G2P GENOMES TO PEOPLE

ARIADNE LABS

the Franca Fund

Empirical Data on the Path to Universal Newborn Sequencing

Robert C. Green, MD, MPH

Professor of Medicine (Genetics)

Harvard Medical School

HARVARD MEDICAL SCHOOL

Mass General Brigham

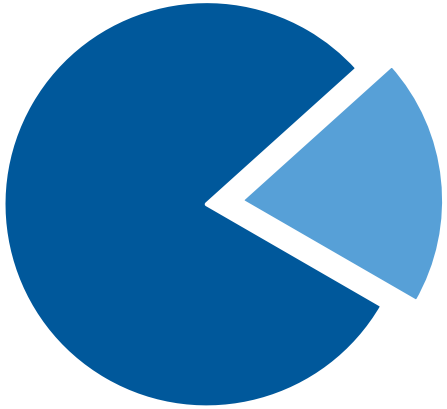
BROAD INSTITUTE

Support and Disclosures

Research:	National Institutes of Health NHGRI, NIA, NICHD, NHLBI, NCATS US Department of Defense Snite Foundation Franca Sozzani Fund for Preventive Genomics
Advisory:	Allelica, Fabric, GenomeWeb, GenomicLife
Co-Founder:	Genome Medical, Nurture Genomics

MedSeq Project

…first randomized trial of comprehensive genome sequencing in healthy adults



80%
NO MDR FOUND

20%
MDR FOUND

Genomic Findings in Healthy Individuals
Based on ~6000 genes

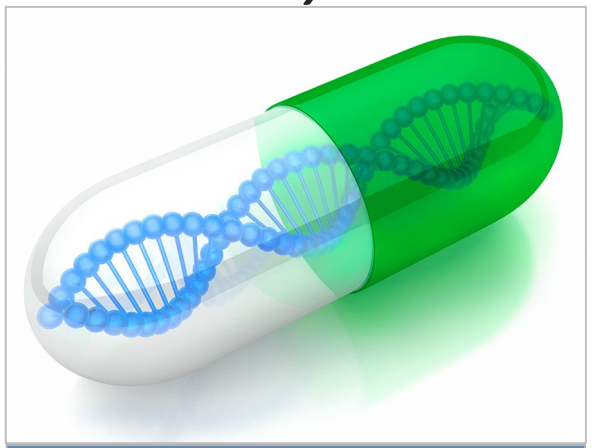
Monogenic dominant/biallelic

20% with dominant mutations

Monogenic recessive carrier

91% with recessive mutations

Pharmacogenomic analyses



80% with atypical responses to meds

Polygenic analyses

50% Elevated polygenic risk in at least one condition

Christensen et al GIM, 2018; Vassy et al Annals 2017; Ceyhan-Birsoy et al. AJHG, 2019; Frampton et al, 2016; Khera et al, 2018; Mahajan et al, 2018; Schmit et al, 2018; Schumacher et al, 2018; Seibert et al, 2018

HARVARD MEDICAL SCHOOL
G2P GENOMES TO PEOPLE ARIADNE LABS

The BabySeq Project

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

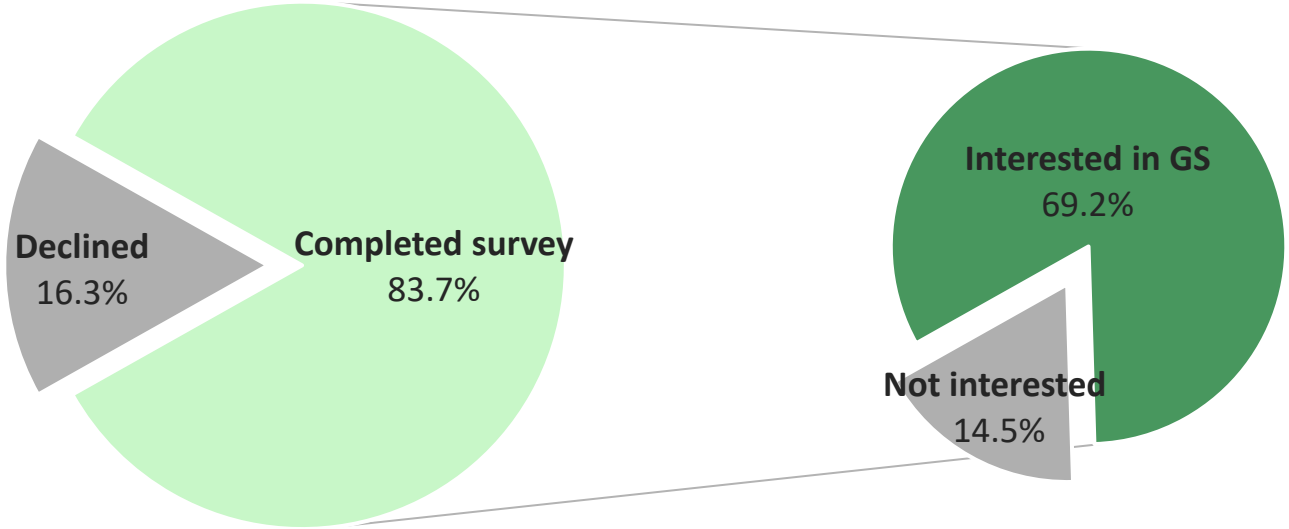
BWH

BCM
Baylor College of Medicine

Mass General Brigham

Parental survey and parental recruitment

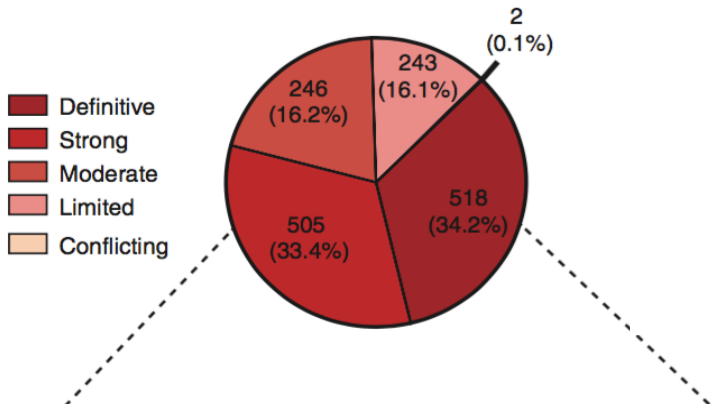
Hypothetical survey
(n= 1309 parents)



Waisbren et al., Genetics in Medicine 2015; Genetti et al., Genetics in Medicine 2019

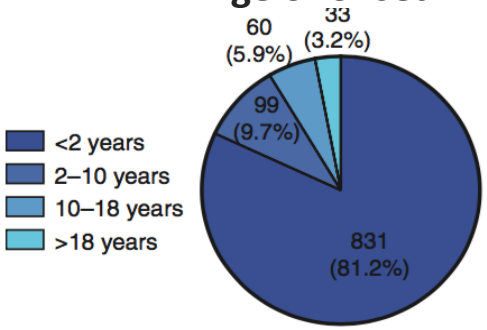
Curating the BabySeq gene list

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

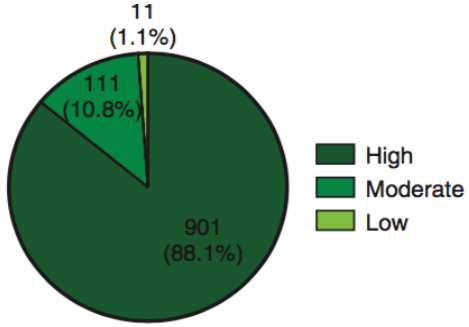


Genes with strong and definitive evidence *(n=1,023)*

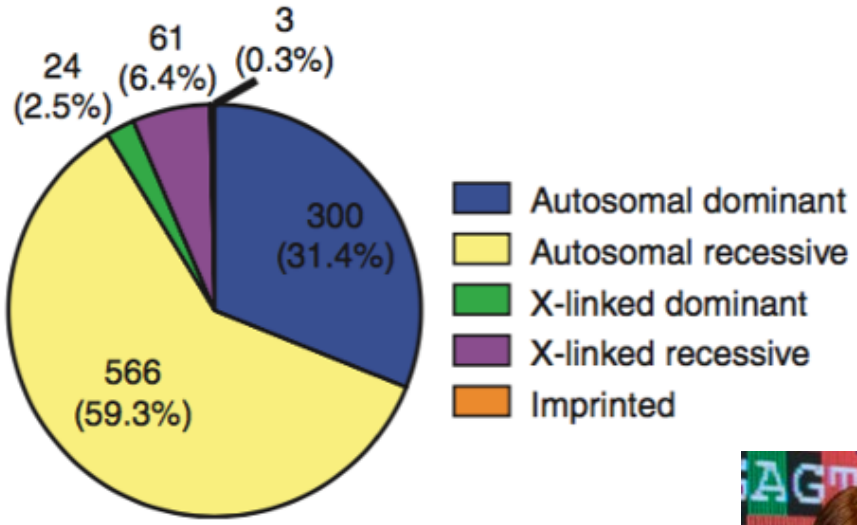
Age of onset



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)*

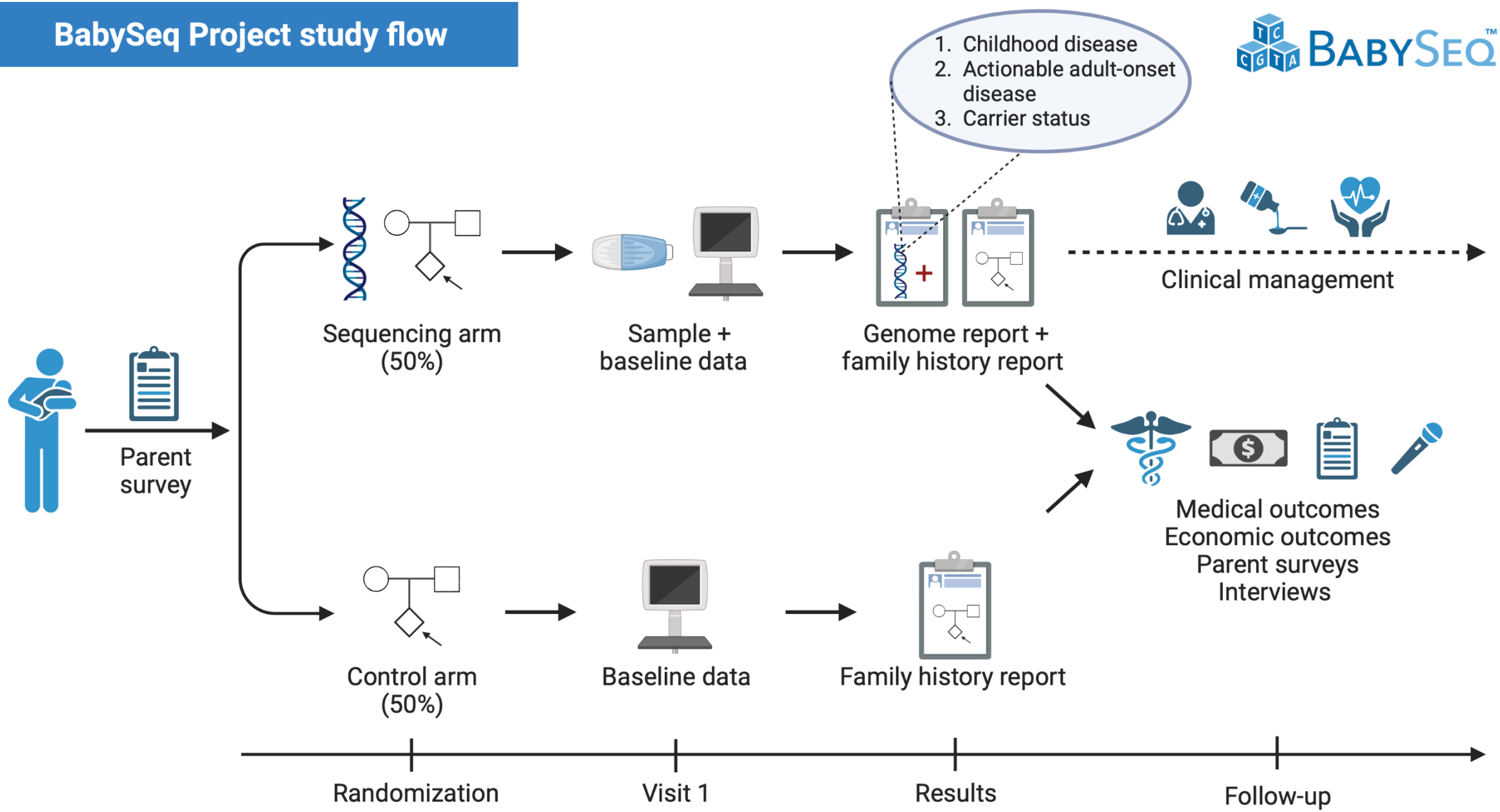
=

954 genes meet BabySeq reporting criteria

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

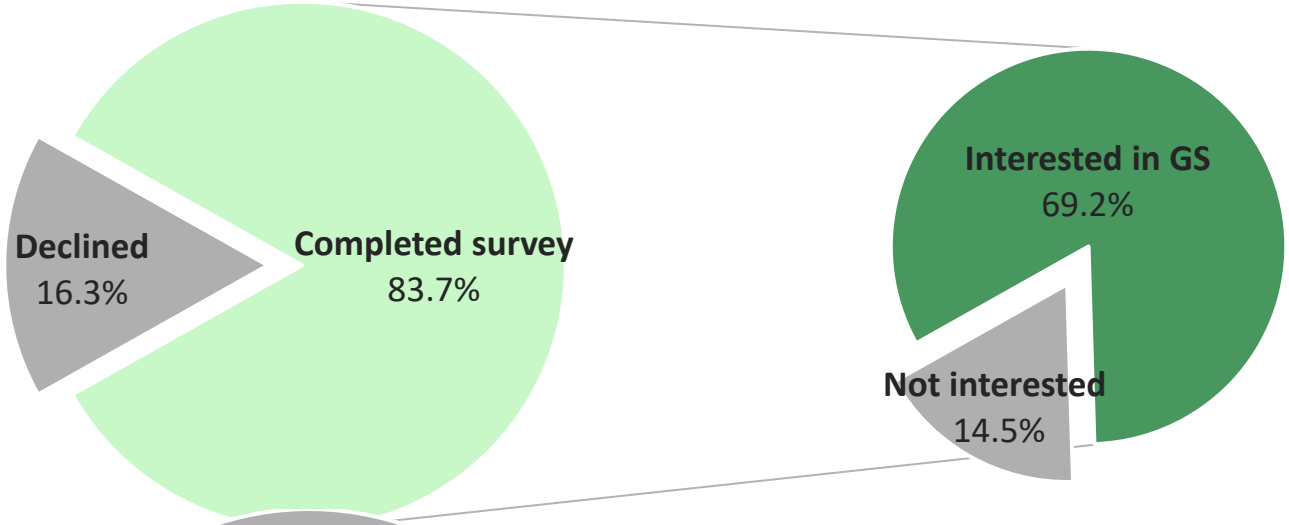
HARVARD MEDICAL SCHOOL
G2P GENOMES TO PEOPLE ARIADNE LABS

BabySeq Project study flow

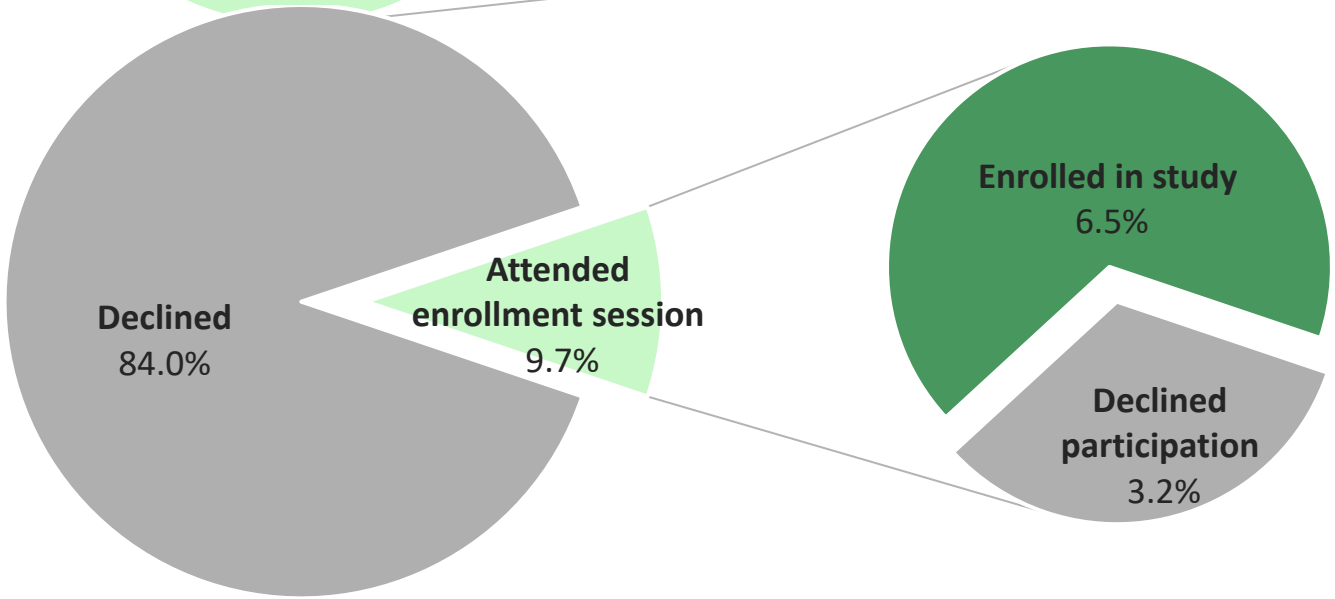


Parental survey and parental recruitment

Hypothetical survey
(n= 1309 parents)



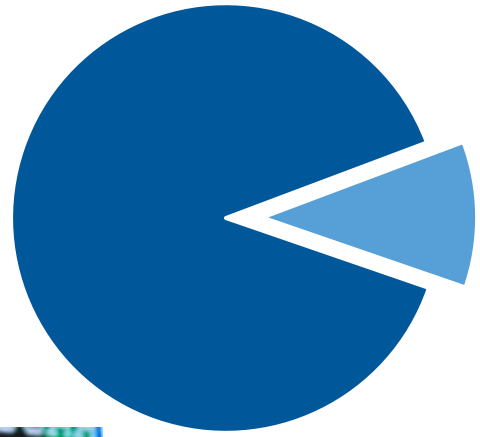
Approached for BabySeq
(n = 3424 parents)



Waisbren et al., Genetics in Medicine 2015; Genetti et al., Genetics in Medicine 2019

Unanticipated monogenic findings

Whole Exome Sequencing Infants (N=159)



89% NO MDR FOUND

11% MDR FOUND

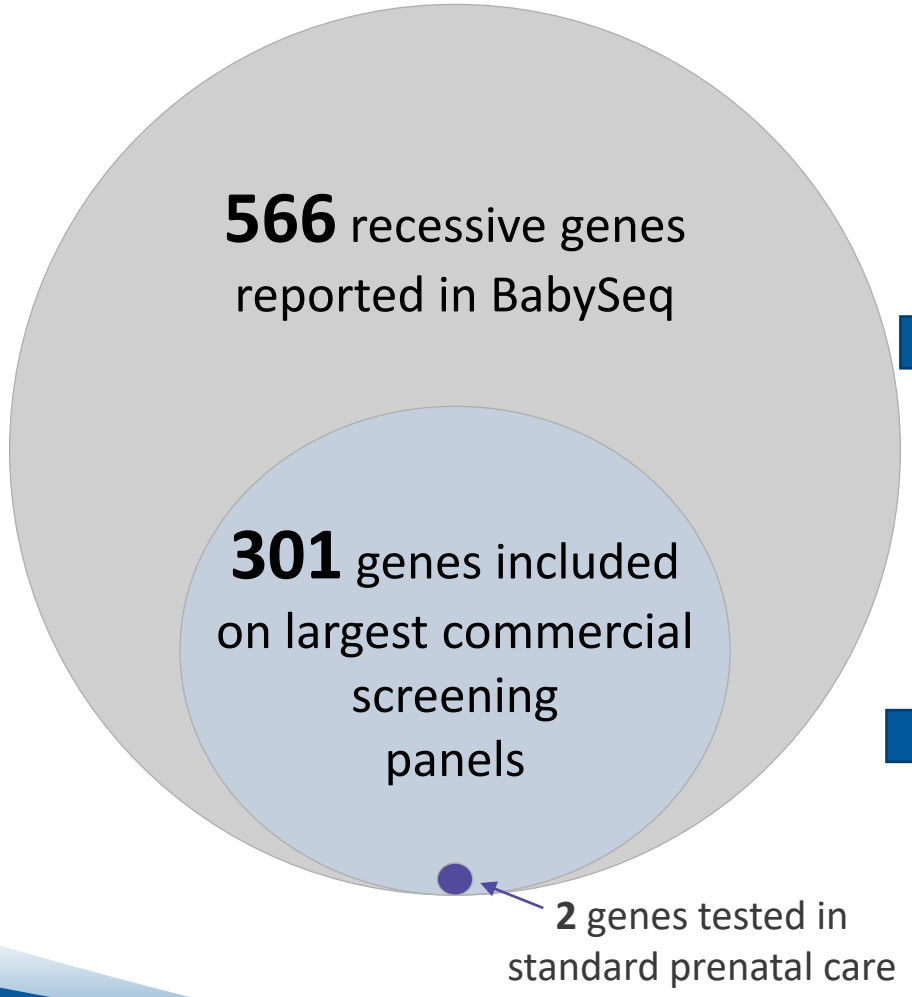
Gene	Condition	Phenotypic evidence
ANKRD11	KBG syndrome; *AD*	Yes
BTD	Biotinidase deficiency; *AR*	Yes
ELN	Supravalvular aortic stenosis; *AD*	Yes
GLMN	Glomuvenous malformations; *AD*	Yes
KCNQ4	Non-syndromic hearing loss; *AD*	Family history
SLC7A9	Cystinuria; *AR*	Family history
TTN (4)	Dilated cardiomyopathy; *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.

HARVARD MEDICAL SCHOOL
G2P GENOMES TO PEOPLE ARIADNE LABS

Comparison with conventional carrier screening

88% of infants had at least 1 PV/LPV for a recessive carrier condition



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

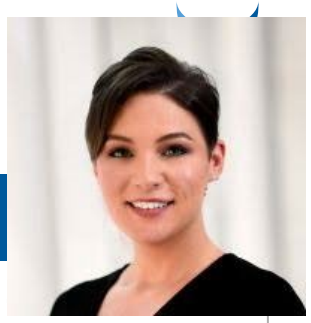
horizon™ natera carrier screen

VanNoy et al. Pediatrics, 2018.

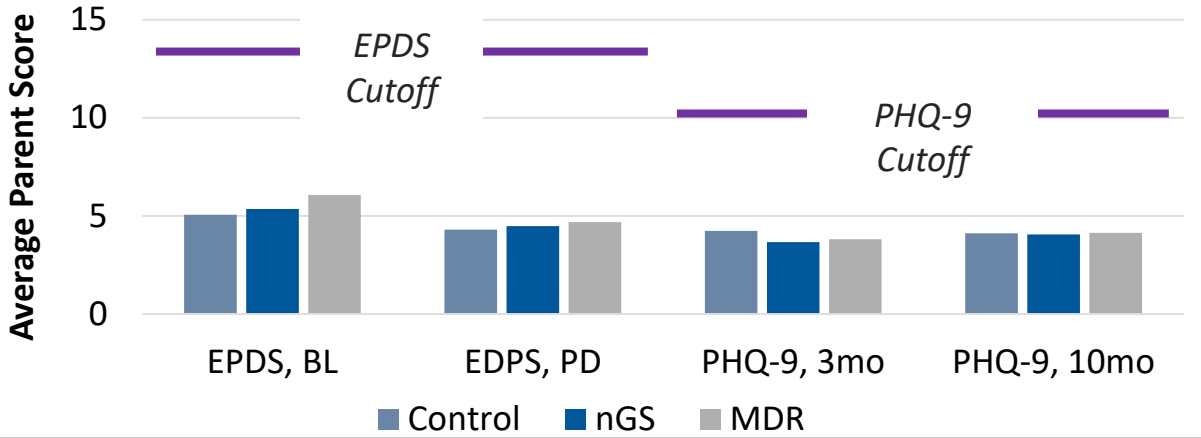
HARVARD MEDICAL SCHOOL

G2P GENOMES TO PEOPLE ARIADNE LABS

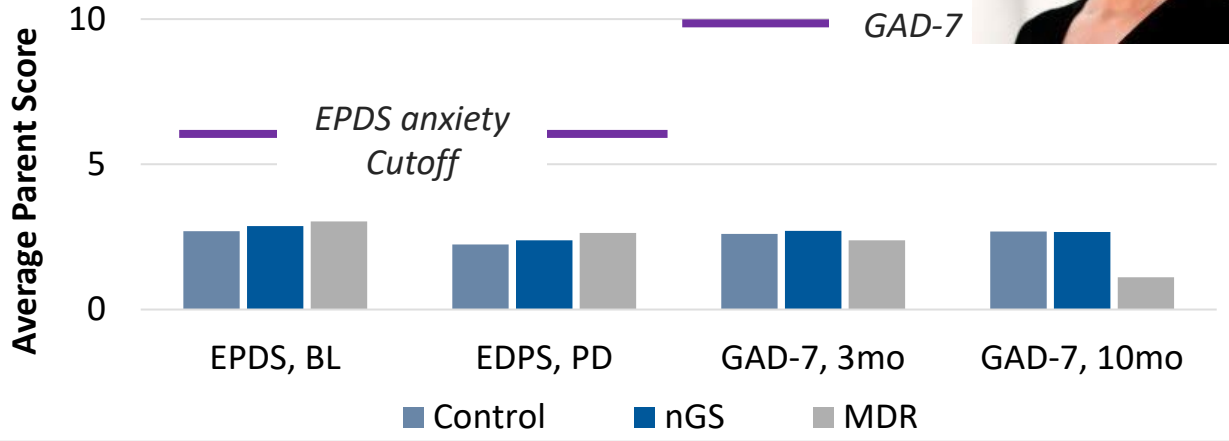
No increased distress



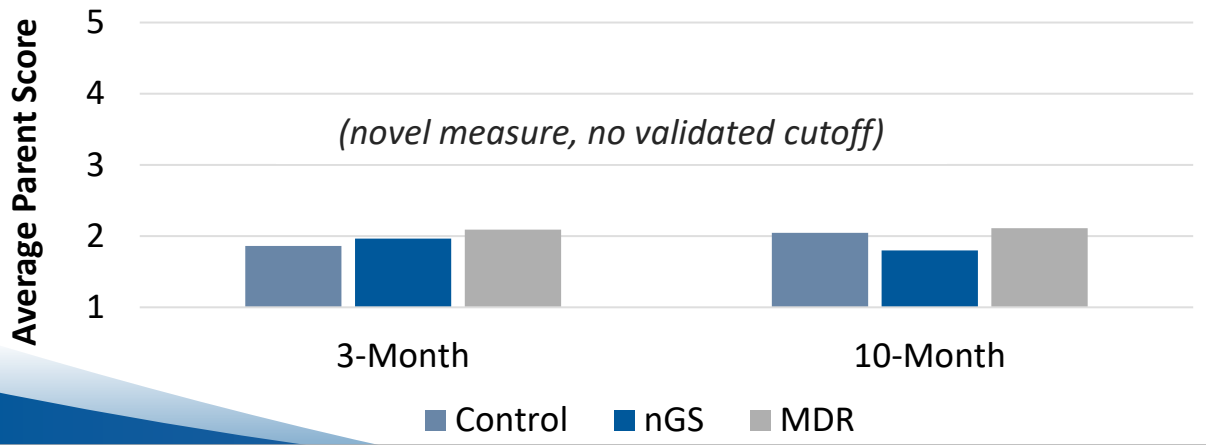
Parental depression



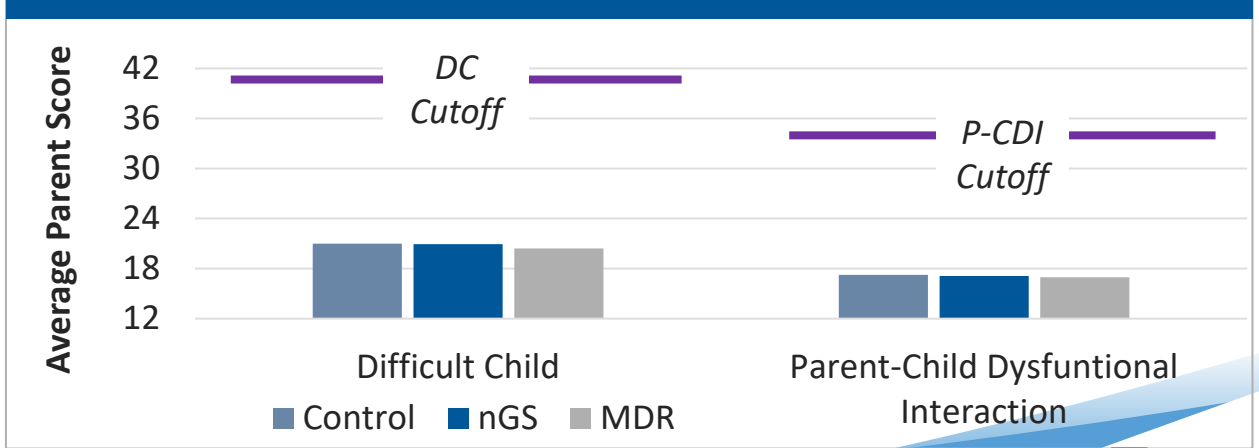
Parental anxiety



Parental self-blame



Parental perception of child & relationship



Pereira et al., JAMA Peds, 2021

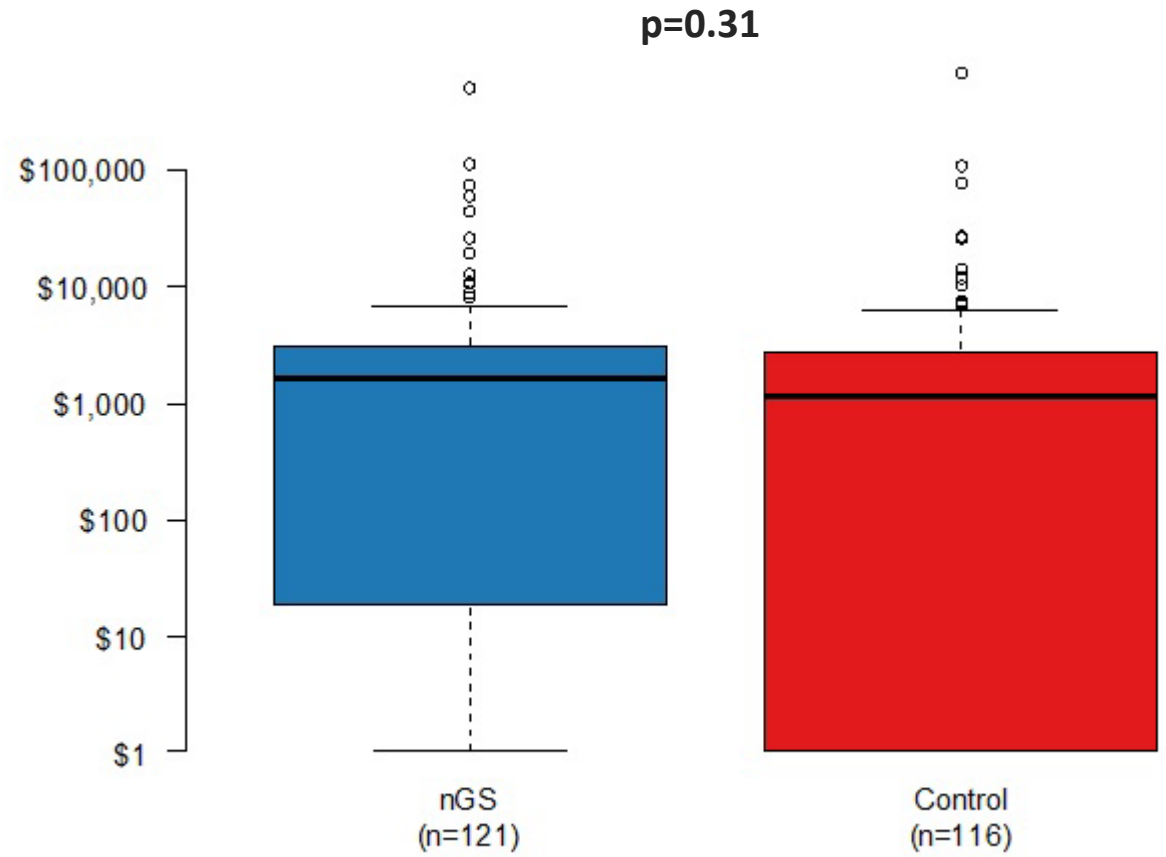
HARVARD MEDICAL SCHOOL
G2P GENOMES TO PEOPLE ARIADNE LABS

Preliminary data: No significant increase in healthcare costs

Healthcare utilization through 10 months

	Well Babies	
	nGS (n=120)	Control (n=116)
Days hospitalized	0.0	0.1
Health care visits	5.9	5.4
Number of medications	1.4	1.7
ER Visits	0.4	0.3

Healthcare costs through 10 months



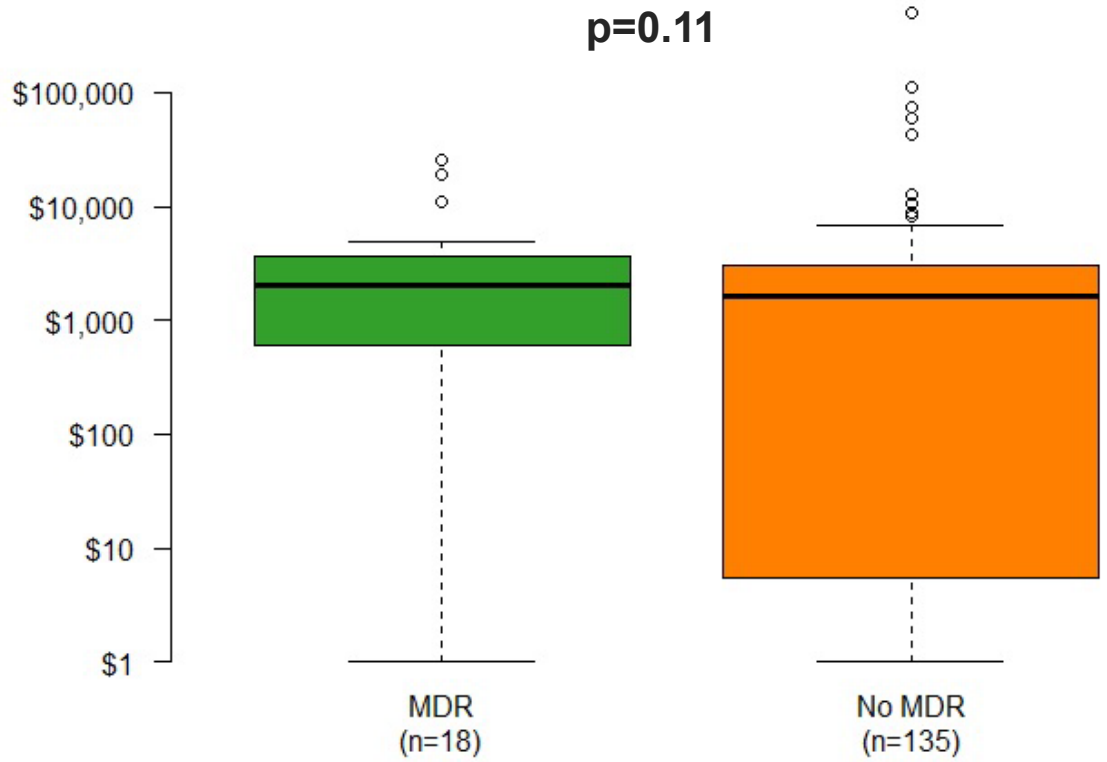
Mean health sector costs: $1,586 for nGS arm and $1,179 for control arm

Christensen et al., in preparation

Preliminary data: Appropriate follow-up for genomic findings

$2,044 for newborns with monogenic disease risks and $1,606 for newborns without.

Variant	Follow-up
BTD (Biotinidase deficiency)	Genetics/metabolics visit (2), biotin supplements
CD46 (Atypical hemolytic-uremic syndrome)	Nephrology visit
ELN (Supravalvular aortic stenosis)	Cardiology visit (3), ECG (3), Echo (2)
TTN x3 (Dilated cardiomyopathy)	Cardiology visit, ECG, Echo
VCL (Dilated cardiomyopathy)	Cardiology visit, ECG, Echo
ANKRD11 (KBG syndrome)	Genetics visit (2)
GLMN (Glomuvenous malformations)	Dermatology visit, CBC



Appropriate follow-up contributed to non-significant increases in healthcare costs

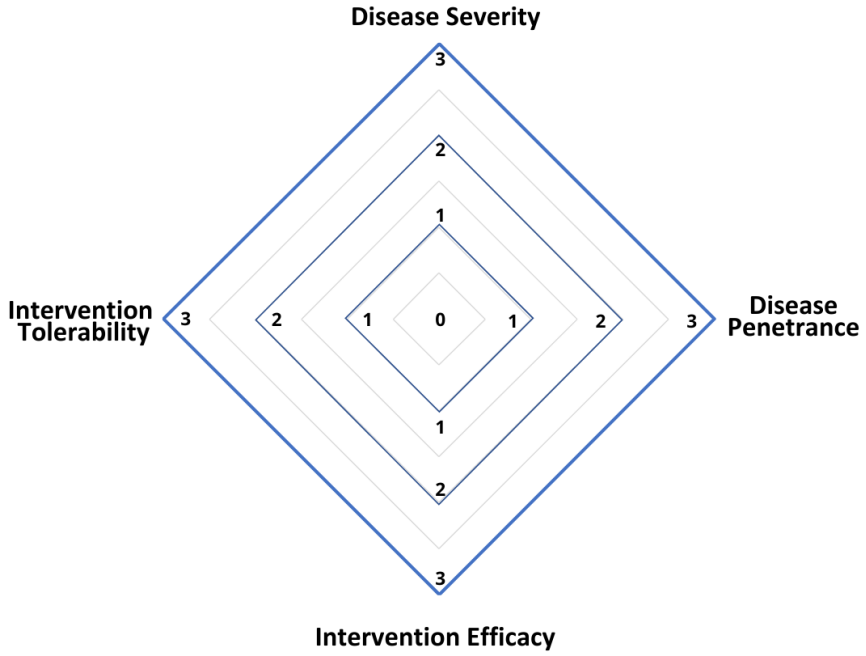
Christensen et al., in preparation

Long term follow-up of infants with uMDR

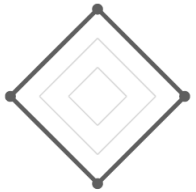
ARTICLE

Actionability of unanticipated monogenic disease risks in newborn genomic screening: Findings from the BabySeq Project

Robert C. Green,[1,2,3,4,16,*] Nidhi Shah,[2,5,6,16] Casie A. Genetti,[5,16] Timothy Yu,[4,5] Bethany Zettler,[1,3] Melissa K. Uveges,[7] Ozge Ceyhan-Birsoy,[8] Matthew S. Lebo,[1,2,4,9] Stacey Pereira,[10] Pankaj B. Agrawal,[4,5,11] Richard B. Parad,[4,12] Amy L. McGuire,[10] Kurt D. Christensen,[4,13] Talia S. Schwartz,[14] Heidi L. Rehm,[2,4,15] Ingrid A. Holm,[4,5] Alan H. Beggs,[2,4,5] and The BabySeq Project Team



Key:



- ✓ Severe genetic condition
- ✓ High penetrance
- ✓ Highly effective intervention
- ✓ Highly tolerable intervention

Example:
FBN1 Marfan syndrome

- ✓ Severe genetic condition
- ✓ High penetrance
- ✗ Highly effective intervention
- ✗ Highly tolerable intervention

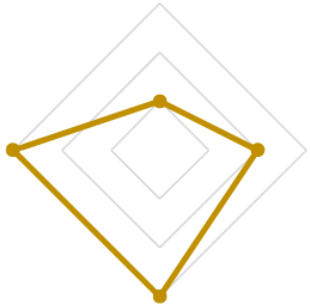
Example:
HD Huntington's disease

Green et al, Am J Hum Genetics, 2023

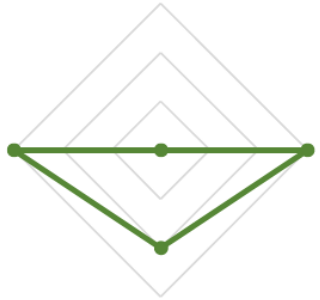
HARVARD MEDICAL SCHOOL
G2P GENOMES TO PEOPLE ARIADNE LABS

Clinical actionability of uMDR genes identified in BabySeq

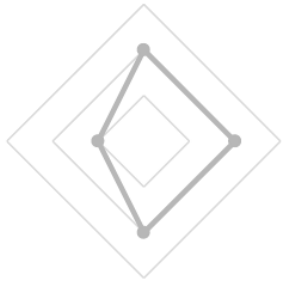
BTD
Biotinidase deficiency



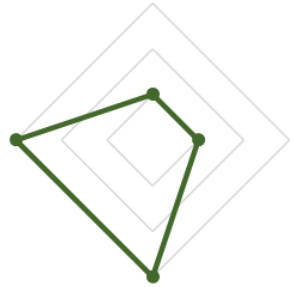
G6PD
Glucose-6-phosphate dehydrogenase deficiency



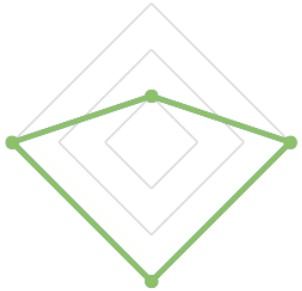
GLMN
Glomuvenous malformations



CD46
Atypical hemolytic-uremic syndrome

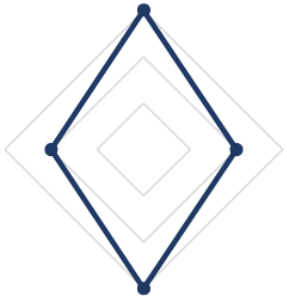


SLC7A9
Cystinuria

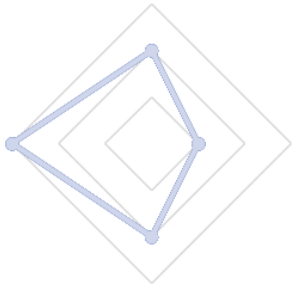


KCNQ4
Non-syndromic hearing loss

CYP21A2
Congenital adrenal hyperplasia due to 21-hydroxylase deficiency

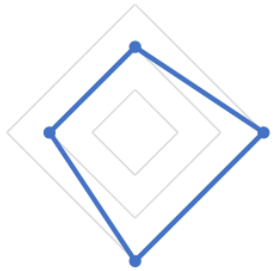


MYBPC3
Hypertrophic cardiomyopathy

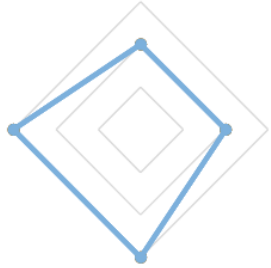


TTN
Dilated cardiomyopathy

VCL
Dilated cardiomyopathy



MSH2
Lynch syndrome

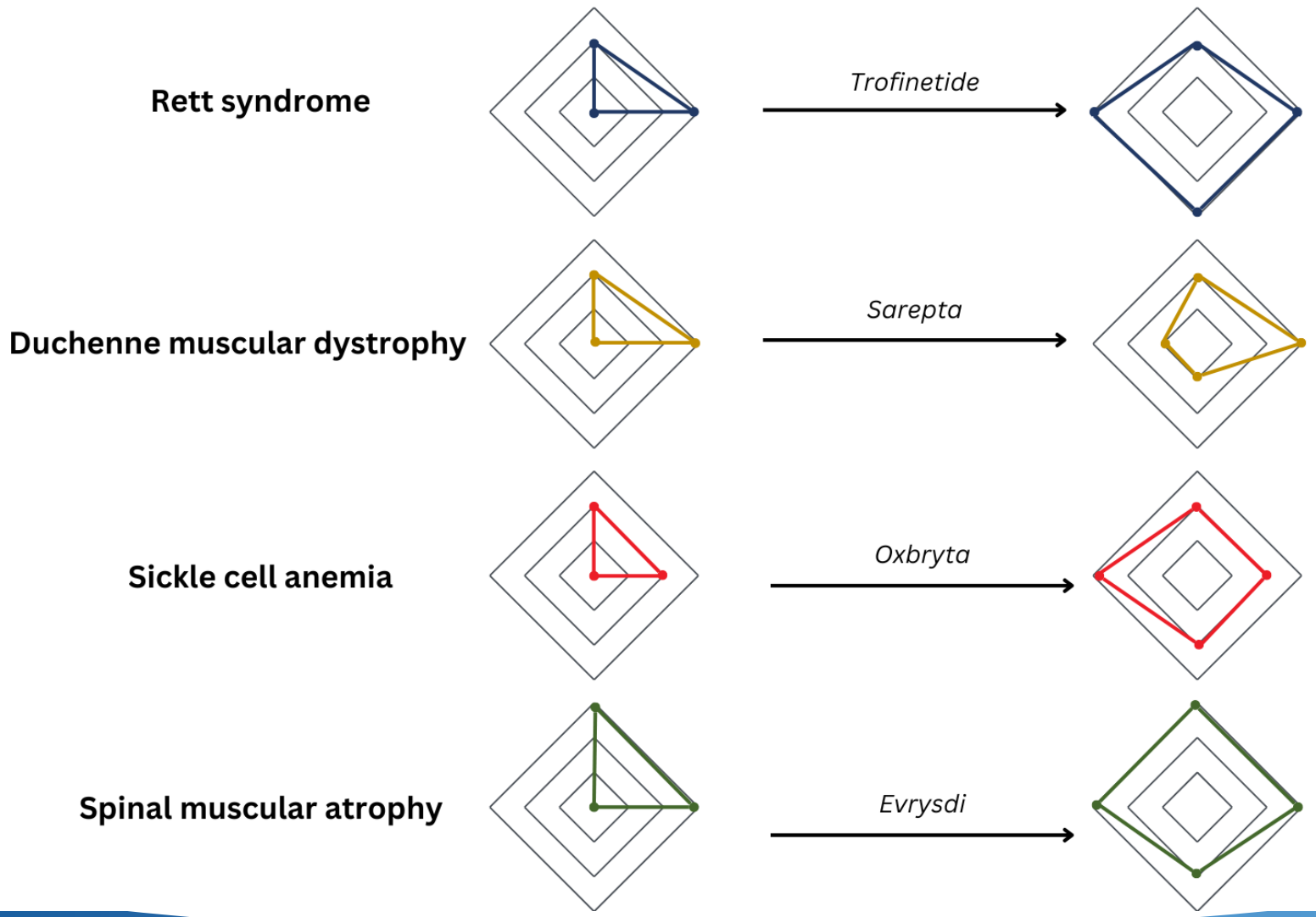


ELN
Supravalvularaortic stenosis

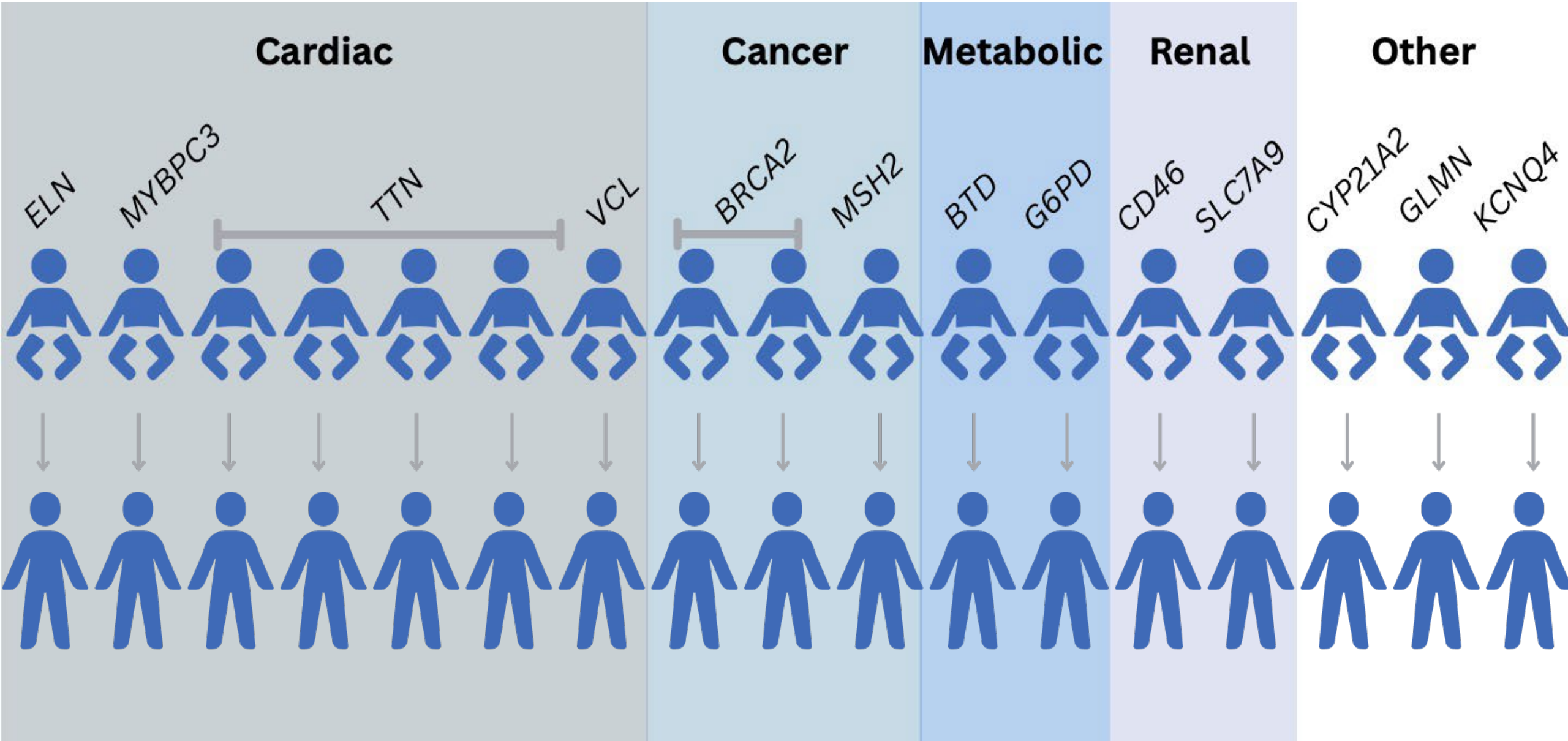
BRCA2
Hereditary breast and ovarian cancer syndrome

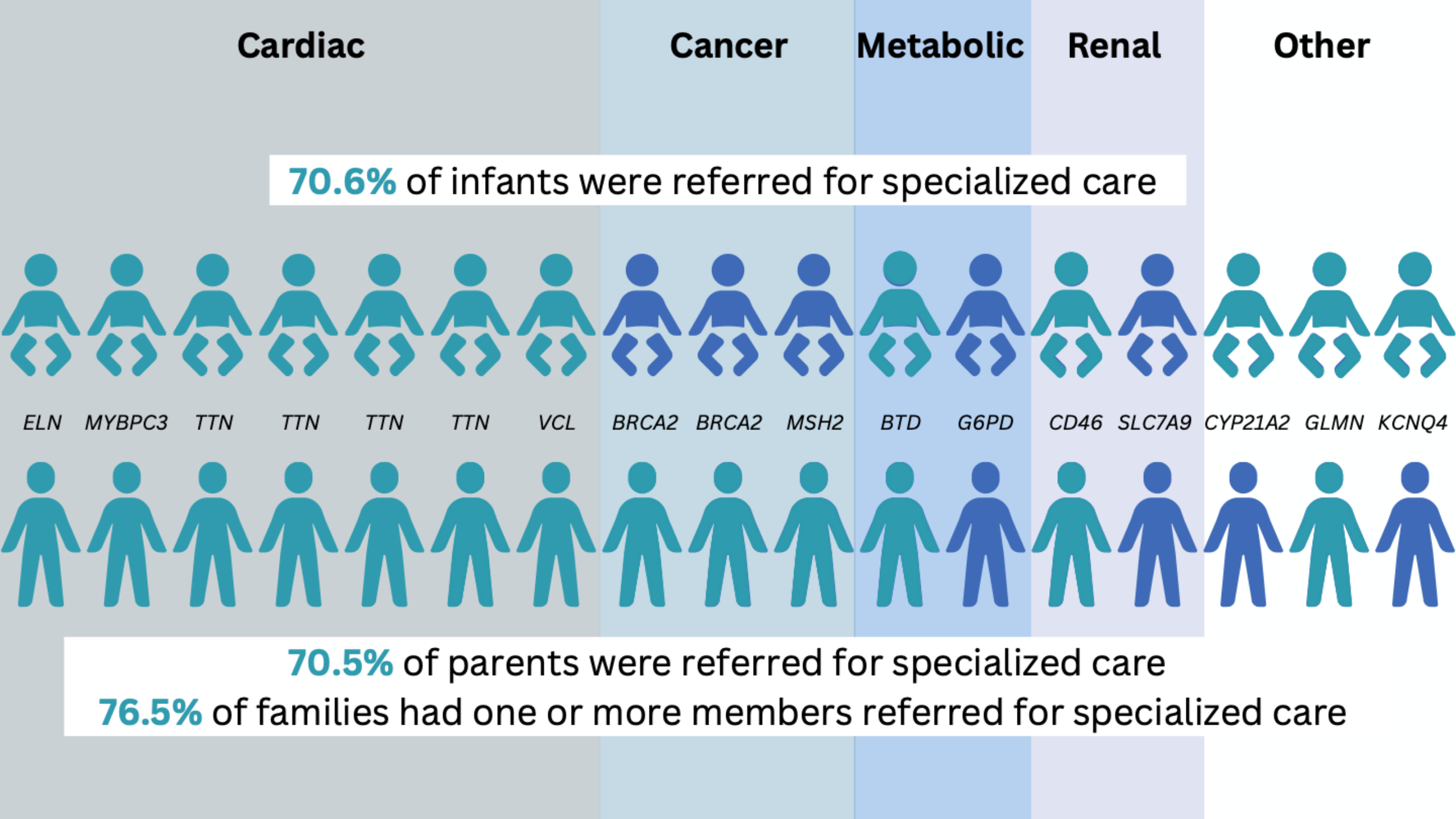
HARVARD MEDICAL SCHOOL
G2P GENOMES TO PEOPLE ARIADNE LABS

Actionability Changes With Treatment

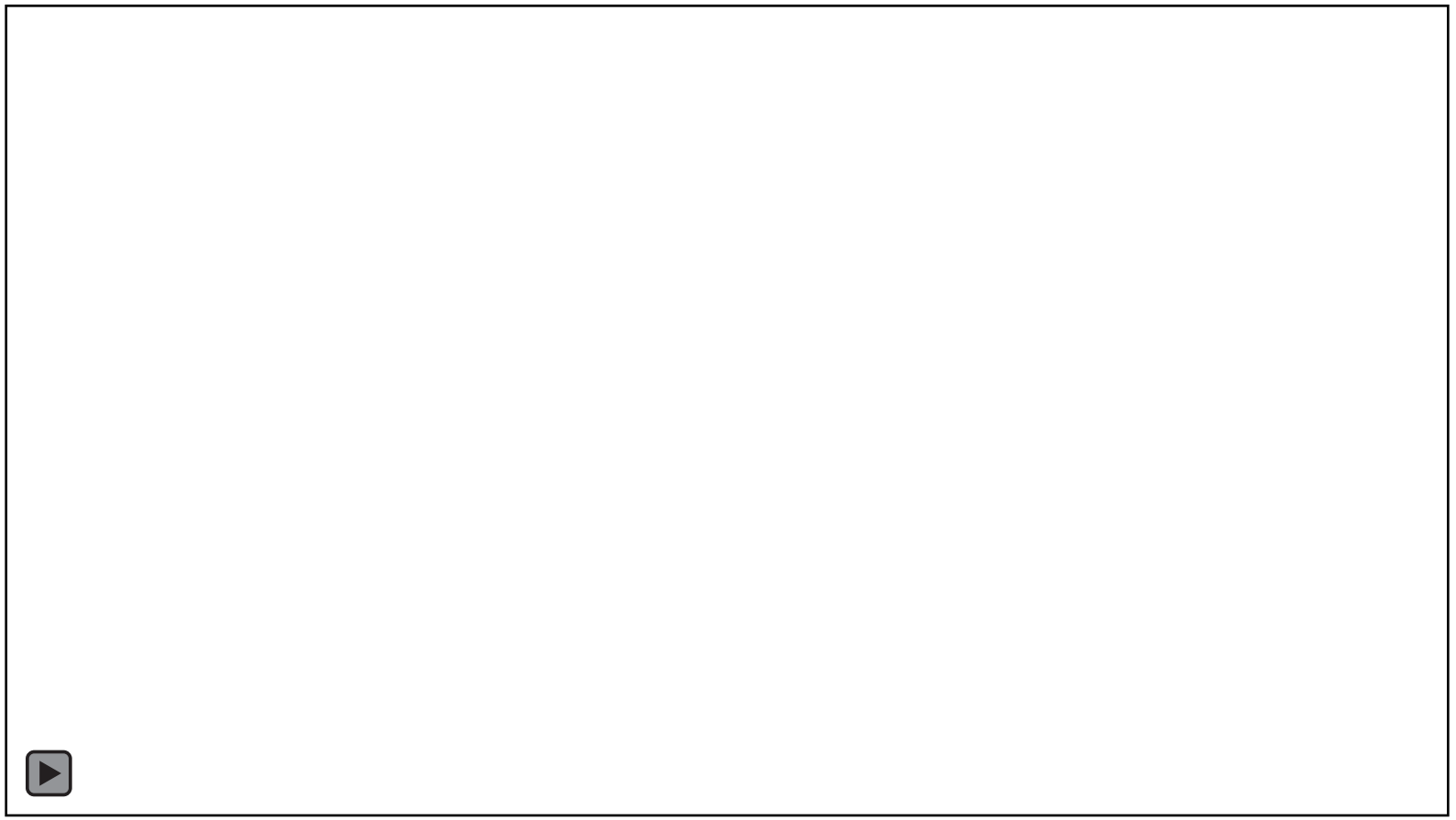


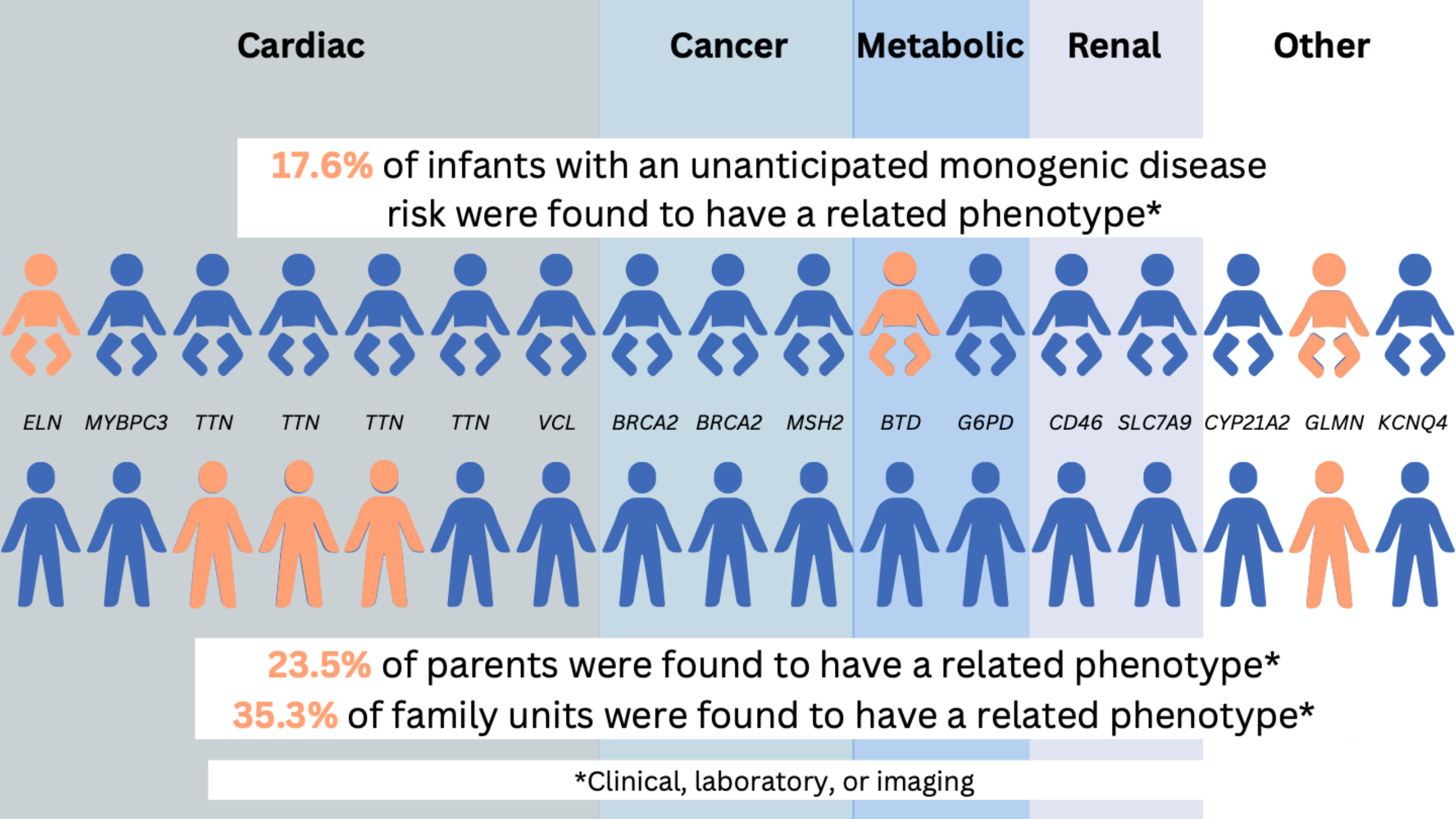
Infants and families with unanticipated monogenic disease risks

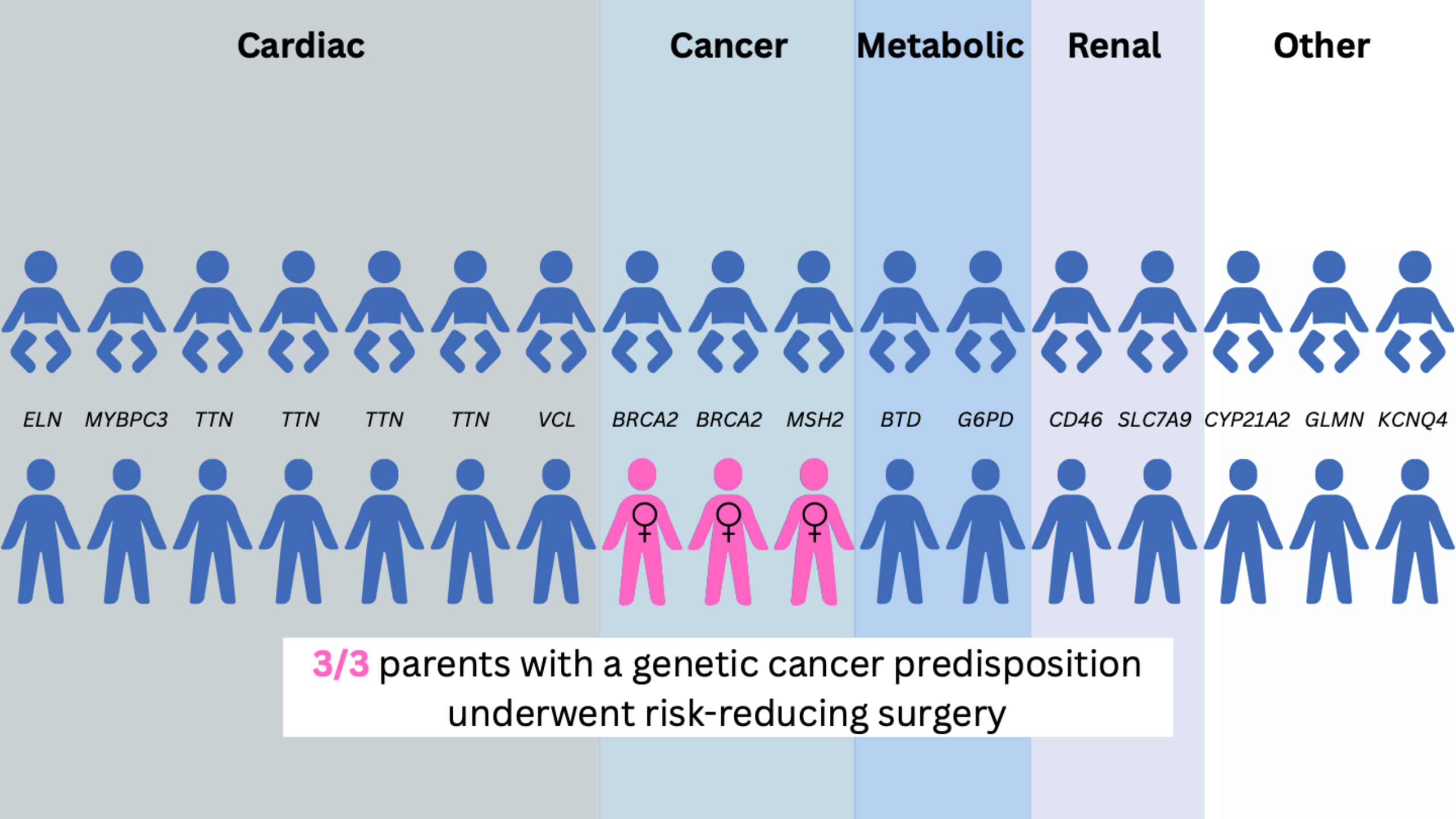



Cardiac
Cancer
Metabolic
Renal
Other
70.6% of infants were referred for specialized care
ELN
MYBPC3
TTN
TTN
TTN
TTN
VCL
BRCA2
BRCA2
MSH2
BTD
G6PD
CD46
SLC7A9
CYP21A2
GLMN
KCNQ4
70.5% of parents were referred for specialized care
76.5% of families had one or more members referred for specialized care

Genomic screening expands within families




Cardiac
Cancer
Metabolic
Renal
Other
17.6% of infants with an unanticipated monogenic disease risk were found to have a related phenotype*
ELN
MYBPC3
TTN
TTN
TTN
TTN
VCL
BRCA2
BRCA2
MSH2
BTD
G6PD
CD46
SLC7A9
CYP21A2
GLMN
KCNQ4
23.5% of parents were found to have a related phenotype*
35.3% of family units were found to have a related phenotype*
*Clinical, laboratory, or imaging

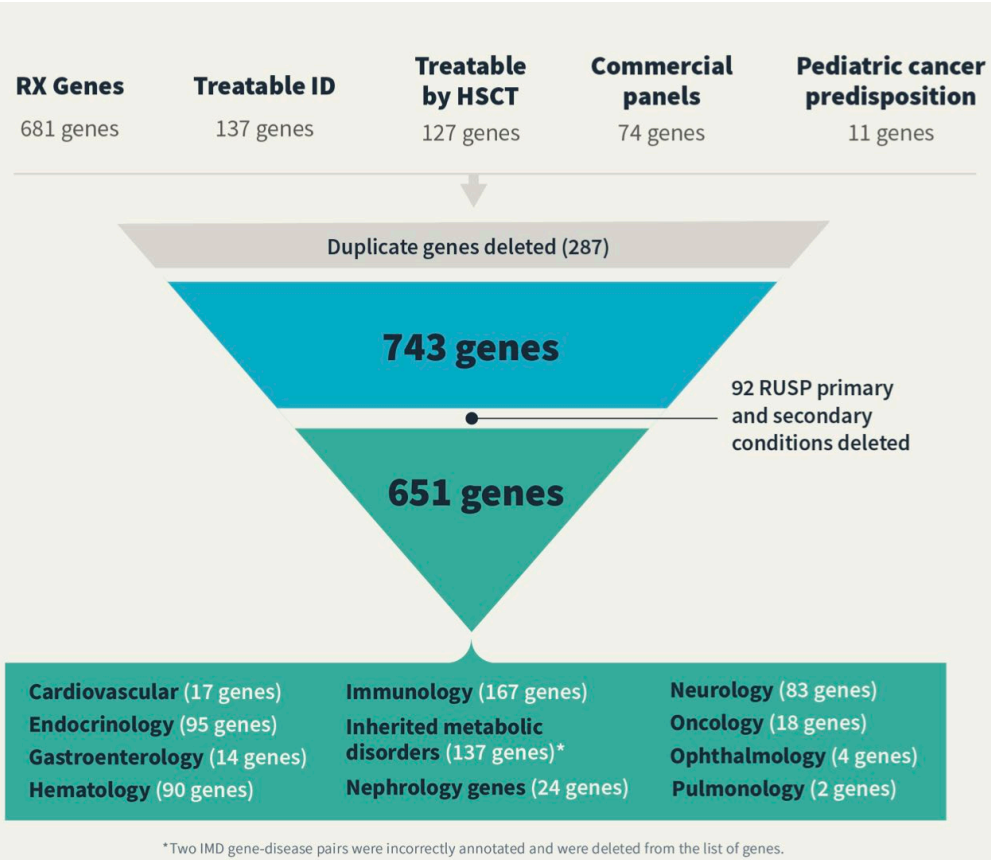

Cardiac
Cancer
Metabolic
Renal
Other
ELN
MYBPC3
TTN
TTN
TTN
TTN
VCL
BRCA2
BRCA2
MSH2
BTD
G6PD
CD46
SLC7A9
CYP21A2
GLMN
KCNQ4
3/3 parents with a genetic cancer predisposition underwent risk-reducing surgery

JAMA Network Open

Original Investigation | Pediatrics

Perspectives of Rare Disease Experts on Newborn Genome Sequencing

Nina B. Gold, MD; Sophia M. Adelson, BA; Nidhi Shah, MD; Shardae Williams, MEd; Sarah L. Bick, MD; Emilie S. Zoltick, ScD, MPH; Jessica I. Gold, MD, PhD; Alanna Strong, MD, PhD; Rebecca Ganetzky, MD; Amy E. Roberts, MD; Melissa Walker, MD, PhD; Alexander M. Holtz, MD, PhD; Vijay G. Sankaran, MD, PhD; Ottavia Delmonte, MD, PhD; Weizhen Tan, MD; Ingrid A. Holm, MD, MPH; Jay R. Thiagarajah, MD, PhD; Junne Kamihara, MD, PhD; Jason Comander, MD, PhD; Emily Place, MS, CGC; Janey Wiggs, MD, PhD; Robert C. Green, MD, MPH



*Two IMD gene-disease pairs were incorrectly annotated and were deleted from the list of genes.

JAMA Network Open

Original Investigation | Pediatrics

Perspectives of Rare Disease Experts on Newborn Genome Sequencing

Nina B. Gold, MD; Sophia M. Adelson, BA; Nidhi Shah, MD; Shardae Williams, MEd; Sarah L. Bick, MD; Emilie S. Zoltick, ScD, MPH; Jessica I. Gold, MD, PhD; Alanna Strong, MD, PhD; Rebecca Ganetzky, MD; Amy E. Roberts, MD; Melissa Walker, MD, PhD; Alexander M. Holtz, MD, PhD; Vijay G. Sankaran, MD, PhD; Ottavia Delmonte, MD, PhD; Weizhen Tan, MD; Ingrid A. Holm, MD, MPH; Jay R. Thiagarajah, MD, PhD; Junne Kamihara, MD, PhD; Jason Comander, MD, PhD; Emily Place, MS, CGC; Janey Wiggs, MD, PhD; Robert C. Green, MD, MPH

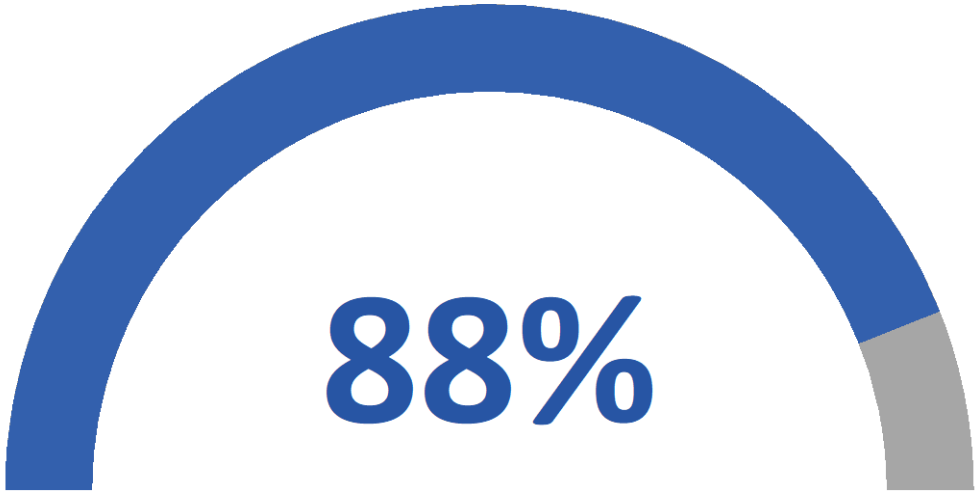
Gene	Disease	Clinical area	No. (%)			Responses, No.	Prevalence of disease (per 100 000)	Age of onset	Orthogonal test for at-risk infants	Intervention
			Yes	No	Unsure					
OTC	Ornithine transcarbamylase deficiency	Metabolism	61 (98.4)	1 (1.6)	0	62	1.5	Infancy to adulthood	Orotic acid level, plasma amino acids	Protein restriction, citrulline, nitrogen scavengers, liver transplant
G6PC	Glycogen storage disease Ia	Metabolism	57 (93.4)	3 (4.9)	1 (1.6)	61	0.04	Infancy	No	Cornstarch, nighttime intragastric continuous glucose infusion, low-carbohydrate and high-protein diet
SLC37A4	Glycogen storage disease Ib	Metabolism	56 (93.3)	4 (6.7)	0	60	0.04	Infancy	No	Cornstarch, nighttime intragastric continuous glucose infusion, allopurinol, statin, granulocyte colony-stimulating factor, immunomodulators, low-carbohydrate and high-protein diet
CYP11B1	Congenital adrenal hyperplasia due to 11-β-hydroxylase deficiency	Endocrinology	35 (92.1)	2 (5.3)	1 (2.6)	38	0.8	Infancy to adolescence	Serum 11-deoxycortisol and 11-deoxycorticosterone levels	Hydrocortisone
ARSB	Mucopolysaccharidosis type VI	Metabolism	54 (91.5)	3 (5.1)	2 (3.4)	59	0.3	Childhood	Arylsulfatase B enzyme activity, urine glycosaminoglycans	Galsulfase enzyme replacement, HSCT
F8	Hemophilia A	Hematology	37 (90.2)	4 (9.8)	0	41	7.5	Infancy to adolescence	Factor VIII level	Factor VIII
F9	Hemophilia B	Hematology	37 (90.2)	4 (9.8)	0	41	1.3	Infancy to adolescence	Factor IX level	Factor IX
SLC2A1	GLUT1 deficiency syndrome 1	Metabolism	55 (90.2)	3 (4.9)	3 (4.9)	61	1.7	Infancy	Blood glucose, cerebrospinal fluid glucose	Ketogenic diet, carnitine supplementation, avoid barbiturates, methylxanthine, valproic acid

HARVARD MEDICAL SCHOOL
G2P GENOMES TO PEOPLE ARIADNE LABS

Expert perspectives on NBSeq

Newborn screening should include…

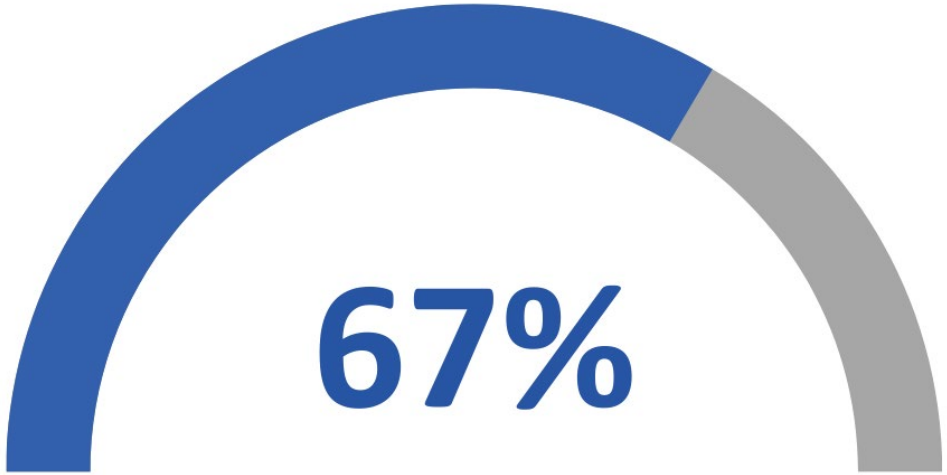
Genome sequencing for treatable conditions



Expert perspectives on NBSeq

Newborn screening should include…

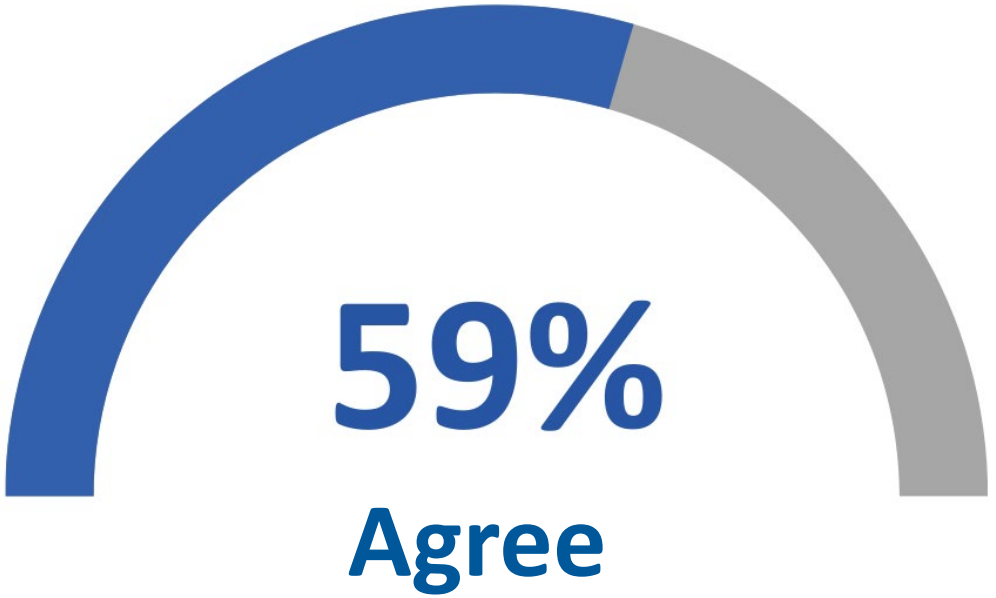
Conditions that are <u>not</u> treatable but have established guidelines for management or surveillance



Expert perspectives on NBSeq

Newborn screening should include…

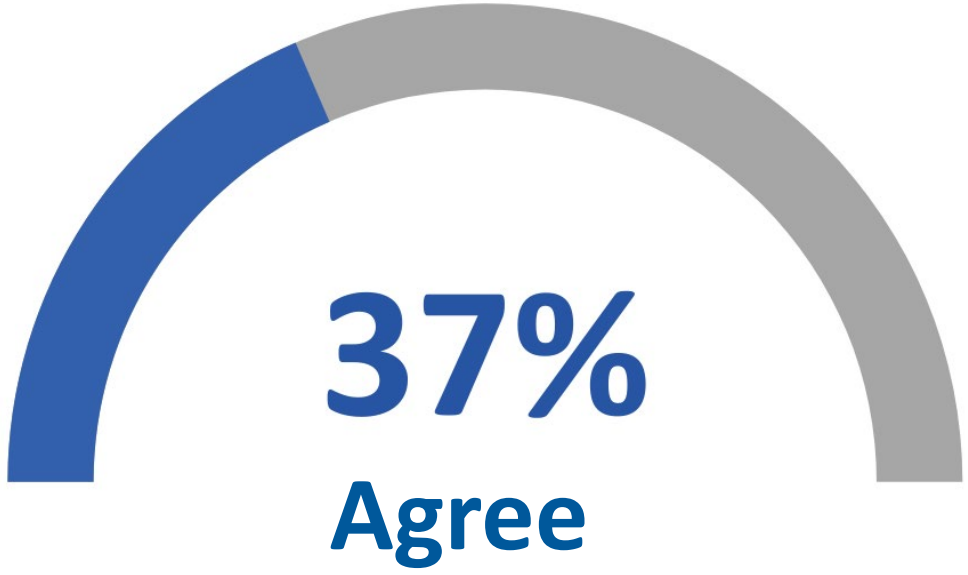
Treatable conditions with low penetrance



Expert perspectives on NBSeq

Newborn screening should include…

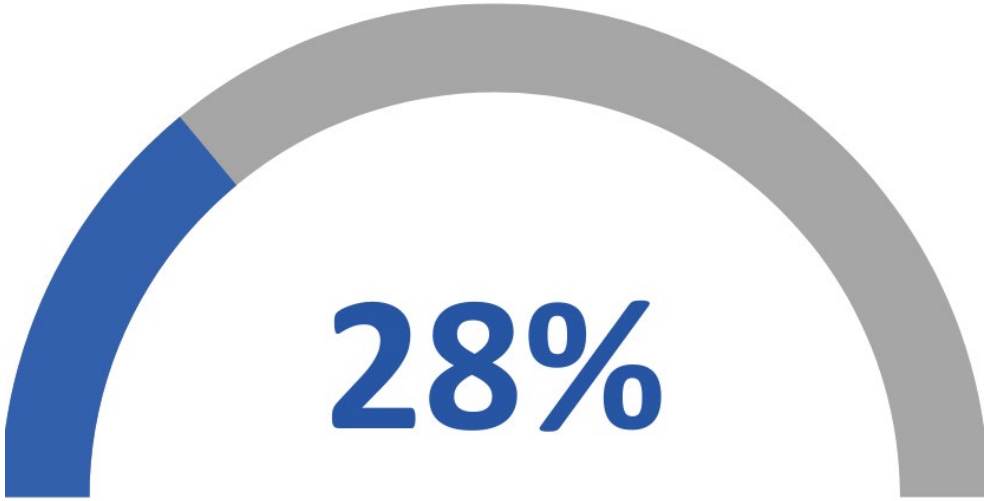
Actionable adult-onset conditions to facilitate cascade testing in parents



Expert perspectives on NBSeq

Newborn screening should include…

Childhood onset conditions with <u>no</u> established targeted therapies or expert management guidelines



National Center
for Advancing
Translational Sciences

The BabySeq2 Project

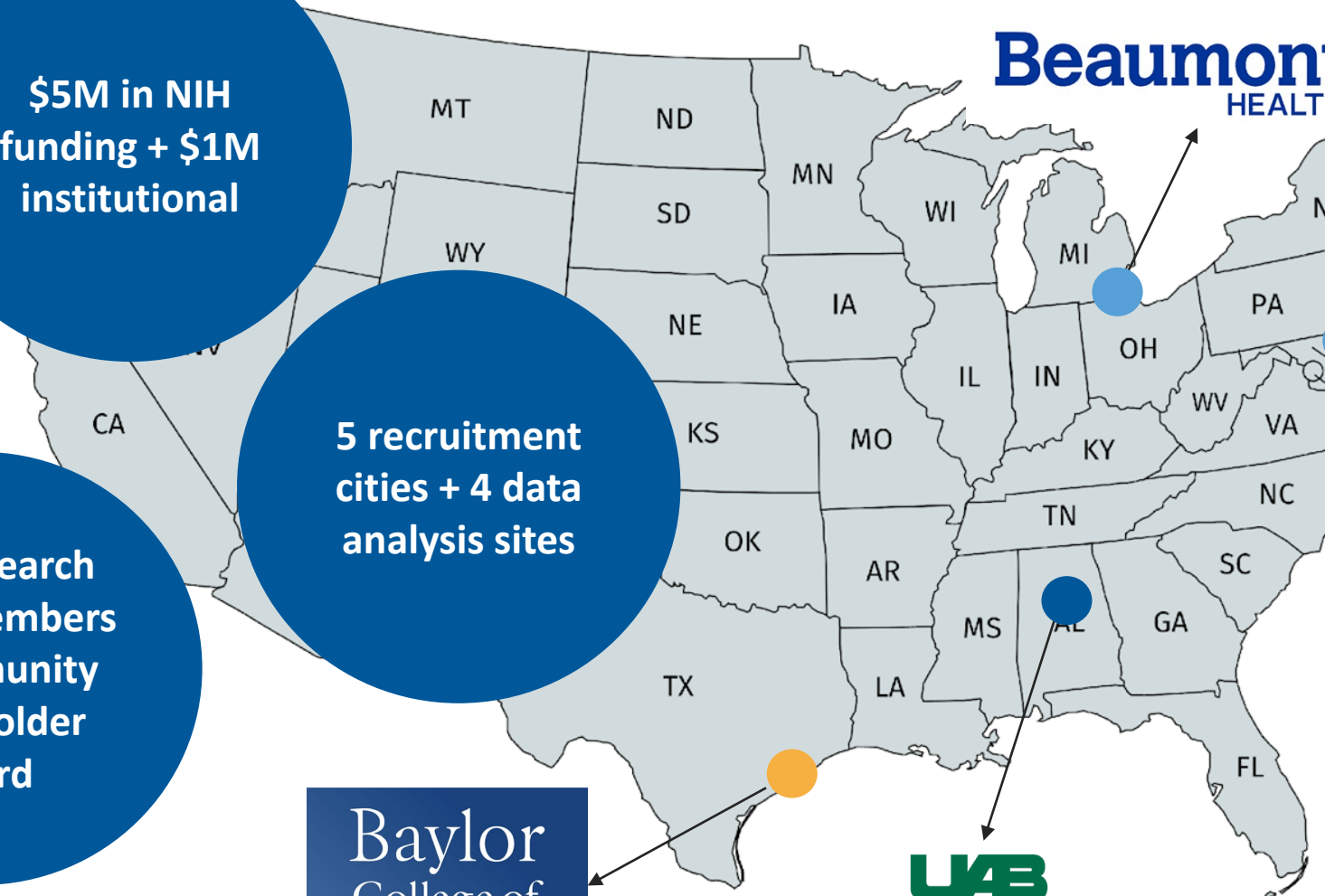
Implementation of preventive genomics in a diverse cohort of healthy infants

BabySeq2: 9 Sites and Growing

$5M in NIH funding + $1M institutional

5 recruitment cities + 4 data analysis sites

100 research team members + community stakeholder board



Beaumont HEALTH

Mass General Brigham

Boston Children's Hospital
Until every child is well™

Harvard Pilgrim Health Care

BROAD INSTITUTE

Mount Sinai Hospital

Children's Hospital of Philadelphia℠

Baylor College of Medicine

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

HARVARD MEDICAL SCHOOL
G2P GENOMES TO PEOPLE ARIADNE LABS

International Consortium/Conference on Newborn Sequencing

ICoNS Steering Committee

Robert C. Green

ICoNS Co-Chair
BabySeq

David Bick

ICoNS Co-Chair
Genomics England

Wendy K. Chung

The GUARDIAN Project

Melissa Wasserstein

ScreenPlus

Allesandra Ferlini

Screen4Care

Stephen Kingsmore

BeginNGS

Holly L Peay

Early Check Program

Lilian Downie

BabyBeyond
BabyScreen+

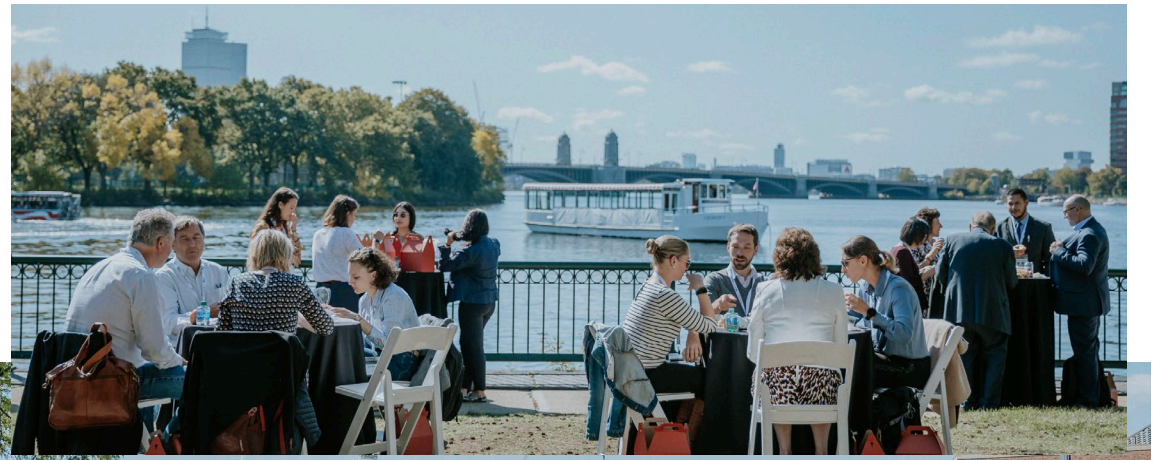
Nicolas Encina

ICoNS Director
Ariadne Labs, Harvard University

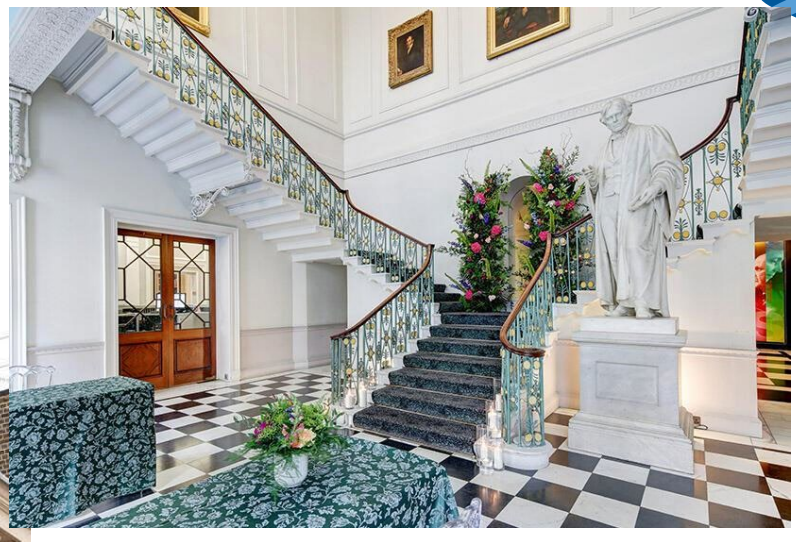
www.iconseq.org

ICONS

INTERNATIONAL CONFERENCE ON NEWBORN SEQUENCING



2023 Conference: The Royal Institution, London October 5-6, 2023



See video at 14:06 in the recording

BabySeq uses genetic testing and family history information to look for risk markers that might cause health problems in childhood.

BabySeq Collaborators

Pankaj B. Agrawal
Sienna Aguilar
Jessica Alfoldi
Heather Andrighetti
Maria Argos
Danielle Renee Azzairiti
Madeleine Ball
Natalie Bartnik
Alan H. Beggs
Marcy Belliveau
Melverta Bender
Tala Berro
Dawn Berry
Wendi N. Betting
Alexander George Bick
Steven Bleyl
Carrie L. Blout
Salvador Borges-Neto
Glenn Braunstein
James Burke
Jeffrey Burns
Deanna Alexis Carere
Maria Carrillo
Rick Caselli
Ozge Ceyhan-Birsoy
Clara Chen
Kurt Christensen
Allison L Cirino
Martha Combs
Adolfo Correa
Mick P. Coupler
Kenneth Covinsky
Scott Crawford

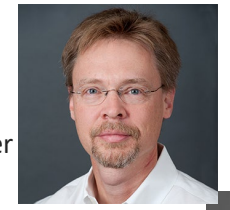
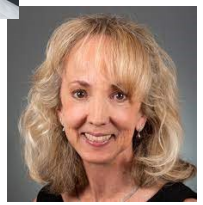
Tshaka Cunningham
Adrienne Cupples
Bridgette Tippin Davis
Mauricio de Castro
Stephanie Deward
Lisa R. Diller
Michael Donohue
Dmitry Dukhovny
Kathryn E. Dunn
Lynette Ekebwe
Ed Esplin
Preston Estep
Altovise Ewing
Romy Fawaz
Shawn Fayer
Candice Finnila
Leslie A. Frankel
Bethany Friedmann
Cubby L. Gardner
Jenny Gauerke
Casie A. Genetti
Nina Gold
Sarah Gollust
Erynn Gordon-Fishman
Chet Graham
Stacy Gray
Joshua Grill
Cynthia Gubbles
Amanda Gutierrez
Maegan Harden
Kristin Harkins
Joe Harrison
Eden Haverfield

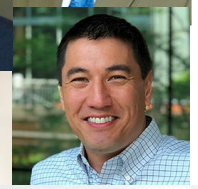
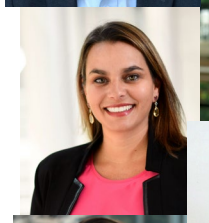
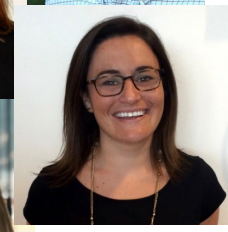
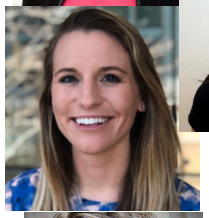
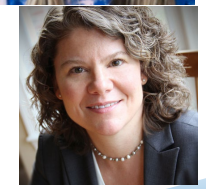
Allison Hazell
Nancy Heard-Costa
Madhuri Hegde
Robyn Heister
Margaret H. Helm
Ally Hempel
Jim Hendrix
Carolyn Y. Ho
Jodi Hoffman
Lillian Hoffman-Andrew
Jennifer Hogan
Ingrid A. Holm
Rebecca Hsu
Jillian Hunsanger
Barbara Inglese
Carmen Isasi
Rubaia Islam
Wiliam Jagust
Anthony Johnson
Jane Juusola
Sarah S. Kalia
Kimberly Kaphingst
Robert Kaplan
Jason Karlawish
Aaron Kesselheim
Amy K. Kiefer
Jacqueline Killian
Scott Kim
Barbara A. Koenig
Robert Koeppe
Peter Kraft
Joel B. Krier
Rebecca C. LaMay

Latrice Landry
William J. Lane
Kenneth Langa
Kostantinos Lazaridis
Lorena de la Vega Lazo
Lan Q Le
Matthew S. Lebo
Justin Leighton
Debra Leonard
Harvey L. Levy
James Lillard
Michael Linderman
Jennifer Lingler
Christina Liu
Courtney Livingston
Xingquan Lu
Daniel MacArthur
Kalotina Machini
Calum Archibald Macrae
Joseph Maher
Mara Mather
Megan Dora Maxwell
Thomas May
Michelle McCart
Molly McGinness
Amy L. McGuire
Zoe McKay
Meredith McNeil
Mollie Minear
Tanya A Moreno
Cynthia Casson Morton
Joanna L. Mountain
Jaclyn B. Murry

Medha Naik
Ilya Nasrallah
Tiffany T. Nguyen
Daiva Nielsen
Jenny Ostergren
Vaibhav Pandya
Richard B. Parad
Peter J. Park
Hayley A. Peoples
Stacey Pereira
Emma Perez
Devan Petersen
Kaela Plant
Laura Raffield
Vasan Ramachandran
Uma Ramamurthy
Vivek Ramanathan
Heidi L. Rehm
Luisel Ricks-Santi
Amy Roberts
Scott Roberts
Jill O. Robinson
Serguei Roumiantsev
Charmaine Royal
Mack T. Ruffin
Laura Saad
David Salmon
Saskia Sanderson
Talia S. Schwartz
John Seibyl
Christian E Seifman
Lisa Slehmann

Julie Smith
Heather Snyder
Tamar Sofer
Benjamin Solomon
Reisa Sperling
Greta Lee Splansky
Elanor B. Steffens
Joan Steyermark
Sheila Sutti
Kathleen Swenson
Gregory Talavera
Meghan C. Towne
Tina K. Truong
Bastian Greshake Tzovaras
Wendy Uhlmann
Melissa Uveges
Maureen Valentino
Grace E. VanNoy
Jason Vassy
Susan E. Waisbren
Catharine Wang
Kareem Washington
Caroline M. Weipert
Kathie Welsh-Bohmer
Keith Whitfield
Angelia Williams
Susan M. Wolf
David Wolk
Timothy W. Yu
Bethany Zettler
Emilie Zoltick


HARVARD MEDICAL SCHOOL
G2P GENOMES TO PEOPLE
ARIADNE LABS

Mass General Brigham

ARIADNE LABS

G2P
GENOMES TO PEOPLE

genomes2people.org

@robertcgreen
@genomes2people

@genomes2people

rcgreen@bwh.harvard.edu