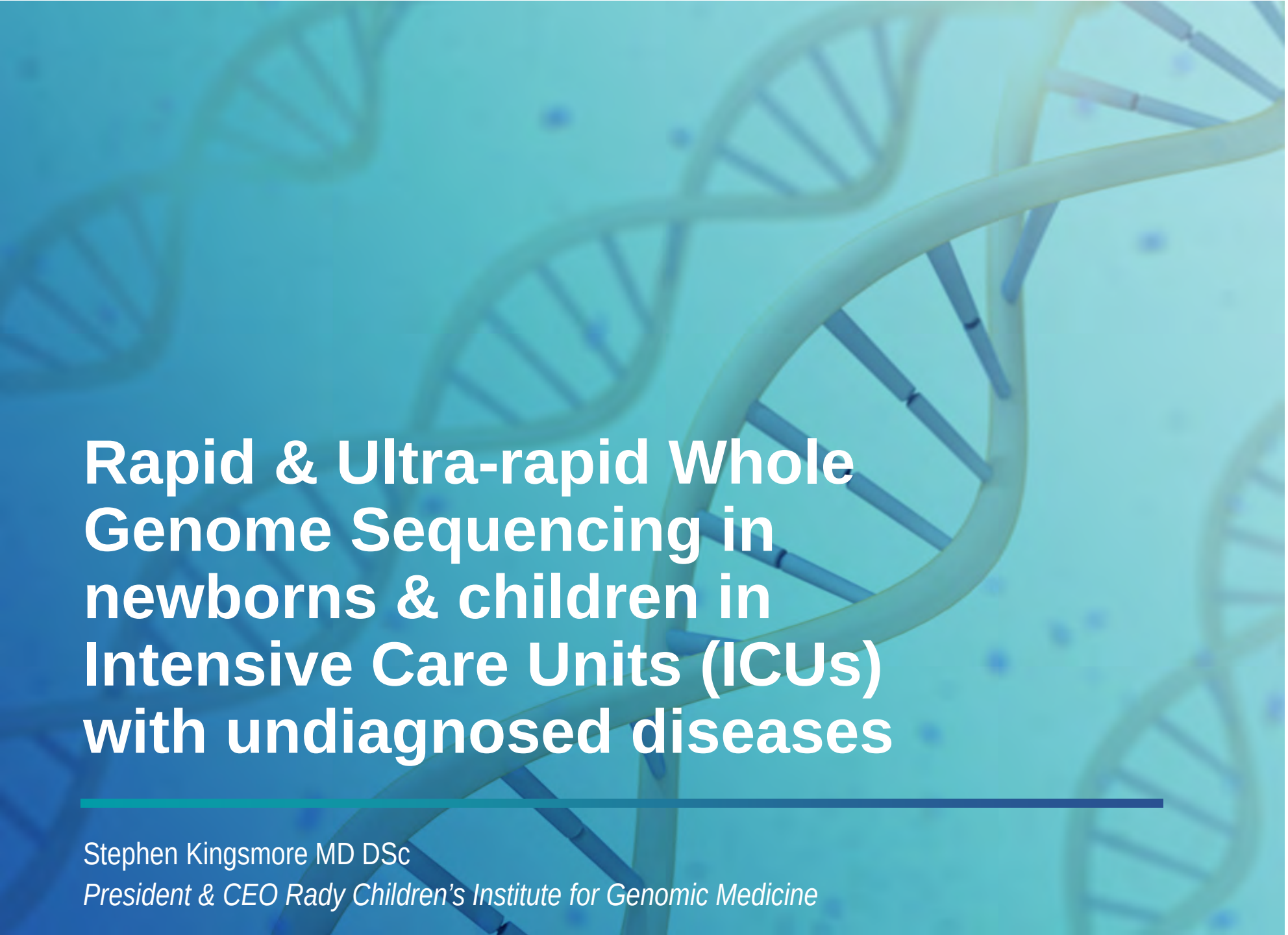

Rapid & Ultra-rapid Whole Genome Sequencing in newborns & children in Intensive Care Units (ICUs) with undiagnosed diseases

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

Rady Children's Institute Genomic Medicine

Over the course of **the next few decades,** the availability of cheap, efficient **DNA sequencing** technology **will lead to** a medical landscape in which **each baby's genome** is **sequenced, and** that information is **used** to shape a lifetime of personalized strategies **for disease** prevention, **detection and treatment**

FRANCIS COLLINS, MD
Director, National Institutes of Health
Wall Street Journal | July 7, 2014

Evolution of genome-informed treatment of heritable conditions in newborns and children

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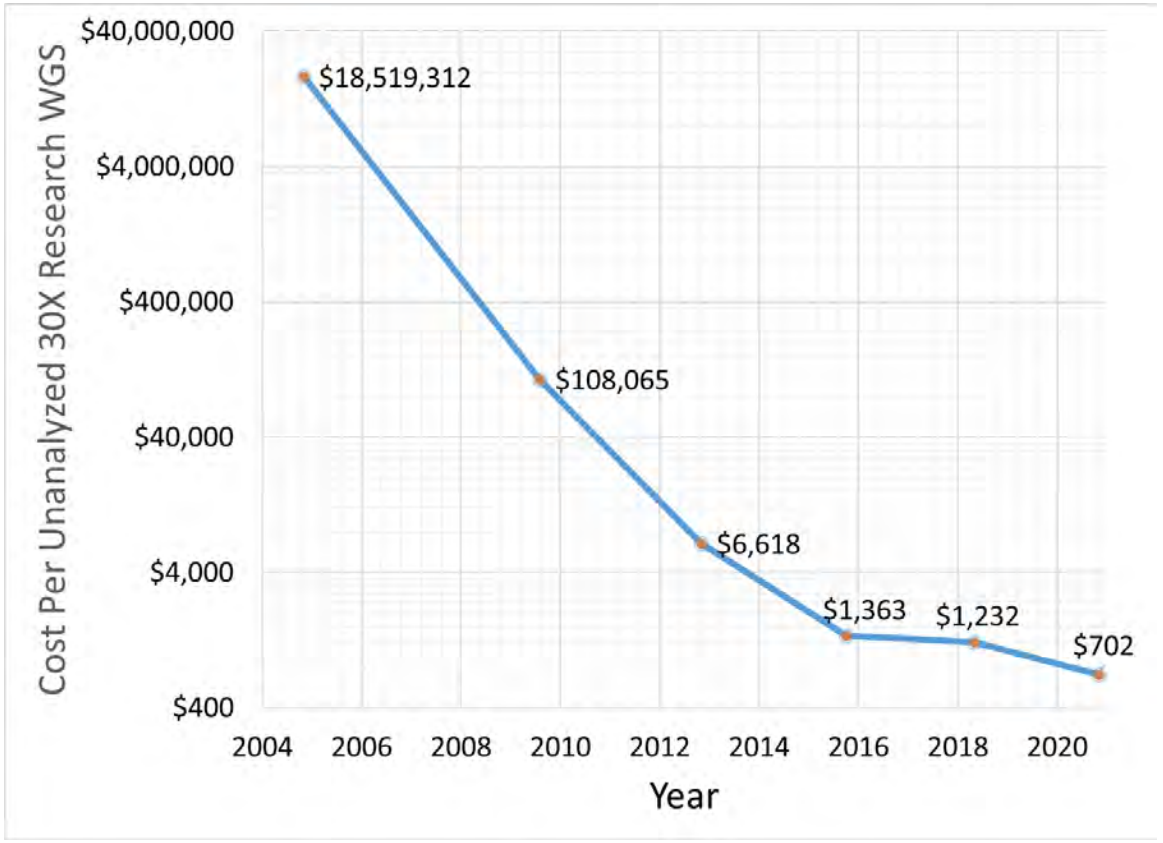

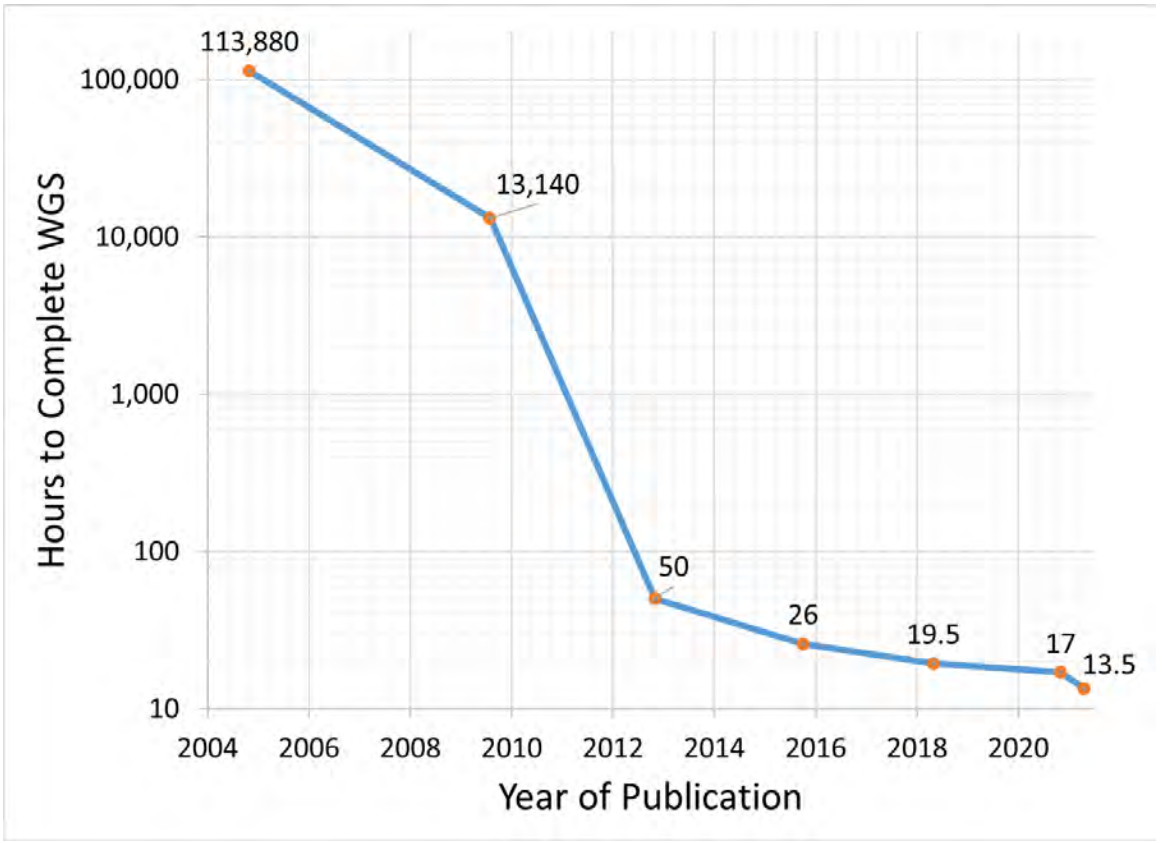

13.5-hour whole genome sequencing from DBS

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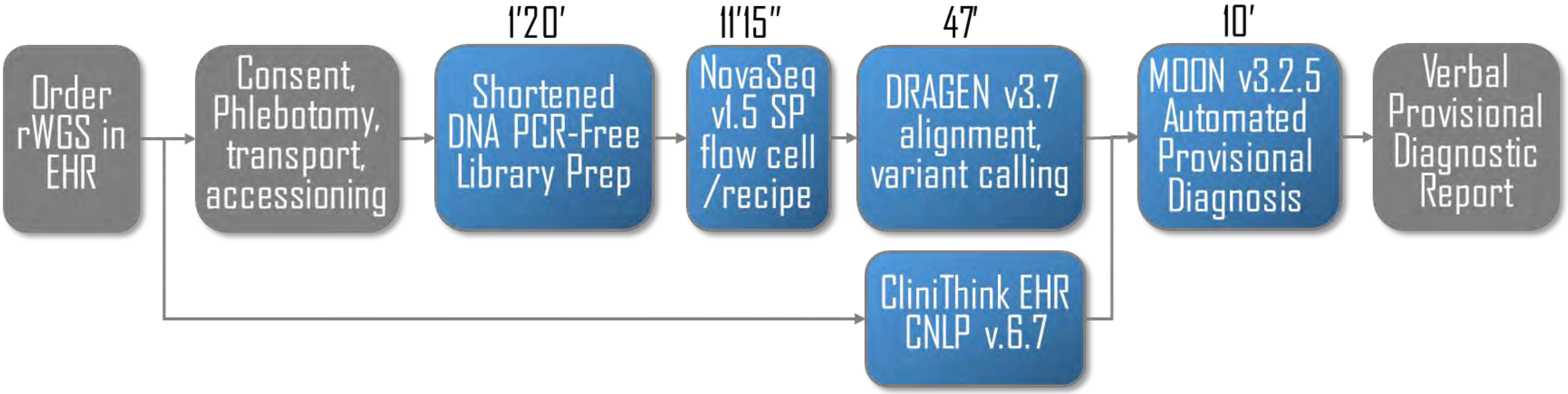

	Precision	Recall
Single nucleotide variants	99.9%	99.9%
Insertion-deletion nucleotide variants	99.6%	99.4%
Structural variant deletions >50 nt	96.8%	61.9%
Structural variant insertions >50 nt	98.1%	48.5%
10-20 kb copy number deletions	66.1%	78.1%
20-50 kb copy number deletions	21.9%	84.0%
>50 kb copy number deletions	16.0%	75.0%

Analytic performance

rWGS & urWGS meet NBS timeliness goals

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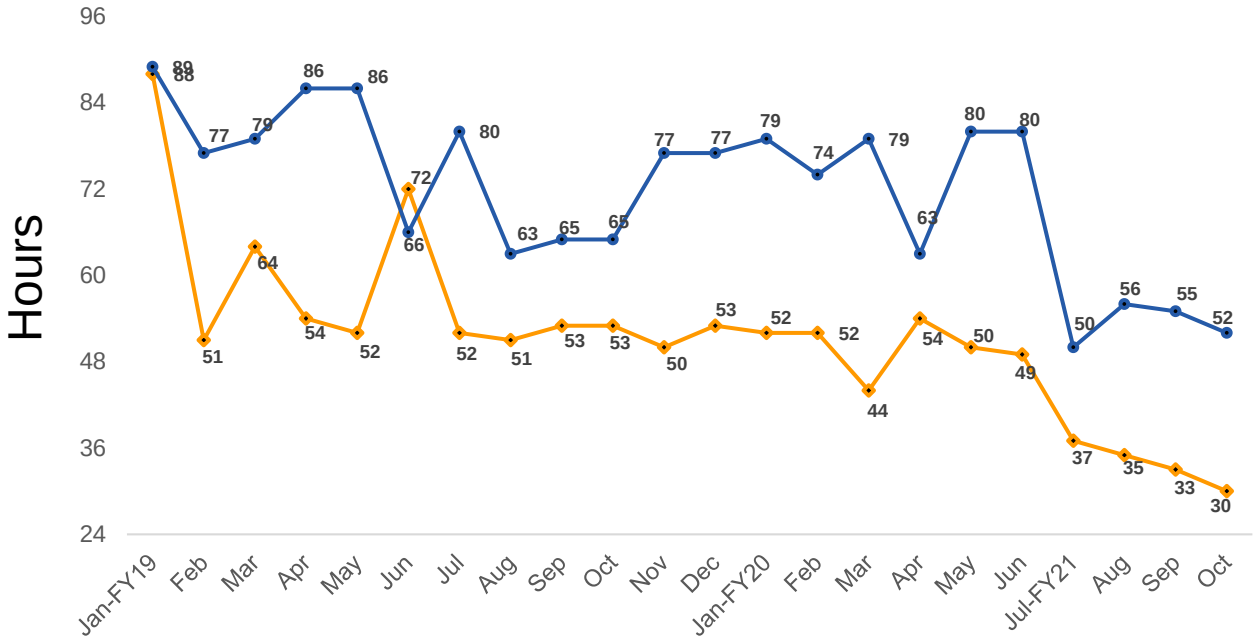
1. DBS collected ≤48 hours after birth.
2. DBS received at laboratory ≤24 hours of collection.
3. Presumptive positive results for time-critical conditions returned @ DOL≤5 (urWGS).
4. Presumptive positive results for other conditions @ DOL≤7 (rWGS).



Median time to provisional positive rWGS result

Median time to provisional positive urWGS result

NSIGHT2 Results

ARTICLE

A Randomized, Controlled Trial of the Analytic and Diagnostic Performance of Singleton and Trio, Rapid Genome and Exome Sequencing in Ill Infants

Stephen F. Kingsmore,[1,*] Julie A. Cakici,[1,2] Michelle M. Clark,[1] Mary Gaughran,[1] Michele Feddock,[1] Sergey Batalov,[1] Matthew N. Bainbridge,[1] Jeanne Carroll,[1,3] Sara A. Caylor,[1] Christina Clarke,[1] Yan Ding,[1] Katarzyna Ellsworth,[1] Lauge Farnaes,[1,3] Amber Hildreth,[1,3,4] Charlotte Hobbs,[1] Kiely James,[1] Cyrielle I. Kint,[5] Jerica Lenberg,[1] Shareef Nahas,[1] Lance Prince,[3] Iris Reyes,[1] Lisa Salz,[1] Erica Sanford,[1,3] Peter Schols,[5] Nathaly Sweeney,[1,3] Mari Tokita,[1] Narayanan Veeraraghavan,[1] Kelly Watkins,[1] Kristen Wigby,[1,3] Terence Wong,[1] Shimul Chowdhury,[1] Meredith S. Wright,[1] David Dimmock,[1] and the RCIGM Investigators

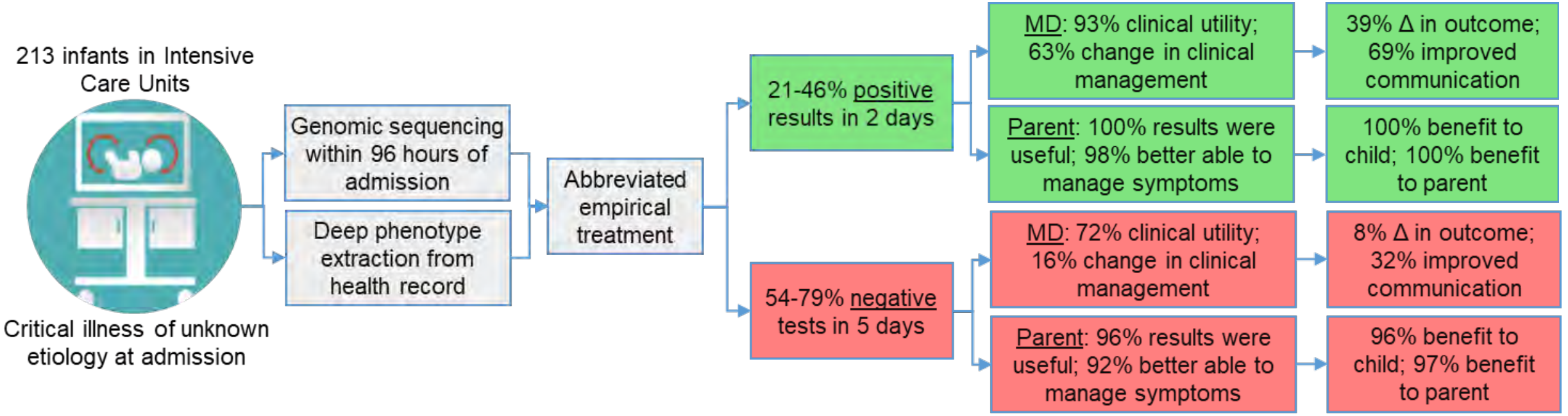
ARTICLE

An RCT of Rapid Genomic Sequencing among Seriously Ill Infants Results in High Clinical Utility, Changes in Management, and Low Perceived Harm

David P. Dimmock,[1,2,*] Michelle M. Clark,[1,2] Mary Gaughran,[1,2] Julie A. Cakici,[1,2,3] Sara A. Caylor,[1,2] Christina Clarke,[1,2] Michele Feddock,[1,2] Shimul Chowdhury,[1,2] Lisa Salz,[1,2] Cynthia Cheung,[3,4] Lynne M. Bird,[2,5] Charlotte Hobbs,[1,2] Kristen Wigby,[1,2,5] Lauge Farnaes,[1,2] Cinnamon S. Bloss,[3,4] Stephen F. Kingsmore,[1,2] and the RCIGM Investigators

A Prospective Study of Parental Perceptions of Rapid Whole-Genome and -Exome Sequencing among Seriously Ill Infants

Julie A. Cakici,[1,2,3] David P. Dimmock,[2] Sara A. Caylor,[2] Mary Gaughran,[2] Christina Clarke,[2] Cynthia Triplett,[4] Michelle M. Clark,[2] Stephen F. Kingsmore,[2] and Cinnamon S. Bloss[1,5,*]



Aggregate evidence: 19 Studies

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PubMed ID	Sequence Method	Neonatal and Pediatric Intensive Care Unit Enrollment Criteria	Patients	Diagnosis Rate	Clinical Utility	Change in Outcome
23035047	Genome	NICU infants with suspected genetic disease	4	75%	n.d.	n.d.
25937001	Genome	<4 mo of age; Suspected actionable genetic disease	35	57%	31%	29%
28973083	Exome	<100 days of life; Suspected genetic disease	63	51%	37%	19%
29449963	Genome	<4 mo of age; Suspected genetic disease	32	41%	31%	n.d.
29644095	Genome	infants; Suspected genetic disease	42	43%	31%	26%
29543227	Exome	Acutely ill children with suspected genetic diseases	40	53%	30%	8%
30049826	Genome	Children; PICU and Cardiovascular ICU	24	42%	13%	n.d.
31246743	Genome	4 months-18 years; PICU; Suspected genetic diseases	38	48%	39%	8%
30847515	Genome	Suspected genetic disease	195	21%	13%	n.d.
31019026	Genome	Infants; Suspected genetic disease	7	43%	43%	n.d.
31780822	Exome	<4 mo of age; ICU; hypotonia, seizures, metabolic, multiple congenital anomalies	50	54%	48%	n.d.
32411386	Exome	NICU & PICU; complex	130	48%	23%	n.d.
32553838	Exome	<6 months; ICU; suspected genetic disease	46	52%	52%	n.d.
32221475	Exome	PICU; < 6 years; new metabolic/neurologic disease	10	50%	30%	n.d.
32336750	Exome	Infants; ICU; Genetic consult	368	27%	22%	n.d.
32573669	Exome	NICU and PICU; Genetic counsult	108	51%	44%	n.d.
32668698	Exome	ICU infants; Severe or progressive conditions	18	72%	n.d.	n.d.
31564432	Genome	Infants; disease of unknown etiology; within 96 hours of admission	94	19%	24%	10%
	Exome		95	20%	20%	18%
	Genome		24	46%	63%	25%
Baby Bear	Genome	MediCal Infants; <1 week of admission	178	43%	31%	n.d.
Weighted Average			**1601**	**37%**	**28%**	**16%**

Global implementation of rWGS in infants & children

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project baby deer

project baby bear

1 Site

2-3 Sites

4-10 Sites

10+ Sites

Project Baby Manatee

Evaluate clinical & economic value of rWGS & urWGS for Medicaid infants receiving critical care

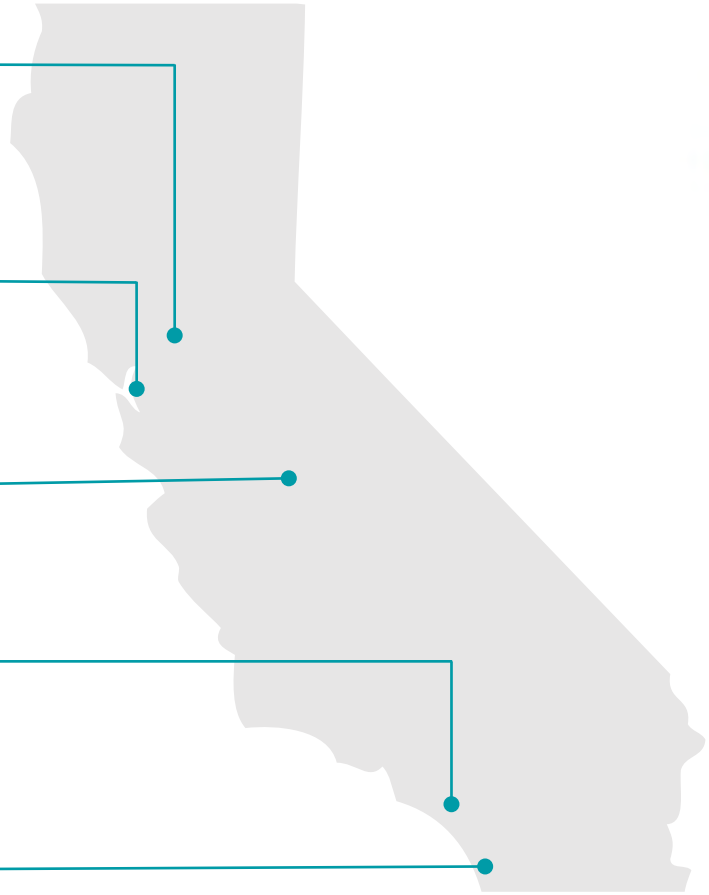
UC Davis Children's Hospital

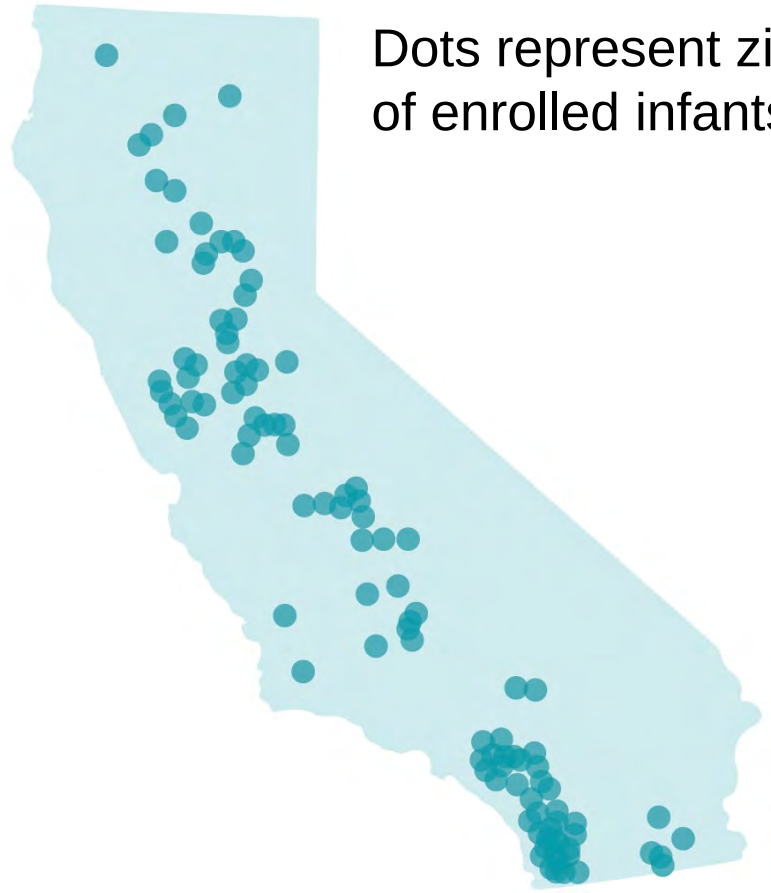
UC San Francisco Benioff Children's Hospital Oakland

Valley Children's Hospital (Madera)'

CHOC Children's (Orange County)

Rady Children's Hospital- San Diego





Dots represent zip codes of enrolled infants

Results

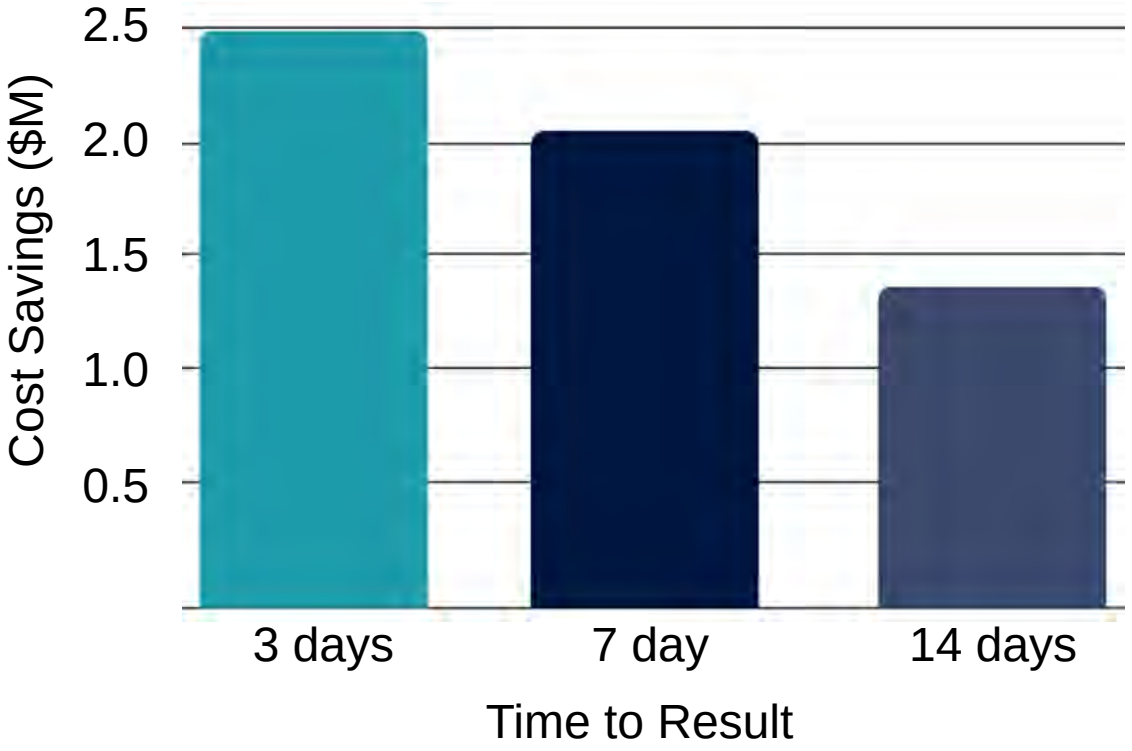
OT SITES	# OF BABIES	DIAGNOSED	WHOSE CARE WAS CHANGED*	RESULT
ILDREN'S HOSPITAL ORANGE COUNTY	23	12 (52%)	9 (39%)	2.5
DY CHILDREN'S HOSPITAL-SAN DIEGO	59	22 (37%)	19 (32%)	3
DAVIS CHILDREN'S HOSPITAL *(Sacramento)*	34	12 (35%)	8 (24%)	2
SF BENIOFF CHILDREN'S HOSPITAL OAKLAND	24	12 (50%)	9 (38%)	3
LLEY 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

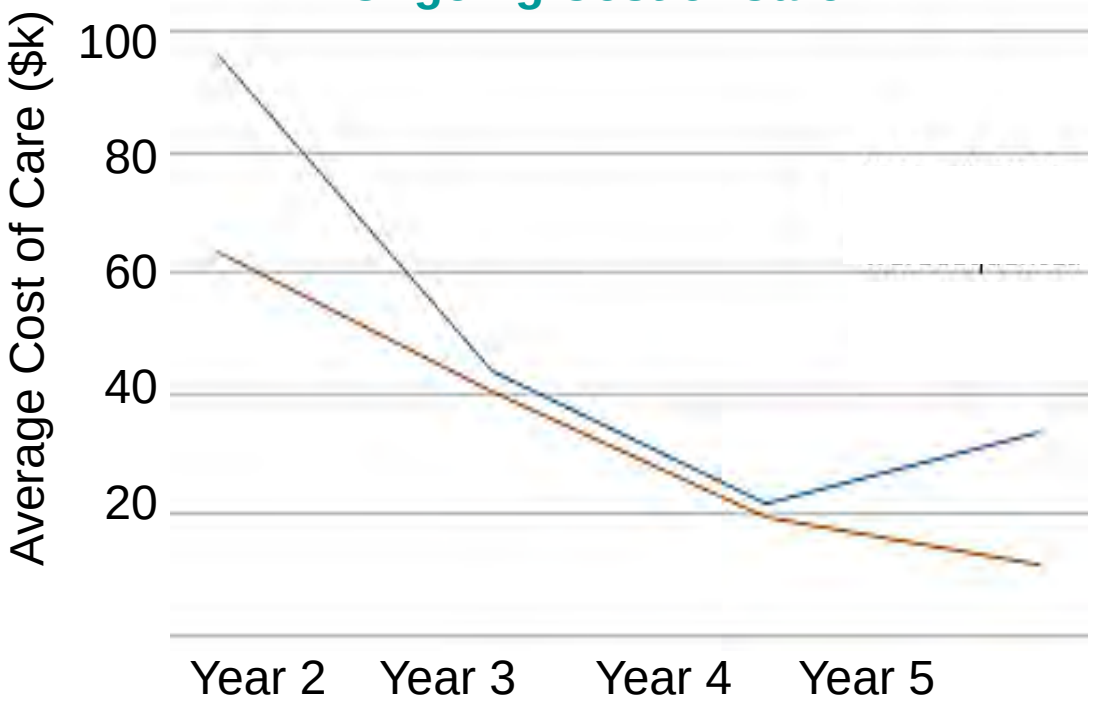
*** Median # days to delivery of provisional positive results*

Results

Cost of 1st Hospitalization



Ongoing Cost of Care



Project Baby Manatee

- Diagnosed 40 (49%) of 82 children & families
- Changed care for 36 (44%) of 82 patients
- Offered mental health counseling to 18 parents experiencing elevated levels of depression
- Saved $6,173,370 ($75,285 per patient)

Return of Results

20%
of patients received UrWGS

AVERAGE TURNAROUND TIME FOR ULTRA-RAPID DIAGNOSES:

- 2.5 days to preliminary report
- 6 days to final report
- 1 day for physician to return results to the family

80%
of patients received rWGS

AVERAGE TURNAROUND TIME FOR RAPID DIAGNOSES:

- 4 days to preliminary report
- 8 days to final report
- 1.4 days for physician to return results to the family

Length of Stay

48
DAYS
On average, length of stay was 48 days for the 50 patients

2-297
Range was 2-297 days

1
WEEK
WGS has shortened LOS for one patient by a week

Changes in Clinical Management

(based on a positive or negative diagnosis)

1
cardiac surgery avoided

1
lung transplant avoided

9
patients had their medication adjusted

8
children started diet therapy for a metabolic condition

1
fundoplication surgery performed

Applying Wilson-Jungner Criteria to NBS by WGS

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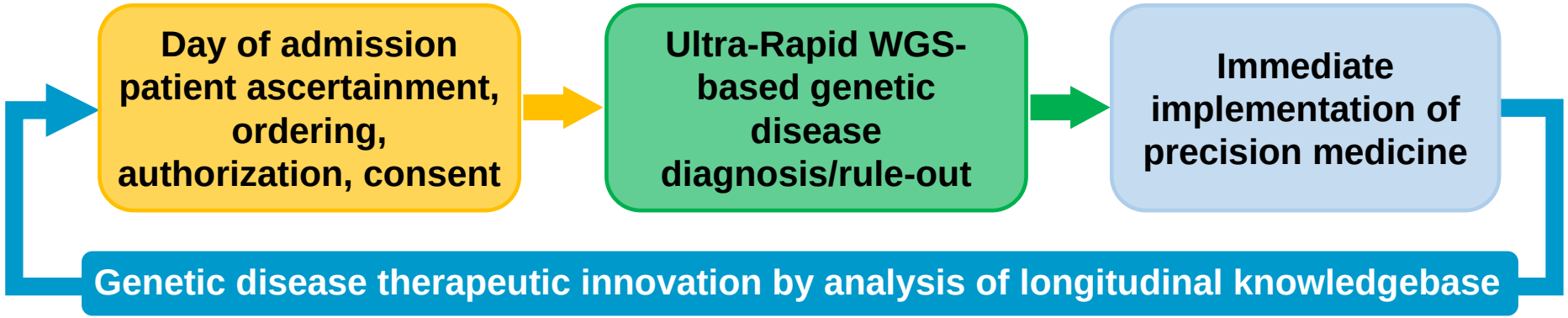
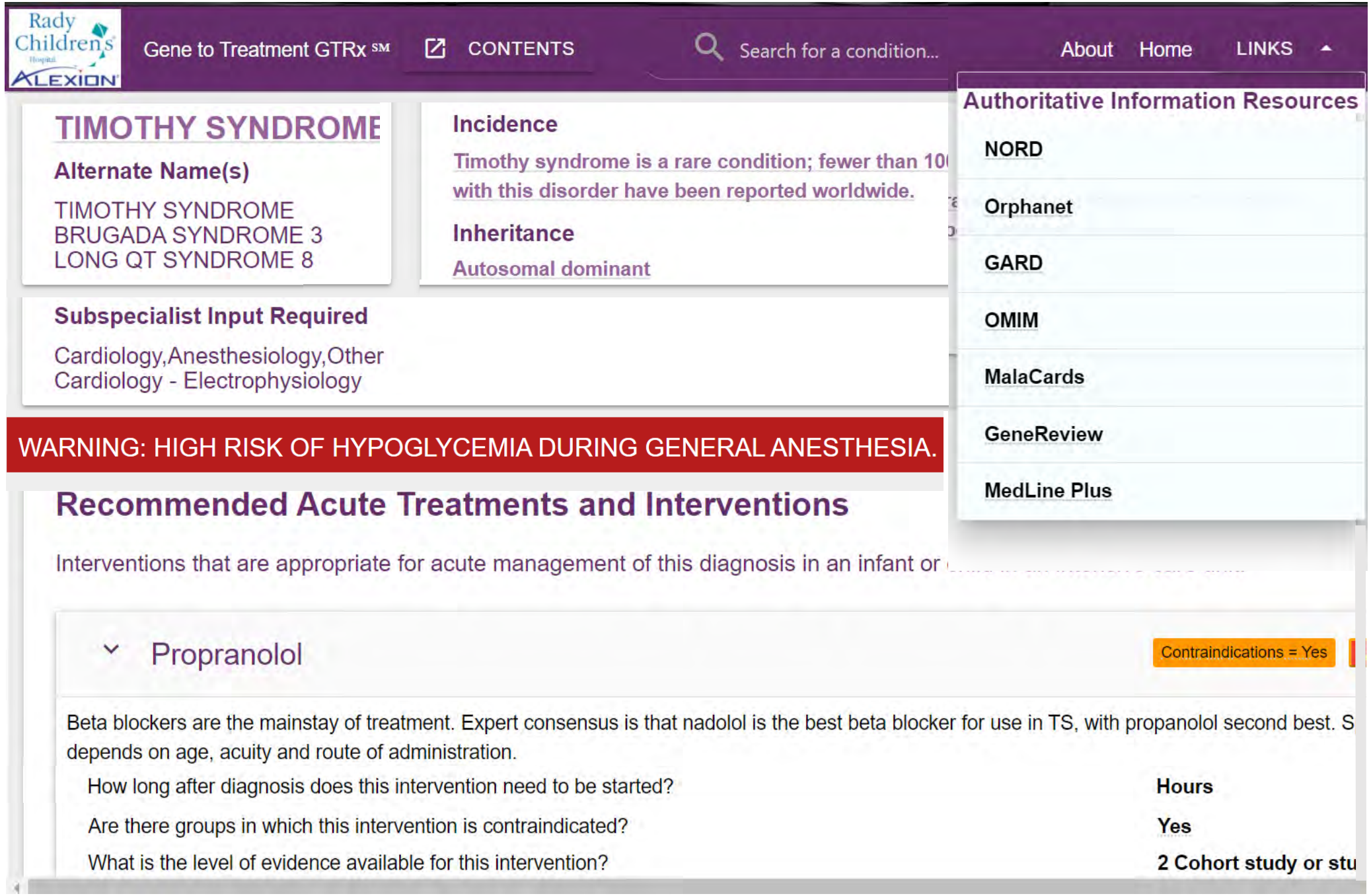


1. Important health problems
2. Well understood natural history
3. Detectable early
4. Early treatment of more benefit than late

5-7. Testable

8. Provision for clinical workload
9. Risk >> benefit
10. Costs balanced with benefit

GTRx: ~500 diseases testable by WGS with effective treatments that present in infancy


Rady Children's Hospital
ALEXION
Gene to Treatment GTRx SM
CONTENTS
Search for a condition...
About
Home
LINKS
TIMOTHY SYNDROME
Alternate Name(s)
TIMOTHY SYNDROME
BRUGADA SYNDROME 3
LONG QT SYNDROME 8
Incidence
Timothy syndrome is a rare condition; fewer than 10
with this disorder have been reported worldwide.
Inheritance
Autosomal dominant
Subspecialist Input Required
Cardiology,Anesthesiology,Other
Cardiology - Electrophysiology
Authoritative Information Resources
NORD
Orphanet
GARD
OMIM
MalaCards
GeneReview
MedLine Plus
WARNING: HIGH RISK OF HYPOGLYCEMIA DURING GENERAL ANESTHESIA.
Recommended Acute Treatments and Interventions
Interventions that are appropriate for acute management of this diagnosis in an infant or
Propranolol
Contraindications = Yes
Beta blockers are the mainstay of treatment. Expert consensus is that nadolol is the best beta blocker for use in TS, with propanolol second best. S
depends on age, acuity and route of administration.
How long after diagnosis does this intervention need to be started?
Hours
Are there groups in which this intervention is contraindicated?
Yes
What is the level of evidence available for this intervention?
2 Cohort study or stu

Summary

Rady Children's Institute Genomic Medicine

- Rapid and ultra-rapid genome sequencing is being adopted widely for infants and children with heritable disorders
- The current application is inpatient infants and children with diseases of unknown etiology
- The technology could be adapted to provide NBS by rWGS for ~500 disorders that meet Wilson-Jungner Criteria for ~$500 per patient