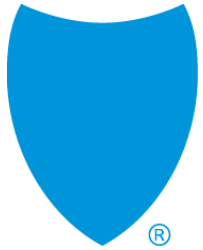


Rapid Whole Genome Sequencing in the NICU

Faster diagnosis. Better outcomes. Reduced healthcare costs

Learning objectives

After completing this webinar, you will be able to:

- Explain the clinical utility of the rWGS test
- List examples of positive health outcomes and cost savings derived from rWGS
- Reference the Blue Shield rWGS medical policy, including criteria to identify babies and children who qualify
- Execute steps needed to implement the test with a qualified patient

This presentation and a link to the recording will be emailed to you within five (5) business days.

Agenda

- Blue Shield of California medical policy overview
- Rady Children's Institute for Genomic Medicine presentation:
  - Rapid Whole Genome Sequencing in the NICU
- Initial steps to implement rWGS testing for a patient
- Q&A

Today's presenters

Erika Allred, MD
Rady Children's Institute for Genomic Medicine

David Dimmock, MD
Senior Medical Director
Rady Children's Institute for Genomic Medicine

Christy Moore, MS, LCGC
Program Manager, Clinical Genetics
Blue Shield of California

Blue Shield of California Policy:
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Policy overview

Rapid whole exome or rapid whole genome sequencing (rWES or rWGS), with trio testing when possible, may be considered **medically necessary** when **all** the following are met:

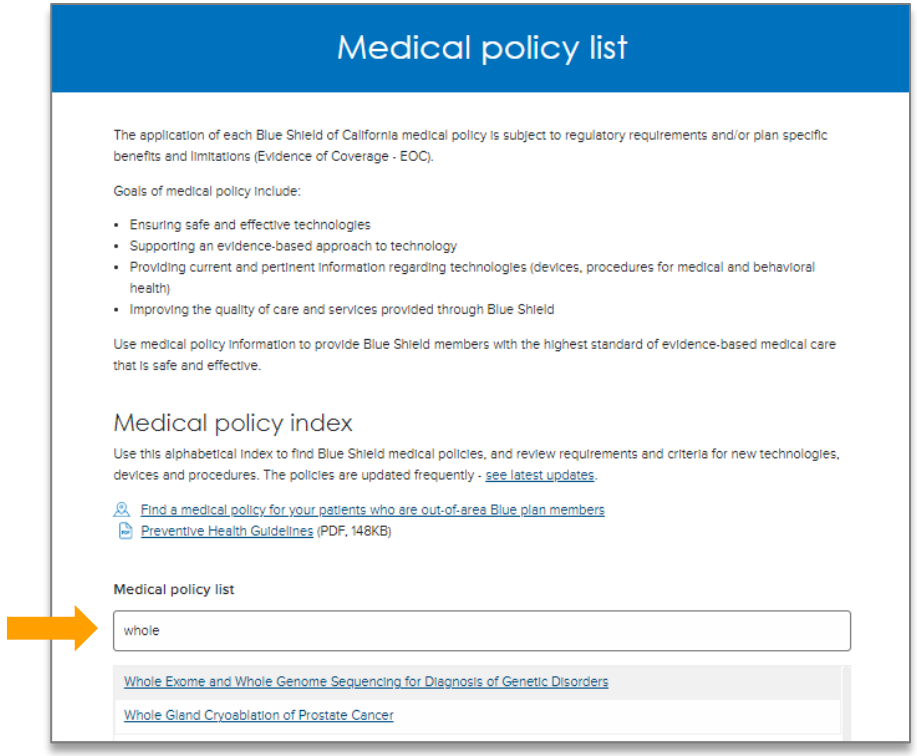
- For the evaluation of critically ill infants or children less than 18 years of age
- Hospitalized in neonatal or pediatric intensive care with illness of unknown etiology
- Documentation that supports at least **one** of the following:
  - Multiple congenital anomalies
  - Specific malformations highly suggestive of a genetic etiology
  - Abnormal laboratory test suggests a genetic disease or complex metabolic phenotype
  - Abnormal response to standard therapy for a major underlying condition
  - Significant hypotonia
  - Persistent seizures
  - Infant with high-risk stratification on evaluation for a Brief Resolved Unexplained Event (BRUE) with **one or more** designated conditions (see policy)
  - Significantly abnormal electrocardiogram (ECG), including but not limited to possible channelopathies, arrhythmias, cardiomyopathies, myocarditis or structural heart disease
  - Family history of one or more designated conditions (see policy)
- Documented exclusion of **all** designated conditions (i.e., infection with normal result to therapy, confirmed genetic diagnosis explains illness, hypoxic Ischemic Encephalopathy – see policy for complete list)

How to find rWGS medical policy

Blue Shield's medical policy:
Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders (12/1/2020).

To access the medical policy on Provider Connection:

- Go to blueshieldca.com/provider – you don't need to be logged in to access medical policies
  - Click the Authorizations from the white navigation bar
  - Click Policies & Guidelines from the blue navigation bar
  - Click the blue Medical policies & procedures box
  - Click Find medical policy for Blue Shield of California plans under the *Medical Policy list*
  - Enter a search term (e.g., "whole" or "genome") in the *Medical policy list* field.
  - Links to any medical policy that aligns with your search will display.



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Genomic Medicine

Rapid Whole Genome Sequencing in the NICU

Faster diagnosis. Better outcomes. Reduced healthcare costs

The Rapid Precision Medicine Paradigm: Example of Neonatal Seizures

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Sebastiana

- Rapid genome sequencing ordered on DOL1
- 3 days of empirical treatment
- Diagnosis on DOL4 Early Infantile Epileptic Encephalopathy 7
- Rapid Precision Medicine: Carbamazepine
- Minor developmental delay
- 17 day hospitalization $79,675
- Search for etiological diagnosis

Newborn 16 Months Earlier

- Search for etiological diagnosis
- 42 days of Empirical treatment
- Continued seizures
- Diagnosis on DOL43 Early Infantile Epileptic Encephalopathy 7
- Natural history of disease
- Severe developmental delay
- 59 day hospitalization $211,484
- Treatment Modification

From: Farnaes L, et al. NPJ Genom Med. 2018 Apr 4;3:10.

Sebastiana and her mom recently came to visit after a routine exam and was dancing, playing and reading

rWGS consistently associated with high clinical utility

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Study Name	Sequencing Type	NICU/PICU enrollment criteria	Study size	Rate of diagnosis	Rate of change in mgmt	Rate in change of outcome
Willig, Children's Mercy, Kansas City	rWGS	<4 mo of age; suspected actionable genetic disease[13]	35	57%	31%	29%
Petrikin, RCIGM	rWGS	<4 mo of age; suspected genetic disease[6]	32	41%	31%	N/D
Farnaes, RCIGM	rWGS	Infants; suspected genetic disease[15]	42	43%	31%	26%
Mestek, UCL Great Ormond Street Institute of Child Health (GOSgene UK)	rWGS	Children; PICU and cardiovascular ICU[9]	24	42%	13%	N/D
Sanford, UCSD, RCIGM	rWGS	4 mo- to 18 yr; PICU; suspected genetic disease[8]	38	48%	39%	8%
French, School of Clinical Medicine, University of Cambridge	rWGS	Suspected genetic disease[7]	195	21%	13%	N/D
Dimmock, RCIGM	rWGS	Infants; disease of unknown etiology; within 96 hr of admission[1]	94	19%	24%	10%
Project Baby Bear, RCIGM	rWGS	Medical infants; <1 wk admission[3]	178	43%	31%	N/D
PBM, Nicklaus Children's Hospital	rWGS, urWGS	Inpatient children <18 yr, 90% in ICUs, primarily PICU[16]	50	40%	38%	N/D
Saunders, Children's Mercy, Kansas City	urWGS	NICU infants; suspected genetic disease[11]	4	75%	N/D	N/D
Clark, RCIGM	urWGS	Infants; suspected genetic disease[6]	7	43%	43%	N/D
Dimmock, RCIGM	urWGS	Infants; disease of unknown etiology; within 96 hr of admission[1]	24	46%	63%	25%
WEIGHTED AVERAGE, rWGS + urWGS			**723**	**35%**	**27%**	**17%**

- **12 studies from multiple institutions**

35%
diagnosed

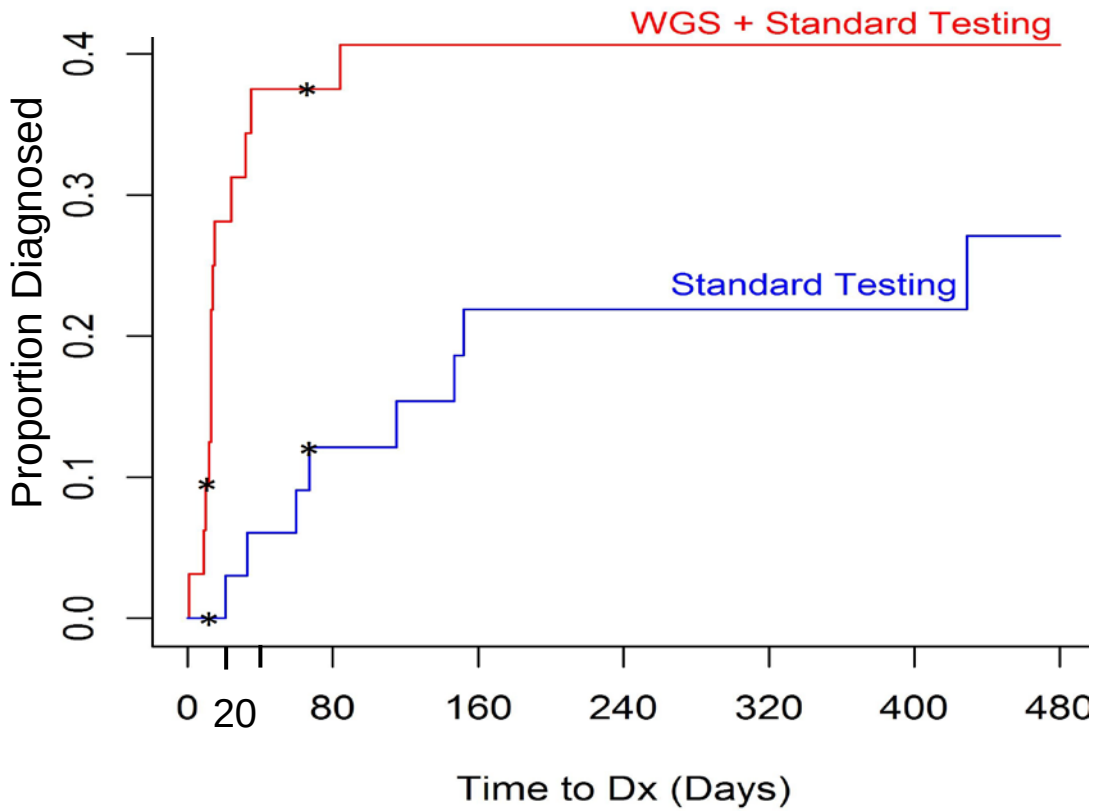
77%
of those diagnosed had a change in management

30%
of those who had a change in management, had a change in outcome*

npj | Genomic Medicine 2018 Feb 9;3:6 www.nature.com/npjgenmed

The NSIGHT1-randomized controlled trial: rapid whole-genome sequencing for accelerated etiologic diagnosis in critically ill infants

Josh E. Petrikin[1,2,3], Julie A. Cakici[4], Michelle M. Clark[4], Laurel K. Willig[1,2,3], Nathaly M. Sweeney[4,5], Emily G. Farrow[1,2,3], Carol J. Saunders[1,3,6], Isabelle Thiffault[1,3,6], Neil A. Miller[1], Lee Zellmer[1], Suzanne M. Herd[1], Anne M. Holmes[2], Serge Batalov[4], Narayanan Veeraraghavan[4], Laurie D. Smith[1,3,7], David P. Dimmock[4], J. Steven Leeder[2,3] and Stephen F. Kingsmore[4]



Near term cost savings outweigh cost of rWGS testing by ~$10K / patient

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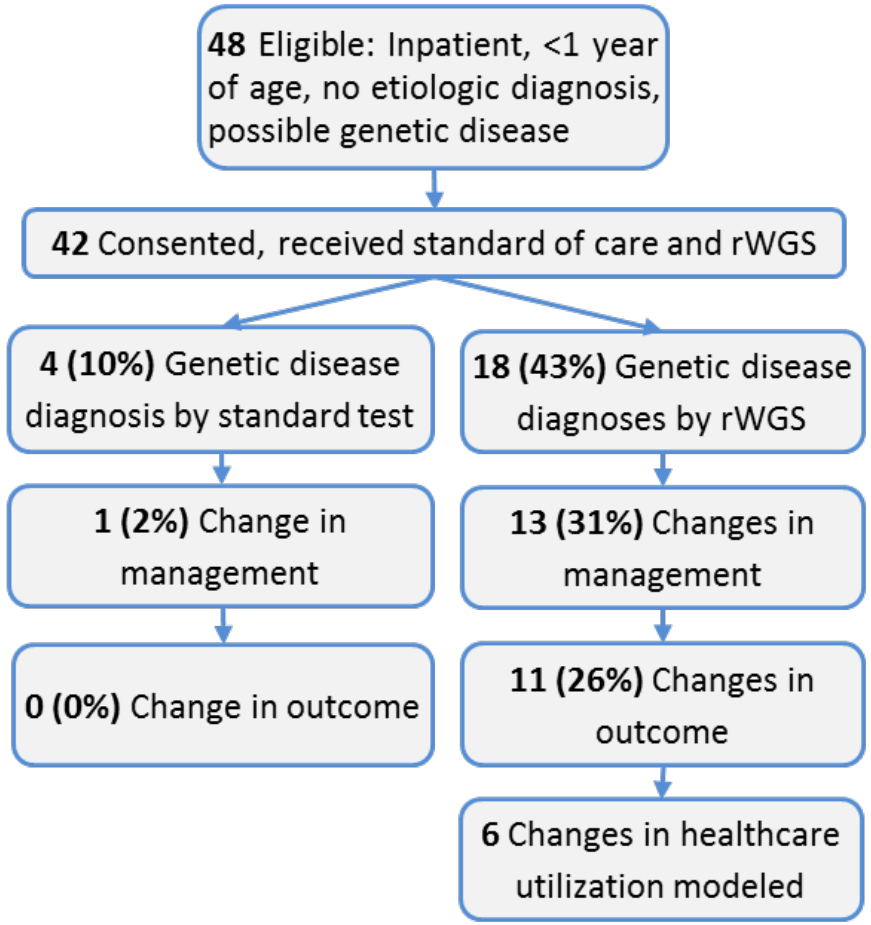

Subject ID	Presentation and modeled change in care	Gene	Time-to-diagnosis, days (method)	Hospital stay, Days	Decreased hospital stay, days (%)	Total cost	Cost avoided
6011	Cholestasis. 1st admision for etiologic Dx	*NPC1*	7 (G)	8	15 (35%)	$ 25,278	$ 27,004
	Cholestasis. 2nd admission for etiologic Dx			15		$ 27,004	
6012	Palliative care started DOL 250	*ARID1B*	26 (G)	250	42 (17%)	$ 1,949,438	$ 327,506
	Palliative care started DOL 292			292		$ 2,276,944	
6014	Hypotonia. Avoided EMG, GA, muscle biopsy	*NEB1*	7 (G)	45	2 (6%)	$ 156,914	$ 9900
Control 1	Electromyogram, GA, muscle biopsy					$ 9900	
6026	Cholestasis and congenital heart disease. Avoided hepatoportoenterosomy	*JAG1*	3 (G)	11	3 (18%)	$ 50,327	$ 131,795
Control 2	Kasai hepatoportoenterostomy					$ 44,451	
Avg cost	Cost of liver transplant × 43% occurrence					$ 87,344	
6041	Seizures. Diagnosis DOL 4	*KCNQ2*	4 (G)	18	41 (69%)	$ 79,675	$ 181,481
	Seizures. Diagnosis DOL 42		42 (S)	59		$ 261,156	
6053	Hypoglycemia. Diagnosis DOL 12	*ABCC8*	7 (G)	10	21 (68%)	$ 59,769	$ 125,514
	Hypoglycemia. Diagnosis DOL 32		28 (S)	31		$ 185,283	
Healthcare savings				398			$ 803,199
Cost of rWGS in 42 families							$ 674,645
Net healthcare savings							$ 128,554

Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization, npj Genomic Medicine (2018) 3:10

NSIGHT2

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When genomic sequencing is limited to children in whom experts suspect a genetic disorder:

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- The total burden of genetic disease is not known
- It is unclear who else might benefit from sequencing
- Care may be inaccessible to infants in a hospital without a genetics service

Primary assumption of NSIGHT2:

- Genetic disorders are suspected to be a key reason for ICU admissions in those without an immediate, identifiable etiology

High clinical utility of rWGS in patients with low suspicion of genetic disease

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Diagnostic rate with suspicion

- 15/25 (60%)
- Consistent with NSIGHT1 and other published series
- Higher positive diagnostic rate / Lower rate of change in care management
- **Two (2)** patients with significant change in management and outcome

Diagnostic rate without suspicion

- 33/189 (17.5%)
- Considerably lower than other series
- Lower positive diagnostic rate / Higher rate of change in care management
- **Eleven (11)** patients with significant change in management and outcome

Historical physician concerns

- Different opinions about whether and how genomic results could be clinically useful
- Potential harms of genomic testing
- Uncertainty about the interpretation of results
- Parental consent and limits on their right to know genomic information

Knapp, B., Decker, C., Lantos, J.D. (2019). Neonatologists' attitudes about diagnostic whole-genome sequencing in the NICU. Pediatrics. 143, 54-7

NSIGHT2 data

Are genomic results clinically useful?

Per physicians

- rWGS was useful in 154 (77%) of 201 infants
- 28% of infants had changes in management as a result of diagnostic genomic sequencing
- Negative tests changed management in 16% of infants

Per parents

- 97% (156) of 161 parents reported that testing was at least somewhat useful

NSIGHT2 data

Potential harms of genomic testing?

Per physicians

- Perceived increased stress in 6 (3%) of 207 cases
- Improved communication with 41% of families

Per parents

- One (0.6%) of 161 parents reported harm from testing due to not receiving positive results
- Decisional regret was low (median 0)

NSIGHT2 data

Uncertainty about the interpretation of results

Per physicians

- Perceived increased confusion for parents in 1 (0.5%) and zero (0) for clinicians in 207 cases
- Led to results not fully understood in 9 (4.5%) of cases

Per parents

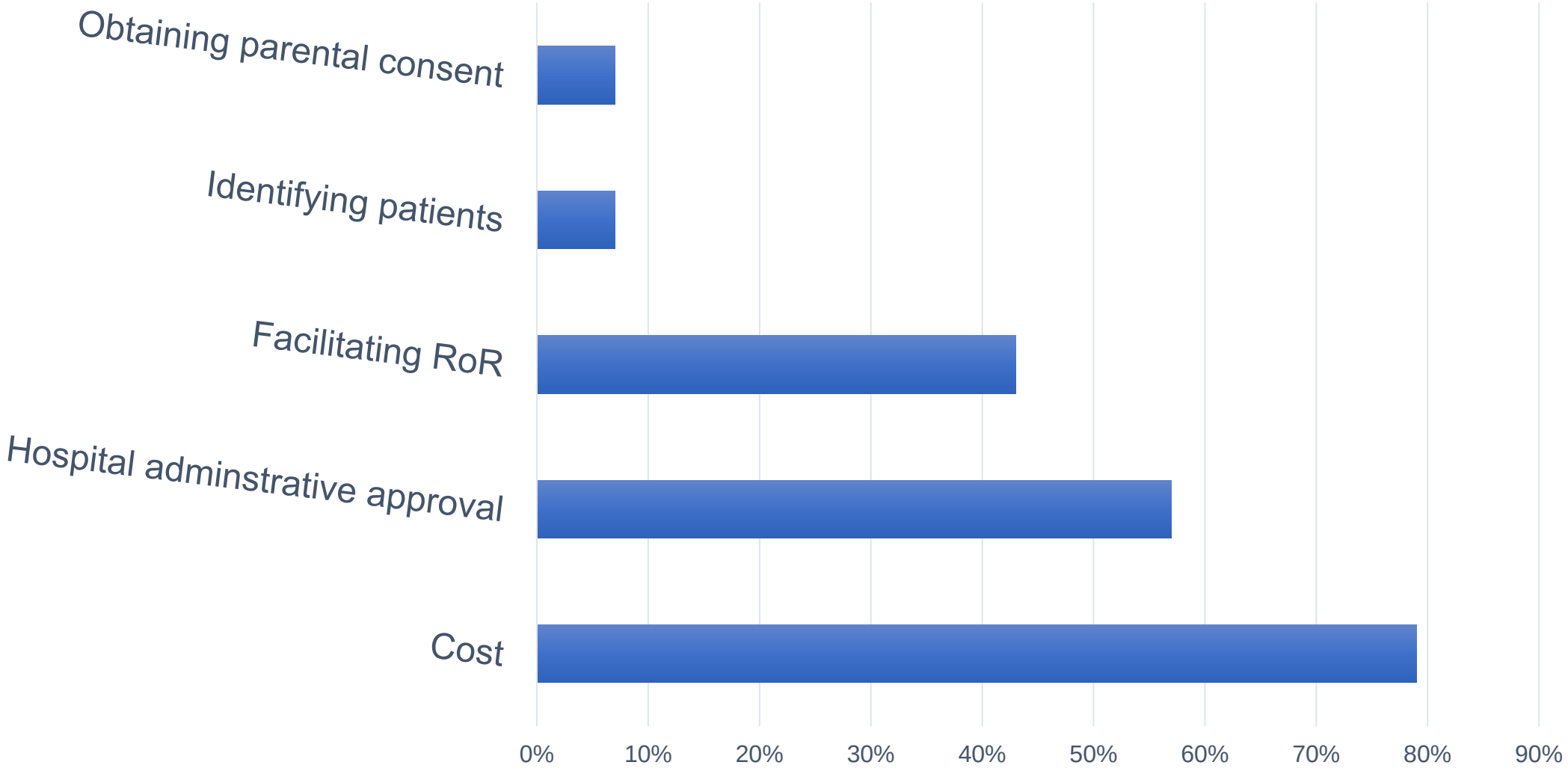
- 79% (127) reported that they understood the results one week after their return
- 80% (129) said that testing made them more knowledgeable about their child's future health
- 66% (106) felt better able to manage their child's potential symptoms

Parental consent and limits on their right to know genomic information

Per parents

- Over 90% reported being adequately informed to consent for diagnostic genomic sequencing

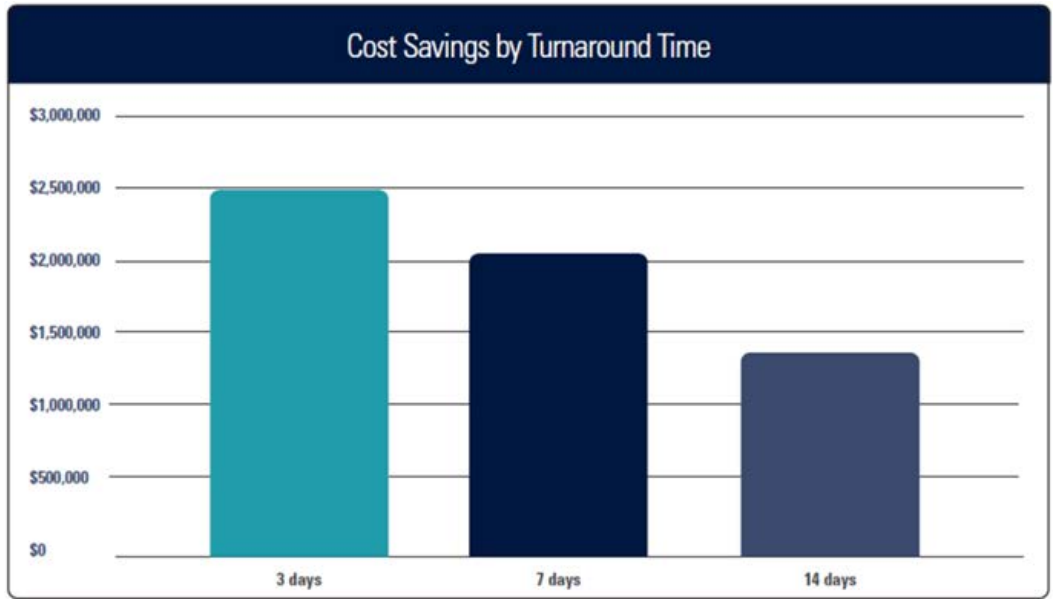
Obstacles to ordering rWGS



Project Baby Bear demonstrated clinical utility and cost-effectiveness of rapid precision medicine

PILOT SITES	# OF BABIES	BABIES DIAGNOSED	BABIES WHOSE CARE WAS CHANGED*	DAYS TO RESULTS**
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*



$2.5M
in healthcare savings

- 513 fewer hospital days
- 11 fewer major surgeries
- 16 fewer invasive diagnostic tests
- Reduction in suffering and unnecessary surgeries and tests

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Initial steps to implement WGS testing for a patient

Initial steps to implementing rWGS testing

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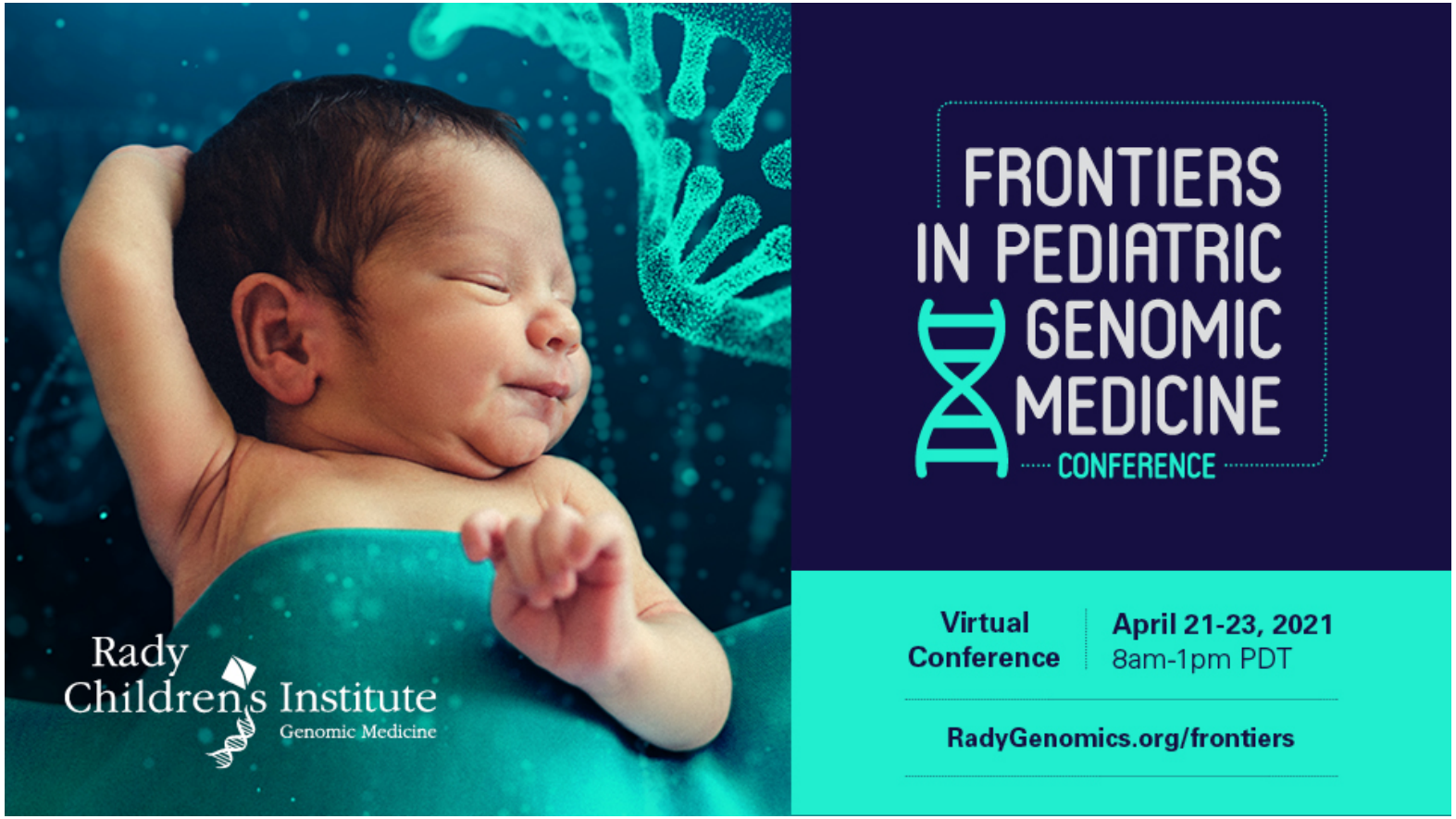
1. Email one of the individuals below to secure a current **Rady's Laboratory Requisition Form (LRF)** from Rady Children's Institute for Genomic Medicine. These individuals will provide support, education, etc., throughout the process.

Kat Chang	KChang1@rchsd.org
Marilyn Brown	MBrown4@rchsd.org
Wes Segal	Wsegal@rchsd.org

   - You may also call the Institute directly at (858) 966-8127.

2. Submit the Laboratory Requisition Form (LRF) to the Institute with pertinent patient clinical notes via fax (858) 966-8092.

3. Send specimen – see requirements below – with a copy of the LRF:
   - For individuals aged 12 months and older, 2-4 ml of whole blood in an EDTA (lavender top) tube: Two (2) tubes of 1-2 ml of whole blood preferred.
   - For infants less than 12 months of age, a minimum of 0.5 ml of whole blood: One (1.0) ml of whole blood preferred.
   - Label each specimen tube with at least two unique identifiers: Name and DOB preferred.
   - Ship specimen tube(s) at room temperature in an insulated container.
   - Submit specimen tube(s) to the Institute within 5 days of collection and store at 4°C within 24 hours of collection through time of packing for shipment.



Rady Children's Institute Genomic Medicine

Free Registration: FrontiersVIP

www.radygenomics.org/frontiers

Process for receiving your CME credit

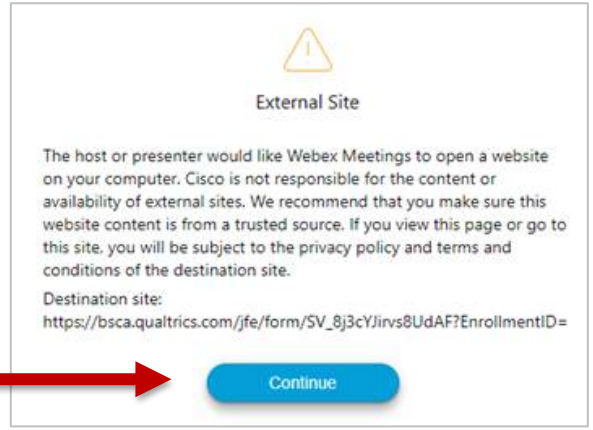
Look for an email from Scripps Health within the next 2-3 days. Scripps Health is Blue Shield's CME provider.

- The **email will provide a link to this webinar's evaluation**, and directions you must follow to complete it and if appropriate, secure your CME credit.
- **First-time users must set up an online CME profile** before you can access the system. The email will provide directions for how to do this. The profile will take approximately 3 minutes to complete.
- **Your profile will house all CME credits earned through Scripps Health,** and you will be able to print and retain certificates.
- Once your profile is established, you can access it for future webinars by entering your login and password.

Remember, you must complete the evaluation to earn your CME.

Please complete the evaluation that displays at the end of the webinar. Your feedback is important!

Click ***Continue*** to access the survey – it takes approximately 3 minutes to complete.



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WGS vs. WES

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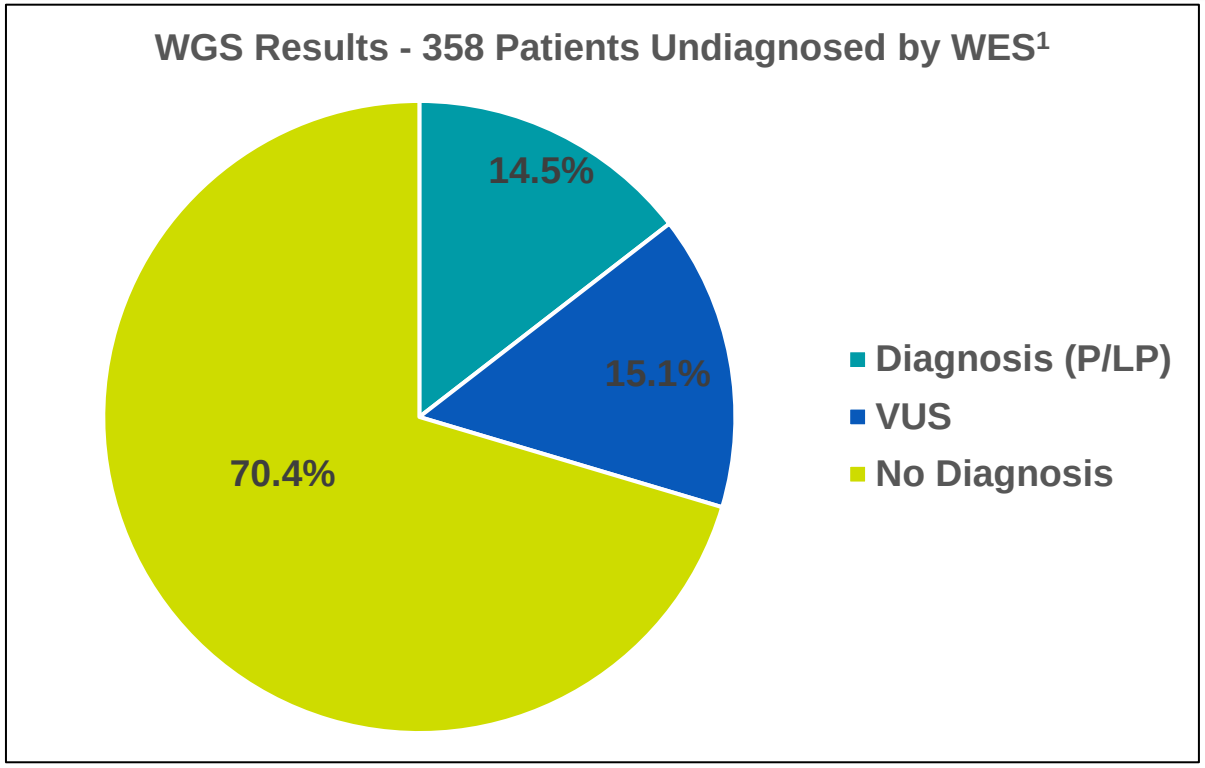
WGS has established itself as having clear benefits over WES

Non-coding variants are often the cause of disease and are not picked up by WES

RCIGM internal data suggests an approximate increased in diagnostic yield of 8-15% from WGS compared to current WES platforms



<u>WGS is an integrated analysis of SNVs, indels, CNVs, SMA, mitochondrial DNA in one test</u>

Examples:

- **Small CNVs** – 30+ cases of CNVs smaller than 30 kB; 15+ cases of CNVs smaller than 5 kB
- **Mitochondrial variants** – 5 diagnoses (Leigh syndrome, Pearson syndrome)
- **Intronic** Variation – 5'UTR in ERCC6 – functionally confirmed; RNU4ATAC – non-coding; Deep intronic in RYR1 (-48) – RNA-seq confirmed
- **Repeat Expansions** – 6 DMPK cases, 1 PHOX2B
- **Mobile Insertion Elements** – ASPA, KARS, other candidates
- **Coverage from PCR-free Genomes** – GREB1L

1. https://www.nature.com/articles/s41431-020-00713-9

WGS vs. WES

- **Small CNVs**
  - 30+ cases of CNVs smaller than 30 kB
  - 15+ cases of CNVs smaller than 5 kB
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