Transforming inpatient children's outcomes by rapid precision medicine

Stephen Kingsmore MD DSc
President & CEO Rady Children's Institute for Genomic Medicine

Rady Children's Institute
Genomic Medicine

No conflict of interest

Rady Children's Institute Genomic Medicine

- Informed consent was obtained for this research.
- Patient and parent photos, videos, and names are used with their permission
- Illumina, Alexion and Diploid provided “in kind” support for part of this research

What is rapid precision medicine?

Rady Children's Institute Genomic Medicine

Acute medical management guided by genome information

Nearly all of my 37 trillion cells contain 2 genomes of 3.3 billion nucleotides

Rady Children's Institute Genomic Medicine

"We are fearfully and wonderfully made"
-- Psalm 139

How do you decode a genome?

Rady Children's Institute
Genomic Medicine

Rapid Whole Genome Sequencing (40-fold, 16 hours)

Rady Children's Institute Genomic Medicine

Glossary: Rapid Whole Genome Sequencing – Rapidly decoding an individual's entire set of DNA molecules

Which children need their genomes sequenced rapidly?

Rady Children's Institute Genomic Medicine

- Inpatient children with diseases of unknown etiology
  - Those suspected of having a genetic disease
    - 5,429 simple (or Mendelian) genetic diseases
    - 19,176 pathogenic structural/chromosomal/copy number variants
  - Leading cause of infant death
  - Leading cause of death in NICU / PICU
  - Many with effective treatments

Autosomal recessive sickle cell disease *HBB* c.20A>T p.Glu6Val, Pathogenic variant

Rady Children's Institute

- **DNA Code**

G_2	G_2	T_1	G_2	T_1	T_1	G_2	G_2	G_2
T_1	T_1	A_1	T_1	C_3	C_3	T_1	A_1	A_1
A_1	G_2	C_3	C_3	A_1	C_3	G_2	G_2	A_1

- **Protein Code**

M_3	V_4	H_4	L_1	T_1	P_3	V_4	E_1	K_5

Why are we focused on speed?

Rady Children's Institute Genomic Medicine

- **Time from receipt of blood sample to report of diagnosis: 19 hours**

3pm, October 25, 2017 – NICU family 243

Rady Children's Institute Genomic Medicine

8-day-old ♂ admitted from ER

Presenting Illness: *Status Epilepticus*

History:

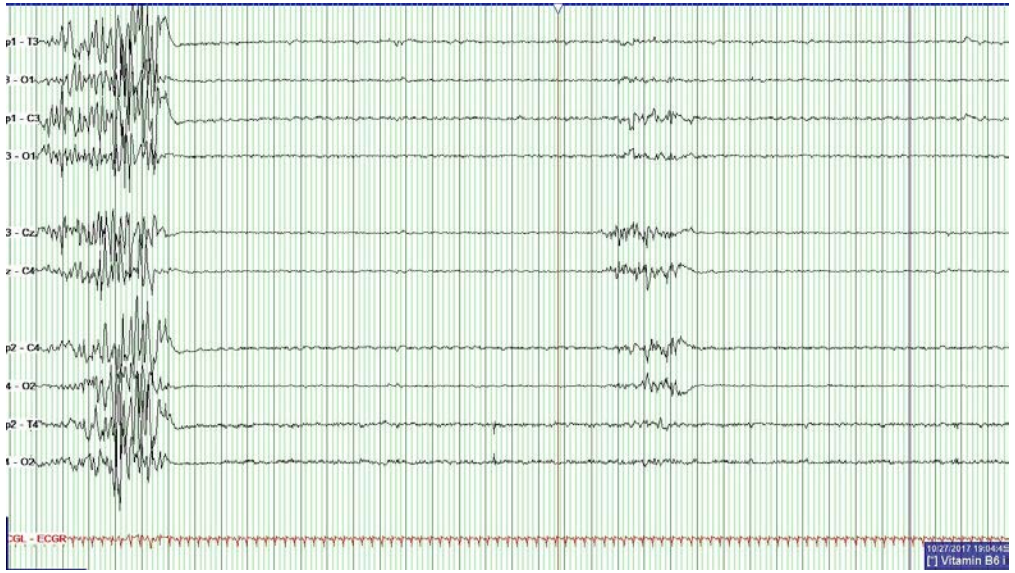
- **23-yo G2P1 healthy mother**
- **Fetal ventriculomegaly detected by ultrasound during pregnancy**
- **Delivery by uncomplicated C-section 39 1/7 weeks**
- **Breast-feeding well, discharged home on day of life 3**

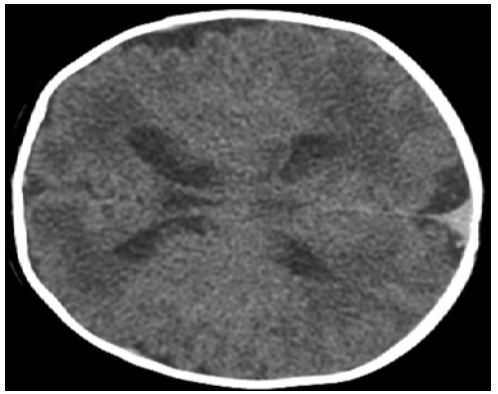
Glossary: Genetic disease – a disease caused by a DNA change(s)

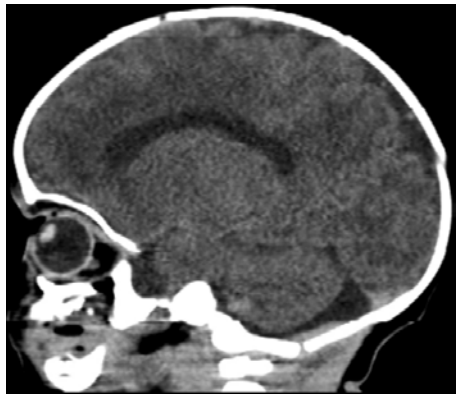
NICU family 243: Initial NICU Workup

Rady Children's Institute Genomic Medicine

- **Electroencephalogram:** seizures & background burst suppression
- **Brain computed tomography:** mild hypoplasia of cerebellum; Borderline lateral ventriculomegaly
- **Infection workup:** negative
- Cerebrospinal fluid lactic acid 6.3 mmol/L (normal 1.1-2.8)
- Serum creatinine kinase 1,195 U/L (normal 13-80, not in acute renal failure range)







Disease Progressed Overnight

Rady Children's Institute Genomic Medicine

"Last night was rough with ongoing…multifocal seizures that continued despite…levetiracetam or phenobarbital"

- Maximal anti-epileptic drugs
- Worsening seizures
- No response to phenytoin, carbamazepine
- Midazolam drip increased until respiratory failure, emergent intubation

"I discussed with his parents the range of outcomes I have seen with Neonatal Burst Suppression encephalopathy which usually entails limited life expectancy and at least moderate to severe developmental disabilities."

Neonatal Seizures

Rady Children's Institute Genomic Medicine

Cause of Neonatal Seizure*	
Hypoxic Ischemic Encephalopathy	38%
Ischemic Stroke	18%
Intracerebral Hemorrhage	12%
Genetic disease	10%
Infection	4%
Brain Malformation	4%
Metabolic disturbance	4%

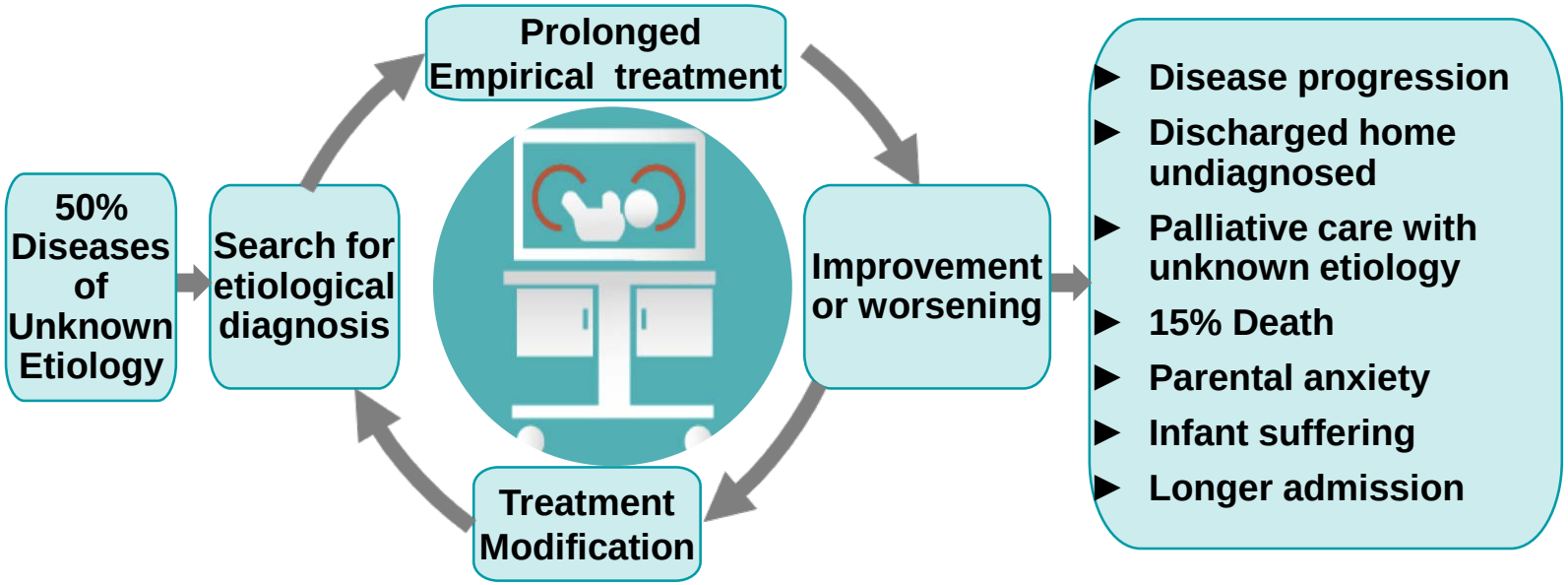
- >1,250 genetic disorders are associated with neonatal seizures

Gene	Specific Treatment
ALDH7A1	Pyridoxine; lysine restriction; valine supplementation
GRIN2A	Memantine or dextromethorphan for gain of function variants
KCNQ2	Ezogabine for loss-of function variants; carbamazepine
KCNT1	Quinidine for gain of function variants
PNPO	Pyridoxal 5'phosphate
PRRT2	Oxcarbazepine; carbamazepine
SCN1A	Avoid sodium channel blockers
SCN2A; SCN8A	Phenytoin; high dose carbamazepine
SLC2A1	Ketogenic Diet
TSC1; TSC2	Vigabatrin
MOCS1	Cyclic pyranopterin monophosphate

60% of the NICU & PICU infants with genetic diseases are misdiagnosed/treated

Rady Children's Institute Genomic Medicine

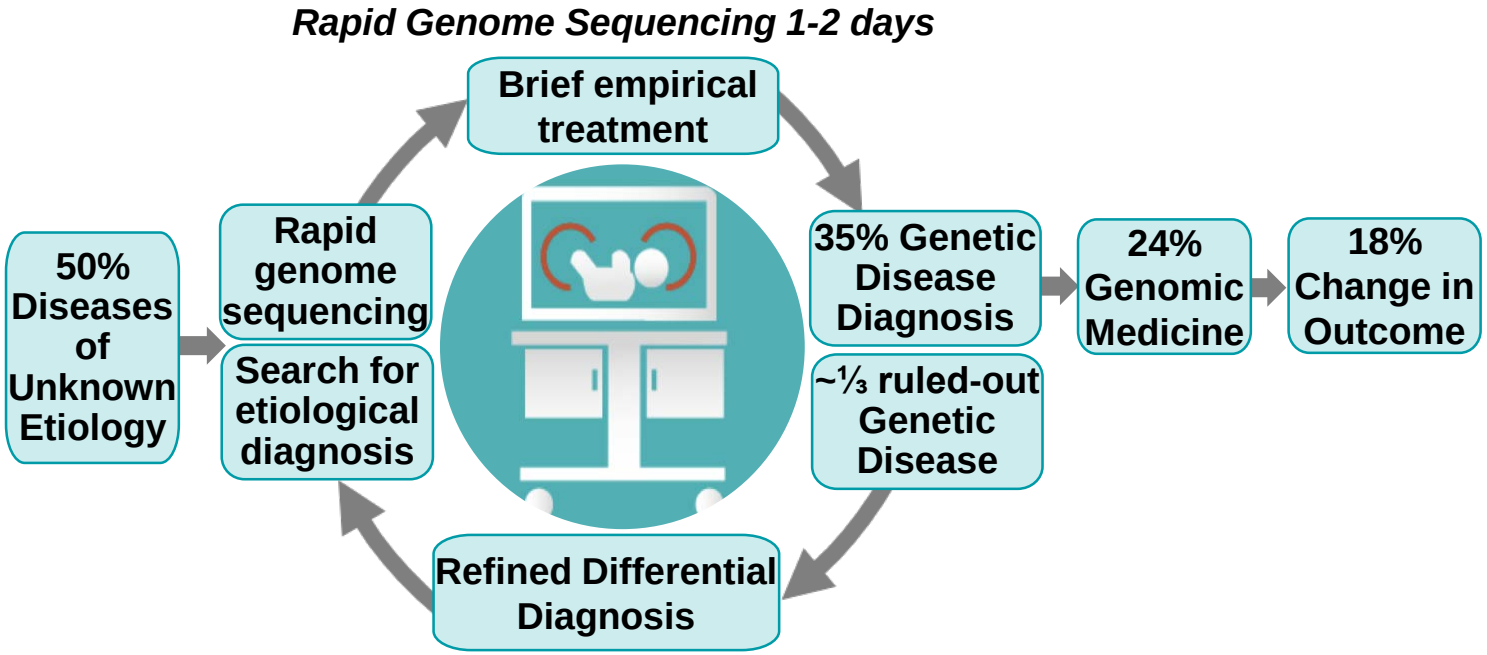
Standard Genetic Testing 6-12 weeks



NSIGHT2, ClinicalTrials.gov ID NCT03211039, 213 enrollees, 47% of NICU eligible, 14% incidence of genetic diseases

Summary: rWGS-based Genomic Medicine improves outcomes in children's ICUs

Rady Children's Institute Genomic Medicine



NSIGHT2, ClinicalTrials.gov ID NCT03211039, 213 enrollees, 47% of NICU eligible, 14% incidence of genetic diseases

Diagnosis reported at 8pm October 27

Rady Children's Institute Genomic Medicine

- **Disease:** Pyridoxine-Dependent Epilepsy
- **Gene:** Aldehyde dehydrogenase 7 family member A1
- **Inheritance Pattern:** Autosomal Recessive
- **Variants:** 2 pathogenic variants

Genome variant (g.)	Gene variant (c.)	Protein variant (p.)
Chr5 g.125,919,689C>T	*ALDH7A1* c.328C>T	p.Arg110Ter
Chr5 g.125887751C>G	*ALDH7A1* c.1279G>C	p.Glu427Gln

C=Cytosine; T=Thymidine; G=Guanine
Arg=Argenine; Ter=Termination Codon; Gln=glutamine; Glu=glutamic acid

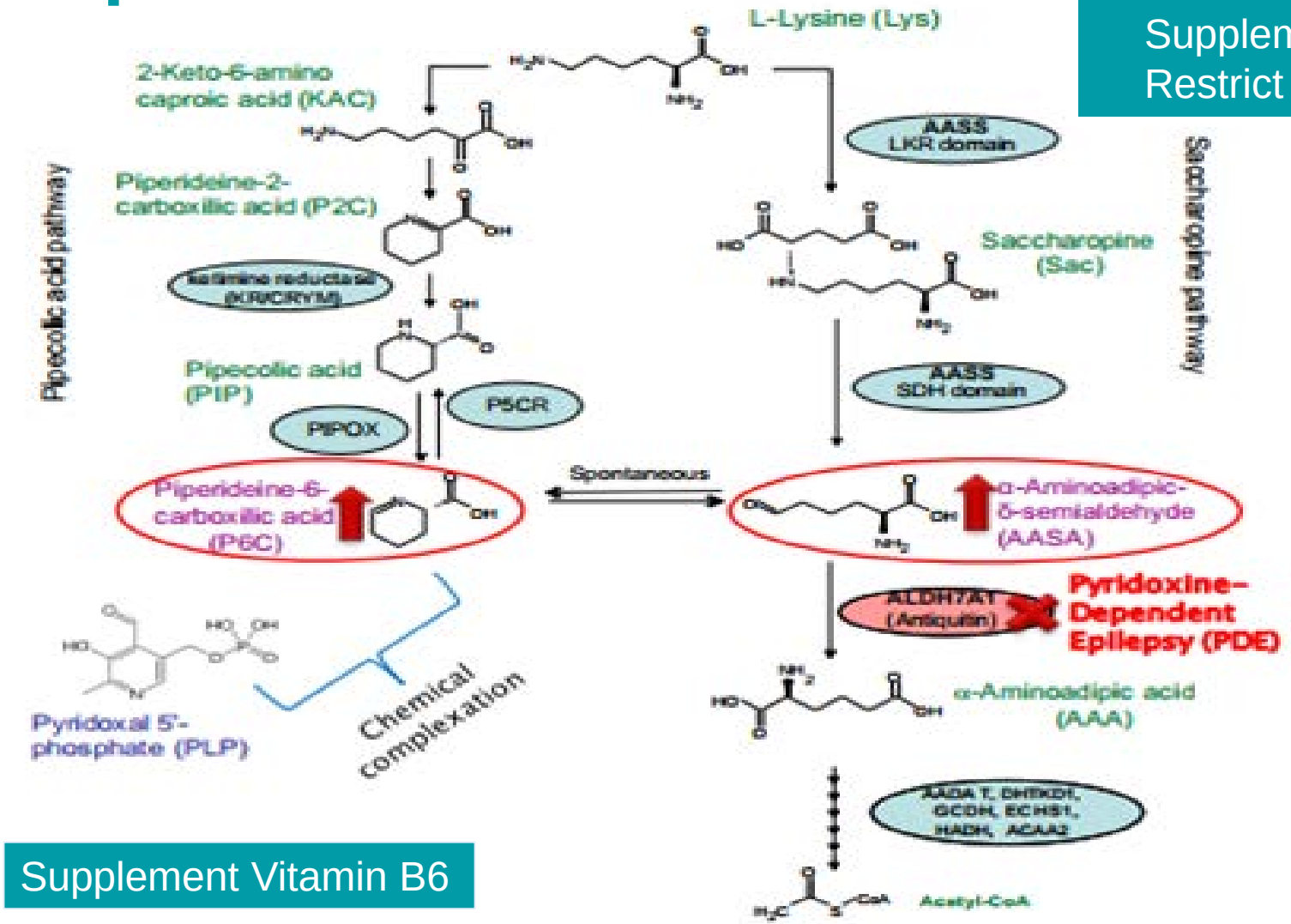
Glossary: Gene – a sequence of nucleotides in a genome that codes for a protein

Recessive – A disease expressed in offspring only when inherited from both parents

Rapid Precision Medicine

Rady Children's Institute Genomic Medicine

Supplement argenine
Restrict dietary lysine



Supplement Vitamin B6

Impact of diagnosis 55 hours after consent

Rady Children's Institute Genomic Medicine

Following triple therapy with pyridoxine, L-arginine supplementation and dietary lysine restriction

- Electroencaphalogram normalized
- Seizures stopped

Within 36 hours

- Extubated
- All anti-epileptic drugs stopped

Discharged Home

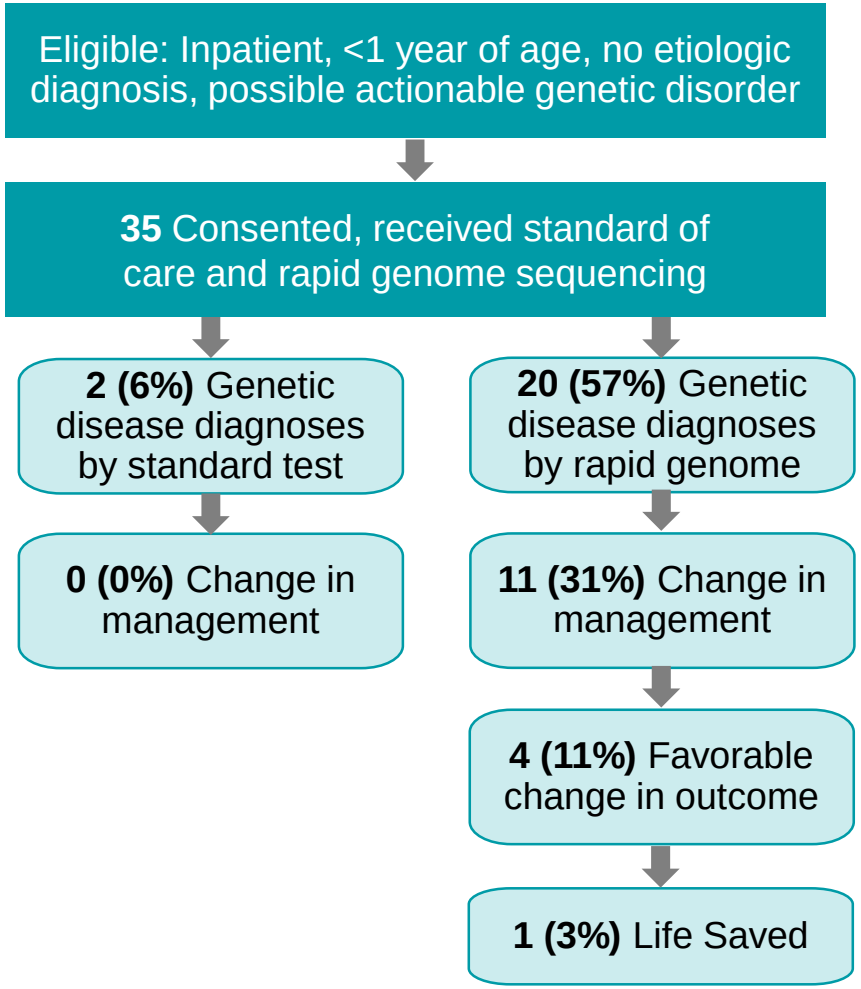
- Meeting milestones @ 22 months of age

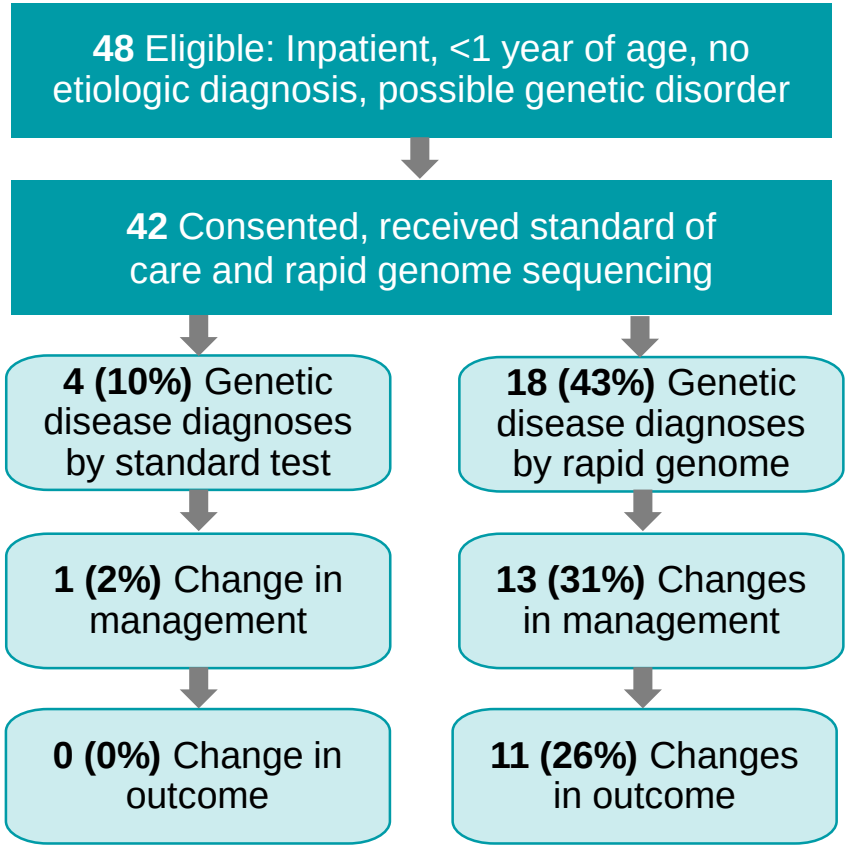
Video of Maverick and his Mum

Rady Children's Institute
Genomic Medicine

Clinical Utility in 2 Studies

Rady Children's Institute Genomic Medicine



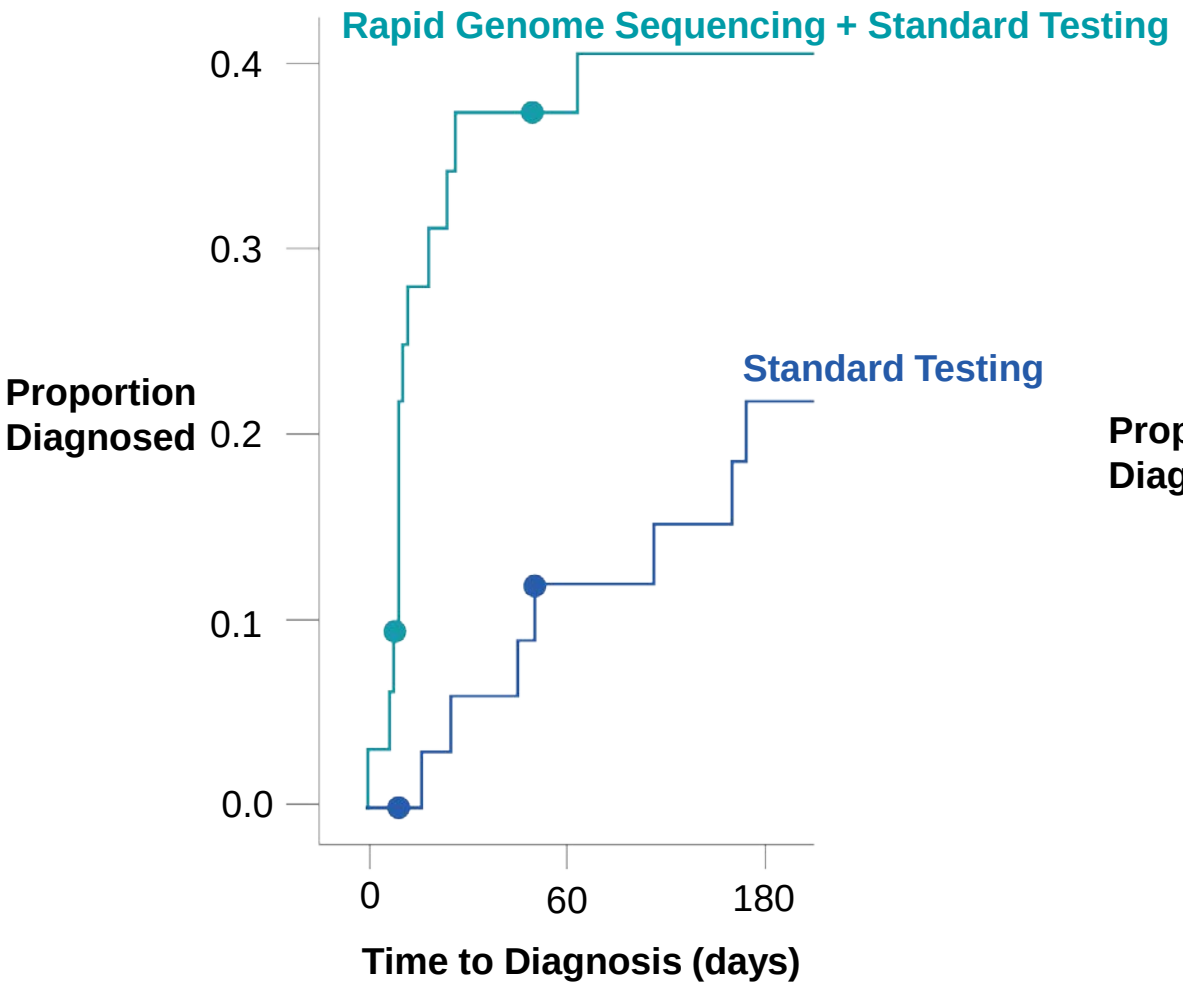


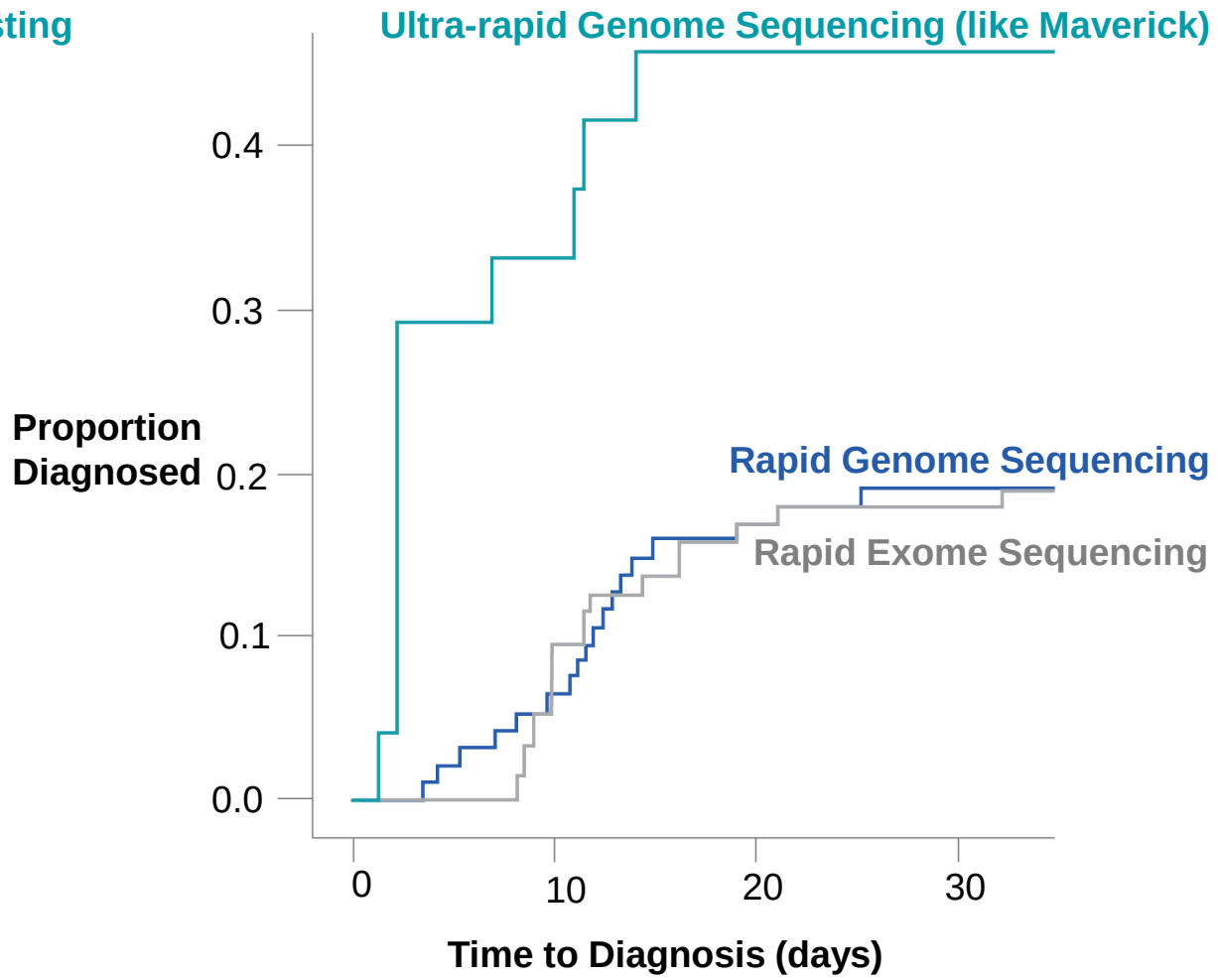
Willig *et al.* Lancet Respir Med 2015 3:377

Farnaes *et al. npgj Genomic Medicine* 2018 3:10

Time to Diagnosis in 2 Studies

Rady Children's Institute Genomic Medicine





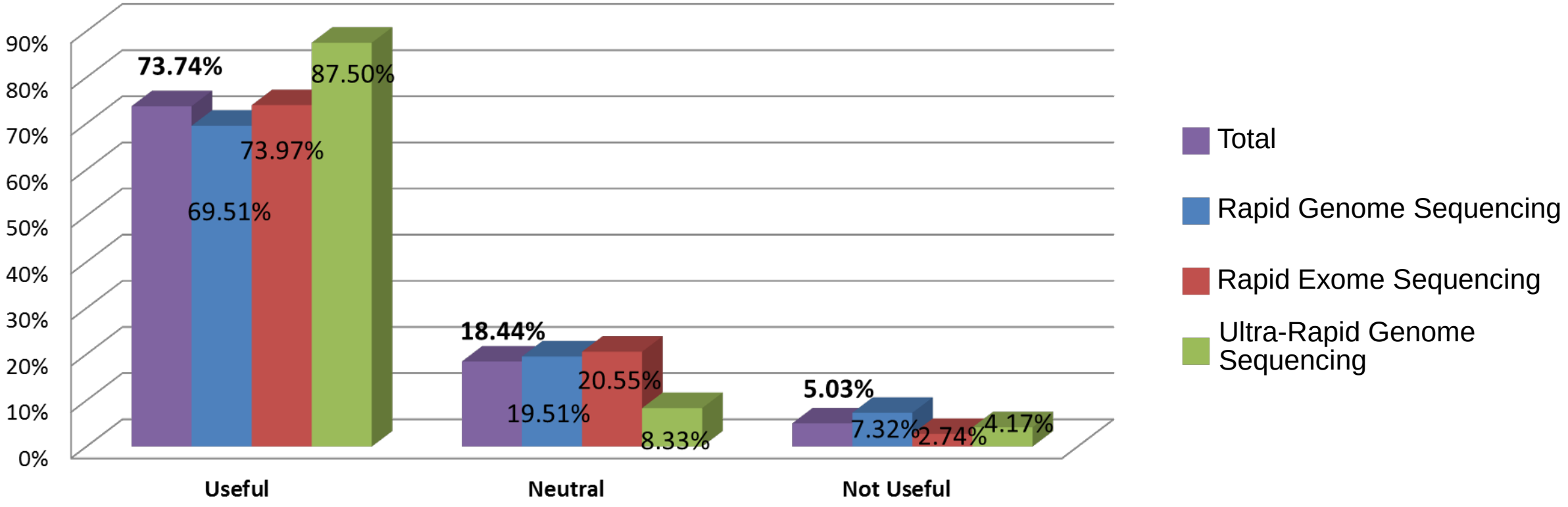
Petrikin *et al. npj Genomic Med* 2018 3:6

Kingsmore et al., AJHG In Press; ClinicalTrials.gov NCT03211039

NSIGHT2 Clinician Survey Results

Rady Children's Institute Genomic Medicine

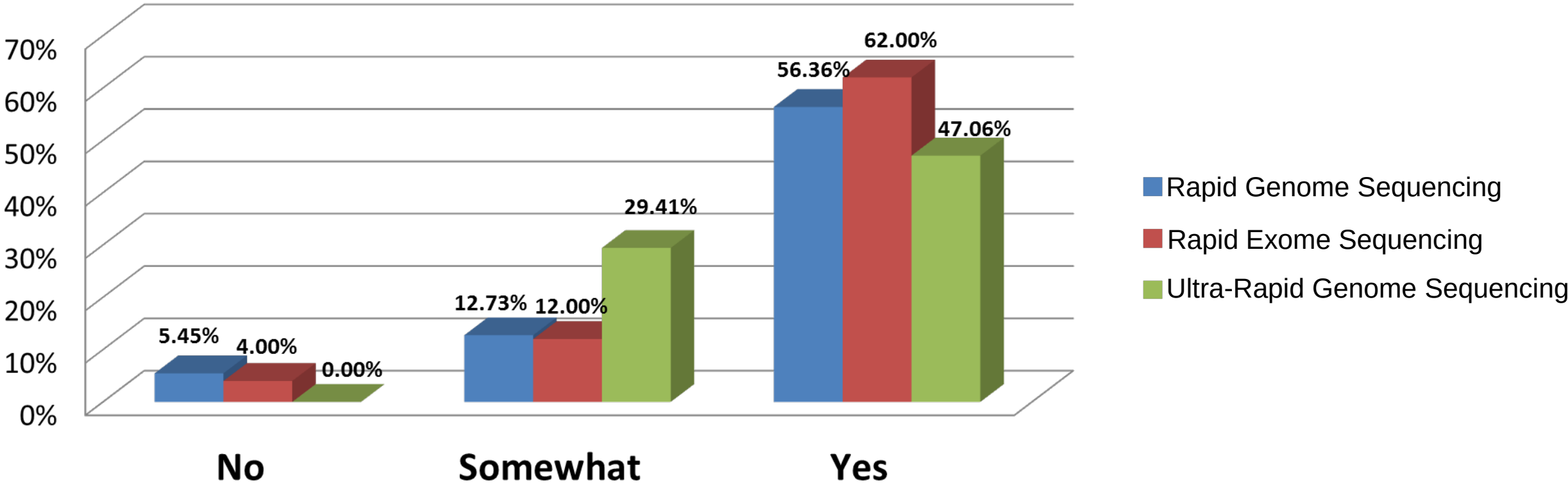
- **Was rapid genome sequencing useful?**



NSIGHT2 Acute Parent Survey Results

Rady Children's Institute Genomic Medicine

- **Did you feel your child's genome sequencing results were useful?**

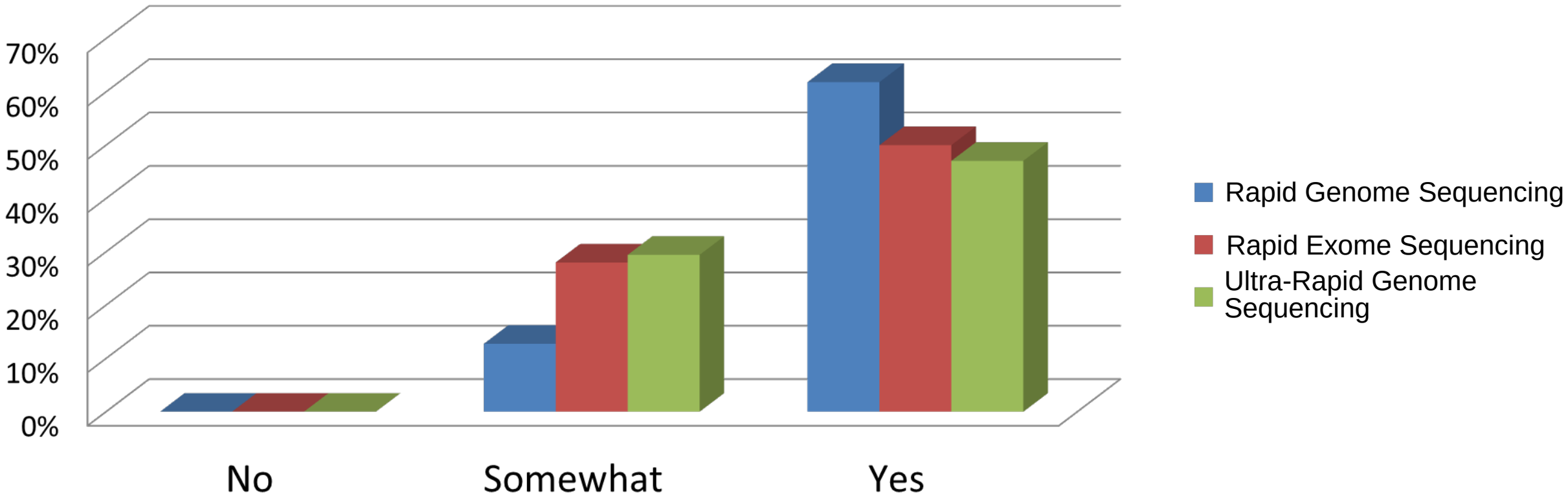


ClinicalTrials.gov NCT03211039

NSIGHT2 Acute Parent Survey Results

Rady Children's Institute Genomic Medicine

- **Did you understand your child's genome sequencing results?**

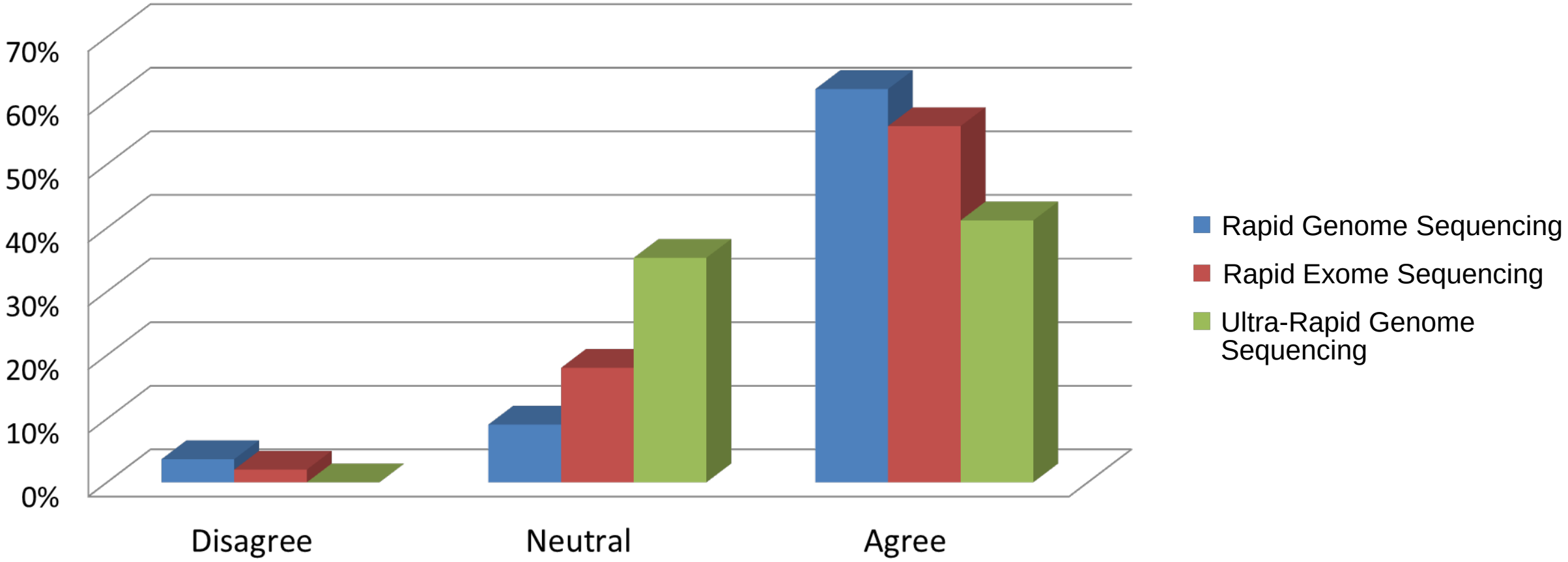


ClinicalTrials.gov NCT03211039

NSIGHT2 Acute Parent Survey Results

Rady Children's Institute Genomic Medicine

- **The choice to sequence did my child a lot of good**

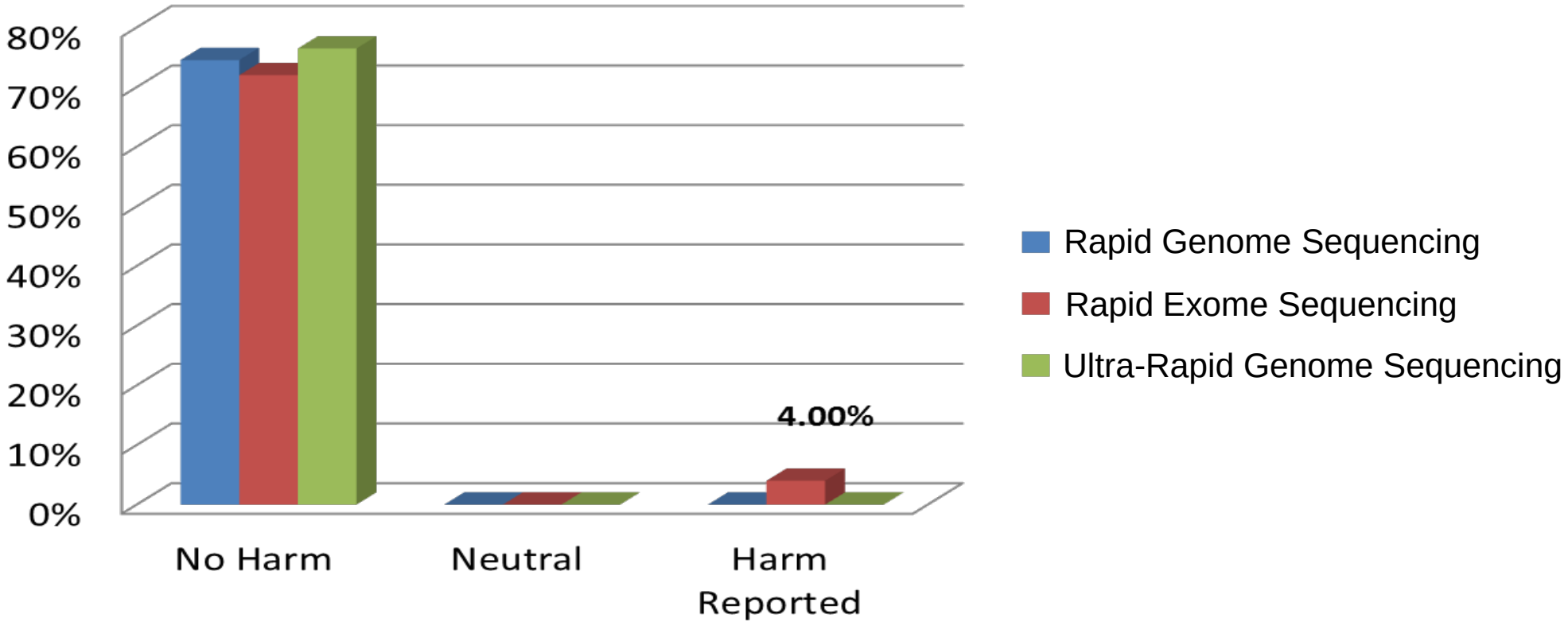


ClinicalTrials.gov NCT03211039

NSIGHT2 Acute Parent Survey Results

Rady Children's Institute Genomic Medicine

- **The choice to sequence did my child a lot of harm**



ClinicalTrials.gov NCT03211039

Literature Review

Rady Children's Institute Genomic Medicine

1st Author	Date	Study Type	Seq Type	NICU and PICU Enrollment Criteria	Size	Dx Rate	Clinical Utility	Change in Outcome	TAT (d)
Saunders	2102	Cases	WGS	NICU infants with suspected genetic disease	4	75%	n.d.	n.d.	2
Willig	2015	Cohort	WGS	<4 mo of age; Suspected actionable genetic disease	35	57%	31%	29%	23
Meng	2017	Cohort	WES	<100 days of life; Suspected genetic disease	63	51%	37%	19%	13
van Diemen	2017	Cohort	Panel	Infants; Suspected genetic disease	23	30%	n.d.	22%	12
Petrikin	2018	RCT	WGS	<4 mo of age; Suspected genetic disease	32	41%	22%	n.d.	13
Farnaes	2018	Cohort	WGS	infants; Suspected genetic disease	42	43%	31%	26%	23
Stark	2018	Cohort	WES	Acutely ill children with suspected genetic diseases	40	53%	30%	8%	16
Ceyhan-Birsoy	2019	RCT	WES	NICU neonates	32	16%	n.d.	n.d.	n.d.
Sanford	2019	Cohort	WGS	4 months-18 years; PICU; Suspected genetic disease	38	48%	39%	8%	14
French	2019	Cohort	WGS	Suspected genetic disease	195	21%	14%	n.d.	21
Clark	2019	Cases	WGS	Infants; Suspected genetic disease	7		100%	n.d.	1
Kingsmore	2019	RCT	WGS	Infants; disease of unknown etiology; within 96 hours of admission	94	19%	in progress		11
			WES		95	20%			11
			WGS		24	46%			5
Baby Bear	2019	Cohort	WGS	MediCal infants; within 1 week of admission; suspected genetic disease	116	50%	30%	in progress	
Average					**840**	**34%**	**26%**	**18%**	

Evolution of Rapid Precision Medicine in Infants in ICUs

Rady Children's Institute Genomic Medicine

2003
$2.7 Billion
13 years

1st Genome Sequence

2009
$2 Million
1.5 years

Nature 460: 1011

1st Medical Genome Sequence

2012
$13,000
50 hours

Sci. Transl. Med. *4*:154ra135

Rapid Genome Sequencing Prototype

2015
$13,000
26 hours

Lancet Respir Med. 3:377

Efficacy Studies

2018
$8,500
19 hours

npj Genomic Medicine 3:10

Effectiveness Studies

2020 Scale-Up, Quality Improvement, Implementation Studies

Explore (contexts, settings)
Identify barriers

Adopt/Prepare

Implement

Sustain / Evolve

Fiscal Year	Partner Hospitals	Children Tested
2017	1	363
2018	11	521
2019	23	488
2020	**40**	**1,546**

Rapid Precision Medicine: A Healthcare System not a Test

Rady Children's Institute Genomic Medicine

Health System and Family Engagement

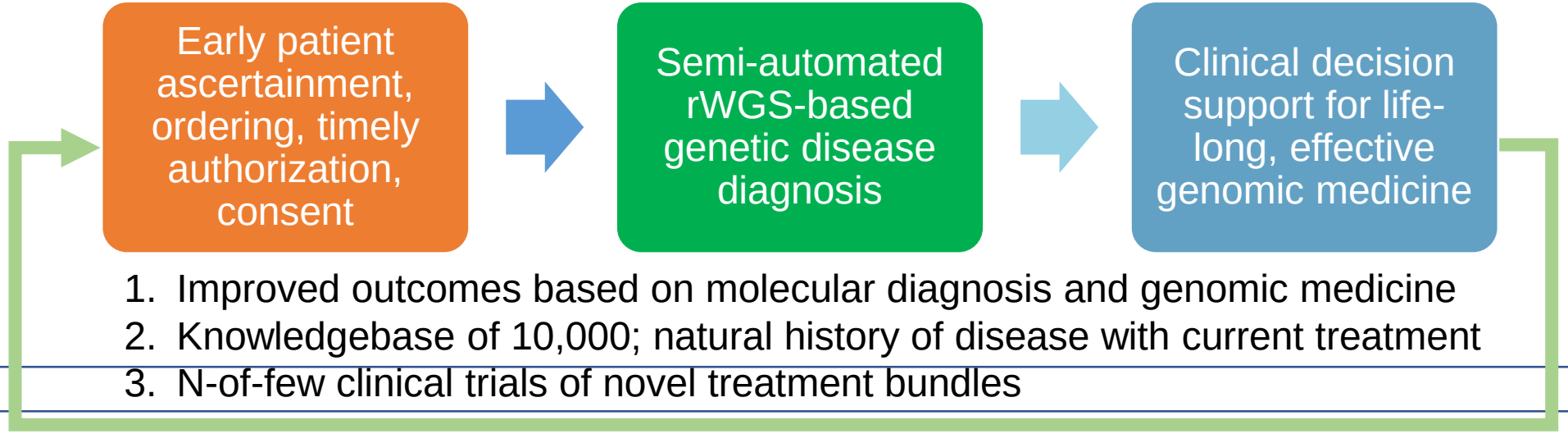
- Indications established
- Intuitive interface in EHR
- Automated site set-up, ascertainment, ordering, phenotyping
- QI: all sites

Rapid Diagnosis

- QI: 1 day to result
- Semi-automated interpretation
- & re-analysis
- Variant, gene, disease dB

Precision Medicine Delivery & Follow Up

- QI: rate/timeliness of NGM, parental counselling, outcomes
- Semi-automated eCDSS
- NGM implementation services
- Automated follow-up of outcomes



1. Improved outcomes based on molecular diagnosis and genomic medicine
2. Knowledgebase of 10,000; natural history of disease with current treatment
3. N-of-few clinical trials of novel treatment bundles

Vermont Oxford Rady Children's Genomic Network

Rady Children's Institute Genomic Medicine

A learning network to shape the future of genomic medicine in newborn care.

Schedule of Activities

April 10, 2019
3:00 PM Eastern
Webinar: Bridging the Genomics Knowledge Gap: Introduction to Rapid Whole Genome Sequencing (rWGS)
Presenting Faculty: Stephen Kingsmore, MD, DSc

July 10, 2019
3:00 PM Eastern
Webinar: The Evolution of Genetic Testing and Its Clinical Application
Presenting Faculty: Nathaly Sweeney, MD

September 11, 2019
3:00 PM Eastern
Webinar: Genomic Network Case #1: Actionable Results to Guide Treatment
Moderating Faculty: Shimul Chowdhury, PhD, FACMG

October 4, 2019
Genomic Medicine: 21st Century Care for Acutely Ill Infants pre-conference session at VON's Annual Quality Congress

November 20, 2019
3:00 PM Eastern
Webinar: Genomic Network Case #2: Parent Perspectives on Genomic Testing
Moderating Faculty: Nathaly Sweeney, MD

Join the Genomic Network

Summary

Rady Children's Institute Genomic Medicine

- Rapid precision medicine can be successfully implemented in the care of inpatient children
- Rapid turnaround allows for timely medical interventions in infants in ICUs
- Infants with seizures and/or encephalopathy of unknown etiology frequently benefit from rapid precision medicine

Acknowledgements: *A Deo lumen, ab amicis auxilium*

Executive Team
Stephen Kingsmore MD, DSc
Wendy Benson
Charlotte Hobbs, MD, PhD
David Dimmock MD

Leadership
Shimul Chowdhury PhD, FACMG, CGMB
Yan Ding MD, MS
Kasia Ellsworth PhD, FACMG
Lauge Farnaes MD, PhD
Karen Garman EdD, MAPP
Shareef Nahas PhD, FACMG, CGMB
Julie Reinke
Grace Sevilla, APR
Mari Tokita MD
Ray Veeraraghavan PhD
Russell Nofsinger, PhD

Clinical Genome Center
Zaira Bezares
Jennie Le
Maria Ortiz-Arechiga
Laura Puckett
Luca Van Der Kraan
Catherine Yamada

Genome Analysts
Michelle Clark PhD
Kiely James PhD
Terence Wong PhD
Meredith Wright PhD

Clinical Trial Team
Sara Caylor RN, BSN
Christina Clarke RN, BSN
Mary Gaughran RN
Jerica Lenberg MS, LCGC
Lisa Salz MS, LCGC
Kelly Watkins MS, LCGC

Clinicians / Researchers
Matthew Bainbridge PhD
Jeanne Carroll MD
Tina Chambers PhD
Michele Feddock, CCRP
Jennifer Friedman MD
Joseph Gleeson MD, PhD
Iris Reyes
Jonathan Sebat PhD
Nathaly Sweeney MD
Robert Wechsler-Reya PhD
Kristin Wigby MD
Amelia Lindgren, MD
Erica Sanford, MD
Kate Perofsky, MD
Kathy Bouic
Linda Luo
Lauren Curley

Information Technology
Josh Braun
Serge Batalov
Carlos Diaz
Raymond Hovey PhD
Dana Mashburn
Patrick Mulrooney, MAS
Danny Oh
Albert Oriol
Dorjee Tamang
Daniken Orendain

Administration
Amanda Abbott Esq
Christine Moran
Ellen Montgomery
Olivia Simonides
Stacey Huynh
Sylvia Breeding
Rachel Burgess
Joey Principato
Leila Schwanemann
Cheyenne Camp
Bryce Waldman

Collaboration with:
Rady Children's Hospital
State of California
UC San Diego Health
Illumina, Inc.
National Institutes of Health
- NICHD
- NHGRI
- NIDDK

The Liguori Family
John Motter and Effie Simanikas
Ernest and Evelyn Rady

Children's Mercy Hospital
John Lantos
Julie Cakici
Josh Petrikin
Laurel Willig
Emily Farrow
Neil Miller
Carol Saunders
Steve Leeder