

On an average week in California

9,404

Births

376

Babies born with 1 of
8,000 genetic diseases

55

Babies die before
1st birthday

Most adult disease is either genetic or has onset in childhood



Rapid Precision Medicine

Accelerating access, transforming outcomes

David Dimmock
Sr. Medical Director

www.radygenomics.org

Goal of Rapid Whole Genome Sequencing in the ICU



Youngest Infant: Opportunity for Biggest Impact

Comprehensive genetic testing



Timely, targeted treatment



Better patient outcomes

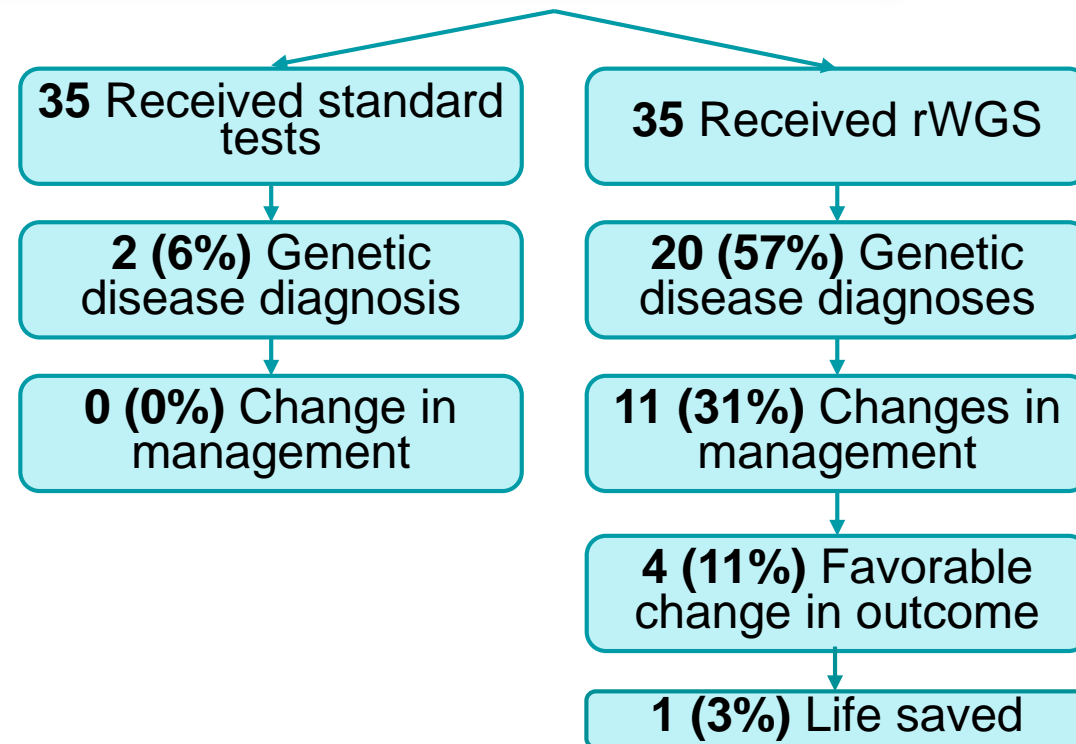
NSIGHT1: First 35 NICU infants to receive rWGS

Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings

Lancet Respir Med. 2015 3:377-87

Laurel K Willig, Josh E Petrikin, Laurie D Smith, Carol J Saunders, Isabelle Thiffault, Neil A Miller, Sarah E Soden, Julie A Cakici, Suzanne M Herd, Greyson Twist, Aaron Noll, Mitchell Creed, Patria M Alba, Shannon L Carpenter, Mark A Clements, Ryan T Fischer, J Allyson Hays, Howard Kilbride, Ryan J McDonough, Jamie L Rosterman, Sarah L Tsai, Lee Zellmer, Emily G Farrow, Stephen F Kingsmore

- Children's Mercy Kansas City
- Selected NICU infants
- Prior to precision medicine mentoring



Case #1 Infant with Seizures

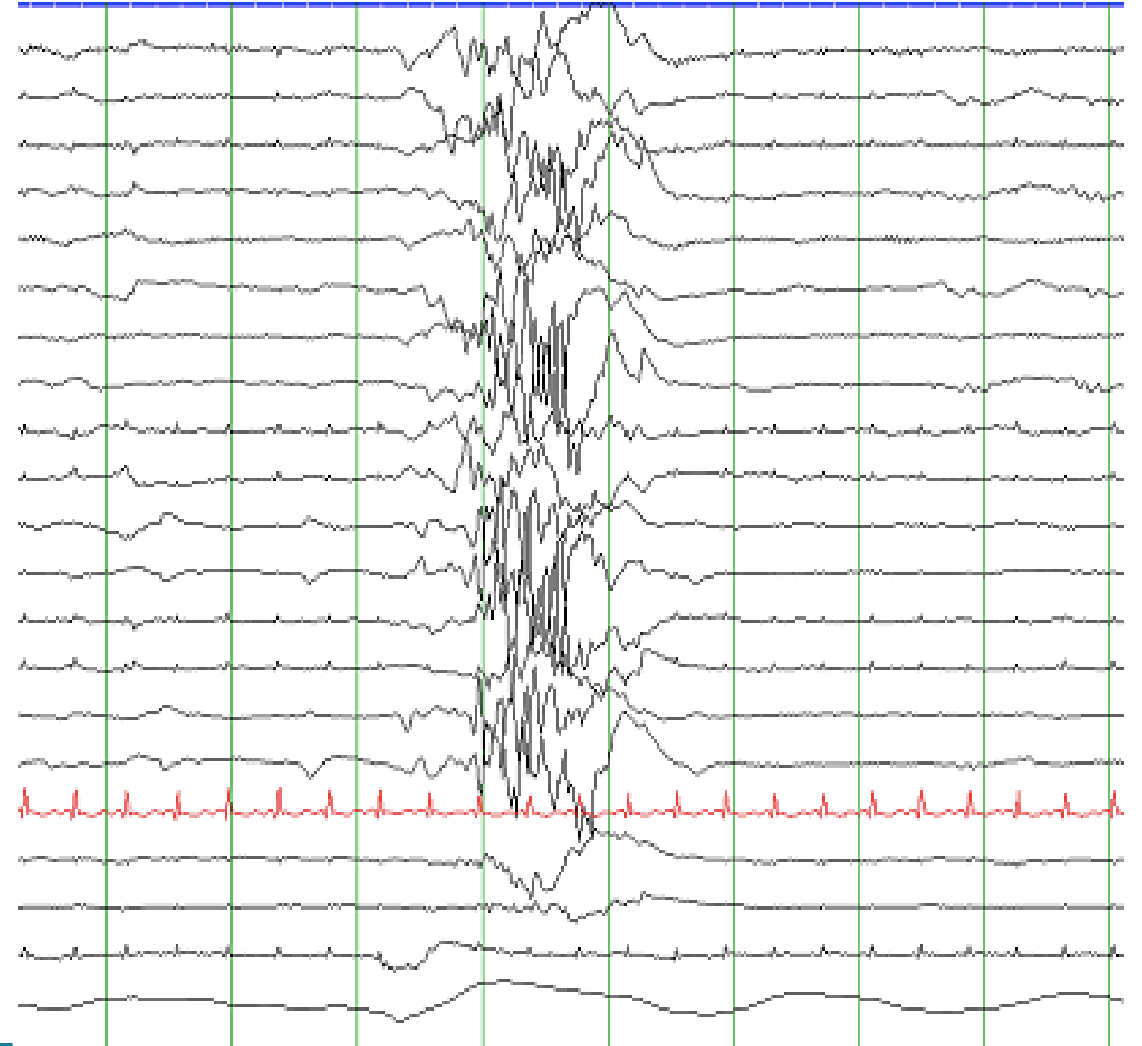
Dec. 2016 Newborn with Seizures

**1-day-old admitted Rady Children's Hospital NICU
within 24 hours of birth**

- **Prior to sequencing**
 - **Treated with top 3 anti-seizure medications**
 - **No impact - seizures continued**
-

DOL 2: Admitted to NICU

- **Tonic and myoclonic seizures**
- **EEG shows burst suppression**
- **Standard anti-epileptics ineffective: phenobarbital, levetiracetam, topiramate**
- **Suspected Ohtahara Syndrome or Early Myoclonic Encephalopathy**



Seizing Baby – Case Evolution

At Rady Children's Hospital NICU

Day 1

Consent,
enrollment
and blood
draw(s)

Day 2

DNA isolation
and library
preparation

Day 3

Sequencing
started

Day 4

Genome
analysis and
interpretation

Variant of Interest Identified

c.875T>C (p.Leu292Pro) in KCNQ2 – de novo

- **Rare variant – not seen in population databases**
 - **Not reported in literature**
 - LP variant found at same position
 - Mutation hotspot in gene
 - **Classified as likely pathogenic**
-

Molecular diagnosis - Ohtahara Syndrome

Targeted medication change

- Promptly stopped seizures on 4th day of life
- Baby went home 12 days after diagnosis - in time for Christmas



Case Comparison 2015

One year earlier, before RCIGM begins rWGS...

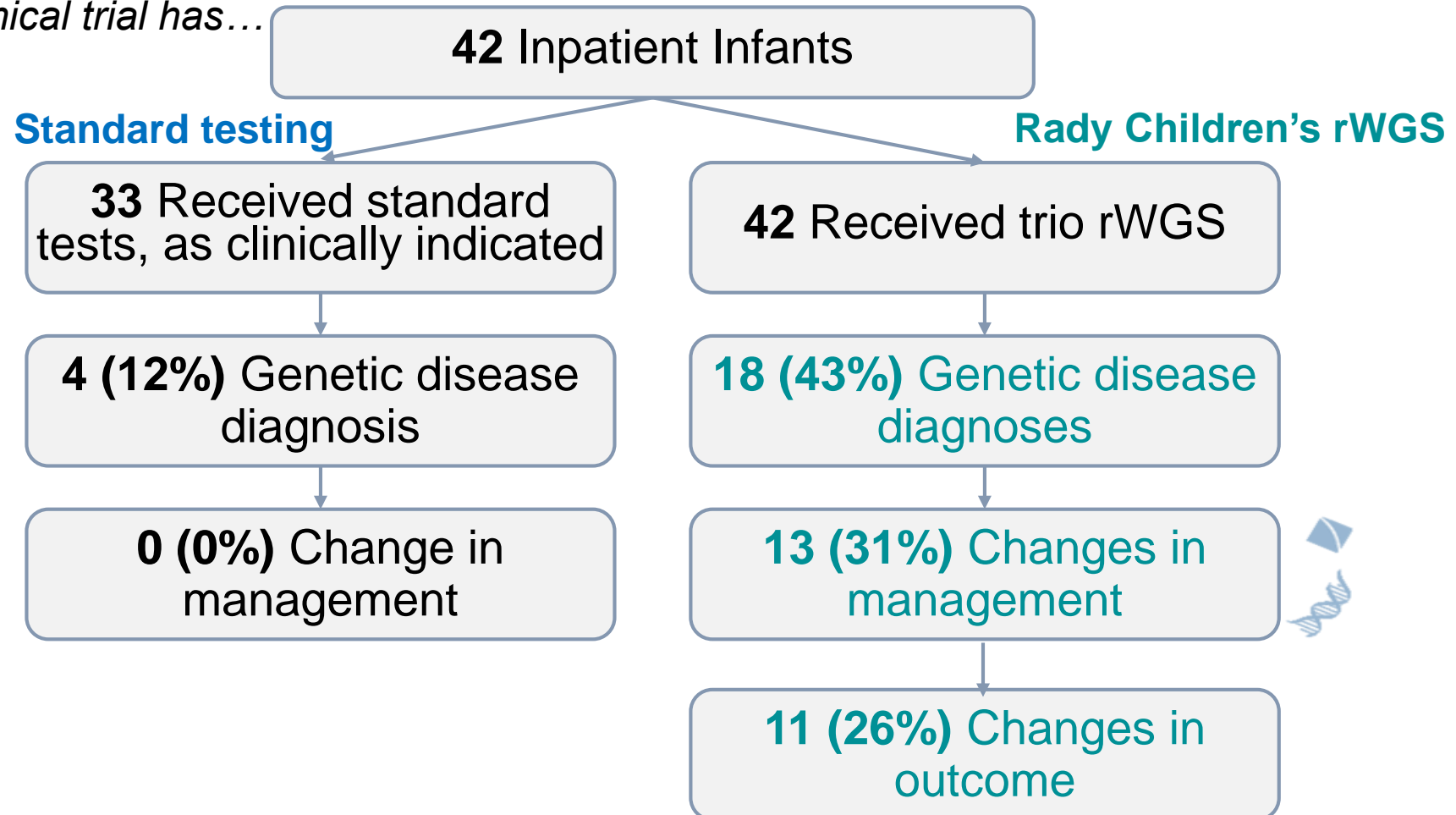
- **Baby with seizures admitted to Rady Children's NICU**
 - Same burst suppression seizures
 - Standard genetic testing
 - Same diagnosis: Ohtahara Syndrome, KCNQ2 mutation

Time to diagnosis: 6 weeks

Result: Neurological devastation

rWGS Enables Precision Care and Improves Outcomes

Subset of our clinical trial has...



Conservative Estimate Shows Near Term Cost Savings Outweigh Cost of rWGS Testing

Subject ID	Presentation and modeled change in care	Gene	Time-to-Diagnosis, Days	Total Cost	Cost Avoided	
6011	Cholestasis. 1 st admission for etiologic Dx (8 days)	NPC1	7	\$ 25,278	\$ 27,004	
	Cholestasis. 2 nd admission for etiologic Dx (7 days)			\$ 27,004		
6012	Palliative care started DOL 250	ARID1B	26	\$ 1,949,438	\$ 327,506	
	Palliative care started DOL 292			\$ 2,276,944		
6014	Hypotonia. Avoided EMG, GA, muscle biopsy	NEB1	7	\$ 156,914	\$ 9,900	
Ctrl 1	EMG, GA, muscle biopsy					
6026	Cholestasis and congenital heart disease. Avoided	JAG1	3	\$ 50,327	\$ 131,795	
Ctrl 2	Kasai hepatoportoenterostomy					
Avg Cost	Cost of Liver Transplant * 43% occurrence			\$ 87,344		
6041	Seizures. Diagnosis DOL 4	KCNQ2	4	\$ 79,675	\$ 181,481	
	Seizures. Diagnosis DOL 42		42	\$ 261,156		
6053	Hypoglycemia. Diagnosis DOL 12	ABCC8	7	\$ 59,769	\$ 125,514	
	Hypoglycemia. Diagnosis DOL 32		28	\$ 185,283		
Healthcare Savings					\$ 803,200	Sequencing Infants only: \$ 256,200
Cost of sequencing all 42 families					\$ 674,645	
Net healthcare savings					\$ 128,555	

Does not include lifetime costs for treated condition, Severe ID Family cost 60K GBP, Disability Services 60K GBP PMID 22339044



NSIGHT2

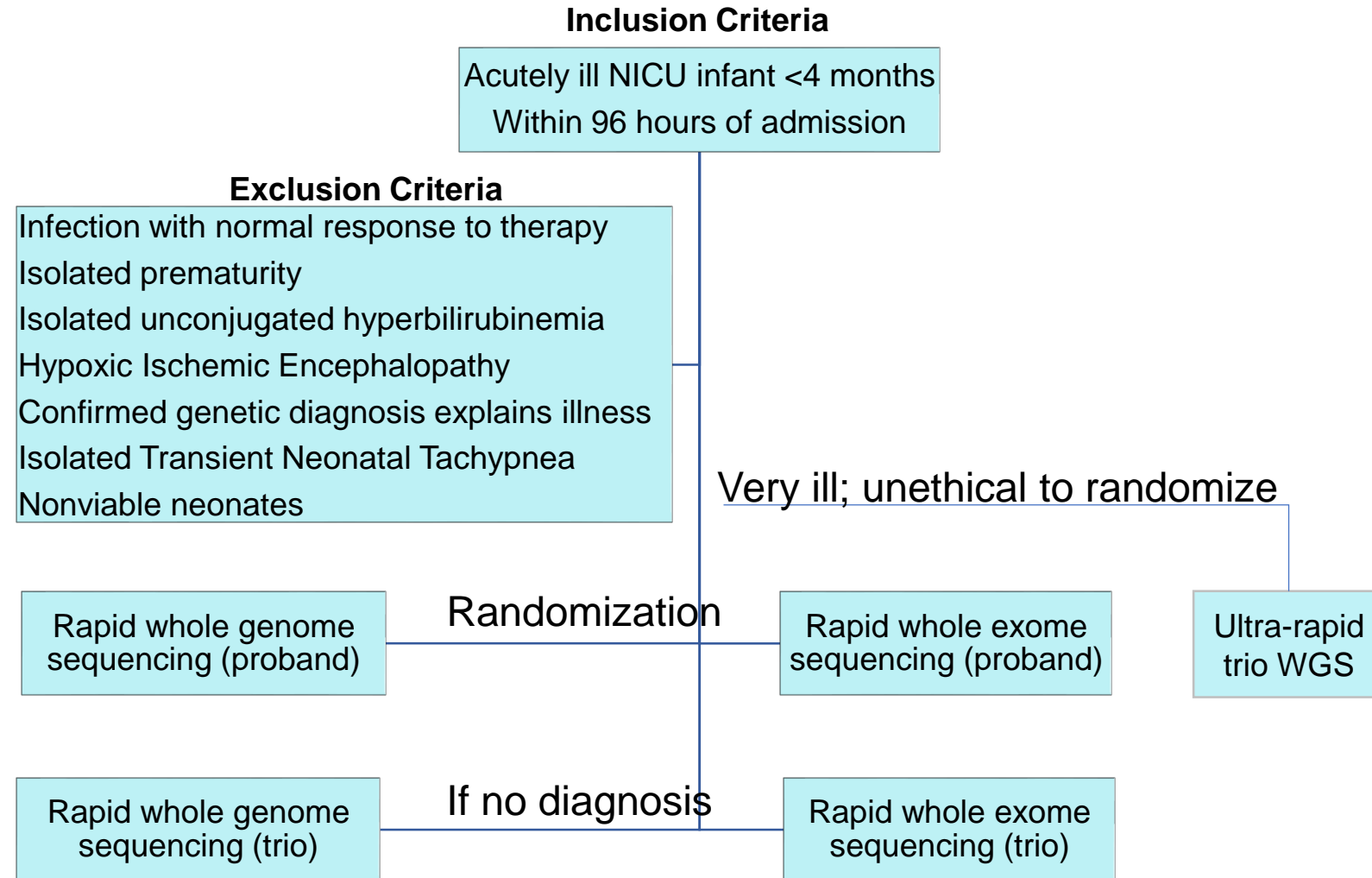
Rady
Children's
Institute
Genomic Medicine

Rady
Children's
Hospital
San Diego

NSIGHT2: Started July 2017

Randomized controlled trial

- **Broad enrollment**
 - Determine prevalence of genetic diseases in a regional NICU
 - Indications for testing/not testing
- **Early enrollment**
 - Maximize potential impact of genomic medicine
- **End-points**
 - Clinical utility, outcomes & cost effectiveness
 - rWGS vs rWES
 - Singleton vs Trio



Strategy/Guidance for Rapid vs Ultra-Rapid

Want to maximize number of patients

Rapid WGS (rWGS)

- Average is ~5 days; positives tend to be quicker but negatives take longer
 - Average interpretation time is 10 hours per case
 - Comprehensive Clinical notes enable rapid TAT
- If findings suggest clinically significant care implications, preliminary report is provided post haste
- All reportable findings are orthogonally confirmed

Ultra Rapid WGS (urWGS)

- May be requested by clinician when patient's status is expected to deteriorate quickly
 - Will load on flow cell on same day if sample received by 8AM
 - Interpretation team will start as soon as alignment is done (weekends, middle of night)
 - Trios are sequenced in UR cases to allow for most efficient path to diagnosis
 - Verbal preliminary reports (when potential care implications are identified) are provided one or two days sooner than in the standard rapid scenario.
-

Prescreening

- Census Review of All Newborns Under 4 Months of Age Admitted to ICU (NICU, PICU, CVICU)
 - 1,022 Patients Prescreened as of July 30, 2018 (~97% of admissions)
 - 52.5% Ineligible
 - 39% Isolated Sepsis/Infection
 - 20% Isolated Prematurity
 - 12% Isolated unconjugated hyperbilirubinemia
 - 7% HIE with Precipitating Event
-

Prescreening

- 485 (47.5%) Eligible Patients
 - 187 (38.6%) Patients Enrolled in NSIGHT2
 - 83 Randomized to rWGS
 - 82 Randomized to rWES
 - 21 Not Randomized- Received Ultra-Rapid WGS
 - 24 Patients Enrolled in General Biorepository Plus Sx-Driven Dx Study
 - Greater than 96 hours
-

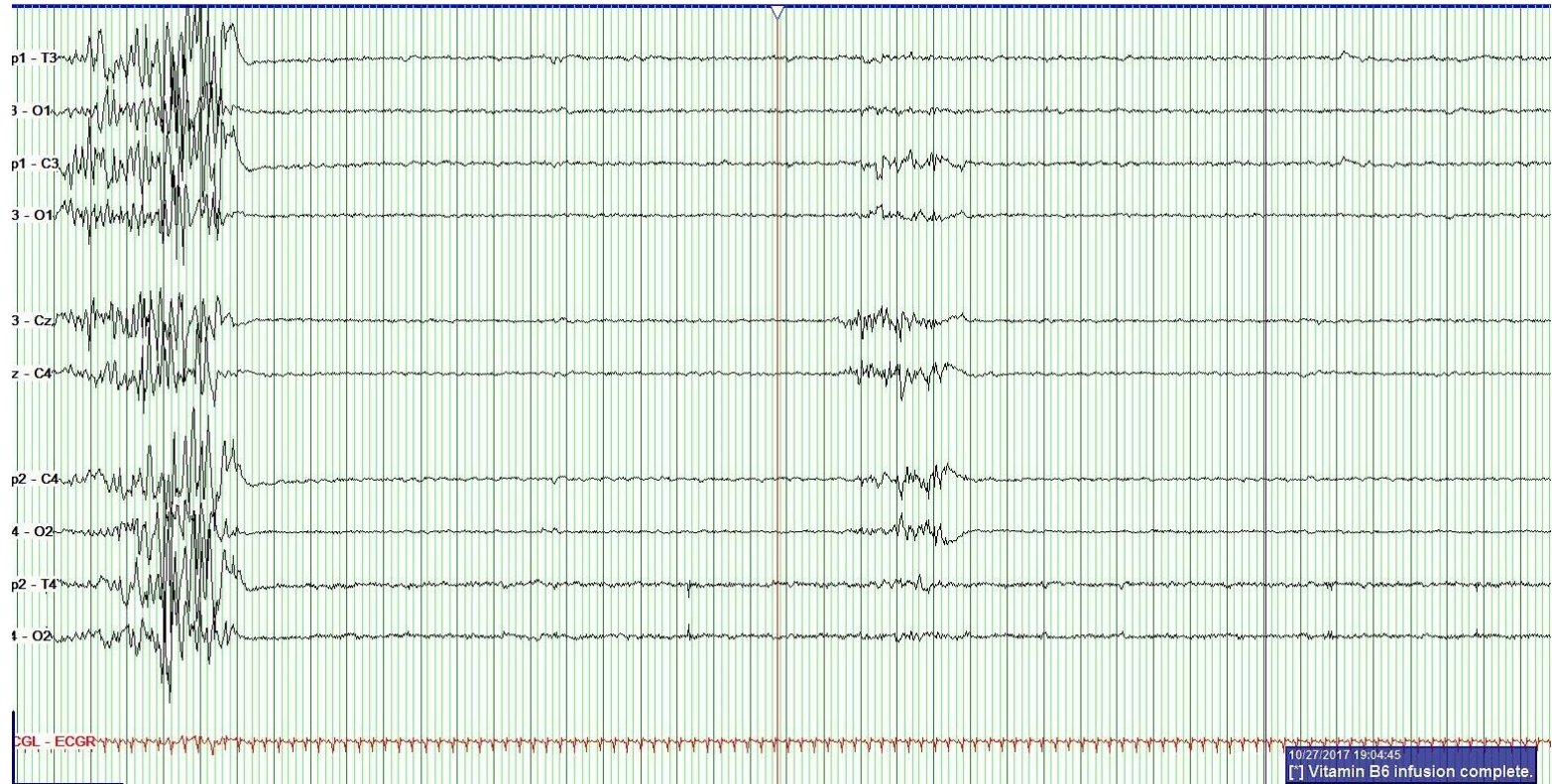
Another Case of Infantile Seizures

The Patient

- 8 day old ♂ admitted from emergency department
 - **PC:** status epilepticus
 - **HPC:**
 - 23 yo G2P1 healthy mother
 - Fetal ventriculomegaly detected by ultrasound during pregnancy
 - Delivery at outside hospital by uncomplicated C-section at 39 1/7 weeks
 - Breast-feeding well, discharged home at day of life 3
-

Initial NICU Workup

- Electroencephalogram – seizures & background burst suppression
 - No change after trial of 100 mg IV pyridoxine
- Brain computed tomography scan: negative for bleed or acute injury
- Infectious workup: negative
- Cerebrospinal fluid lactic acid 6.3 mmol/L (normal 1.1-2.8)
- Serum creatinine kinase 1,195 U/L (normal 13-80, not in rhabdomyolysis range)



Disease Progression Overnight Led to Poor Prognosis Without a Genetic Diagnosis

- “Unfortunately last night was rough with ongoing...multifocal seizures that continued despite...levetiracetam or phenobarbital”
- **Maximal antiepileptic drugs**
 - Worsening seizures
 - No response to phenytoin, carbamazepine
 - Midazolam drip increased until respiratory failure, emergent intubation

“I discussed with his parents the range of outcomes I have seen with Neonatal Burst Suppression encephalopathy which usually entails limited life expectancy and at least moderate to severe developmental disabilities. ”

Provisional Diagnosis

The patient's phenotype might be caused by:

ALDH7A1 ▾

5:125,887,751 ▾

rs121912707

ClinVar

CG

ref: C

missense

p.Glu427Gln

Epilepsy, pyridoxine-dependent

AR

ALDH7A1 ▾

5:125,919,689 ▾

rs121912708

ClinVar

GA

ref: G

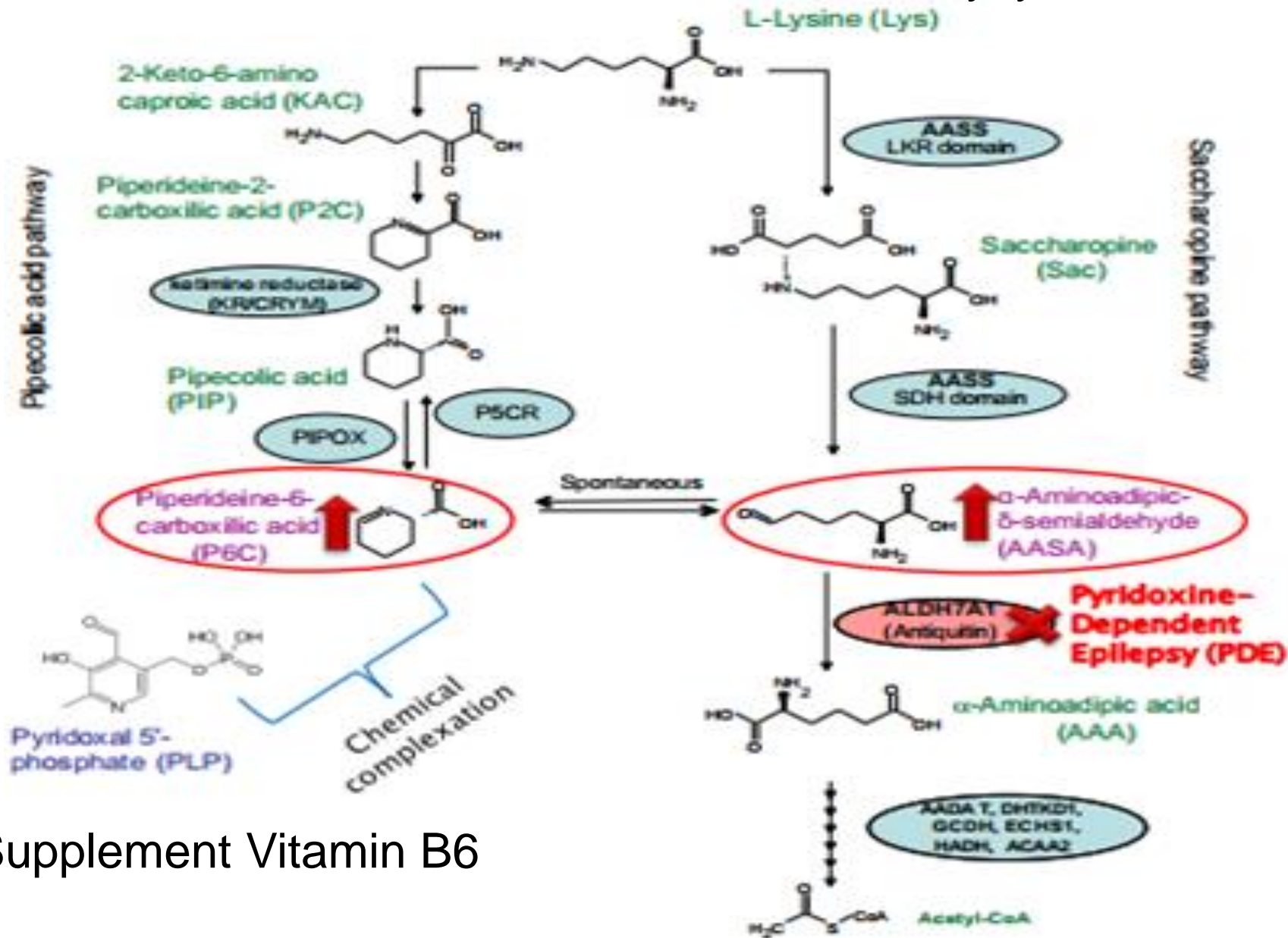
stop gained

p.Arg110*

Epilepsy, pyridoxine-dependent

AR

Restrict dietary lysine



Supplement Vitamin B6

Impact of Diagnosis in 55 Hours

- Triple therapy with pyridoxine, L-arginine supplementation and dietary lysine restriction
- Electroencephalogram normalized
- Seizures stopped
 - All anti-epileptic drugs stopped within 36 hours
 - Extubated within 36 hours
- Discharged home
- Meeting milestones @ 7 months of age

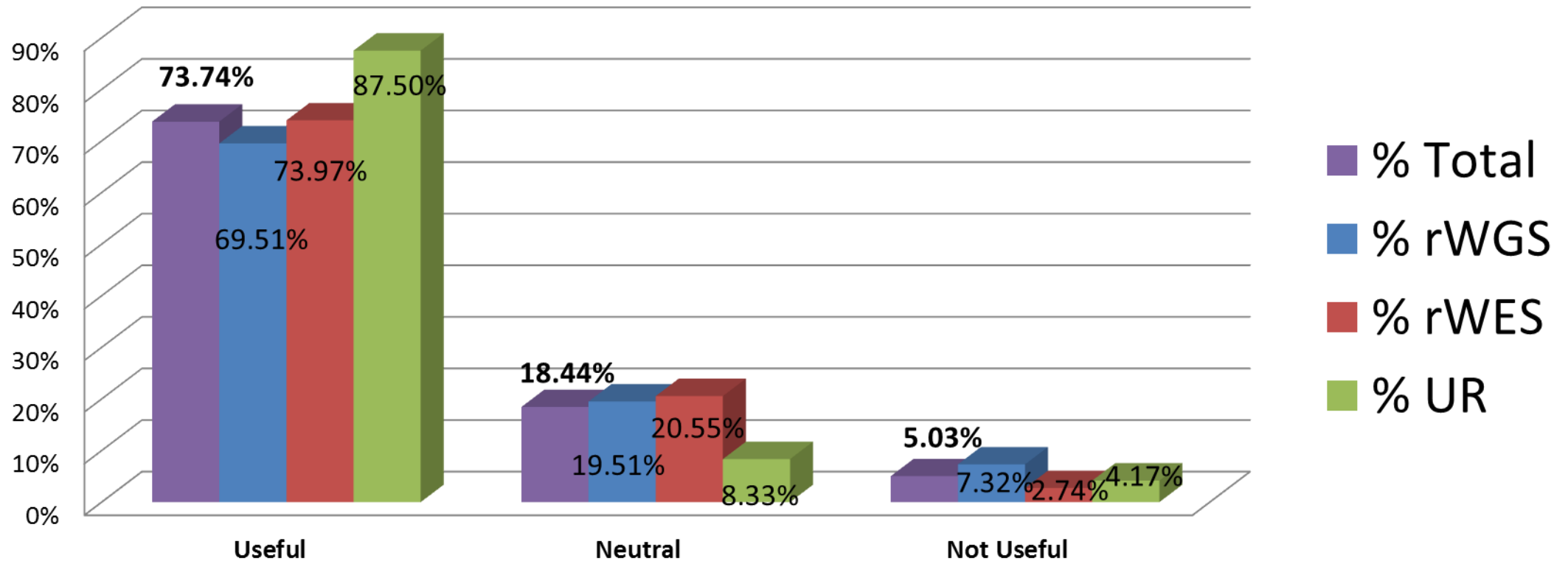


Enrollment Update (9/20/18)

Project	# GN+EX Seq	Genomes	Exomes	Enrollment	Completed Testing	Diagnosed		Change in Management		Break the Glass		
						#	Rate	#	Rate	#	Rate (of Diagnosed)	TAT (days)
External rWGS	152	152	0	94	91	41	45%	31	76%	31	76%	3
Western IRB (rWGS)	133	133	0	55	55	22	40%	18	82%	12	55%	3
RCHSD babies (BloRepos)	483	483	0	223	223	79	35%	53	67%	33	42%	3.3
RCT (WES, WGS)	533	288	245	203	203	48	24%	35	73%	20	42%	4
NeuroGenomics	99	100	0	45	45	13	29%	10	77%	5	38%	6
NeuroOncology	31	31	0	26	24	16	67%	7	44%	1	6%	N/A
Total	1431	1187	245	646	641	219	34%	154	70%	102	47%	3.86

Clinician Survey Post- Results

Clinical Utility of Genomic Testing



Clinician Survey Post- Results

Genomic findings...(select all that apply):	Total	rWGS	rWES	Ultra-Rapid WGS
Allowed avoidance of complications.	15	4	7	4
Enabled targeted treatment that may improve long-term outcomes.	20	6	8	6
Enabled improved communication of outcomes/expectations/prognosis with families.	73	29	28	16
Increased stress for family.	4	1	2	1
Increased confusion for family.	1	1	0	0
Increased confusion among clinical staff.	0	0	0	0
Enabled cessation of additional testing.	35	14	13	8
Required additional testing to confirm diagnosis.	12	7	3	2
Required additional testing to screen for comorbidities.	7	2	3	2
Did not lead to/require additional testing.	100	46	42	12
Resulted in a diagnosis not fully understood at this time.	9	2	4	3
Other	22	10	11	1

Clinician Survey Post- Results

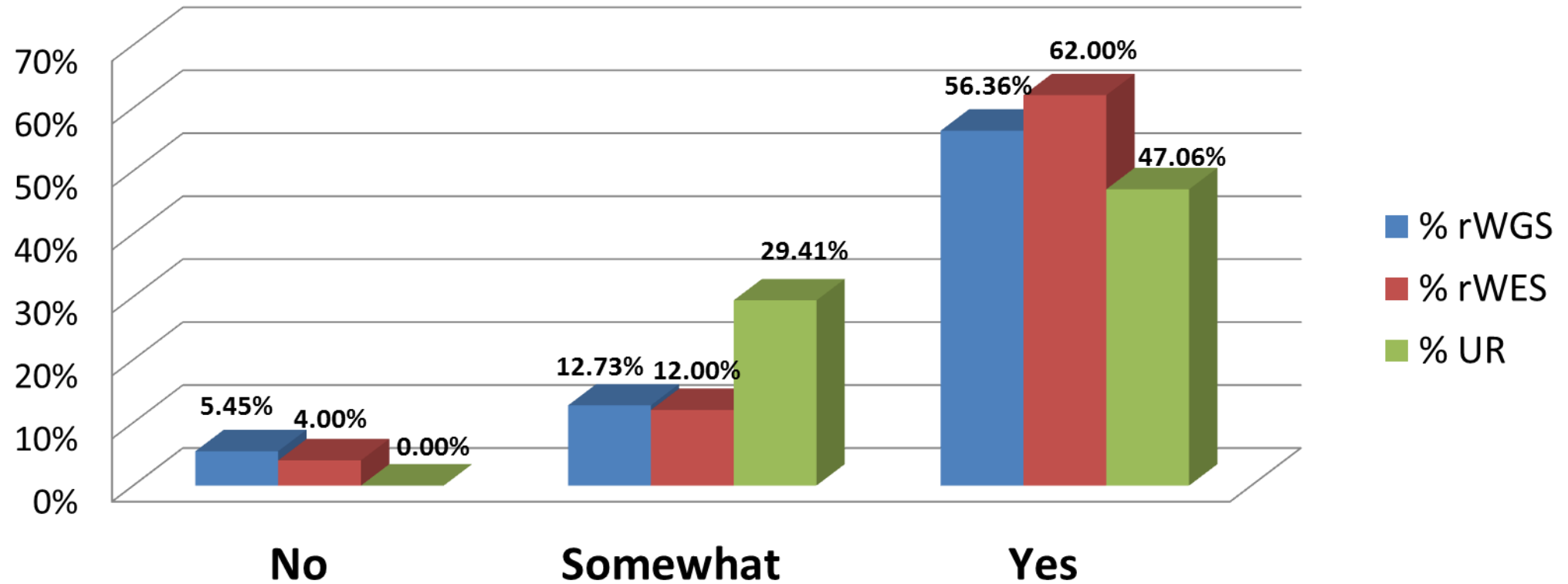
Change in clinical management (select all that apply):	Total	rWGS	rWES	Ultra-Rapid WGS
Surgical intervention added	2	1	1	0
Surgical intervention removed	2	2	0	0
Surgical intervention changed	2	1	1	0
Medication added	7	2	2	3
Medication removed	3	0	0	3
Medication changed	5	0	1	4
Diet changed	4	1	0	3
New specialty service sought	11	3	6	2
Prior specialty service no longer required	2	2	0	0
New imaging sought	3	1	1	1
Prior imaging cancelled	0	0	0	0
New test ordered	8	3	3	2
Prior testing cancelled	0	0	0	0
Screening for additional comorbidities added	12	4	4	4
Screening for additional comorbidities removed	10	6	4	0
Palliative care initiated	2	0	1	1
Palliative care withdrawn	0	0	0	0
Other	85	39	39	7

Clinician Survey Post- Results

	Total	rWGS	rWES	Ultra-Rapid WGS
Other care changes (select all that apply):				
Genetic Counseling to understand risks for the individual or family members recommended.	38	15	16	7
Clinical monitoring of family members recommended.	5	3	1	1
Genetic testing of family members recommended.	8	3	2	3
Family planning counseling recommended.	7	3	3	1
Patient eligible for new research study	0	0	0	0
Patient and/or family members enrolled into a new research study	3	3	0	0
Other	75	38	32	5

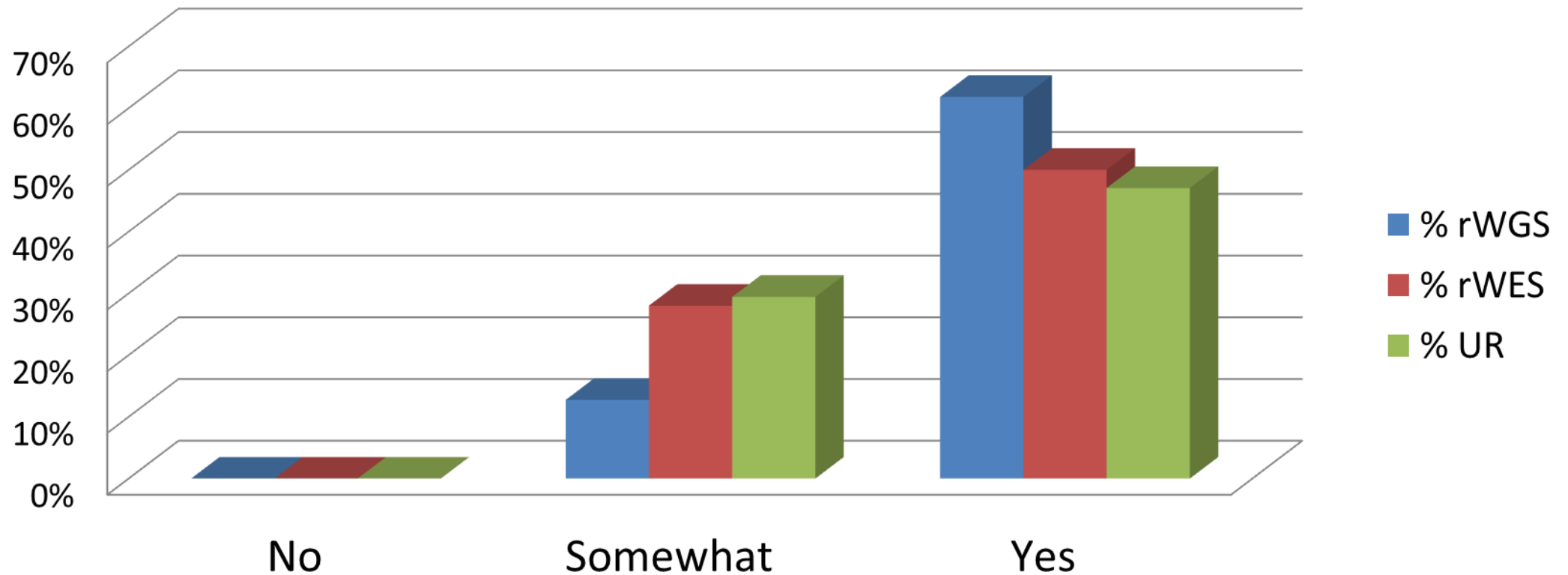
Post-Results Parent Surveys

In general, do you feel your child's genomic sequencing results are useful?



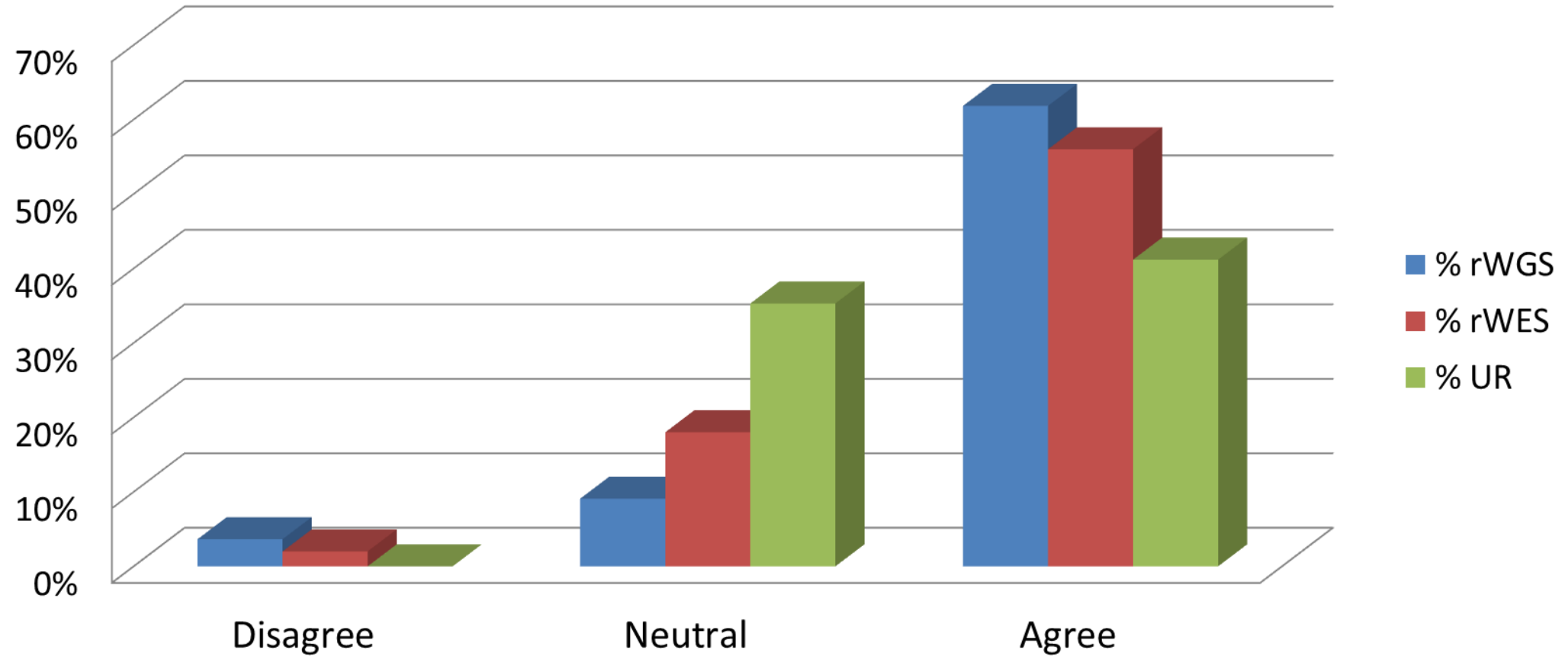
Parent Post-Results

Do you feel you understand your child's genomic sequencing results?



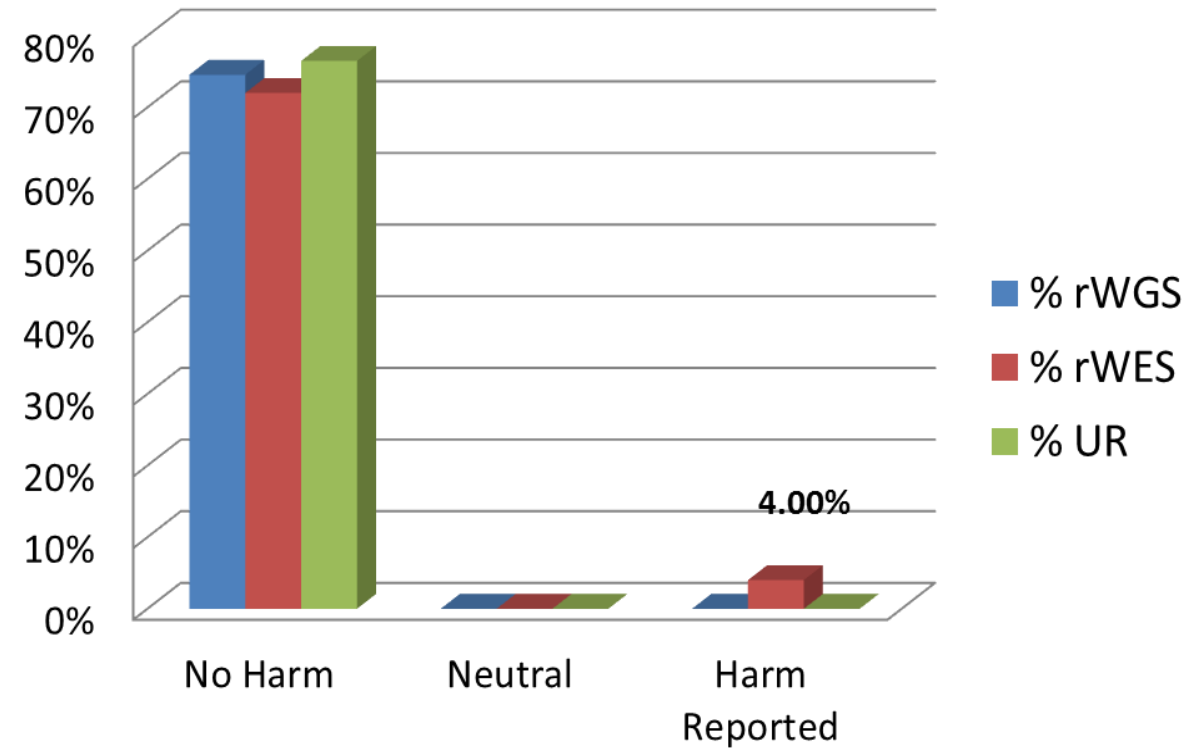
Parent Post-Results

The Choice Did My Child a Lot of Good



Parent Post-Results

The Choice Did My Child a Lot of Harm



	Total	% Total	rWGS	% rWGS	rWES	% rWES	UR WGS	% UR
No Harm	90	73.77%	41	74.55%	36	72.00%	13	76.47%
Neutral	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Harm Reported	2	1.64%	0	0.00%	2	4.00%	0	0.00%

How many patients would benefit?

- RCIGM retained Milliman to provide a benchmark for the number of infants in a standard commercial population that may be good candidates for rapid whole genome sequencing (rWGS) using retrospective claims-based criteria
- Found that about 4% of infants had one or more NICU or PICU admissions, and of these 15% would be potential candidates for rWGS testing
- For the State of California or England & Wales:
 - 400,000 live births/year => 2,400 likely to benefit from rWGS



The Near Future



California Department of
Health Care Services

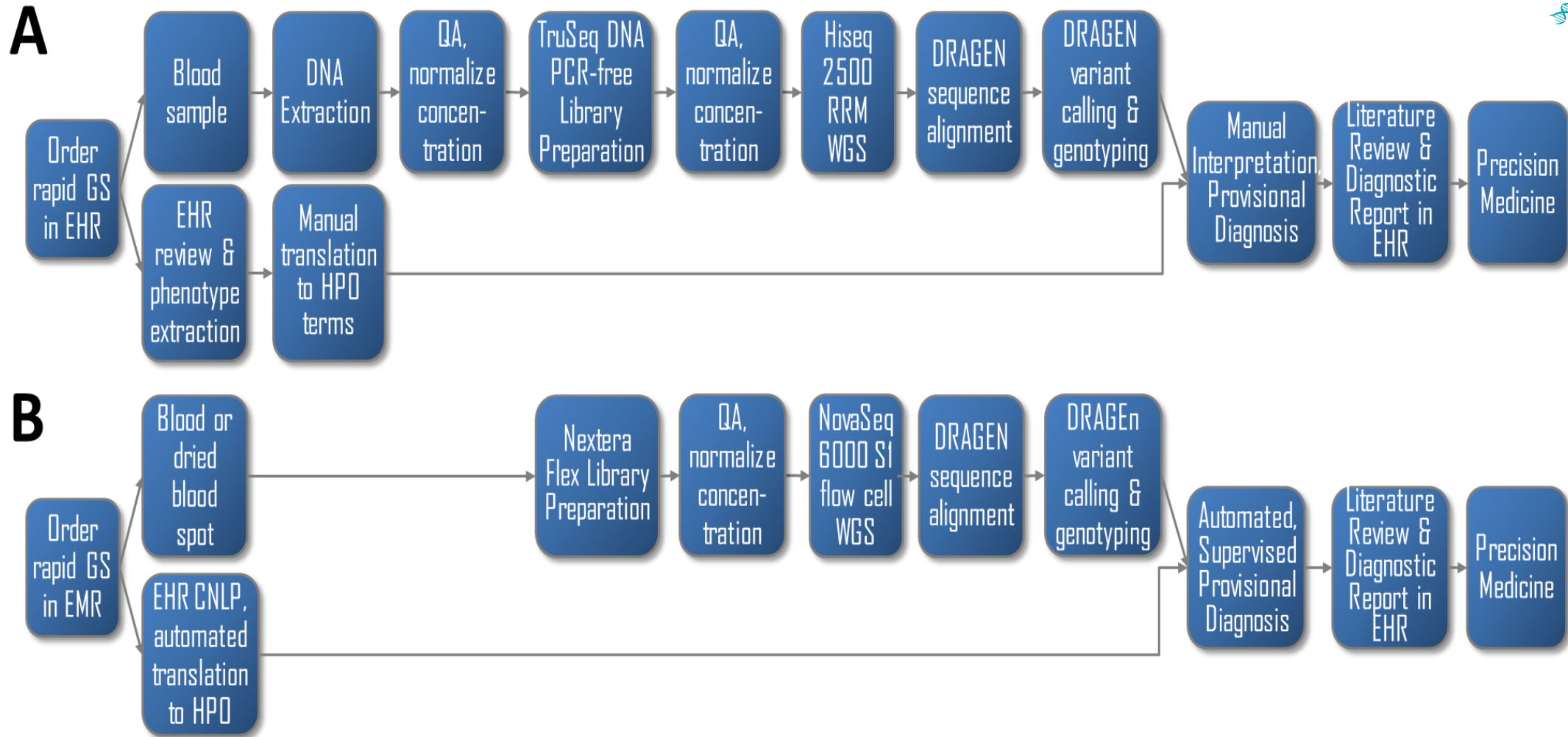
Rady Children's Hospital - San Diego

- **\$2M State appropriation, in collaboration with Illumina**
- **MediCal patients in 4 California Children's Services-certified NICUs and PICUs**
- **Pilot project of rapid whole genome sequencing**
 - **Clinical utility, Cost effectiveness**
- **Press Event September 26th Carly's Garden:**
 - **State Sen. President pro Tem Toni Atkins (D-39)**
 - **Asm. Brian Maienschein (R-77)**
 - **Asm. Todd Gloria (D-78)**
 - **Michael Wilkening, Secretary, California Health and Human Services Agency**

The Government's mandate to NHS England for 2018-19

- Population: 53 million
- July 2018: 70th anniversary of National Health Service
- 100,000 Genomes Project, UK Strategy for Rare Diseases
- Spring 2019: rapid whole genome sequencing of acutely ill children
- Centralized testing, 7 day results





Phenotyping automated by Natural Language Processing of EMR: 20 sec

CLIXENRICH

Welcome back mclark3@rchsd.org (rchsd Administrator)

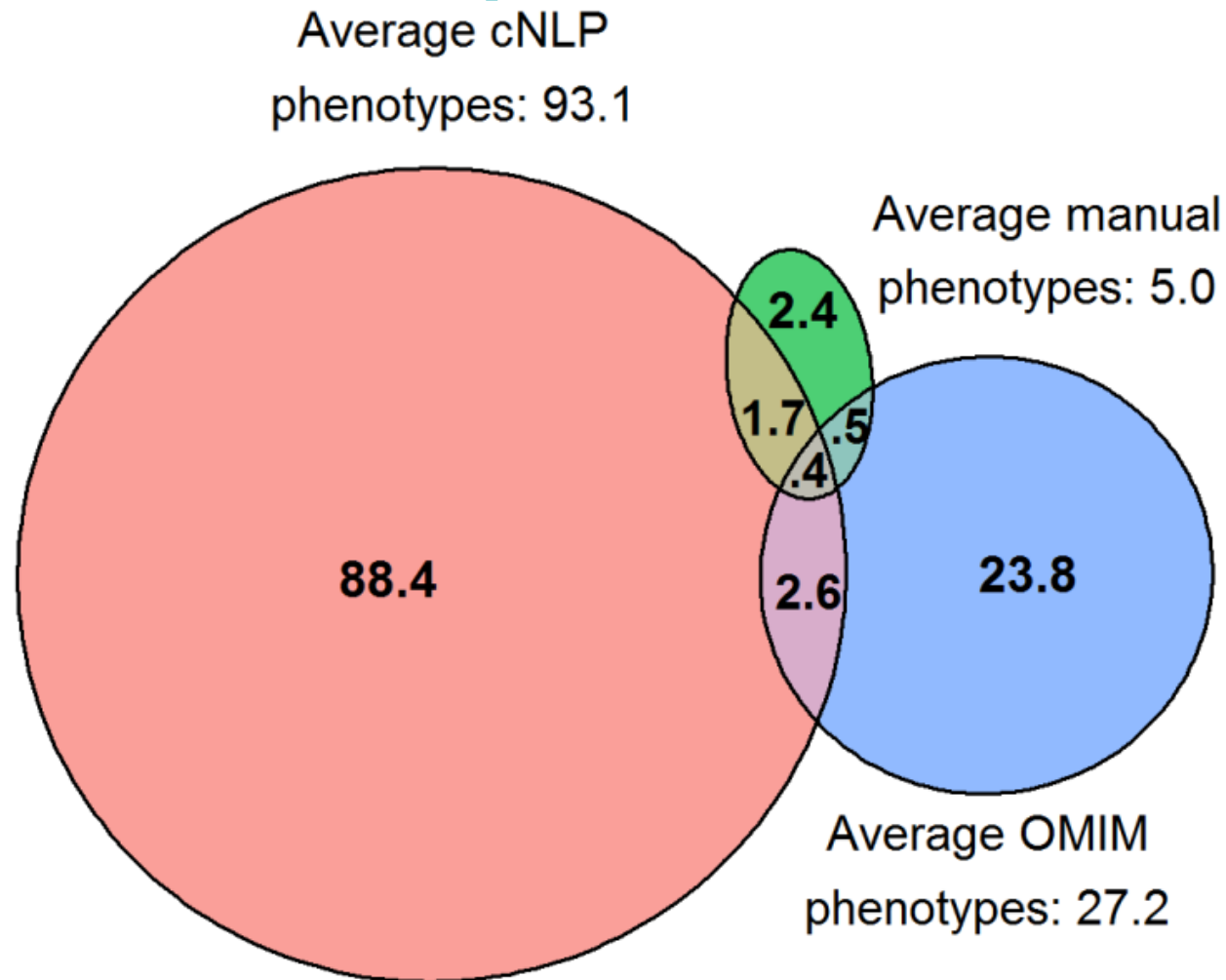
🔔 Clinithink Exchange Dark UI Light UI Fullscreen

- 🏠 Home
- 📄 Import Records
- 👤 Manage Filters
- ▶ Run Jobs
- 🔍 View Results
- 🔧 Interactive Testpad
- 📊 View Status
- 🔒 Manage API Keys
- 🚪 Logout

- nervous system (100%)
- HP0001041 Facial erythema (100%)
- HP0001250 Seizures (100%)
- HP0001298 Encephalopathy (100%)
- HP0001336 Myoclonus (100%)
- HP0001438 Abnormality of abdomen morphology (100%)
- HP0001941 Acidosis (100%)
- HP0001942 Metabolic acidosis (100%)
- HP0002011 Morphological abnormality of the central nervous system (100%)
- HP0002060 Abnormality of the cerebrum (100%)
- HP0002329 Drowsiness (100%)
- HP0002353 EEG abnormality (100%)
- HP0002373 Febrile seizures (100%)
- HP0002521 Hypsarrhythmia (100%)
- HP0002527 Falls (100%)
- HP0002790 Neonatal breathing dysregulation (100%)
- HP0002928 Decreased activity of the pyruvate dehydrogenase complex (100%)
- HP0003128 Lactic acidosis (100%)
- HP0004305 Involuntary movements (100%)

10 mg TID depending on kidney function Step 5: Reload levetiracetam 20 mg/kg and then maintenance of 45 mg/kg divided BID or 15 mg TID depending on kidney function Step 6 Reload Dilantin 20 mg/kg and start IV maintenance 5 mg/kg/day divided BID for a goal level of 10 Step 7: Initiate a midazolam drip Step 8: Consider topiramate or lacosamide 2) Metabolic testing: Urine organic acids Serum amino acids Plasma acylcarnitine profile Ammonia, lactate From a metabolic standpoint, there are a number of time-dependent, treatable conditions that need to be addressed including: 1) Vitamin dependent epilepsies including Pyridoxine-dependent seizures, Pyridoxal 5 phosphate dependent seizures and biotinidase deficiency. --Children with these conditions and others need specific vitamin supplementation as soon as possible to prevent permanent brain injury (for example, pyridoxine, P5P, biotin) 2) Transporter disorders including GLUT1 deficiency and cerebral folate deficiency. --Children with GLUT1 need the ketogenic diet started as soon as possible to prevent long-term disability. Folate supplementation may help children with cerebral folate deficiency. CSF glucose and folate levels should be sent in children with refractory epilepsy and no identified cause of seizures 3) Amino and organic acidopathies, most notably maple syrup urine disease. --Dietary avoidance may be required in some conditions. Metabolic testing including newborn screening, urine organic acids, plasma amino acids, serum acylcarnitine profile are needed in all children with seizures and no identified cause. 4) Mitochondrial disorders, most notably Leigh's disease and pyruvate dehydrogenase deficiency. All children with seizures and no identified cause should have serum and CSF lactate and pyruvate testing. Treatment may include vitamins and supplements such as co-enzyme Q10. 5) Urea cycle defects. All children with seizures and no identified cause should have serum ammonia testing. Dietary avoidance may be needed. 6) Neurotransmitter disorders. All children with refractory seizures and no identified cause should have CSF neurotransmitters sent, including CSF biopterin. 3) Genetic testing: CGH, epilepsy genetic panel, genetics institute From a genetic standpoint, there is a growing list of neonatal onset epilepsies that have been identified, some with specific treatments. Recent series have found diagnosable genetic epilepsies in 12% (EuroEPINOMICS-RES Consortium, Am J Hum Gen, 2014), 18% (Trump et al, J Med Genet 2016), 23% (Moller et al, Mol Syndromol, 2016), 28% (Mercimek-Mahmutoglu et al, Epilepsia 2015), to 33% (Heibig et al, Genet Med, 2016) in patients with no clear provoking cause of seizures. Many of those source report their highest yield in neonatal seizures: in the Trump study, the overall hit rate was 18% but the neonatal hit rate was 39%, while the Hieberg study had a hit rate of 43% in children with epileptic encephalopathy. Most common were the SCN family of mutations, STXBP1 and the KCNQ family of genetic epilepsies. Most importantly, identification of these genetic epilepsies can have profound implications for immediate and long-term clinical care. For example, one review (Poduri et al, Nat Rev Neurol, 2014) included the table below showing how specific mutations influence care: From our experience and discussion with other providers (especially utilizing data from Dr. Poduri), we recognize AT LEAST the following mutations that may influence care: Gene Treatment ALDH7A1 Pyridoxine GRIN2A Memantine (potentially) KCNQ2 Ezogabine (potentially) KCNT1 Quinidine (potentially) PLCB1 Inositol PNPO Pyridoxal-5-phosphate PRRT2 Carbamazepine SCN1A Avoid phenytoin and lamotrigine SCN2A High-dose phenytoin SCN8A High-dose phenytoin SLC2A1 Ketogenic diet TSC1/TSC2 Everolimus (and potentially other migration disorders) 4) MRIS If this testing is negative, we will consider LP for CSF glucose and neurotransmitter work-up 6) We will continue to monitor Jeffrey Gold, MD, PhD UCSD and RCHSD Pager: 858-494-2196

In most NICU patients, there is little overlap between the observed clinical features and the classical textbook description of that disease



Sample/Library Prep (hours)	3:20	2:55	2:24	2:22	2:10	23:54	2:12	22:05	2:13	15:42	2:31	18:30	3:30	10:10	4:30	12:10
NovaSeq Loading (hours)	0:20	0:17	0:16	0:20	1:38*	0:20	0:29	0:22	0:30	0:53	0:15	2:30	0:45	0:35	1:00	1:00
2x101 nt Sequencing (hours)	15:36	15:31	15:34	15:27	15:26	24:13	15:25	24:08	15:21	22:44	15:17	33:36	15:17	21:07	15:19	22:46
1 ⁰ & 2 ⁰ Analysis (hours)	1:03	1:02	0:59	0:59	1:07	3:05	1:00	1:57	1:01	2:30	1:02	2:30	1:02	2:30	1:09	2:25
3 ⁰ Analysis Processing (hours)	0:06	0:05	0:07	0:05	0:06	0:15	0:08	0:14	0:06	0:15	0:05	0:15	10:28**	0:16	0:06	0:16
Total (hours)	20:25	19:56	19:20	19:14	20:42	56:03	19:29	48:46	19:11	42:04	19:10	57:21	31:02	34:38	22:04	38:37

