Transforming Healthcare for Children through Genomic Medicine

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Rady Children's Hospital San Diego

Rady Children's Institute Genomic Medicine®

Rady Children's At a Glance

Rady Children's includes:

- 35 locations
- 505 total beds
- >5,400 employees

2021 Market Presence:[1]

- San Diego County: 88%
- Imperial County 68%
- Southern Riverside County: 61%

2022, we managed:

- >240k patients
- >18k inpatient discharges
- >18k total surgeries
- >97k emergency department visits
- >260k specialty care visits
- >550k primary care visits

Our medical network consists of:

- >800 medical staff
- 35 medical specialties
- >150 primary care providers

[1] Based on inpatient discharges

The approach to diagnosing + managing childhood genetic disease is unacceptably inefficient + inequitable

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to end the diagnostic odyssey

Burden of Rare Genetic Disease

1 in 20

children have a rare genetic disease[1]

On average, reaching a diagnosis takes

4.8 Years

AND

7.3

Specialists

and some children never get diagnosed

>$1 T

annual burden of rare disease on U.S. healthcare system[2] with an average PPPY cost between $9 – 140K[3]

Management of rare disease patients is a **global issue** that needs to be addressed by **integrated healthcare systems**

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[1] Estimates of number of rare diseases are 5000 – 8000, and U.S. rare disease prevalence are 1 in 10, where children are about half. [2] ~$1 T annual cost of subset of 379 rare diseases, comprised of direct and indirect costs, non-medical costs, and healthcare costs not covered by insurance. [3] Range from rare diseases diagnostic / treatment costs, compared to <$6 K annual cost for non-rare disease pts. PPPY: Per patient per year. Source: Bavisetty. *Rare Dis.* 2013; Marwaha. *Genome Medicine.* 2022; Tisdale et al. *Orphanet Journ. Rare Disease.* 2021; Yang et al. *Orphanet Journ. Rare Disease.* 2019; RCIGM Prior Materials; NIH; ClearView Analysis.

Childhood Genetic Diseases Are Grossly Underdiagnosed

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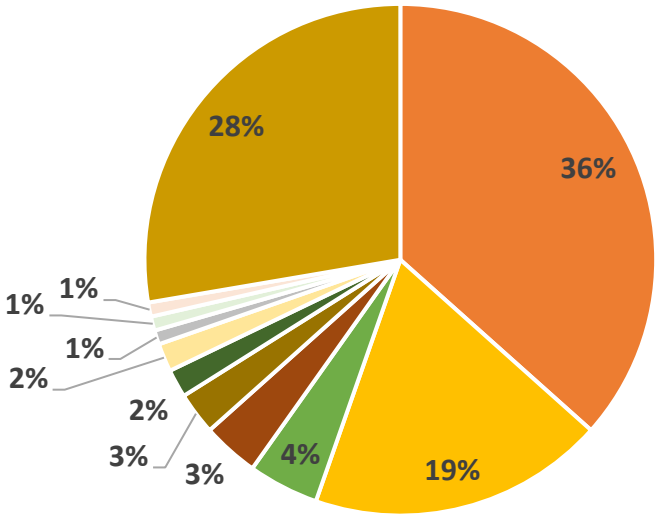
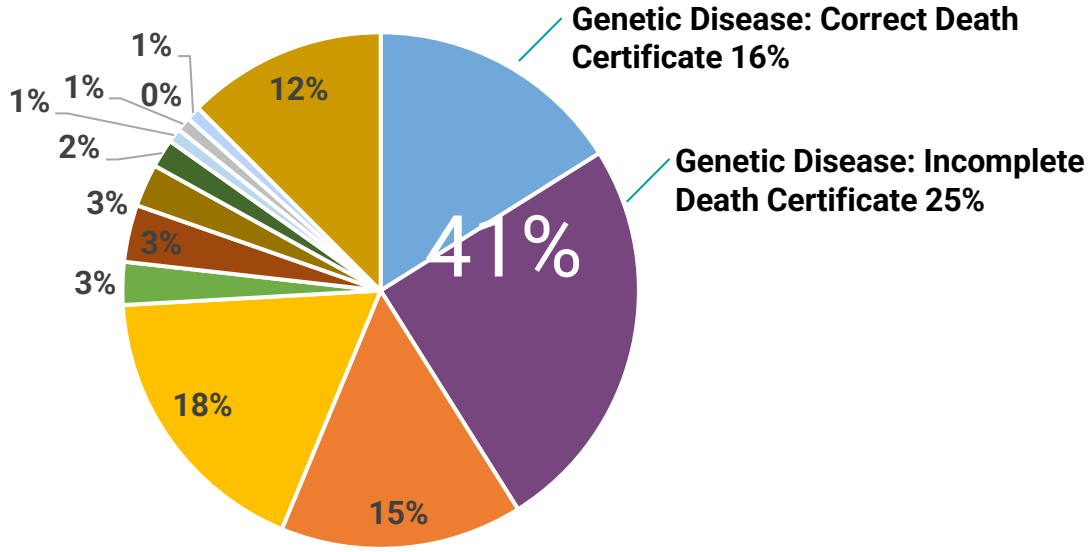
US infant mortality rate 5.5/1,000 (highest of high-income countries)

Leading causes of infant mortality in San Diego

Before diagnostic genome sequencing



After diagnostic genome sequencing



- Congenital malformations, deformations, + chromosomal abnormalities
- Short gestation + low birth weight
- Sudden infant death syndrome
- Affected by complications of placenta, cord + membranes
- Intrauterine hypoxia + birth asphyxia
- Affected by maternal pregnancy complications
- Bacterial sepsis
- Accidents
- Neonatal hemorrhage
- Respiratory Distress
- All other causes

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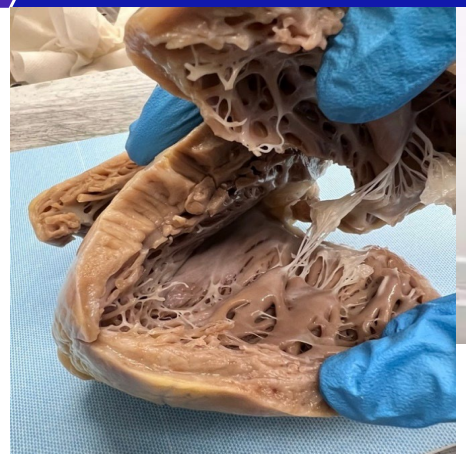
14-year-old ♀ with cardiac arrest at home

Day 0
- Admitted to PICU
- Placed on ECMO
- Rhinovirus positive
- Ejection Fraction 3%
- Rapid Diagnostic Genome Sequence ordered

Day 2
- Rapid Diagnostic Genome Sequence Preliminary result:
- *LMNA*-Dilated cardiomyopathy 1A

Day 3
- Listed for heart transplant

Day 7
- Received heart transplant



Day 22
- Discharged home with normal cardiac + neurologic function

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44 Clinical Studies of Diagnostic Rapid Genome Sequencing

37% diagnosis

26% change in management

18% change in outcome

$14,265 net savings per admission

Ref.	Year	Country	Number of probands	Dx rate	Cost per test	Cost per Diagnosis	Net savings per test
48	2018	USA	42	43%	$16,063	$37,480	$18,741
68	2021	USA	184	40%	$9,239	$23,602	$6,294
6	2022	USA	61	33%	$9,758	$29,570	$11,286
85	2022	USA	38	45%	$6,300	$14,082	($1,436)
75	2022	USA	65	40%	$11,029	$27,573	$100,440
86	2022	Australia	40	53%	$8,088	$15,406	$17,243
77	2023	USA	89	39%	$7,564	$19,234	$4,155
87	2023	USA	184	40%	$14,450	$36,125	$22,395
78	2023	USA	400	49%	$8,000	$16,326	nd
		Median		**40%**	**$9,239**	**$23,602**	**$14,265**

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Ref.	Year	Country	Study Type	Test	Enrollment Criteria	Size	Dx Rate	Δ Mx	Δ Outcome	TAT (days)
7	2012	USA	Cases	URGS	NICU infants; Susp. genetic disease	4	75%	n.d.	n.d.	2
44	2015	USA	Cohort	RGS	<4 months of age; Susp. actionable genetic disease	35	57%	31%	29%	23
45	2017	USA	Cohort	RES	<100 days old; Susp. genetic disease	63	51%	37%	19%	13
46	2017	Holland	Cohort	RGS	Infants; NICU, PICU; Susp. genetic disease	23	30%	22%	22%	12
47	2018	USA	RCT	RGS,SOC	<4 months of age; Susp. genetic disease	32	41%	31%	n.d.	13
48	2018	USA	Cohort	RGS	Infants; Susp. genetic disease	42	43%	31%	26%	23
49	2018	Aust	Cohort	RES	Acutely ill children with susp. genetic disease	40	53%	30%	8%	16
50	2018	UK	Cohort	RGS	Children; PICU and Cardiovascular ICU	24	42%	13%	n.d.	9
51	2019	USA	Cohort	RGS	4 months-18 years; PICU; Susp. genetic disease	38	48%	39%	8%	14
52	2019	UK	Cohort	RGS	Susp. genetic disease	195	21%	13%	n.d.	21
12	2019	USA	Cases	URGS	Infants; ICU; Susp. genetic disease	7	43%	43%	n.d.	0.8
53	2020	USA	Cohort	RES	<6 months old; ICU; hypotonia, seizures, metabolic, multiple congenital anomalies	50	58%	48%	n.d.	5
54	2019	Canada	Cohort	RES	NICU; infants; susp. genetic disease	25	72%	60%	n.d.	7.2
55	2019	Taiwan	Cohort	RES	PICU and other; children; susp. genetic disease	40	53%	43%	n.d.	6
56	2020	China	Cohort	RES	NICU & PICU; complex	130	48%	23%	n.d.	3.8
57	2020	USA	Cohort	RES	Critical illness; medical genetics selected	46	43%	52%	n.d.	9
58	2020	USA	Cohort	RES	PICU; < 6 years; new metabolic/neurologic disease	10	50%	30%	n.d.	9.8
59	2020	USA	Cohort	RES	ICU; infants	368	27%	n.d.	n.d.	n.d.
60	2020	China	Cohort	RES	Infants; ICU and inpatient	102	31%	27%	n.d.	11
61	2020	USA	Cohort	RES	Various	41	32%	n.d.	n.d.	7
62	2020	Aust	Implem	URES	<18 year; NICU and PICU	108	51%	44%	n.d.	3
63	2020	Poland	Cohort	RES	Infants; NICU, PICU; susp. genetic disease	18	83%	61%	n.d.	14
64	2020	China	Cohort	URES	Infants; NICU, PICU; susp. genetic disease	33	70%	30%	30%	1
33,65, 66	2019, 2020	USA	RCT	RGS	Infants; disease of unknown etiology; within 96 hours of admission	94	19%	24%	10%	11
				RES		95	20%	20%	18%	11
				URGS		24	46%	63%	25%	4.6
68	2021	USA	Implem	URGS	Medicaid infants; unknown etiology; within 1 week c	184	40%	32%	n.d.	3
69	2021	China	Cohort	RES	Critically ill; 6 days - 15 years; susp. genetic disease	40	43%	31%	n.d.	5
70	2021	Germany	Cohort	RES	NICU, PICU, infants; sup. Genetic disease	61	43%	11%	n.d.	60
71	2021	USA	RTDCT	RGS,WGS	<120 days old; ICU; susp. genetic disease	354	31%	25%	n.d.	15
43	2021	China	Crossover	RES	Critically ill infants with conditions suggestive of gene	202	20%	n.d.	n.d.	20
				RGS		202	37%	7%	n.d.	7
72	2022	France	Cohort	RGS	NICU, PICU with probable genetic disease; urgent ne	37	57%	n.d.	n.d.	43
73	2022	UAE	Cohort	URGS	Infants in ICU with complex multisystem disease	5	60%	20%	20%	1.5
74	2022	USA	Implem	RES	NICU infants with susp. genetic disease	80	28%	18%	n.d.	13
75	2022	USA	Cohort	RGS	Children in ICU with disease of unknown etiology	65	40%	n.d.	n.d.	12
76	2022	France	Cohort	RES	Infants in ICU with susp. genetic disease	15	40%	53%	n.d.	16
77	2023	USA	Implem	RGS	NICU, PICU with disease of unknown etiology	89	39%	27%	n.d.	n.d.
67,78	2021, 2023	USA	Crossover	RGS, panel	NICU with disease of unknown etiology	400	49%	19%	n.d.	6
79	2023	USA	Cohort	RGS	Acutely ill inpatient infants; susp. genetic disease	188	35%	32%	n.d.	6
80	2023	Belgium	Cohort	URGS	NICU, PICU, neurologic inpatients with susp. genetic	21	57%	57%	n.d.	1
Weighted Average						**3609**	**37%**	**26%**	**18%**	

Progress in Medicaid Coverage + Reimbursement of Rapid Diagnostic Genome Sequencing

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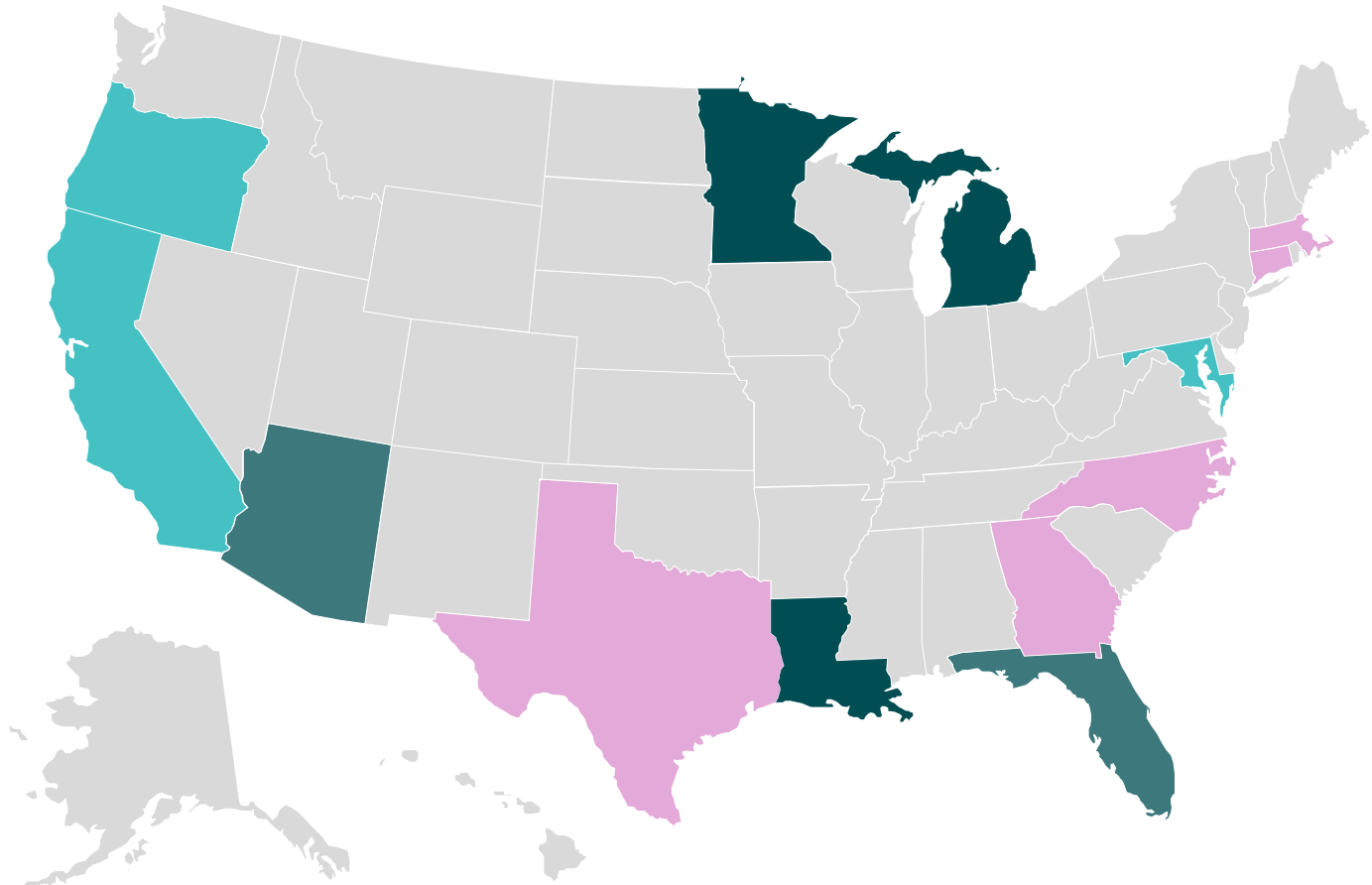
11 Anthem/BlueCross/Blue Shield Plans & Cigna: Coverage & Payment

Medicaid Coverage & Bundled Payment

Medicaid Coverage & Payment

Medicaid Coverage Policy in Progress



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Trends in Genomic Medicine

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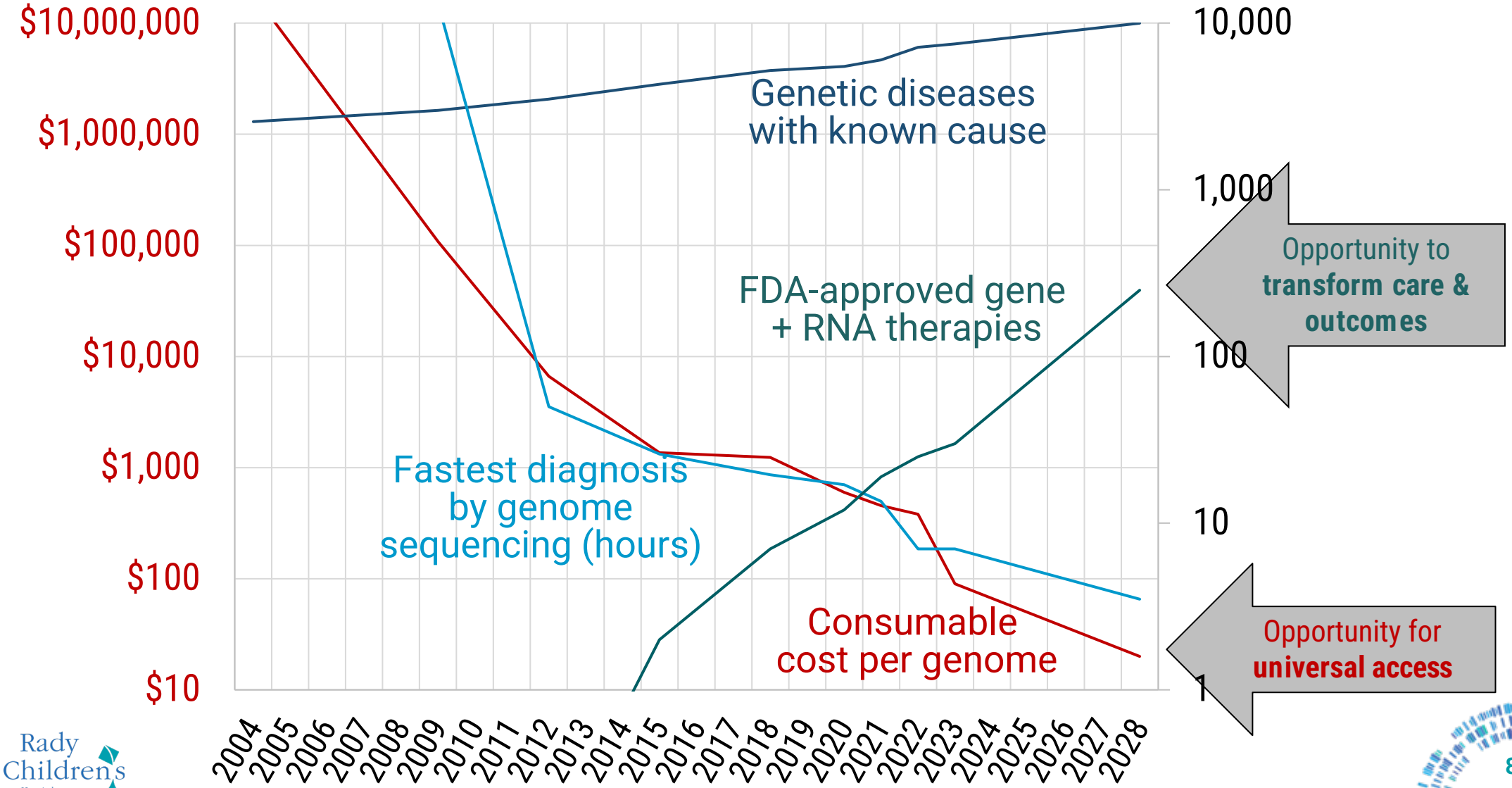

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Transforming Healthcare for Children through Diagnostic Rapid Genome Sequencing + BeginNGS

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	Microarray + Karyotype	Diagnostic Rapid Genome Sequencing	Genome-based Newborn Screening	Newborn Screening of Dried Blood Spots (California)
Annual need	200k children in ICUs with disorders of uncertain etiology		3.7M newborns	
Genetic disorders evaluated	~500	~7,500	~750	80
Average cost per test today	$1,887	$7,000	~$500	$211
Average diagnostic rate today	14%	37%	~5%	0.18%
Average cost per diagnosis today	$13,978	$18,919	~$10,000	$118,688
Median net incremental cost per test	n.d.	($14,265)	?	n.d.
Proportion of annual need currently met		~2%	0%	98%

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Achieving Equitable Access to Genomic Medicine

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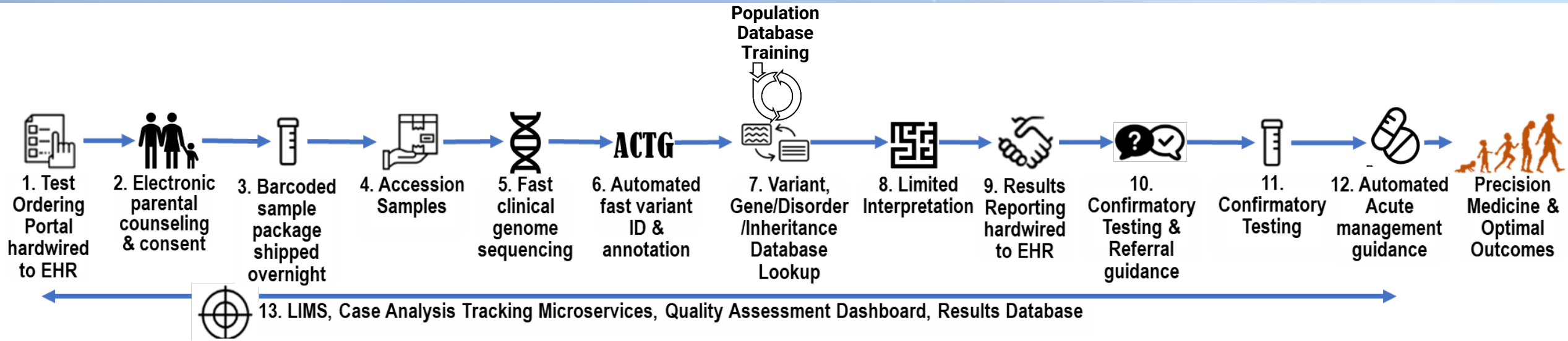

Implementation barriers:

1. Parental ability to navigate healthcare delivery system
2. Hospital/provider/parental understanding of benefits of genomic medicine
3. Provider index of suspicion for genetic disease
4. Hospital/provider reimbursement
5. Genetic counseling expertise
6. Provider ability to translate genome findings into improved outcomes

Fitz: NBS + Rapid Diagnostic Genome Sequencing + Gene Therapy = Optimal Outcome

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- Appeared healthy at birth
- Newborn screen positive for Severe Combined Immunodeficiency (SCID)
- Rapid diagnostic genome sequencing identified *DCLRE1C*-Athabascan SCID in 1st week of life
- Precise diagnosis allowed Fitz to qualify for an *ex-vivo* gene therapy clinical trial during infancy
- Lentivirus/*DELRE1C* phase 1 transduction of autologous $CD34^+$ cells successful
- Now 4 years old with healthy immune system

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