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Improving the Diagnostic Odyssey for Rare Disease Patients

July 29, 2021

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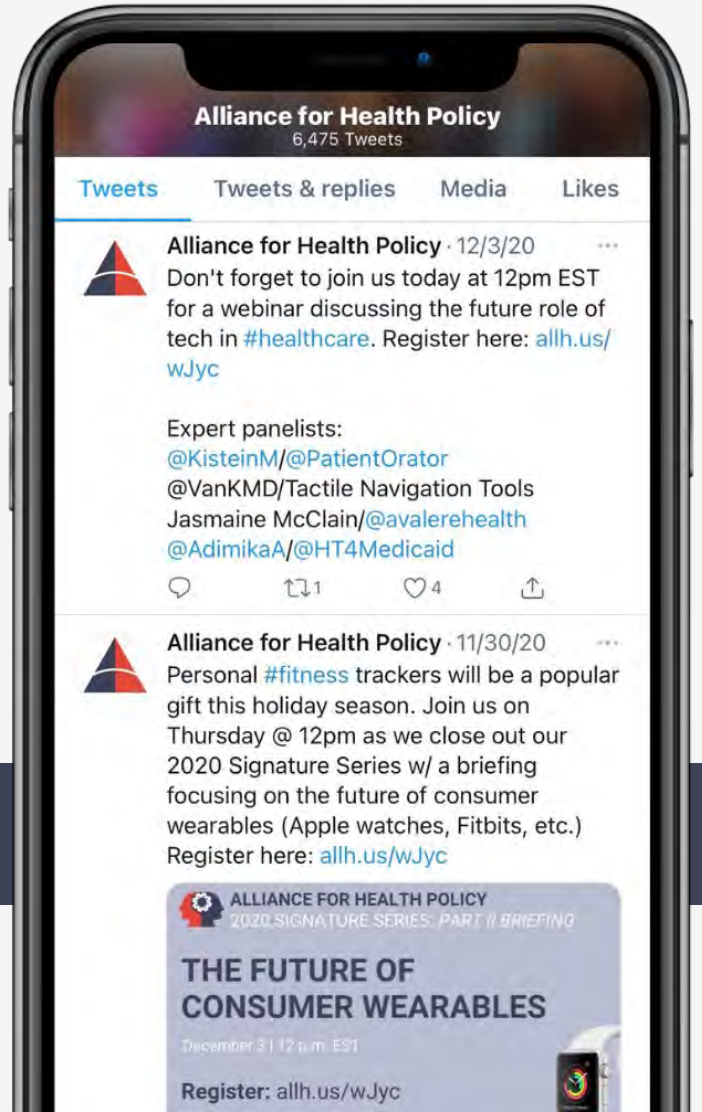

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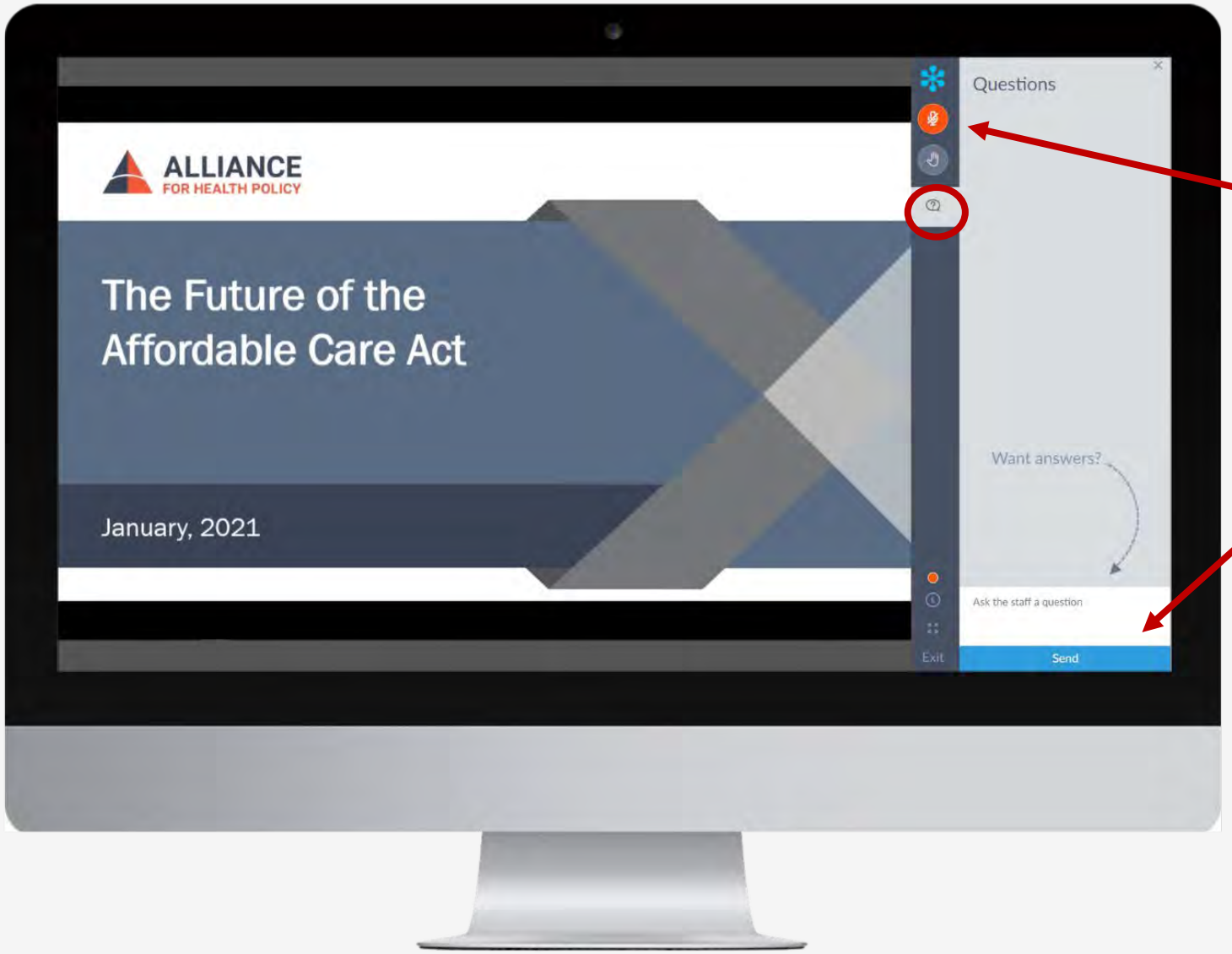

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Panelists

Matthew Might, Ph.D.
Professor, Department of Medicine
Director
Hugh Kahl Precision Medicine Institute

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Moderator

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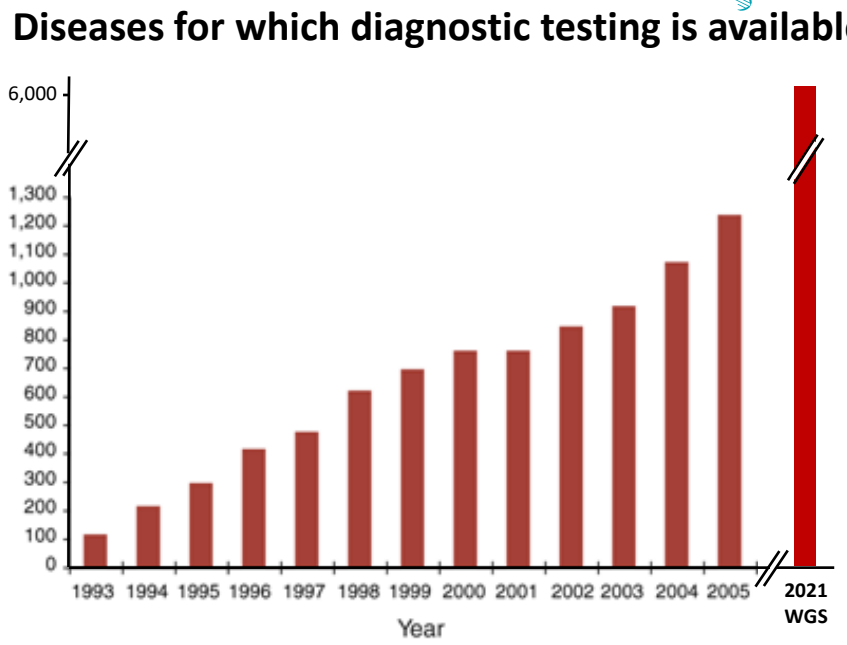
President & CEO

Rady Children's Institute of Genomic Medicine

We now know 6,000 genetic diseases

Rady Children's Institute Genomic Medicine

- Genetic diseases for which molecular basis is known: 6,138
- Increase in known genetic diseases: ~1 per day
- **MANY causes of common childhood disorders:**
  - Seizures: 1,283 genetic diseases
  - Intellectual disability: 1,681 genetic diseases
  - Recurrent infection: 699 genetic diseases
  - Congenital heart disease: 1,889 genetic diseases
  - Metabolic abnormalities: 3,402 diseases

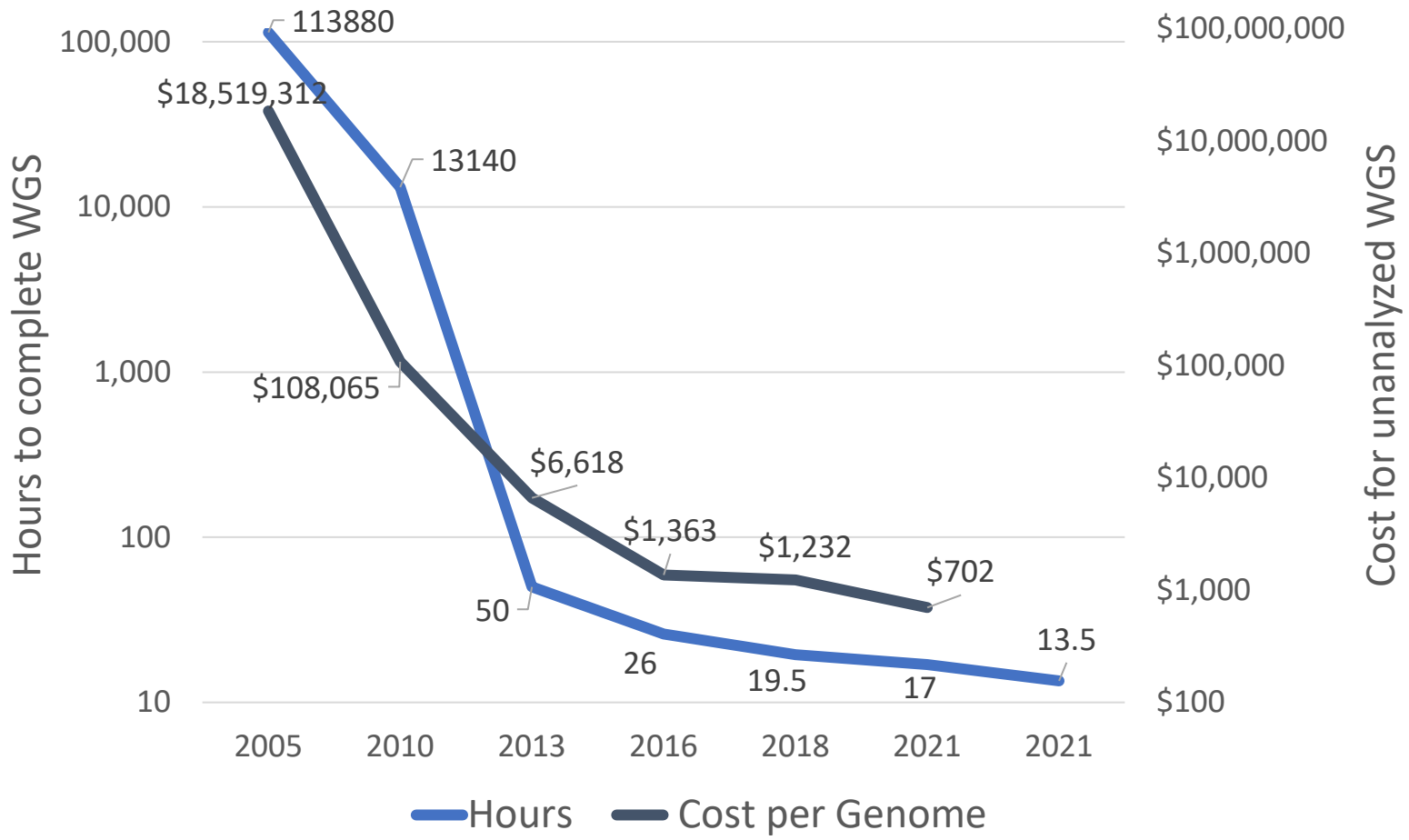


https://www.omim.org/statistics/entry, accessed June 2021.
Modified from Hudson K. et al. *Nat Biotechnol*. 2006;24(9):1083-1090.

There is an ongoing technology revolution

Rady Children's Institute Genomic Medicine

- Genome sequencing now possible for ~$700
- Automated, diagnostic whole genome sequencing now possible in 13.5 hours



Owen MJ et al. Submitted

Genome Sequencing Saves Lives

Rady Children's Institute Genomic Medicine

213 infants in Intensive Care Units [1-3]

Critical illness of unknown etiology at admission

Genomic sequencing within 96 hours of admission

Deep phenotype extraction from health record

Abbreviated empirical treatment

21-46% positive results in 2 days

12% of admissions

MD: 93% clinical utility; 63% change in clinical management

39% Δ in outcome; 69% improved communication

Parent: 100% results were useful; 98% better able to manage symptoms

100% benefit to child; 100% benefit to parent

54-79% negative tests in 5 days

41% of admissions

MD: 72% clinical utility; 16% change in clinical management

8% Δ in outcome; 32% improved communication

Parent: 96% results were useful; 92% better able to manage symptoms

96% benefit to child; 97% benefit to parent

1. Kingsmore SF, et al. *Am J Hum Genet.* 2019;105:719-733.
2. Dimmock DP, et al. *Am J Hum Genet*. 2020;107:942-952.
3. Cakici JA, et al. *Am J Hum Genet.* 2020;107:953-962.

The Evidence Is Overwhelming

Rady Children's Institute Genomic Medicine

Ref.	Date	Study Type	Seq Type	Neonatal & Pediatric Intensive Care Unit Enrollment Criteria	Size	Dx Rate	Change in Management	Change in Outcome	TAT (d)
1	2012	Cases	urWGS	NICU infants with suspected genetic disease	4	75%	n.d.	n.d.	2
2,3	2015	Cohort	rWGS	<4 months of age; Suspected actionable genetic disease	35	57%	31%	29%	23
4	2017	Cohort	rWES	<100 days of life; Suspected genetic disease	63	51%	37%	19%	13
5	2018	RCT	rWGS	<4 months of age; Suspected genetic disease	32	41%	31%	n.d.	13
6	2018	Cohort	rWGS	infants; Suspected genetic disease	42	43%	31%	26%	23
7	2018	Cohort	rWES	Acutely ill children with suspected genetic diseases	40	53%	30%	8%	16
8	2018	Cohort	rWGS	Children; PICU and Cardiovascular ICU	24	42%	13%	n.d.	9
9	2019	Cohort	rWGS	4 months-18 years; PICU; Suspected genetic diseases	38	48%	39%	8%	14
10	2019	Cohort	rWGS	Suspected genetic disease	195	21%	13%	n.d.	21
11	2019	Cases	urWGS	Infants; Suspected genetic disease	7	43%	43%	n.d.	0.8
13	2020	Cohort	rWES	<4 mo of age; ICU; hypotonia, seizures, metabolic, multiple congenital anomalies	50	54%	48%	n.d.	5
14	2020	Cohort	rWES	NICU & PICU; complex	130	48%	23%	n.d.	3.8
15	2020	Cohort	rWES	Critical illness; medical genetics selected	46	43%	52%	n.d.	9
16	2020	Cohort	rWES	PICU; < 6 years; new metabolic/neurologic disease	10	50%	30%	n.d.	9.8
17	2020	Cohort	rWES	ICU	368	27%	n.d.	n.d.	n.d.
18	2020	Cohort	rWES	>1 year; ICU and inpatient	102	31%	27%	n.d.	11
19	2020	Cohort	rWES	Various	41	32%	n.d.	n.d.	7
20	2020	Implement	rWES	<18 yr; NICU and PICU	108	51%	44%	n.d.	3
12, 21	2019	RCT	rWGS	Infants; disease of unknown etiology; within 96 hours of admission	94	19%	24%	10%	11
			rWES		95	20%	20%	18%	11
			urWGS		24	46%	63%	25%	4.6
22	2021	Cohort	rWGS,panel	Infants; disease of unknown etiology	113	33%	26%	n.d.	n.d.
23	2021	Implement	rWGS	Medicaid infants; unknown etiology; within 1 week of admission	178	43%	31%	n.d.	3
Weighted Average					1839	36%	29%	25%	

References at the end of this presentation.

Implement, Implementation science study
RCT, randomized, controlled trial. rWES, rapid whole exome sequencing.

Legislative Action Is Needed

Rady Children's Institute Genomic Medicine

blue california

1

project baby bear

2

project baby deer

1 Site

2-3 Sites

4-10 Sites

10+ Sites

Project Baby Manatee

3

Speaker's own illustration.

1. https://www.radygenomics.org/our-work/project-baby-bear/, accessed March 2021.
2. http://community.mha.org/browse/announcements?AnnouncementKey=ef2cf136-3f73-4c99-afa8-dc908a7661cd, accessed March 2021.
3. https://www.nicklauschildrens.org/medical-services/personalized-medicine-initiative-(pmi)/genomic-medicine, accessed March 2021.

California Medicaid Example

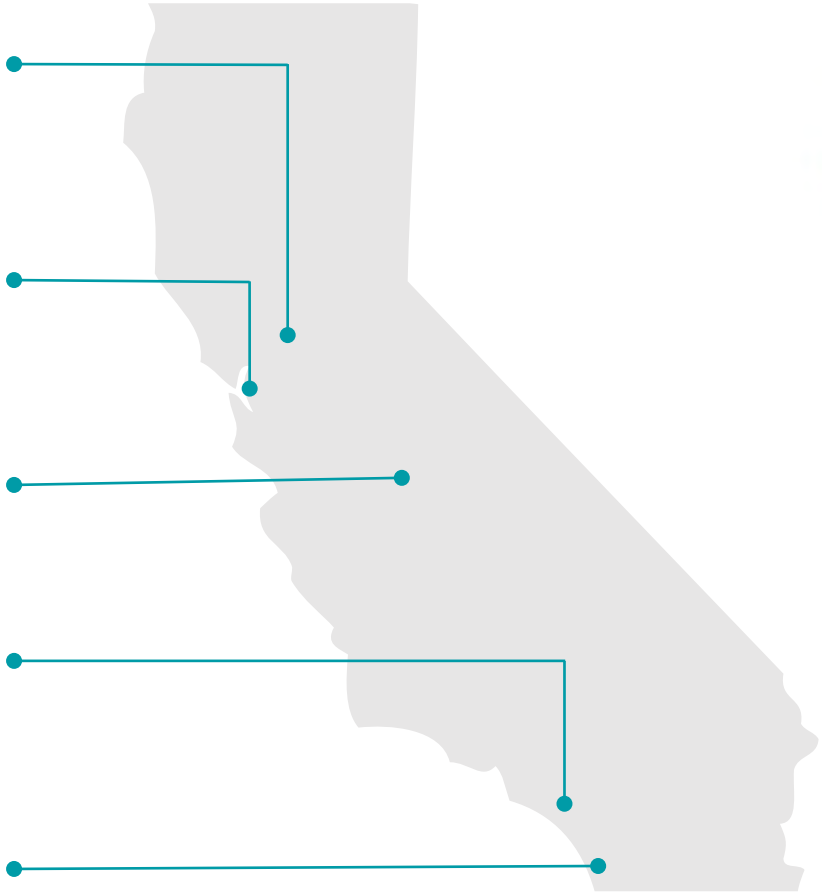
UC Davis Children's Hospital

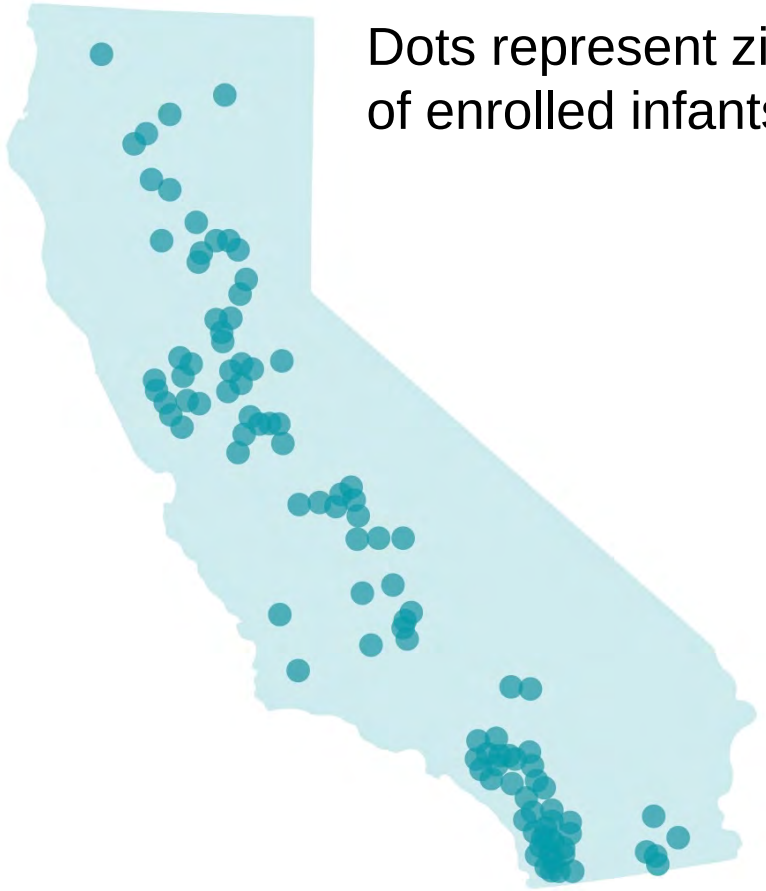
UC San Francisco Benioff Children's Hospital Oakland

Valley Children's Hospital (Madera)'

CHOC Children's (Orange County)

Rady Children's Hospital- San Diego



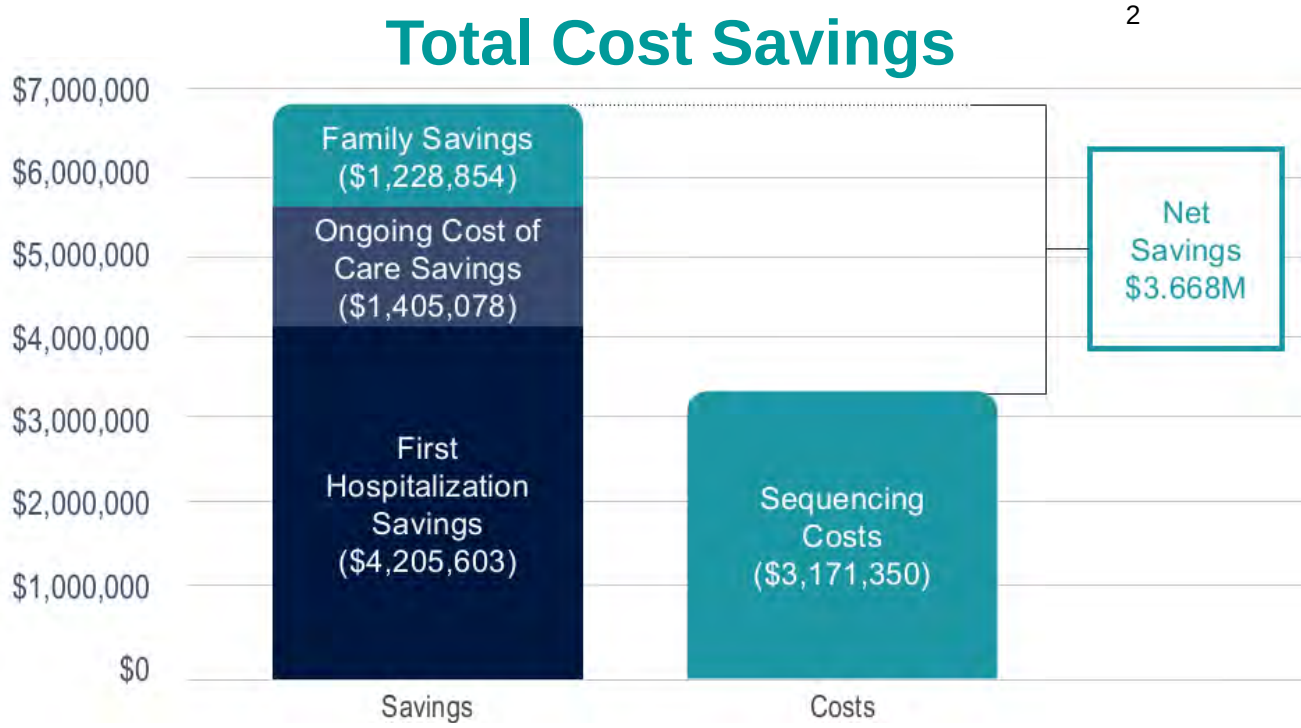


Dots represent zip codes of enrolled infants

Dimmock D, et al. *Am J Hum Genet.* May 29:S0002-9297(21)00192-0.
https://www.radygenomics.org/our-work/project-baby-bear/, accessed March 2021.

CHOC, Children's Hospital of Orange County;
UC, University of California; ZIP, zone improvement plan.

Results: Genome Sequencing Decreases Medicaid Cost of Care



Speaker's own illustration.

1. https://www.radygenomics.org/our-work/project-baby-bear/, accessed March 2021. Final report.
2. Dimmock D, et al. *Am J Hum Genet.* In Press. .

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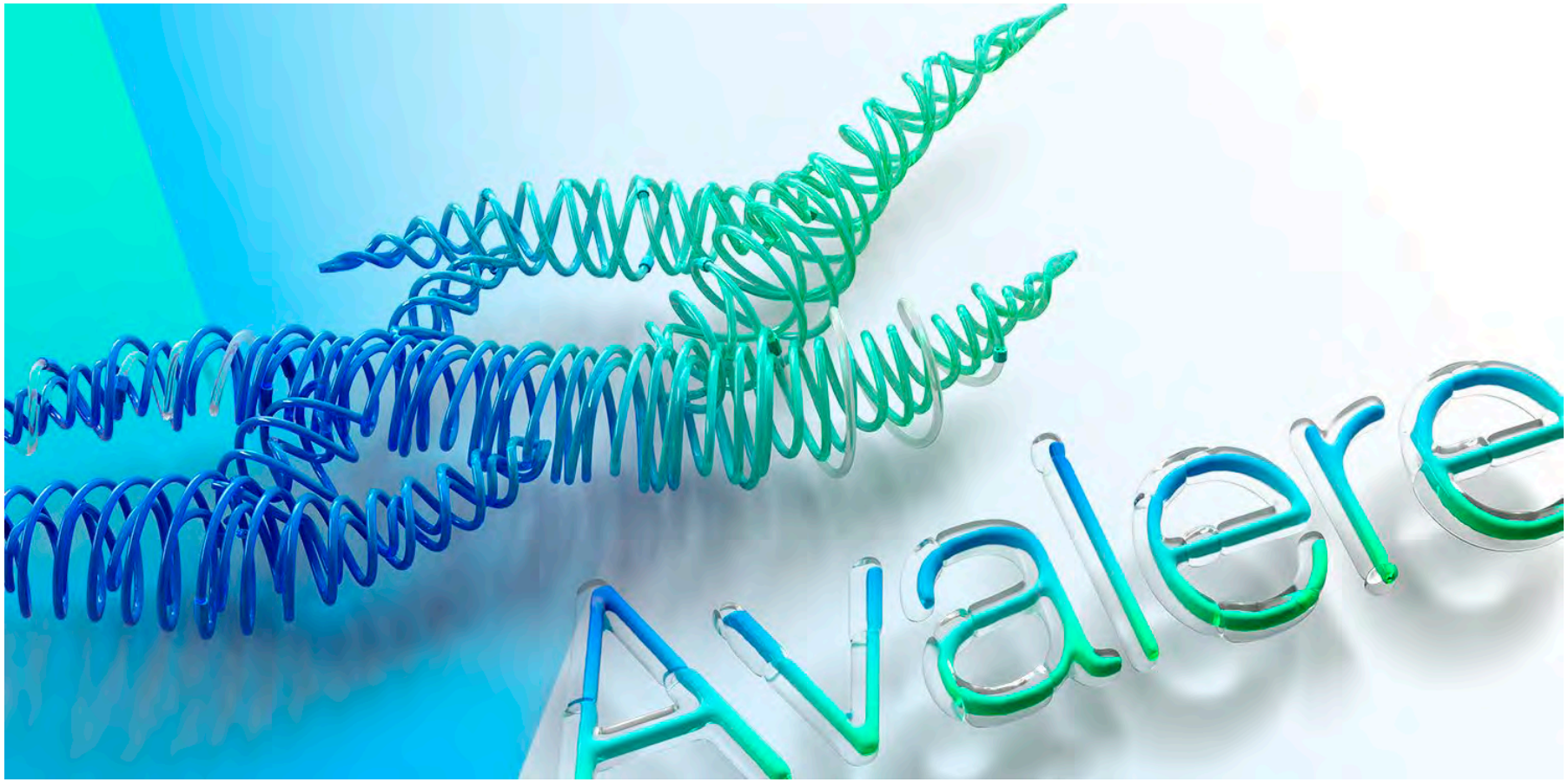

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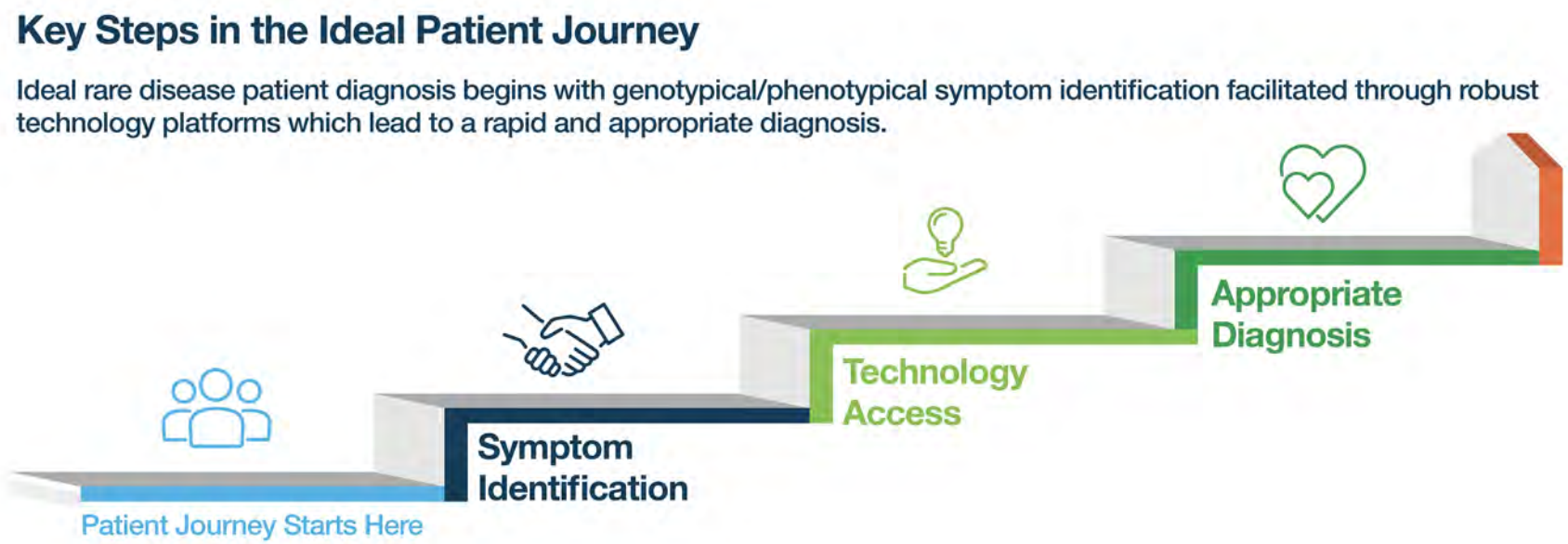
The Diagnostic Journey for Rare Disease Patients: Scaling Sustainable Solutions

What Does Good Look Like?



Challenges and Barriers to Scale and Spread

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A Technology Solution

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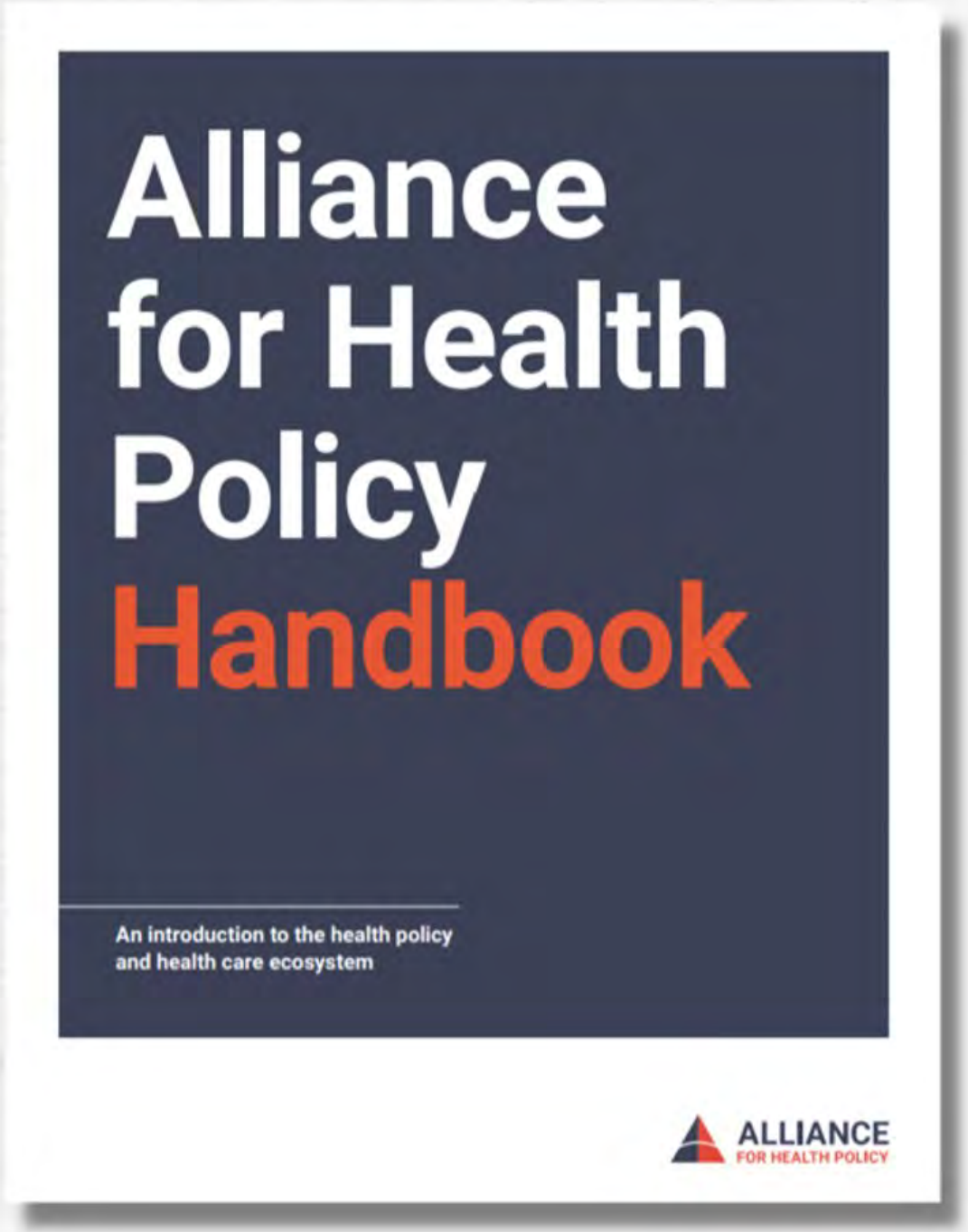

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