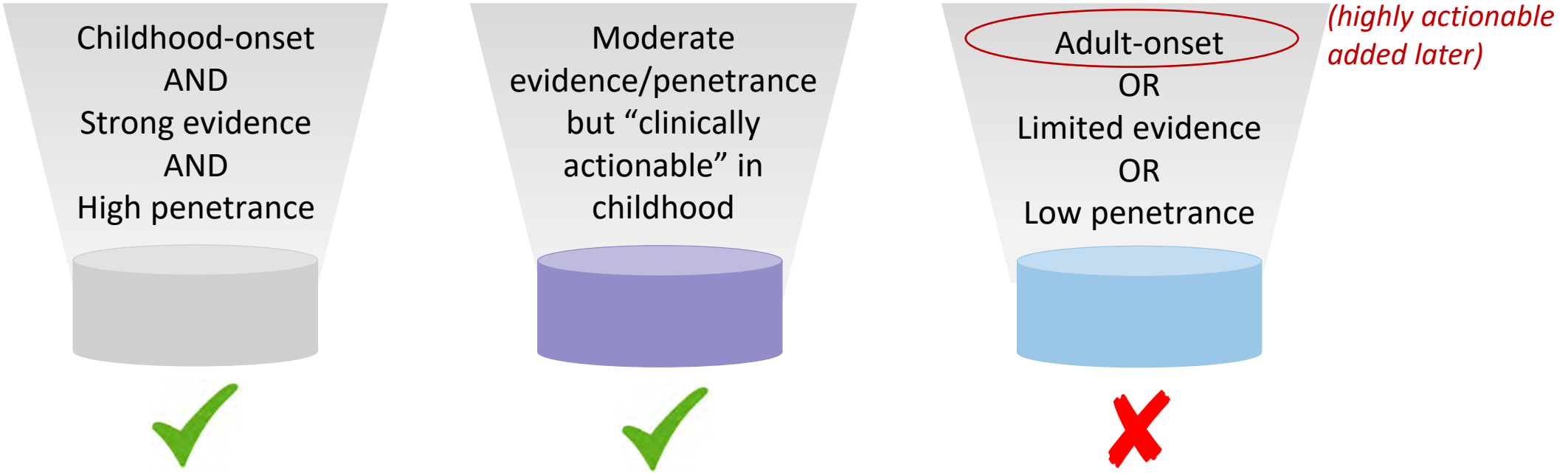
The BabySeq Project: A controlled trial of WES and comprehensive interpretation



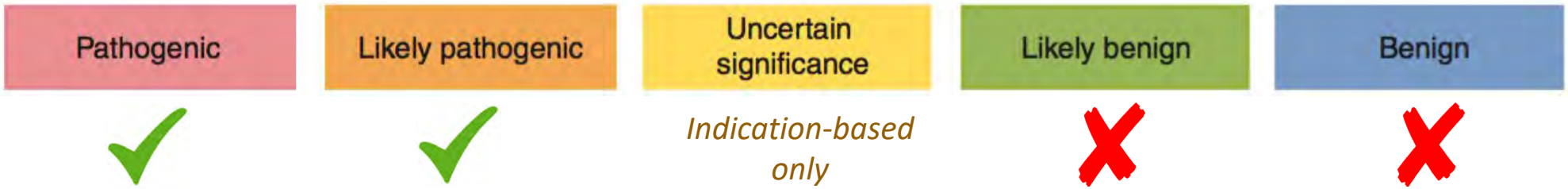
Holm et al. *BMC Pediatrics*, 2018.

Newborn Genomic Sequencing Report

~1000 genes analyzed based on disease validity, penetrance, and age of onset:



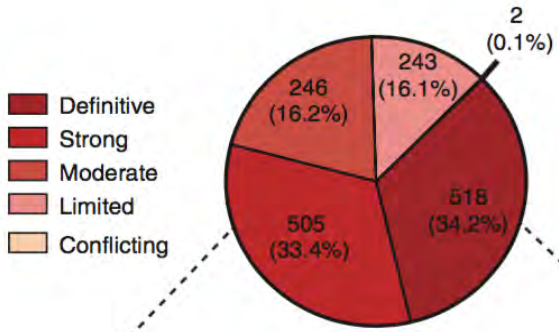
Variants reported based on evidence for harm:



Ceyhan-Birsoy et al. *Genetics in Medicine*, 2017.

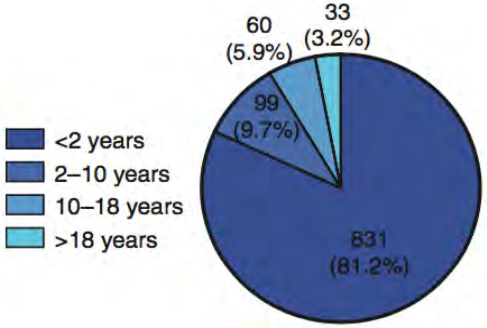
Curation of BabySeq gene list

Gene-disease validity *(n=1,514)*

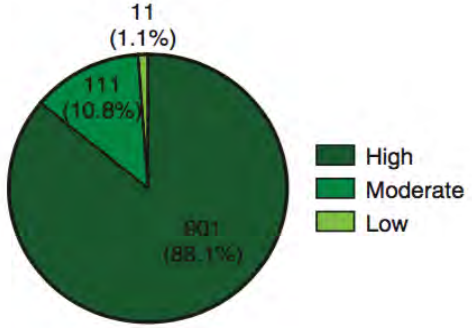


Genes with strong and definitive evidence *(n=1,023)*

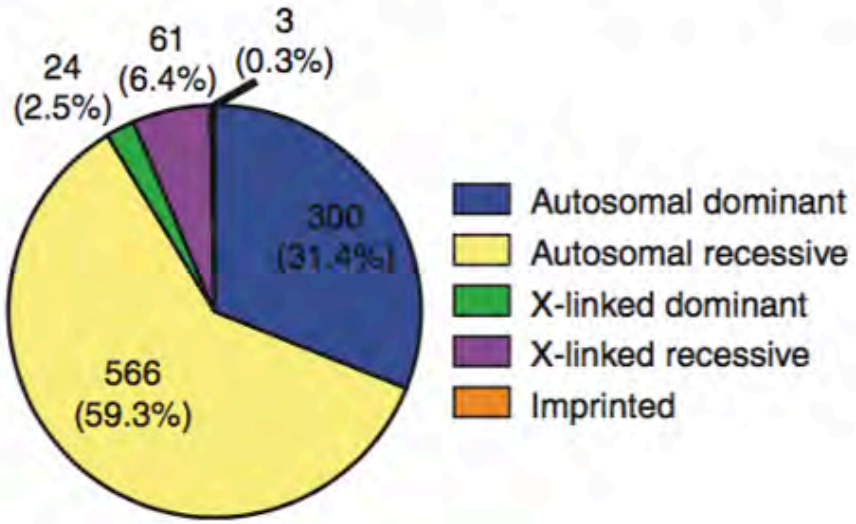
Age of onset



Penetrance



Inheritance pattern of genes meeting BabySeq reporting criteria (954)



Genes with highly penetrant, childhood onset disease *(i.e. Duchenne muscular dystrophy, n=884)*

+

Genes with high actionability *(i.e. cancer predisposition syndromes, n=70)*

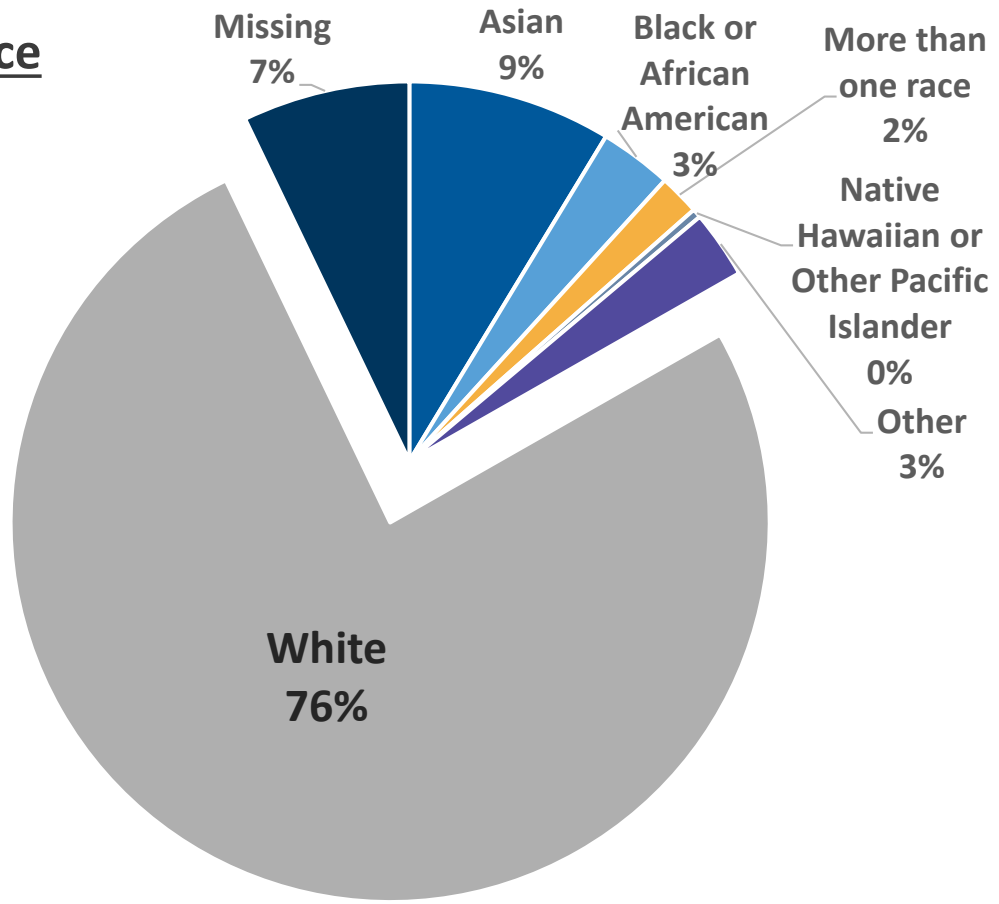
=

954 genes meet BabySeq reporting criteria

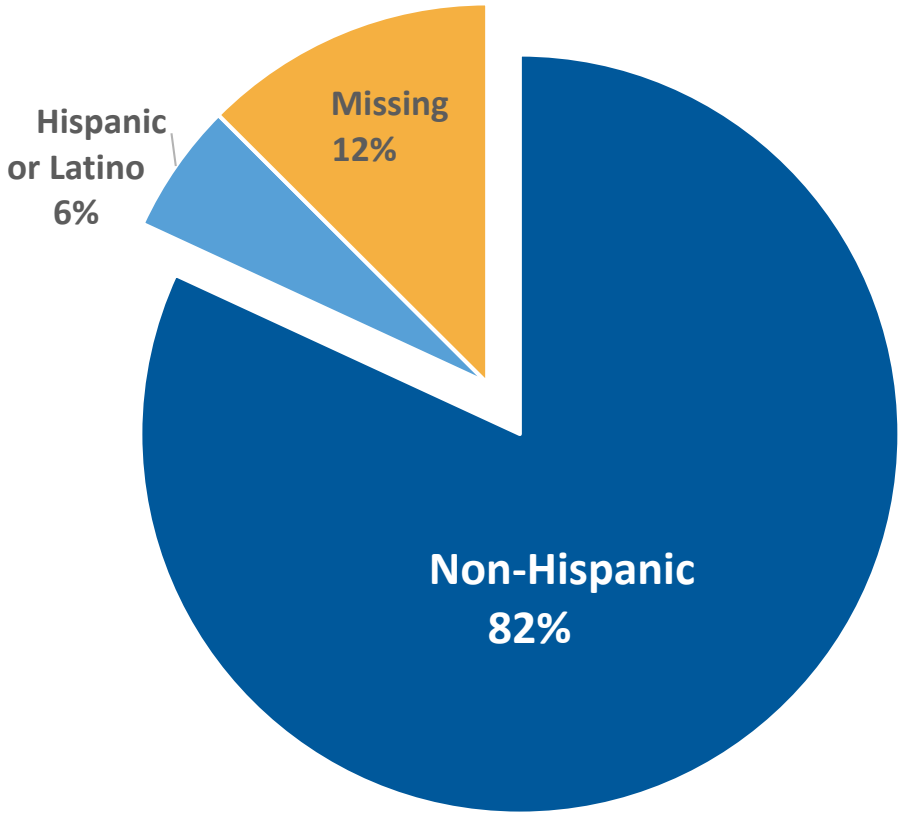
Ceyhan-Birsoy et al. *Genetics in Medicine*, 2017.

Demographics of Enrolled Parents in BabySeq

Race

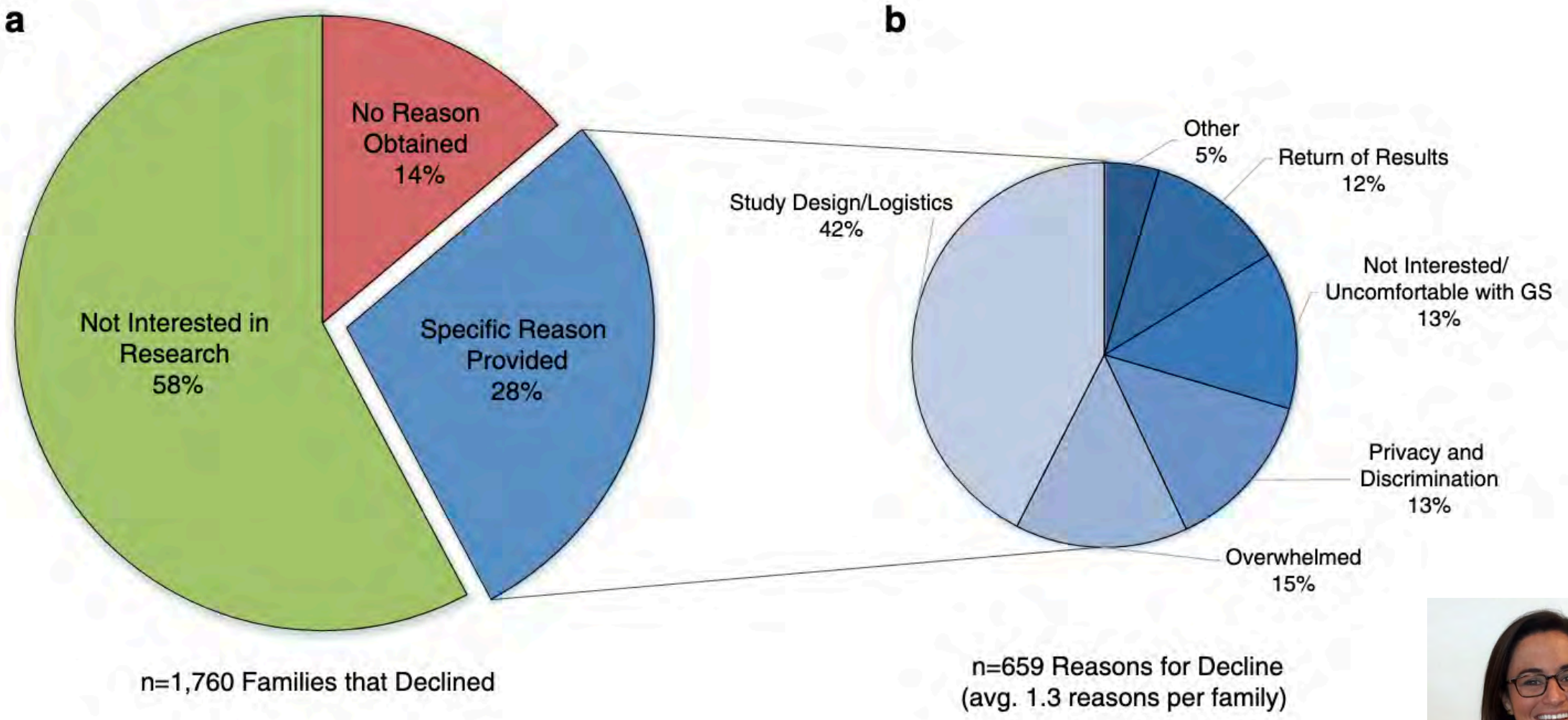


Ethnicity



Genetti et al. *Genetics in Medicine,* 2019.

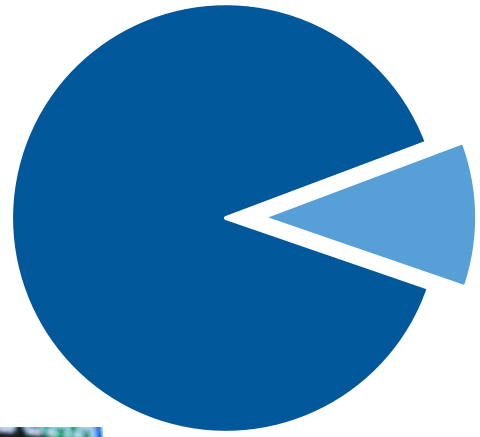
Reasons parents declined participation



Genetti et al. *Genetics in Medicine,* 2019.

The BabySeq Project: Unanticipated monogenic findings

Whole Exome Sequencing Infants (N=159)



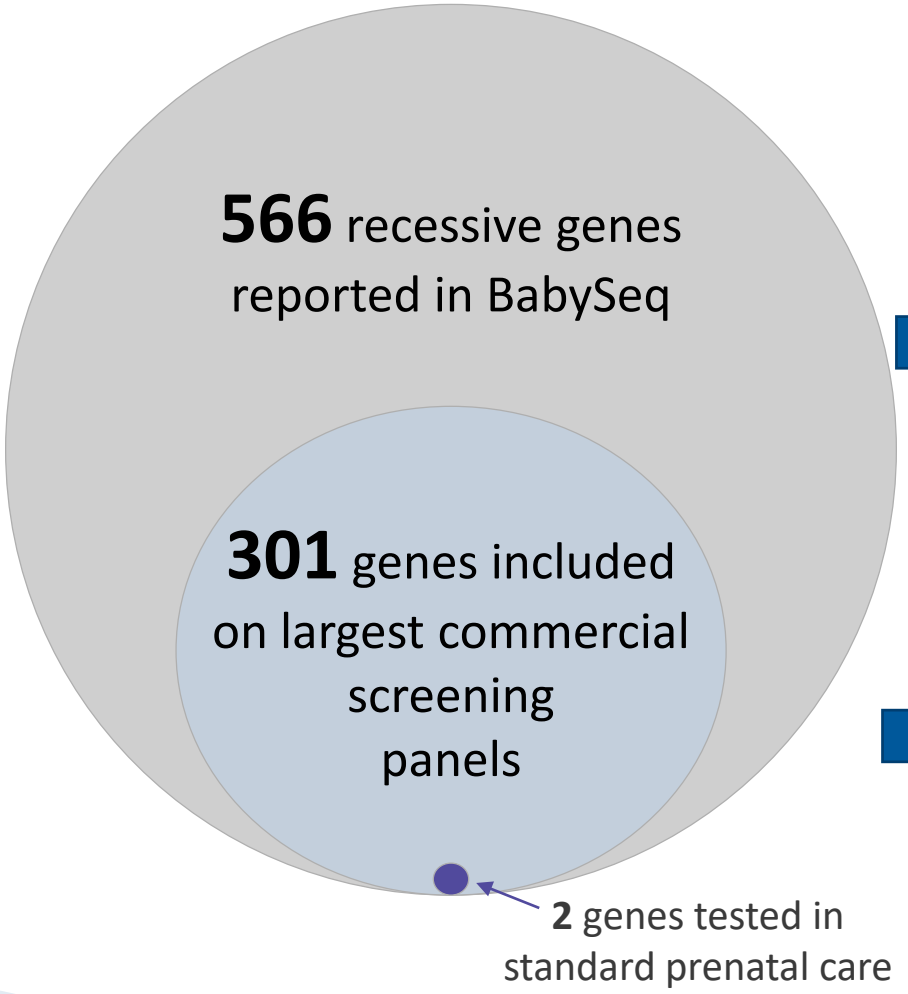
89% NO MDR FOUND

11% MDR FOUND

Gene	Condition	Phenotypic evidence
ANKRD11	KBG syndrome; *AD*	Yes
BTD	Biotinidase deficiency; *AR*	Yes
ELN	Supravalvular aortic stenosis; *AD*	Yes
GLMN	Glomuvenous malformations; *AD*	Yes
KCNQ4	Non-syndromic hearing loss; *AD*	Family history
SLC7A9	Cystinuria; *AR*	Family history
TTN (4)	Dilated cardiomyopathy; *AD*	Family history (2/4)
BRCA2 (2)	Hereditary breast and ovarian cancer; *AD*	Family history
MSH2	Lynch syndrome; *AD*	Family history
MYBPC3	Hypertrophic cardiomyopathy; *AD*	No
VCL	Dilated cardiomyopathy; *AD*	No
CD46	Atypical hemolytic-uremic syndrome; *AD*	No
CYP21A	Congenital adrenal hyperplasia due to 21-hydroxylase deficiency; *AR*	No
G6PD	Glucose-6-phosphate dehydrogenase deficiency; *XL*	No

Ceyhan-Birsoy et al. *Am J Hum Genet*, 2019.

88% of infants had at least 1 PV/LPV for a recessive carrier condition: Comparison with conventional carrier screening



47% of reported variants would have been missed by commercial "expanded screening" panels

INVITAE | GoodStart Genetics

sema4

HerediT UNIVERSAL

Counsyl

99% of reported variants would have been missed by routine care

horizon™ natera carrier screen

VanNoy et al. *Pediatrics*, 2018.

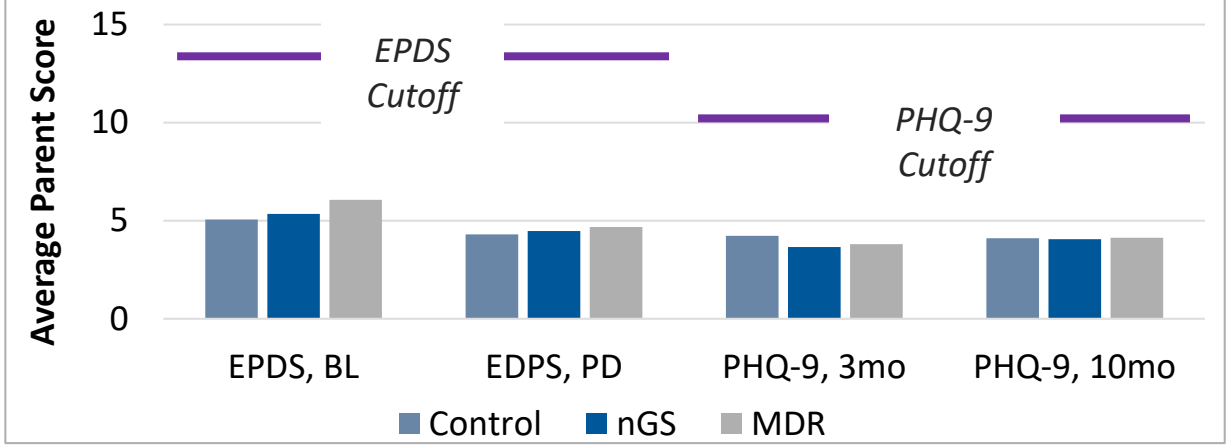
The BabySeq Project: Comparison with conventional NBS

(n=159)	Sequencing positive	NBS positive
True positive	**Phenotype positive: 4** • KBG syndrome • Biotinidase deficiency* • Supravalvular aortic stenosis • Glomuvenous malformations **Family history supported: 7** • Non-syndromic hearing loss • Cystinuria • Dilated cardiomyopathy (2) • Hereditary breast and ovarian cancer (2) • Lynch syndrome	**Phenotype positive: 3** • Biotinidase deficiency* • (Hemoglobin FAV) • (Hemoglobin FAB)
False positive	**No phenotype or family history: 7** • Hypertrophic cardiomyopathy • Dilated cardiomyopathy (3) • Atypical hemolytic-uremic syndrome • Congenital adrenal hyperplasia • Glc-6-phosphate dehydrogenase deficiency	**False positive: 9 (7 NICU)** • Thyroid abnormality (5) • Amino acid abnormalities + thyroid abnormality + severe combined immunodeficiency • Thyroid abnormalities + homocystinuria • Phenylketonuria • Amino acid abnormalities
Total	**18/159 = 11.3%**	**12/159 = 7.5%**

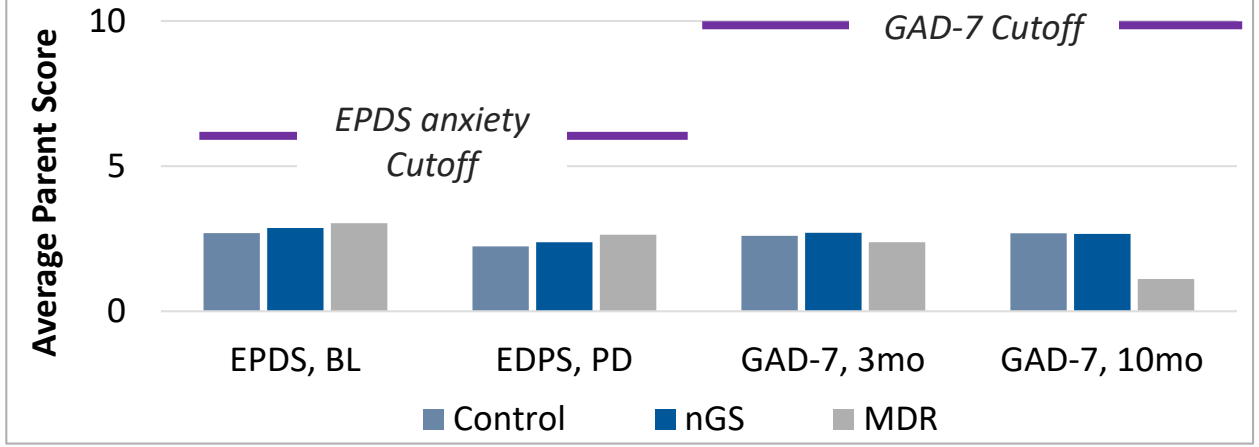
Wojcik et al. in submission.

BabySeq Project: No increased depression/anxiety, self-blame, or relationship dysfunction by randomization arm or MDR

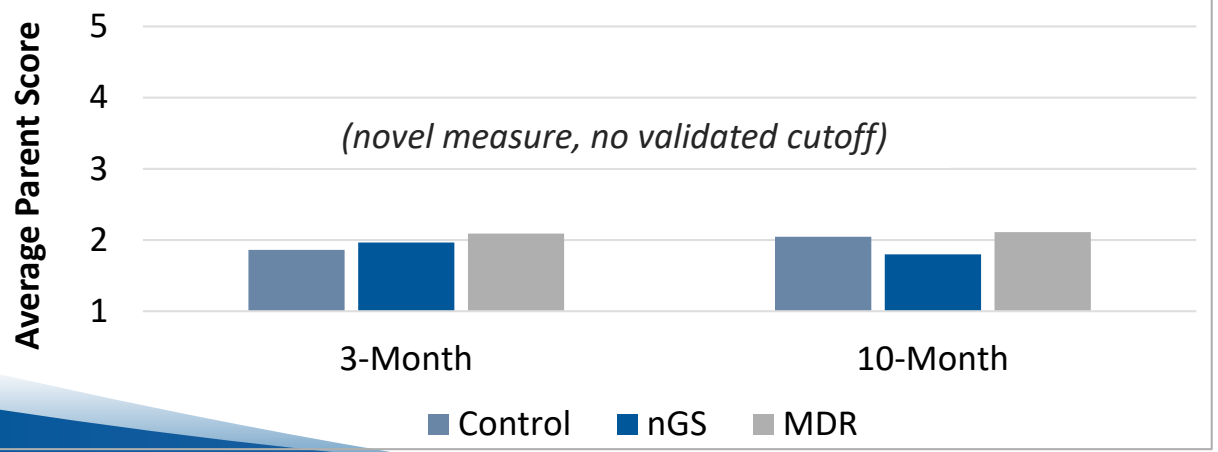
Parental depression



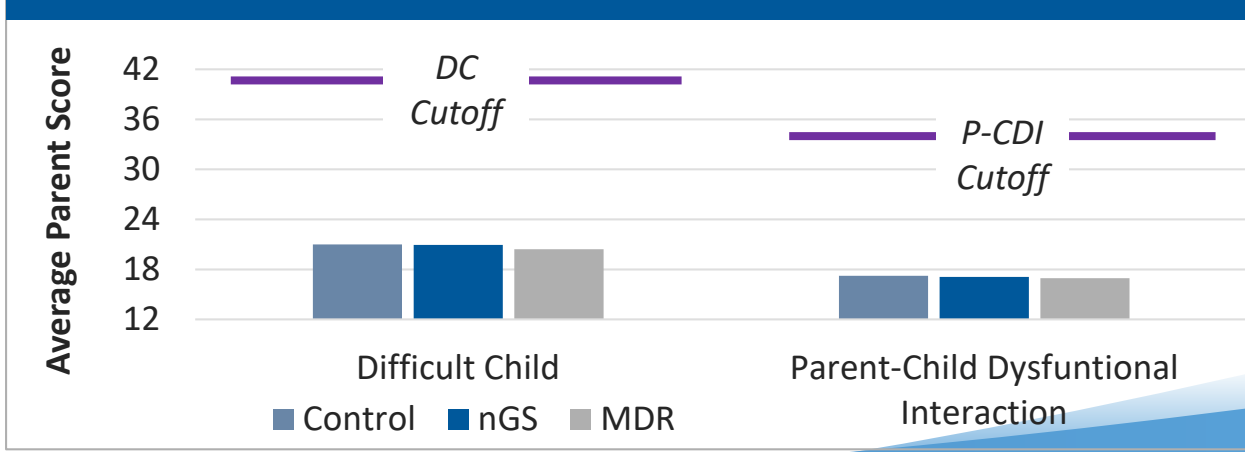
Parental anxiety



Parental self-blame



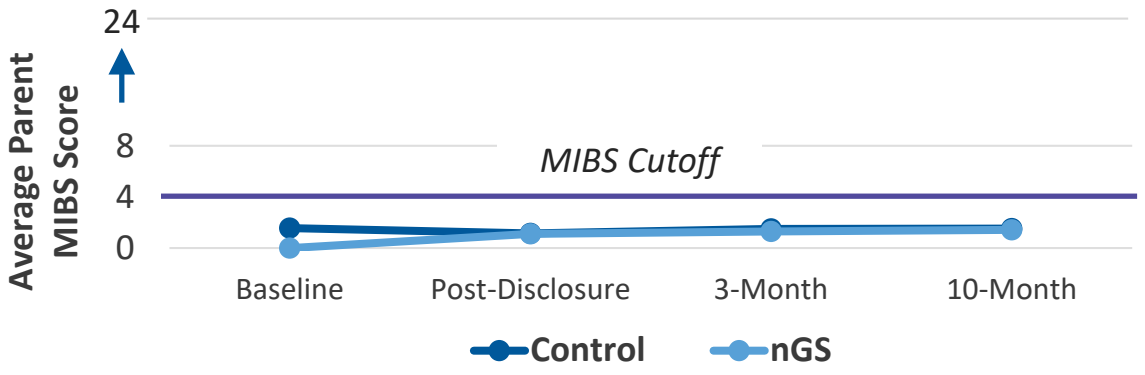
Parental perception of child & relationship



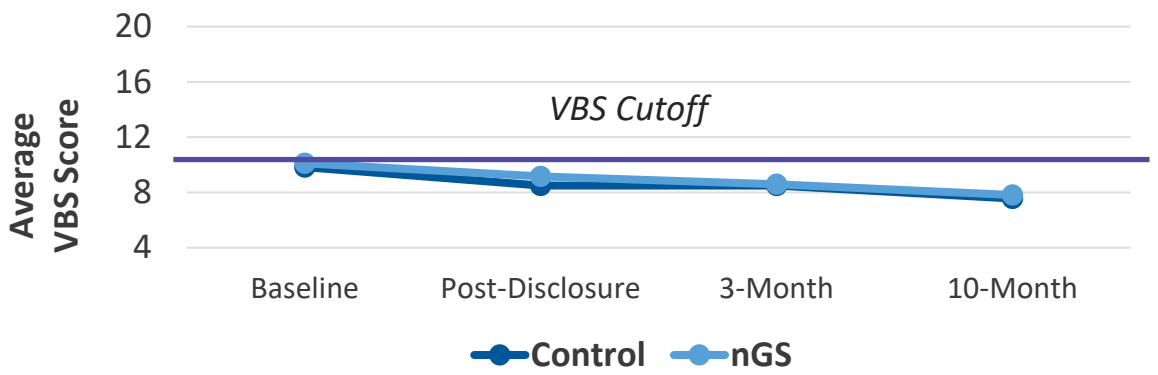
Pereira et al. in submission.

The BabySeq Project: No disruption of parent-child bond or increased perception of child vulnerability

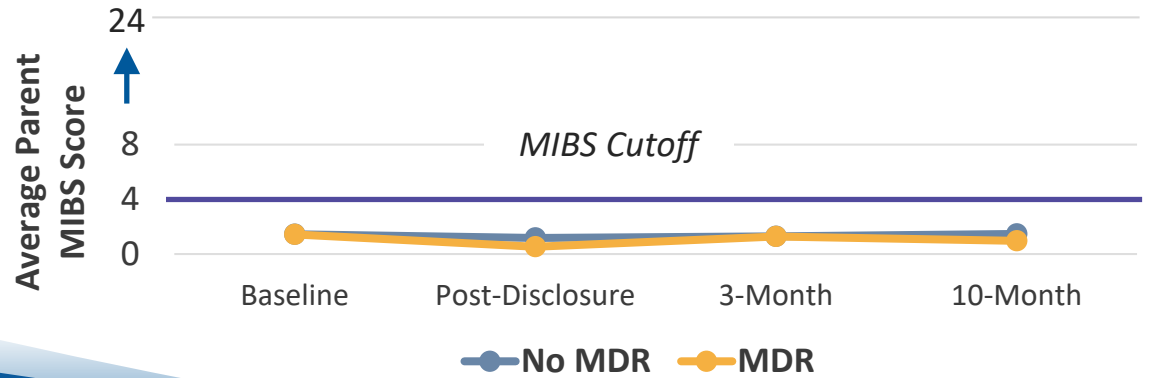
Parent-child bond



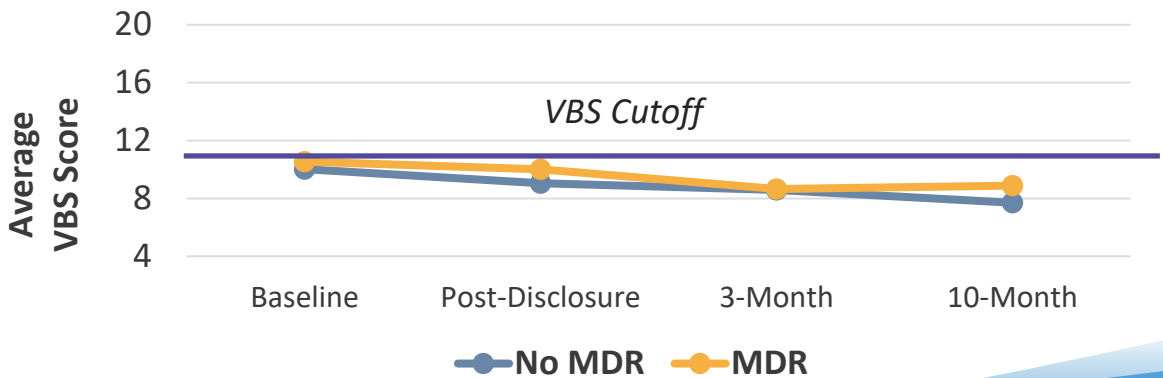
Child vulnerability



Parent-child bond



Child vulneratiliby

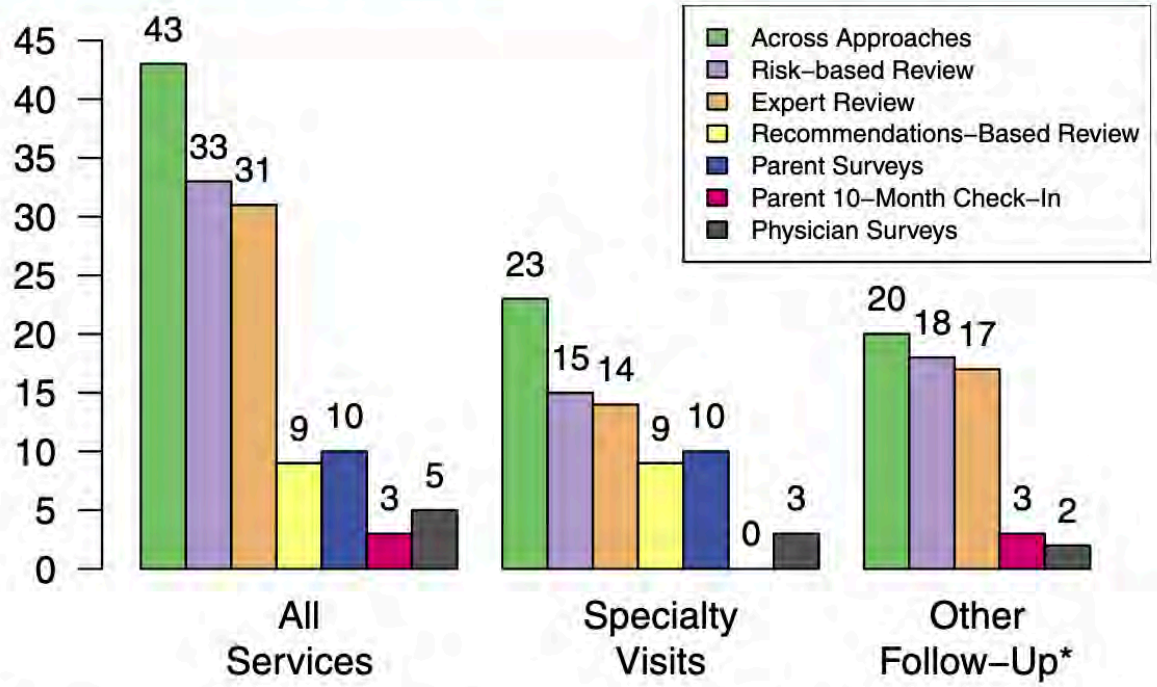


Pereira et al. in submission.

Assessing downstream medical impact of genomic sequencing

- 17 newborns with unanticipated genomic findings
- 43 services associated with follow-up care
- 23 specialty visits
- 20 other resources *(i.e. labs, imaging)*

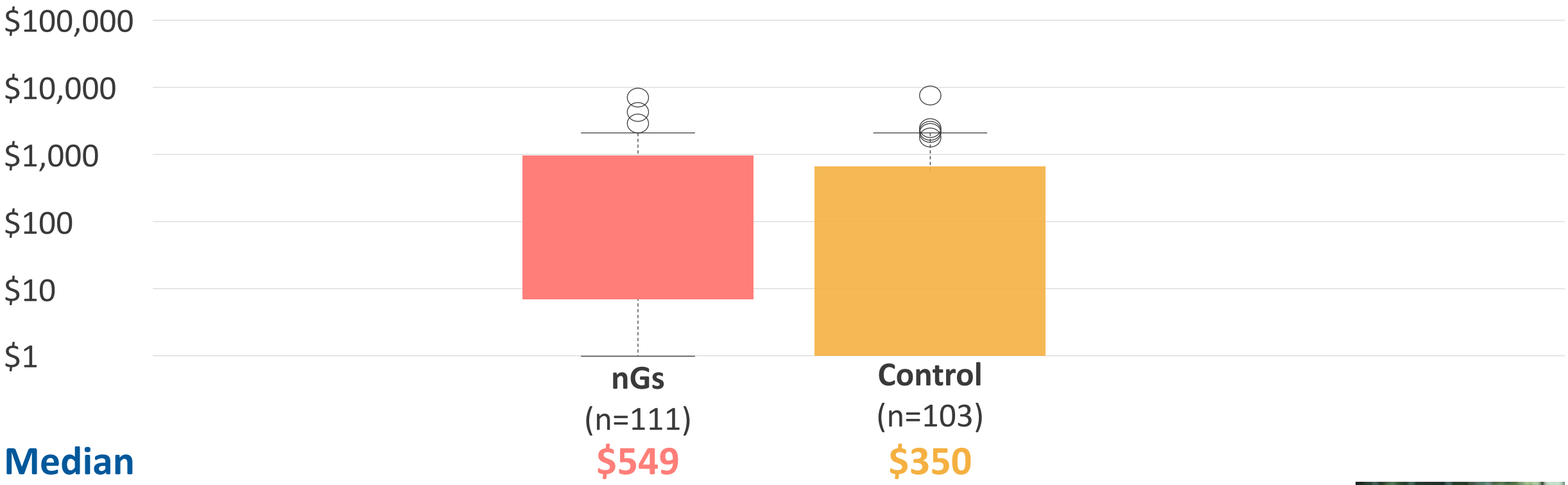
Figure 1. Number of healthcare services associated with follow-up of secondary findings from newborn genomic sequencing using different approaches.



*Parent surveys were omitted because they included no items to assess healthcare utilization other than specialist visits.

Mackay, et al. *Value in Health*, 2020.

Health care spending in newborns after sequencing



Median

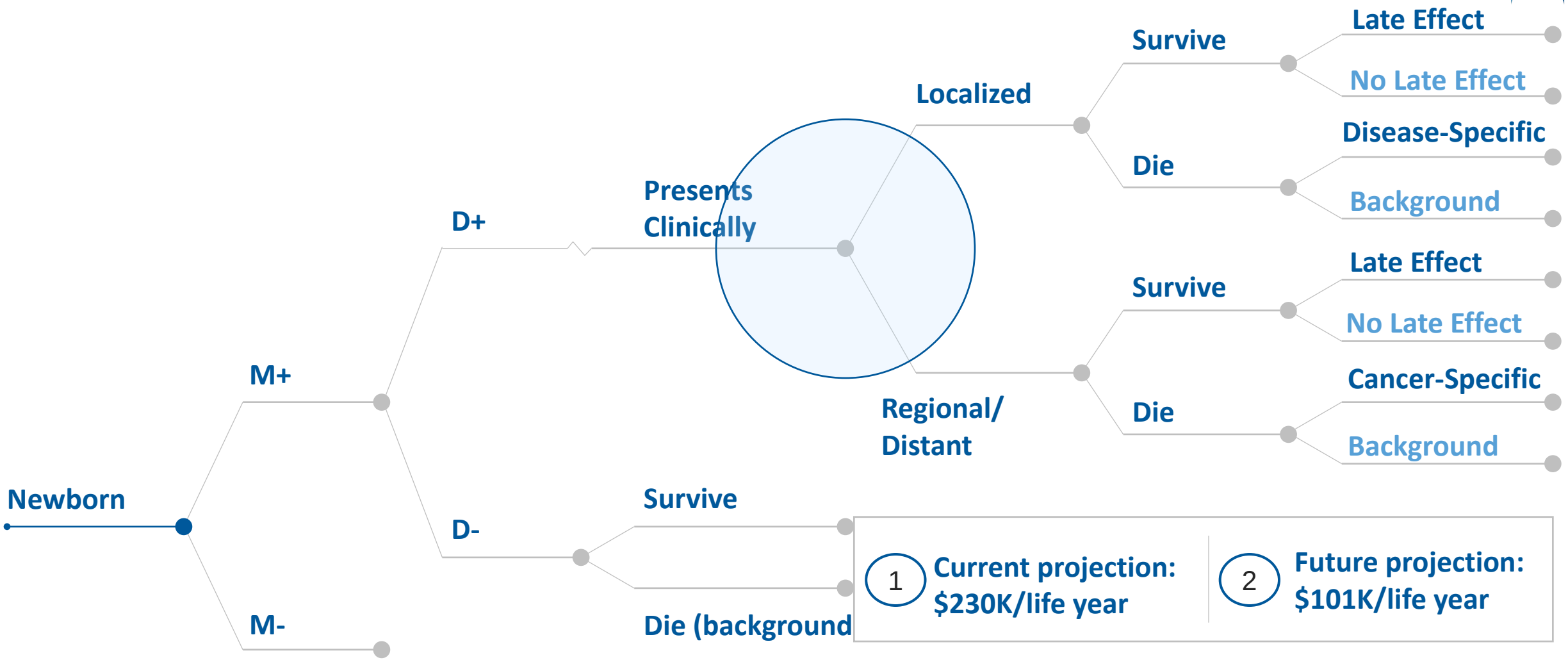
Well Newborns

No significant differences in healthcare costs

Christensen et al., in preparation.

Modeling lifetime benefits and costs

(slide courtesy Kurt Christensen)



Christensen et al., in preparation.

Comprehensive sequencing and analysis of many genes

	MedSeq™	BabySeq™	MilSeq™
Monogenic (Strong effect)	21%	11%	15%
Monogenic (Weak effect)			54%
Polygenic (>2 OR)	62%		
Carrier Status	92%	88%	88%
Pharmacogenomics (atypical)	80%	5% (limited to childhood relevance)	100%

Christensen et al. *Genetics in Medicine*, 2018; Vassy et al. *Annals of Internal Medicine*, 2017; Ceyhan-Birsoy et al. *Am J Human Genetics*, 2019.

Mass General Brigham

G2P
GENOMES TO PEOPLE

Thank You!

genomes2people.org

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