From NSIGHT2 to BeginNGS

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Disclosures

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NONE

Leading Causes US Infant Mortality

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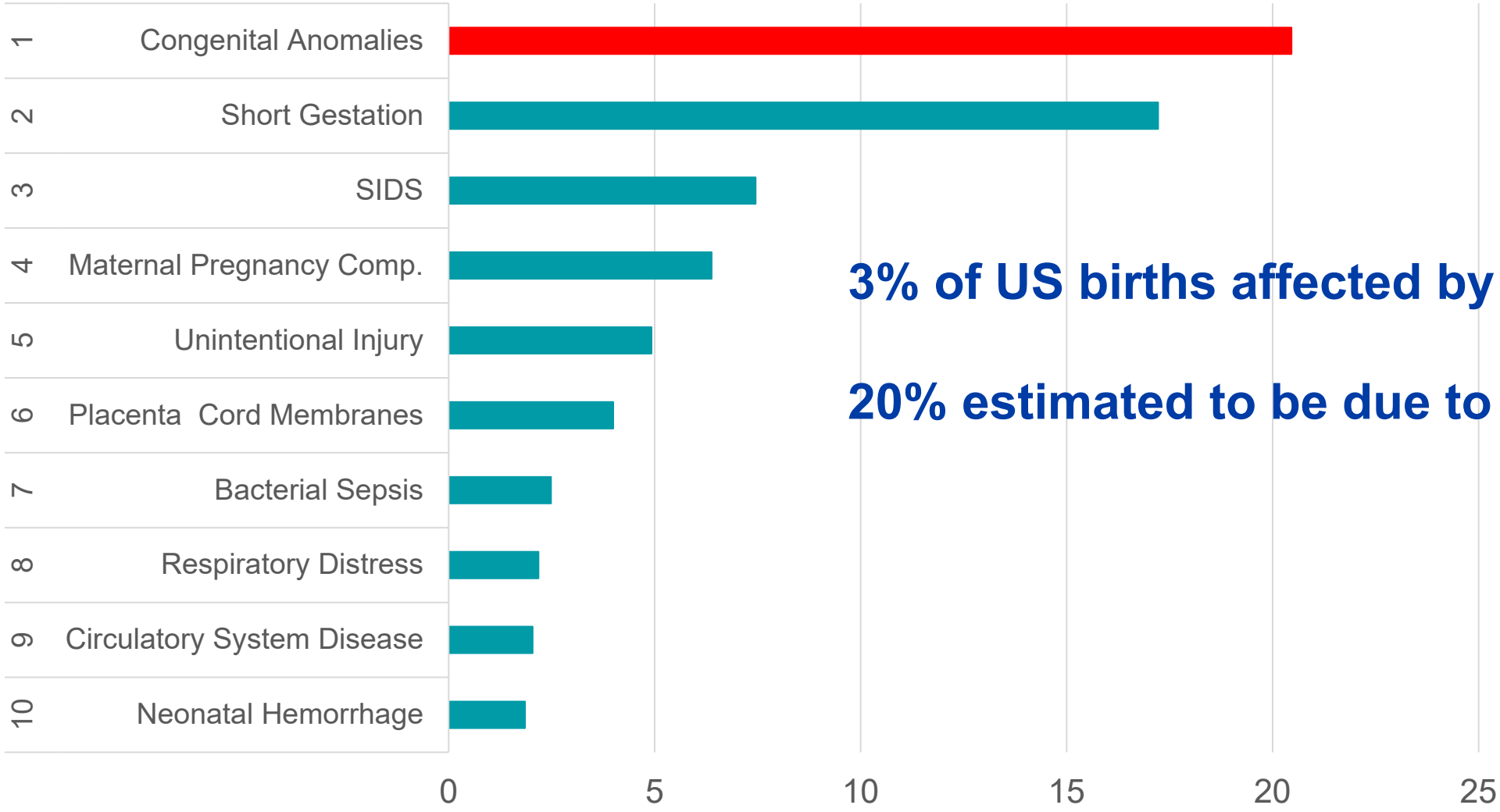
Percent of All Infant Deaths



3% of US births affected by birth defects

20% estimated to be due to genetic factors

Produced By: National Center for Injury Prevention and Control, Centers for Disease Control and Prevention
Data Source: National Center for Health Statistics (NCHS), National Vital Statistics System

The state of healthcare for children with genetic diseases

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Today, diagnosing a genetic disease is long and tedious

7,350 known genetic diseases

70% start in children

2.5% of children affected

On average, reaching a diagnosis takes

4.8 YEARS

AND

7.3 SPECIALISTS

And some people never get a diagnosis at all.

Early diagnosis is a significant unmet need

Rapid diagnosis is a critical factor in saving lives. Babies simply can't afford the current delays.

J Rare Diseases 1:1-15 (2013)

NSIGHT 2: Rady Children's Hospital (RCHSD)

A Randomized, controlled trial of the diagnostic utility of rapid genome and exome sequencing in ill infants

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NSIGHT2- Rady Children's Hospital

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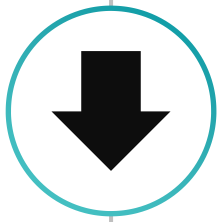
Molecular diagnosis



End Points

- Diagnostic rate
- Time to report
- Clinical utility
- Cost effectiveness
- Outcomes

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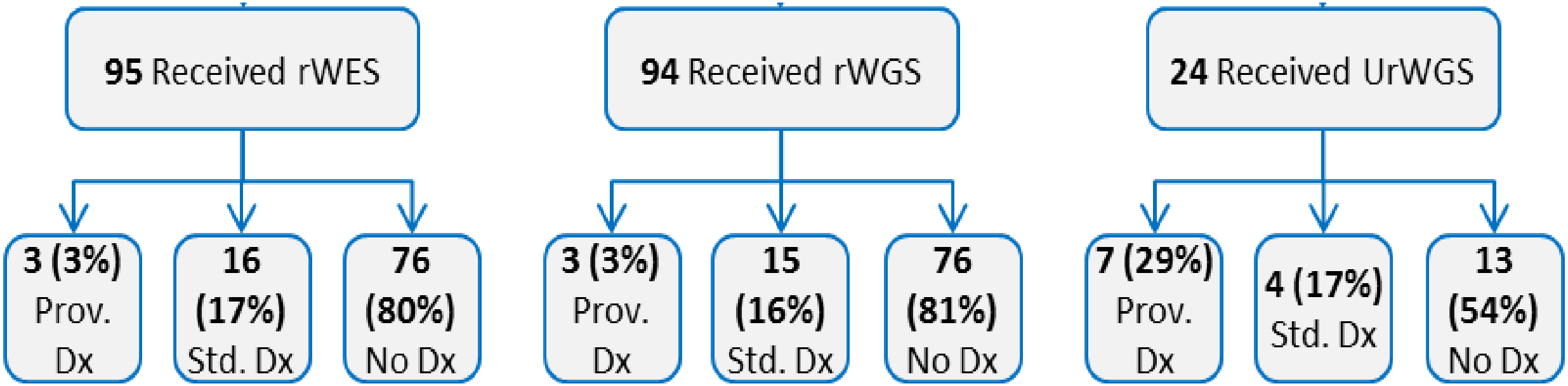
NSIGHT2- Rady Children's Hospital



NSIGHT2- Rady Children's Hospital

213 infants in Intensive Care Units

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
  - 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
  - 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

NSIGHT2- Rady Children's Hospital

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Reference/1st Author	Date	Study Type	Seq Type	NICU and PICU Enrollment Criteria	% ICU eligible	Size of Study	Rate of Dx	Dx	TAT (d)
18	2015	Cohort	rWGS	<4 mo of age; Suspected actionable genetic disease	1.50%	35	57%	20	23
14	2017	Cohort	rWES	<100 days of life; Suspected genetic disease	5%	63	51%	32	13
van Diemen	2017	Cohort	Rapid Panel	Infants; Suspected genetic disease	2.50%	23	30%	7	12
17	2018	RCT	rWGS	<4 mo of age; Suspected genetic disease	7%	32	41%	13	13
16	2018	Cohort	rWGS	infants; Suspected genetic disease	10%	42	43%	18	23
29	2018	Cohort	rWES	Acutely ill children with suspected genetic diseases	10%	40	53%	21	16
30	2018	Cohort	rWGS	PICU children with suspected genetic disease	10%	24	42%	10	9
Sanford	2019	Cohort	rWGS	4 months-18 years; PICU; Suspected genetic disease	5%	38	48%	18	14
28	2019	Cohort	rWGS	Suspected genetic disease	20%	195	21%	40	21
NSIGHT2		**RCT**	**urWGS/rWGS/ rWES**	**<4 mo of age, w/in 96h of admission or development of abnormal response to standard therapy, suspected genetic disease**	**46%**	**213**	**23%**	**48**	**4/11**

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Study Type	Test	Enrollment Criteria	Size	Dx Rate	Δ Mx	Δ Outcome	TAT (days)
Cases	URGS	NICU infants; Susp. genetic disease	4	75%	n.d.	n.d.	2
Cohort	RGS	<4 months of age; Susp. actionable genetic disease	35	57%	31%	29%	23
Cohort	RES	<100 days old; Susp. genetic disease	63	51%	37%	19%	13
Cohort	RGS	Infants; NICU, PICU; Susp. genetic diseases	23	30%	22%	22%	12
RCT	RGS,SOC	<4 months of age; Susp. genetic disease	32	41%	31%	n.d.	13
Cohort	RGS	Infants; Susp. genetic disease	42	43%	31%	26%	23
Cohort	RES	Acutely ill children with susp. genetic diseases	40	53%	30%	8%	16
Cohort	RGS	Children; PICU and Cardiovascular ICU	24	42%	13%	n.d.	9
Cohort	RGS	4 months-18 years; PICU; Susp. genetic diseases	38	48%	39%	8%	14
Cohort	RGS	Susp. genetic disease	195	21%	13%	n.d.	21
Cases	URGS	Infants; ICU; Susp. genetic disease	7	43%	43%	n.d.	0.8
Cohort	RES	<6 months old; ICU; hypotonia, seizures, metabolic, multiple congenital anomalies	50	58%	48%	n.d.	5
Cohort	RES	NICU; infants; susp. genetic disease	25	72%	60%	n.d.	7.2
Cohort	RES	PICU and other; children; susp. genetic disease	40	53%	43%	n.d.	6
Cohort	RES	NICU & PICU; complex	130	48%	23%	n.d.	3.8
Cohort	RES	Critical illness; medical genetics selected	46	43%	52%	n.d.	9
Cohort	RES	PICU; < 6 years; new metabolic/neurologic disease	10	50%	30%	n.d.	9.8
Cohort	RES	ICU	368	27%	n.d.	n.d.	n.d.
Cohort	RES	Infants; ICU and inpatient	102	31%	27%	n.d.	11
Cohort	RES	Various	41	32%	n.d.	n.d.	7
Implem	URES	<18 year; NICU and PICU	108	51%	44%	n.d.	3
Cohort	RES	Infants; NICU, PICU; susp. genetic diseases	18	83%	61%	n.d.	14
Cohort	URES	Infants; NICU, PICU; susp. genetic diseases	33	70%	30%	30%	1
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
Implem	URGS	Medicaid infants; unknown etiology; within 1 week of admission	178	43%	31%	n.d.	3
Cohort	RES	Critically ill; 6 days - 15 years; susp. genetic diseases	40	43%	31%	n.d.	5
Cohort	RES	NICU, PICU, infants; sup. Genetic diseases	61	43%	11%	n.d.	60
RTDCT	RGS,WGS	<120 days old; ICU; susp. genetic disease	354	31%	25%	n.d.	15
Crossover	RES	Critically ill infants with conditions suggestive of genetically heterogeneous disorders	202	20%	n.d.	n.d.	20
	RGS		202	37%	7%	n.d.	7
Cohort	RGS	NICU, PICU with probable genetic disease; urgent need for etiological diagnosis to guide are	37	57%	n.d.	n.d.	43
Cohort	URGS	Infants in ICU with complex multisystem disease	5	60%	20%	20%	1.5
Implem	RES	NICU infants with susp. genetic disease	80	28%	18%	n.d.	13
Cohort	RGS	Children in ICU with diseases of unknown etiology	65	40%	n.d.	n.d.	12
Cohort	RES	Infants in ICU with susp. genetic disease	15	40%	53%	n.d.	16
Implem	RGS	NICU, PICU with disease of unknown etiology	89	39%	27%	n.d.	n.d.
Crossover	RGS, panel	NICU with disease of unknown etiology	400	49%	19%	n.d.	6
Cohort	RGS	Acutely ill inpatient infants; susp. genetic diseases	188	35%	32%	n.d.	6
Cohort	URGS	NICU, PICU, neurologic inpatients with susp. genetic diseases	21	57%	57%	n.d.	1
Median			3603	38%	26%	18%	

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Paradigm informed by this literature

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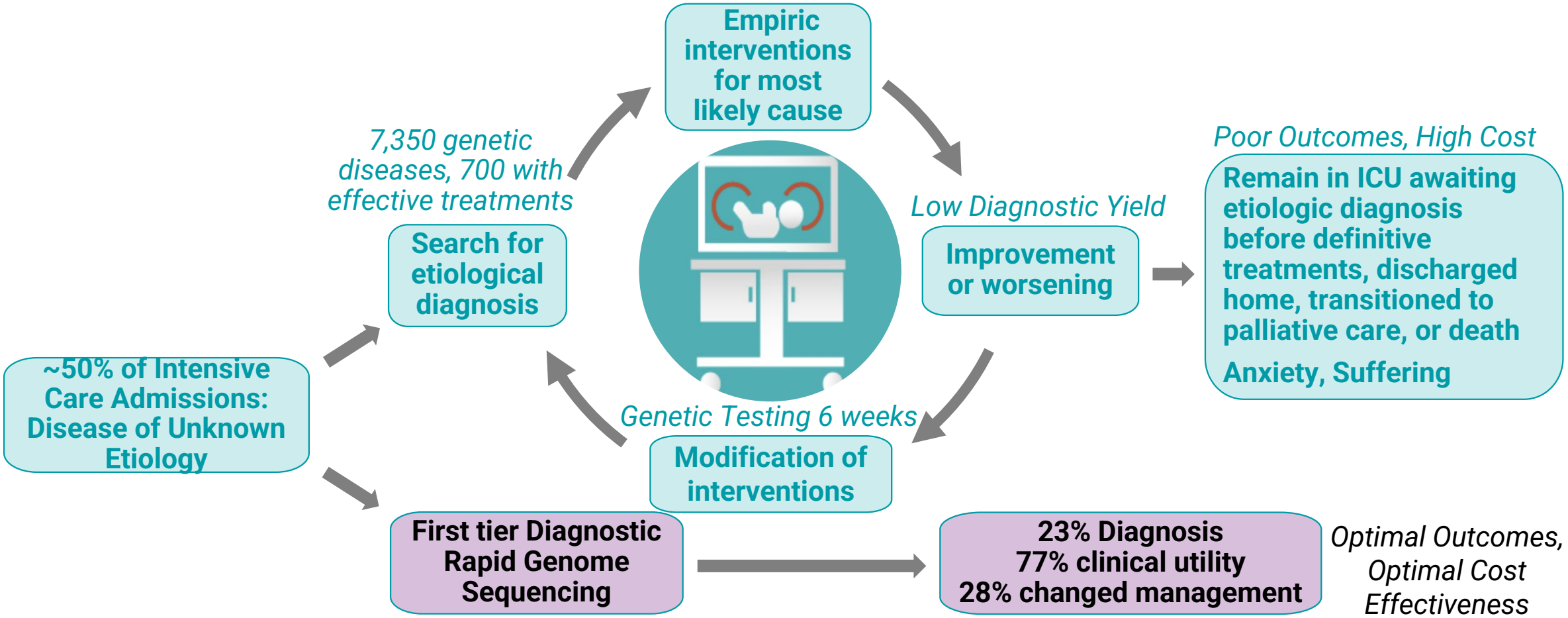


Am J Hum Genet 2019, 105:1 and 2020, 107: 942
NSIGHT2, ClinicalTrials.gov NCT03211039, 213 enrollees, 47% of NICU, 15% genetic disease incidence

Project Baby Bear: Real-world Implementation Study of Clinical Utility & Cost Effectiveness

PILOT SITES	# OF BABIES	BABIES DIAGNOSED	BABIES WHOSE CARE WAS CHANGED*	DAYS TO RESULTS**
CHOC CHILDREN'S HOSPITAL (ORANGE COUNTY)	23	12 (52%)	9 (39%)	2.5
RADY CHILDREN'S HOSPITAL-SAN DIEGO	59	22 (37%)	19 (32%)	3
UC DAVIS CHILDREN'S HOSPITAL *(Sacramento)*	34	12 (35%)	8 (24%)	2
UCSF BENIOFF CHILDREN'S HOSPITAL OAKLAND	24	12 (50%)	9 (38%)	3
VALLEY CHILDREN'S HOSPITAL *(Madera)*	38	18 (47%)	10 (26%)	3
TOTAL PROJECT BABY BEAR CASES	178	76 (43%)	55 (31%)	3

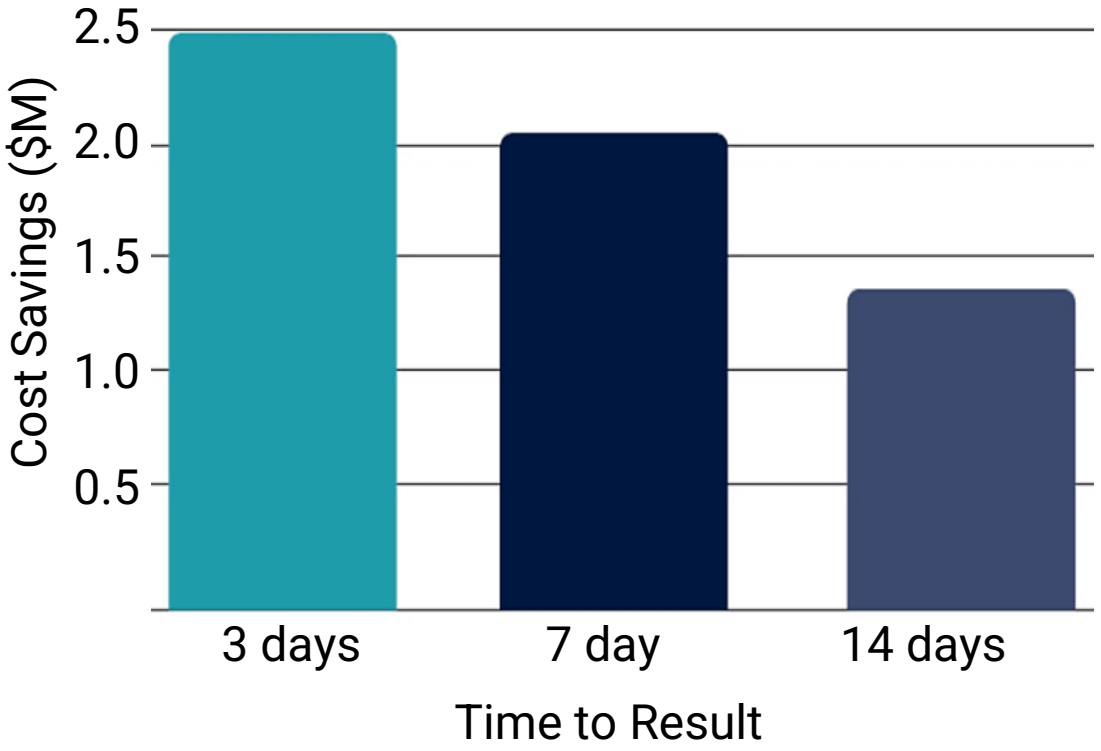
** Results confirmed 21 babies were already receiving appropriate care*

*** Median # days to delivery of provisional positive results*

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. Final report.

Cost effectiveness dependent on time to result

Cost Savings: 1st Hospitalization[1]



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

Demonstrating Value for Payors (US$)

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Ref.	Subjects	Dx rate	Δ Mx rate	Cost per proband	Cost per Dx	TAT (days)	Net Savings/child
46	42	43%	33%	$16,063	$37,480	23	$18,741
68	184	40%	32%	$9,239	$22,973	3	$15,711
16	61	33%	n.d.	$9,758	$29,570	n.d.	$11,286
85	38	45%	34%	$6,300	$14,082	14	-$1,436
75	370	40%	n.d.	$11,029	$27,573	12	$100,440
86	40	53%	39%	$8,088	$15,406	3	$17,243
77	89	39%	27%	$7,564	$19,234	n.d.	$4,155
Median	824	40%	33%	$9,239	$22,973	n.d.	$15,711
Controls							
75	305	14%	n.d.	$1,887	$13,978	Microarray, Karyotype	
78	400	28%	n.d.	$6,500	$23,636	Gene Panel	

Progress in Coverage and Reimbursement

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11 Anthem/BlueCross/Blue Shield Plans & United Health Group: Infants ≤ 1 year old in ICU; Reimbursed

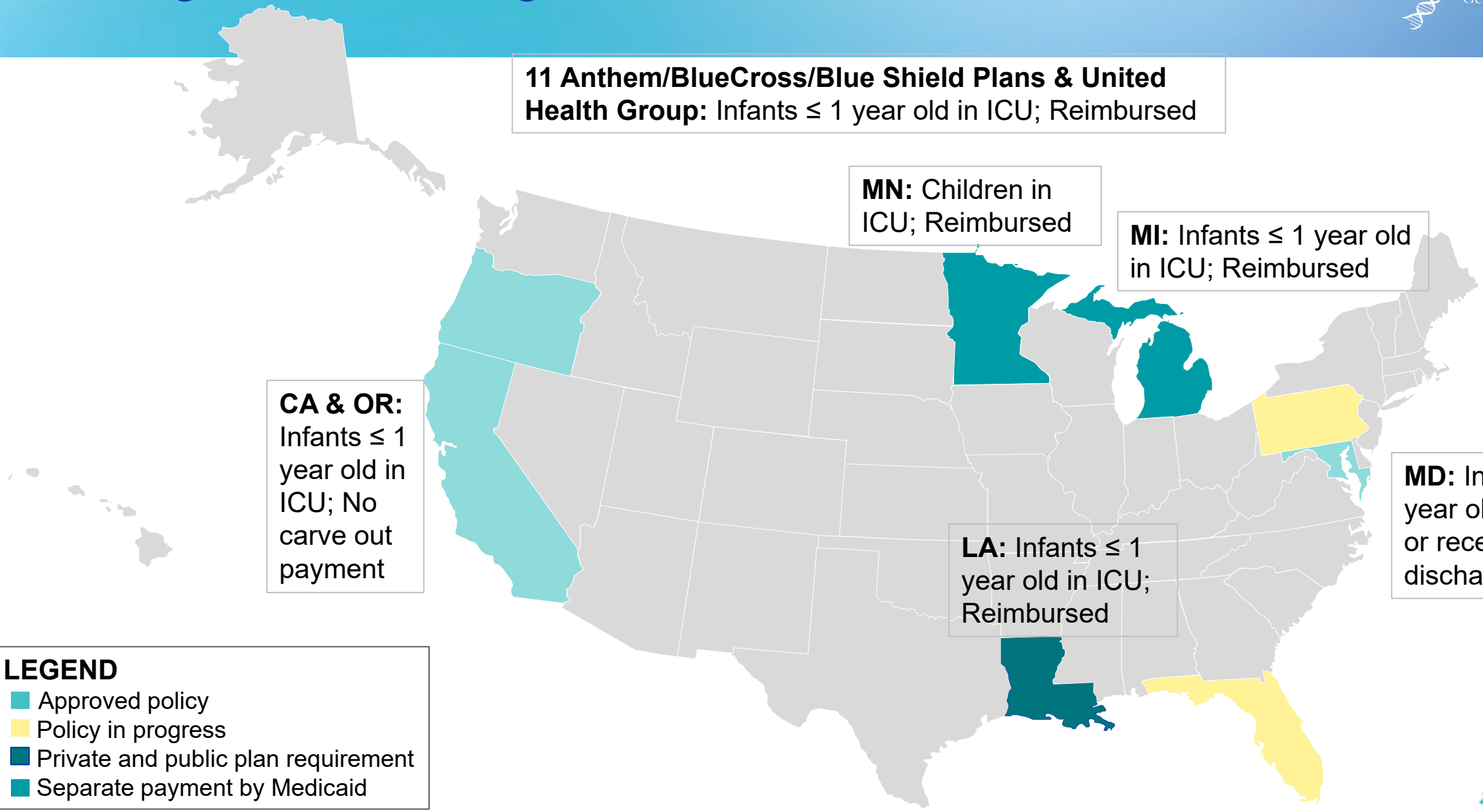
MN: Children in ICU; Reimbursed

MI: Infants ≤ 1 year old in ICU; Reimbursed

CA & OR: Infants ≤ 1 year old in ICU; No carve out payment

MD: Infants ≤ 1 year old in ICU or recently discharged

LA: Infants ≤ 1 year old in ICU; Reimbursed



LEGEND

- Approved policy
- Policy in progress
- Private and public plan requirement
- Separate payment by Medicaid

Which Medicaid Beneficiaries benefit from diagnostic rWGS?

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- **Critically-ill children** with suspected genetic diseases for which effective therapies exist
- **Critically-ill children** with suspected genetic diseases
- **Critically-ill children** for whom a rapid diagnosis may change go/no-go decision about high-cost or high-risk interventions
- Infants and children in **intensive care units** (NICU, PICU, CVICU) without a unifying (etiologic, molecular) diagnosis at admission
- **Inpatient children who have failed to receive a diagnosis despite extensive work-up**
- Inpatient children who have had multiple hospitalizations or **readmission** within 30 days of discharge for an unexplained condition
- Infants or children with **prolonged hospital stay** (outliers)

Patients who receive the biggest impact from fastest testing

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- **Intractable seizures**
- **Suspected inborn error of metabolism** including profound hypoglycemia
- **Unexplained cardiac arrest**
- Invasive diagnostic procedures or heroic measures being considered during current hospitalization that may be avoided based on results (ECMO, transplant)
- Avoidance of high-cost inappropriate therapy or delay of high-cost therapy
- Other condition for which a delayed diagnosis has a high likelihood of adverse effects (due to inappropriate therapy) or severe morbidity or mortality (due to delayed specific treatment)

Genome sequencing for newborn screening

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BeginNGS

A learning precision medicine delivery system for newborns + children for ~700 rare diseases

BeginNGS is not just a test. It is a learning healthcare delivery system.

1 Education + Engagement

2 Screening + Diagnosis

3 Precision Interventions at/before symptoms

4 Optional insights across the lifespan

5 Acceleration of rare disease therapy development & access

Principles Setting the Stage for Genomic Sequencing of All Newborns

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Principle	Genomic Sequencing of Newborns
Conditions should be important health problems	**Single locus Mendelian diseases**
Natural history of the conditions should be adequately understood	Incomplete for many
There should be a recognizable latent or early symptomatic stage	**Recognizable by genome sequence**
There should be a suitable test	**Genome sequencing**
The test should be acceptable to the population	Parental consent & control
There should be an agreed policy on whom to treat as patients	Diagnosed neonates
There should be accepted treatments	True for ~700 Mendelian disorders
Facilities for diagnosis and treatment should be available	True in USA
Cost should be balanced with possible expenditure on medical care	$196,000 per diagnosis by NBS
Case-finding should be a continuing process, not “once and for all”	Opt-in for age-appropriate reanalysis

Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: World Health Organization; 1968.

BeginNGS: Collaboration and Cooperation

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1. Broad adoption requires engagement and participation by many stakeholders

1. No single entity can achieve the scale required for BeginNGS (testing of >1 million newborns).
    i. Acceptance requires equity*. Disorder incidence & mutation spectrum vary between races, ethnicities, & ancestries. Genome information currently under-represents non-northern Europeans.
    ii. The incidence, natural history, and clinical utility of interventions for ultra-rare disorders are poorly understood.

2. Significant technology innovation and investment is needed to develop a scalable, cost-effective system

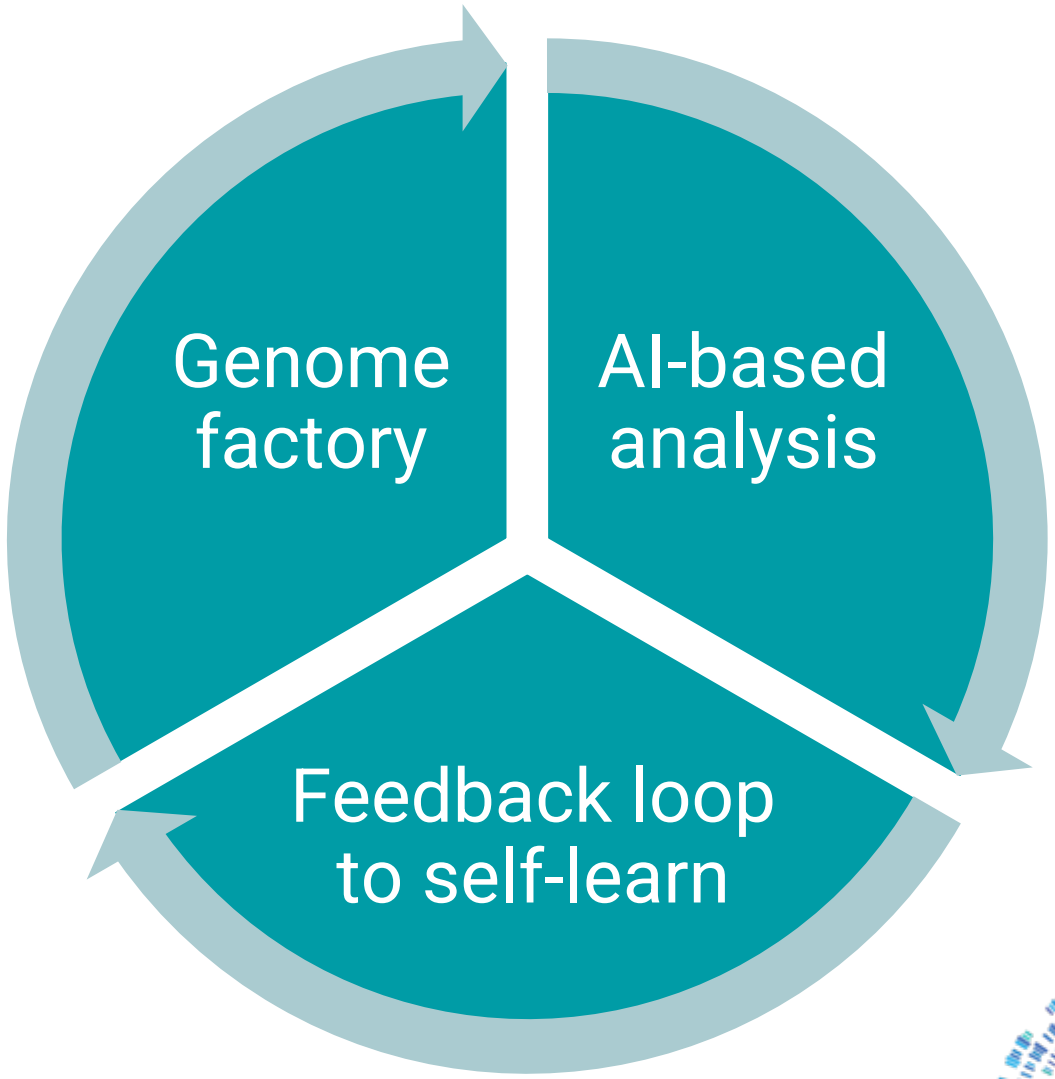
*Equality = everyone is treated the same exact way, regardless of need or other individual difference. Equity = everyone is provided with what they need to succeed.

https://Begin-NGS.org

How difficult is it to develop a screening test for a number of ultra-rare genetic diseases?

BeginNGS™
NEWBORN GENOMIC SEQUENCING
to end the diagnostic odyssey

	Diagnostic genome for critically ill child	Newborn screening genome for all babies
How many?	80,000/year	3.6 million/year
Cost	$9,499	$300
Pre-test probability of genetic disorder	40%	1%
Time to result	2 days	1-2 weeks
Test rationale	Diagnosis for answers	Screening for early treatment
Performance target	Few false negatives	Few false positives
# Diseases	7300	700



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Artificial-intelligence-Analyzed Genome Sequencing is A Suitable Test

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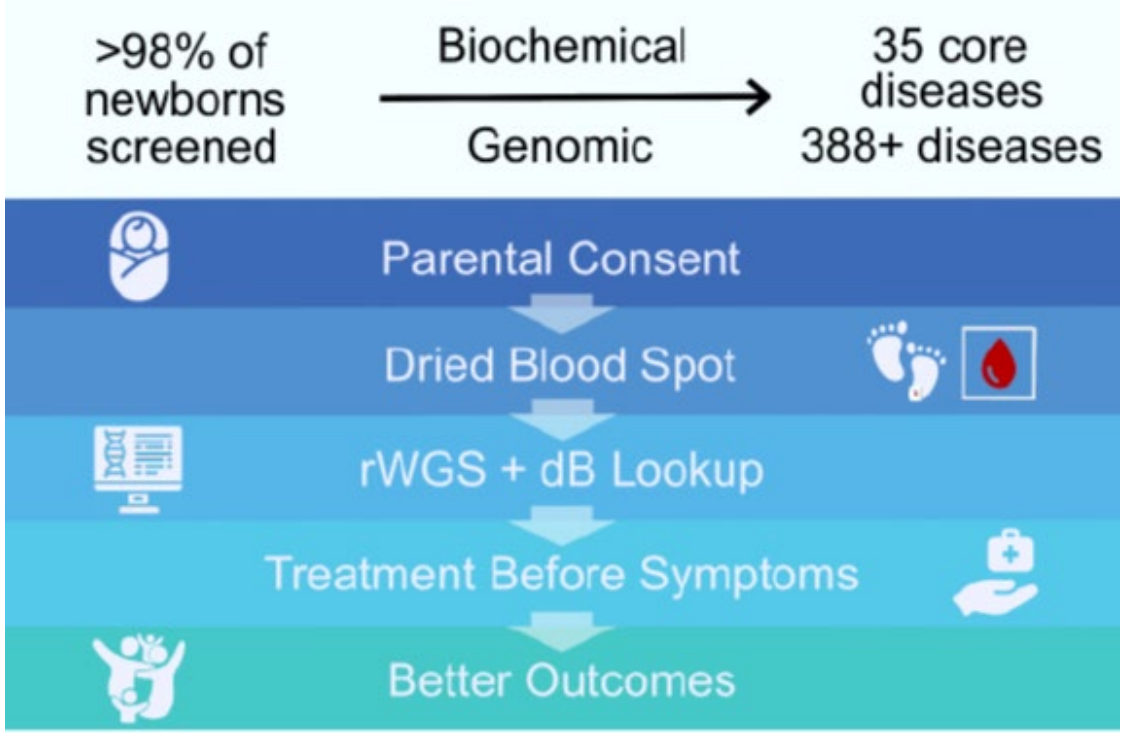

Train in 454k UKBB subjects: 99.7% specificity

Test in 4k+ ill children/parents: 88.8% sensitivity

Critical illnesses avoided in 7 infants

Am J Hum Genet. 2022 109:1605-1619.

Genome-to-Treatment, gtrx.rbsapp.net or gtrx.radygenomiclab.com

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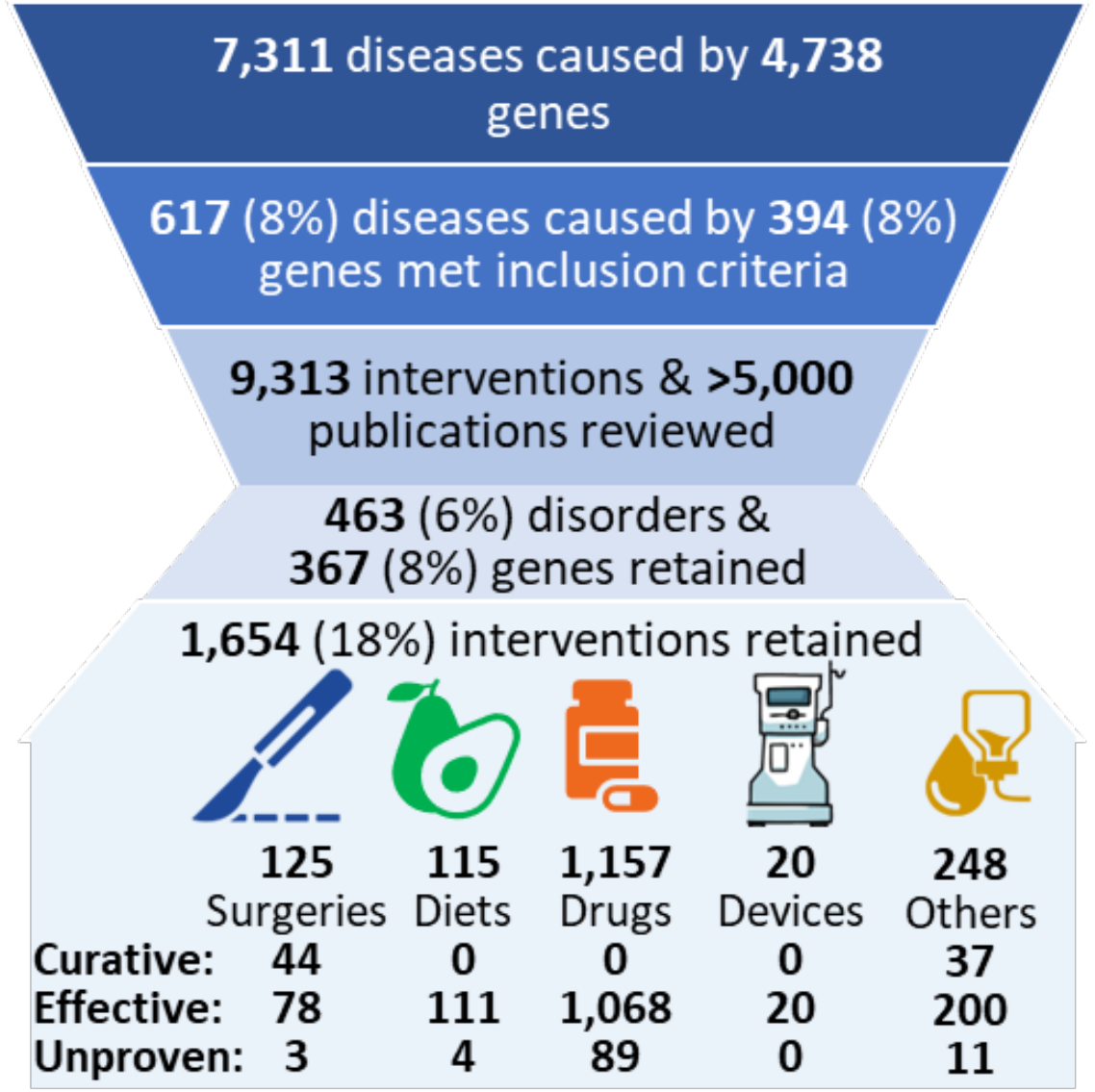

Nat Commun. 2022 Jul 13:4057.

Summary

- We are at an inflection point in genome-informed healthcare delivery for genetic diseases
- Diagnostic rapid GS has been demonstrated to be both clinically and cost effective and is being implemented as a 1st-tier healthcare delivery system for genetic diseases in hospitalized children with illnesses of unknown etiology
- The feasibility of BeginNGS – a population healthcare delivery system for childhood genetic diseases – has been demonstrated
- Clinical trials of BeginNGS are starting which will evaluate clinical and cost effectiveness of >700 diseases in diverse racial, ethnic and ancestral groups

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