On an average week in California

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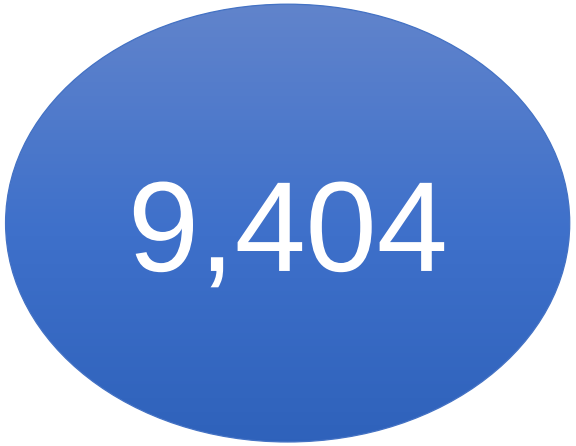

Births

Babies born with 1 of 8,000 genetic diseases

Babies die before 1st birthday

Most adult disease is either genetic or has onset in childhood

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Rapid Precision Medicine

Accelerating access, transforming outcomes

David Dimmock
Sr. Medical Director

www.radygenomics.org

Goal of Rapid Whole Genome Sequencing in the ICU

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Youngest Infant: Opportunity for Biggest Impact

Comprehensive genetic testing

↓

Timely, targeted treatment

↓

Better patient outcomes

NSIGHT1: First 35 NICU infants to receive rWGS

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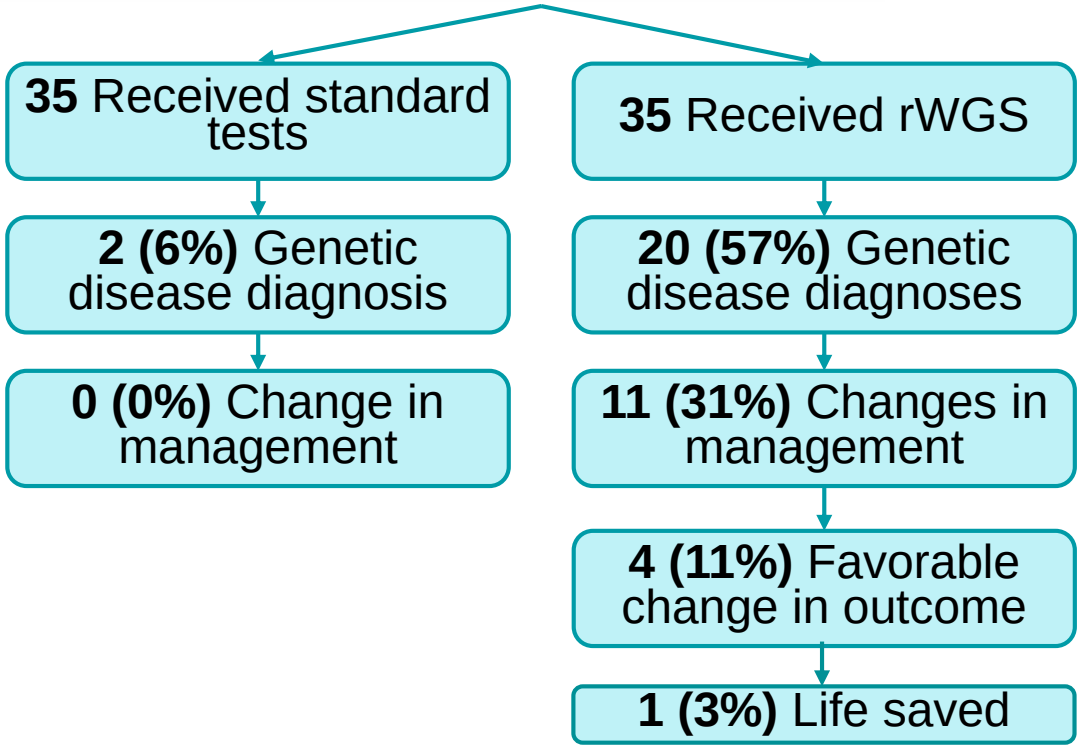
Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings

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



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Case #1 Infant with Seizures

Dec. 2016 Newborn with Seizures

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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

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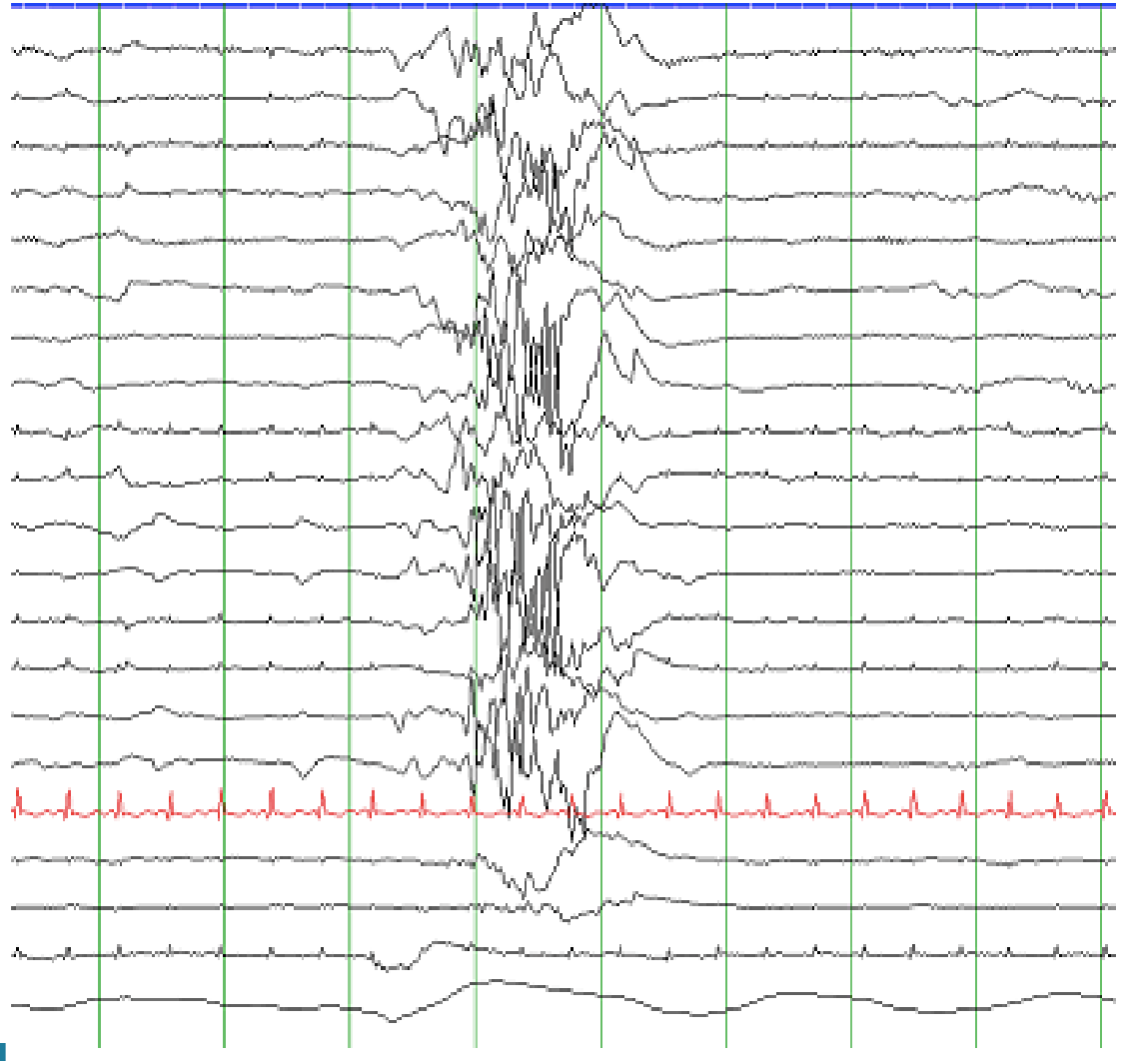
- **Tonic and myoclonic seizures**
- **EEG shows burst suppression**
- **Standard anti-epileptics ineffective: phenobarbital, levetiracetam, topiramate**
- **Suspected Ohtahara Syndrome or Early Myoclonic Encephalopthy**



Seizing Baby – Case Evolution

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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

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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 Sydrome

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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

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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

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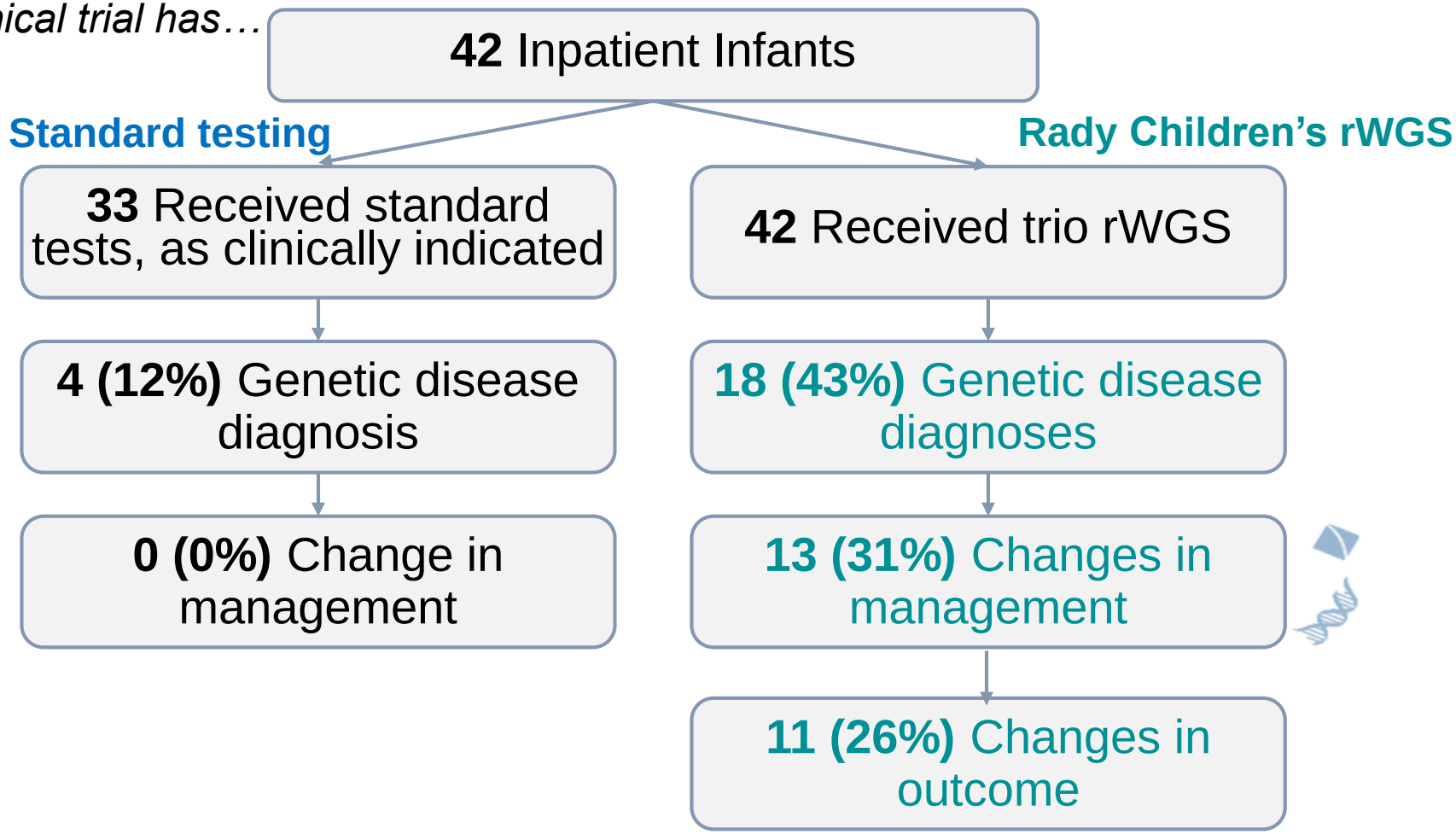
Subset of our clinical trial has…



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

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Subject ID	Presentation and modeled change in care	Gene	Time-to-Diagnosis, Days	Total Cost	Cost Avoided
6011	Cholestasis. 1st admision for etiologic Dx (8 days)	*NPC1*	7	$ 25,278	$ 27,004
	Cholestasis. 2nd 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	
Ctrl 2	Kasai hepatoportoenterostomy			$ 44,451	$ 131,795
Avg Cost	Cost of Liver Transplant * 43% occurrence			$ 87,344	
6041	Seizures. Diagnosis DOL 4	*KCNQ2*	4	$ 79,675	
	Seizures. Diagnosis DOL 42		42	$ 261,156	$ 181,481
6053	Hypoglycemia. Diagnosis DOL 12	*ABCC8*	7	$ 59,769	$ 125,514
	Hypoglycemia. Diagnosis DOL 32		28	$ 185,283	
Healthcare Savings					$ 803,200
Cost of sequencing all 42 families					$ 674,645
Net healthcare savings					$ 128,555

Sequencing Infants only:

$ 256,200

$ 547,000

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

NSIGHT2

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Genomic Medicine

Rady Children's Hospital San Diego

NSIGHT2: Started July 2017

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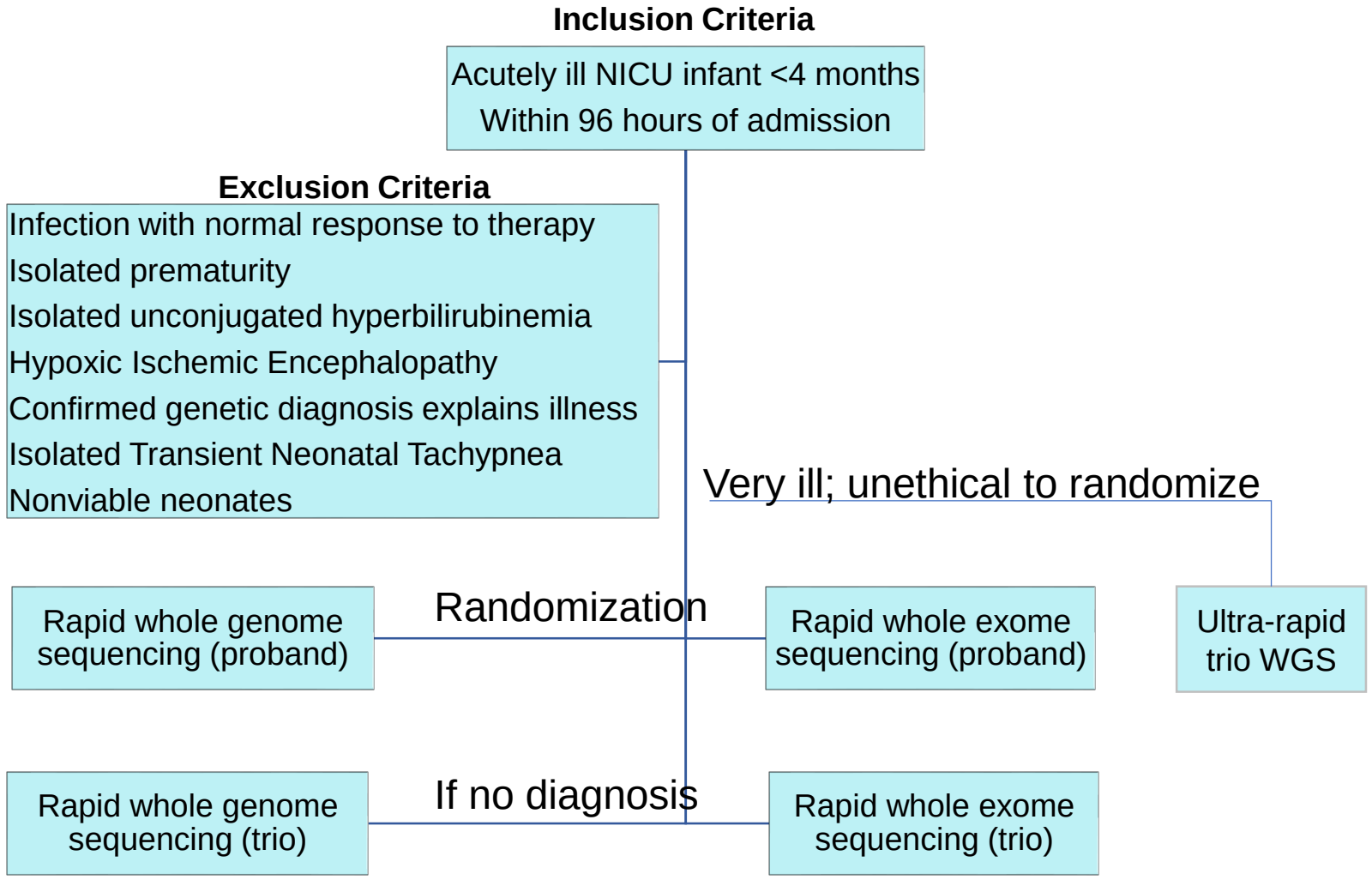
Randomized controlled trial

- **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

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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 starts 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

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- 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

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- 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

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The Patient

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- 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

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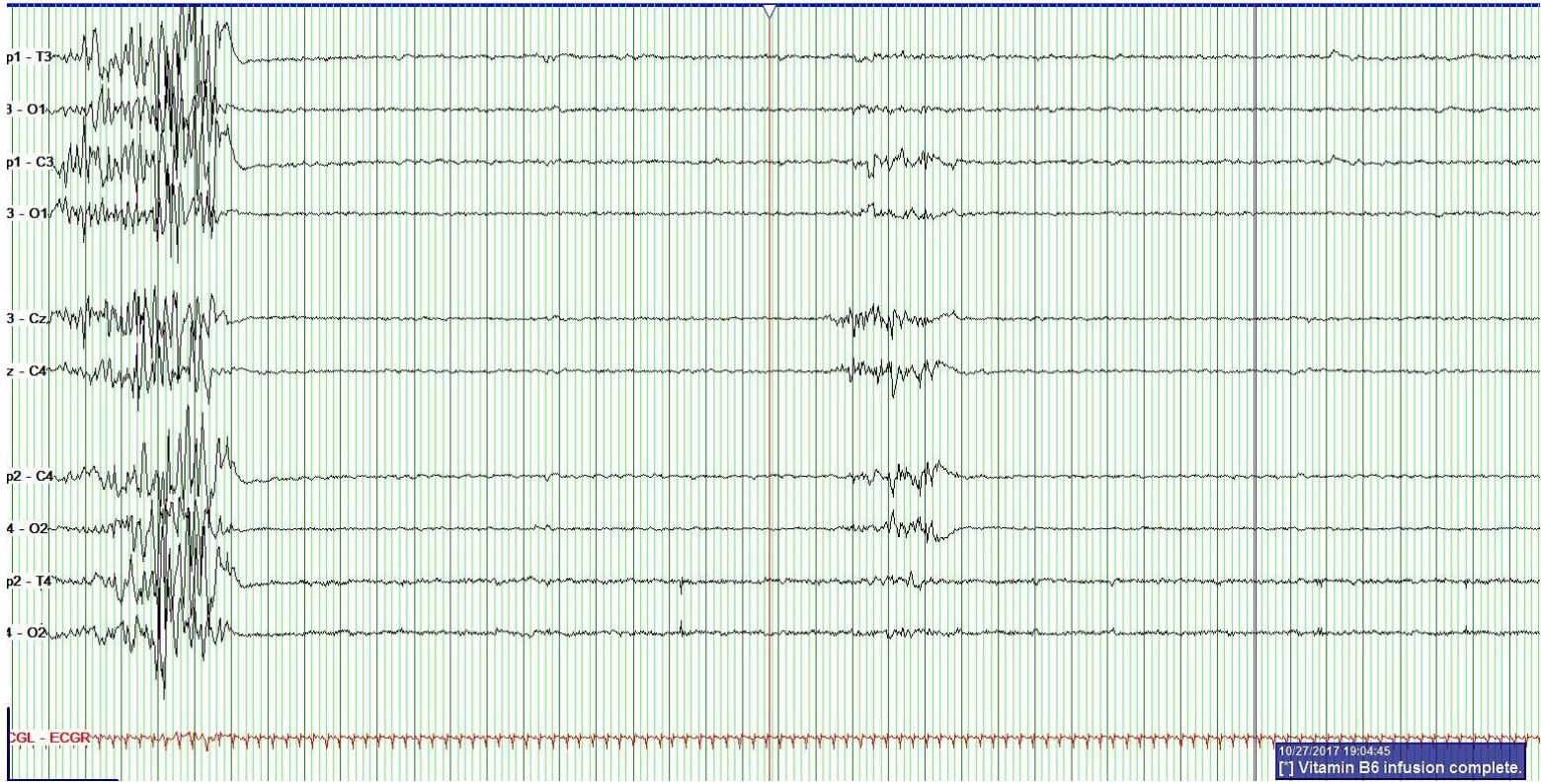
- Electroencephalogram – seizures & background burst supppression
  - No change after trial of 100 mg IV pyridoxine
- Brain computed tomography scan: negative for bleed or acute injury
- Infectious workup: negative
- Cerebrospinal fluid lactic acid 6.3 mmol/L (normal 1.1-2.8)
- Serum creatinine kinase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



Disease Progression Overnight Led to Poor Prognosis Without a Genetic Diagnosis

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- "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

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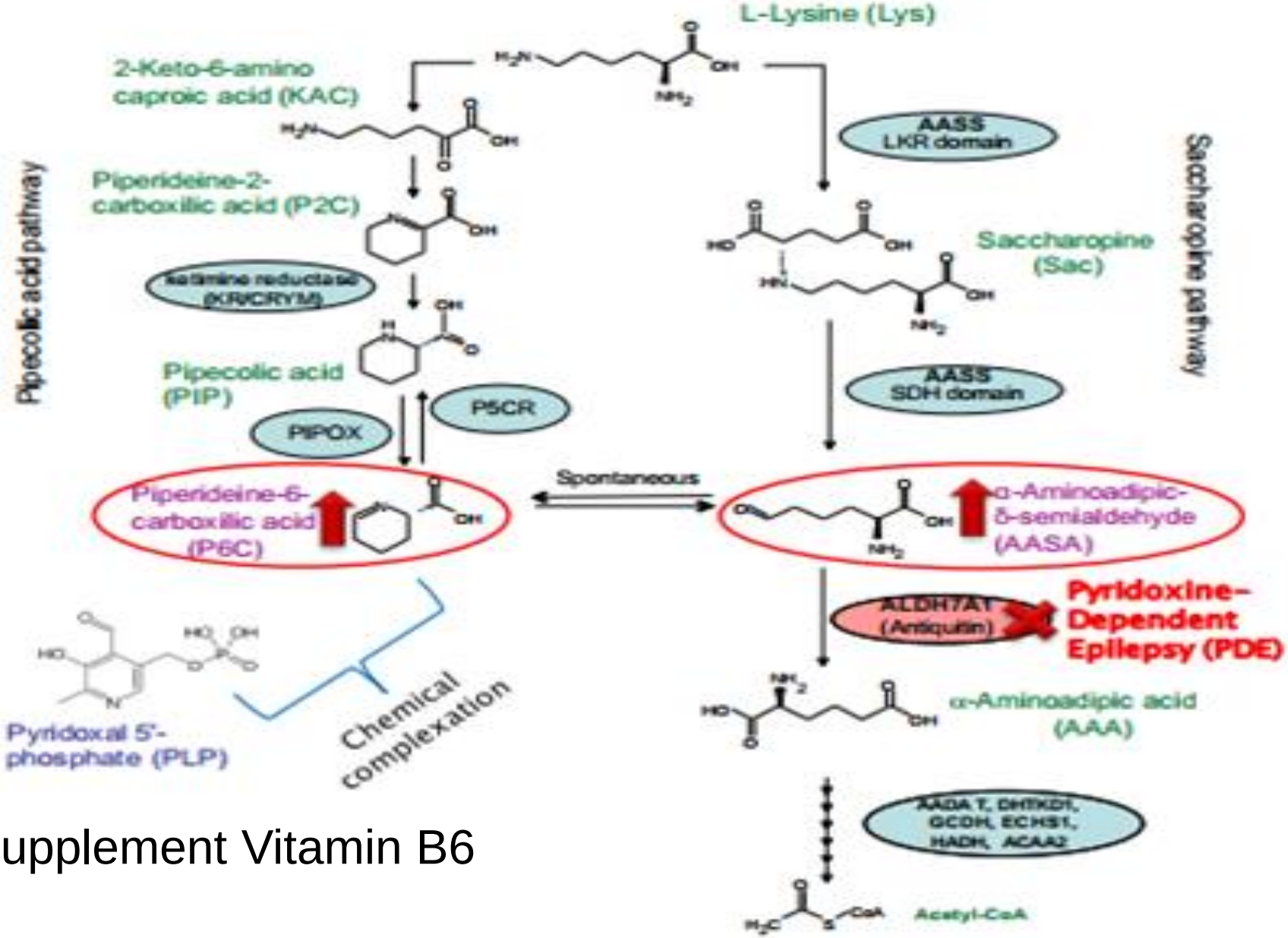
The patient's phenotype might be caused by:

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

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- Triple therapy with pyridoxine, L-arginine supplementation and dietary lysine restriction
- Electroencaphalogram 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)

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						Diagnosed		Change in Management		Break the Glass		
Project	# GN+EX Seq	Genomes	Exomes	Enrollment	Completed Testing	#	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 (BIoRepos)	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

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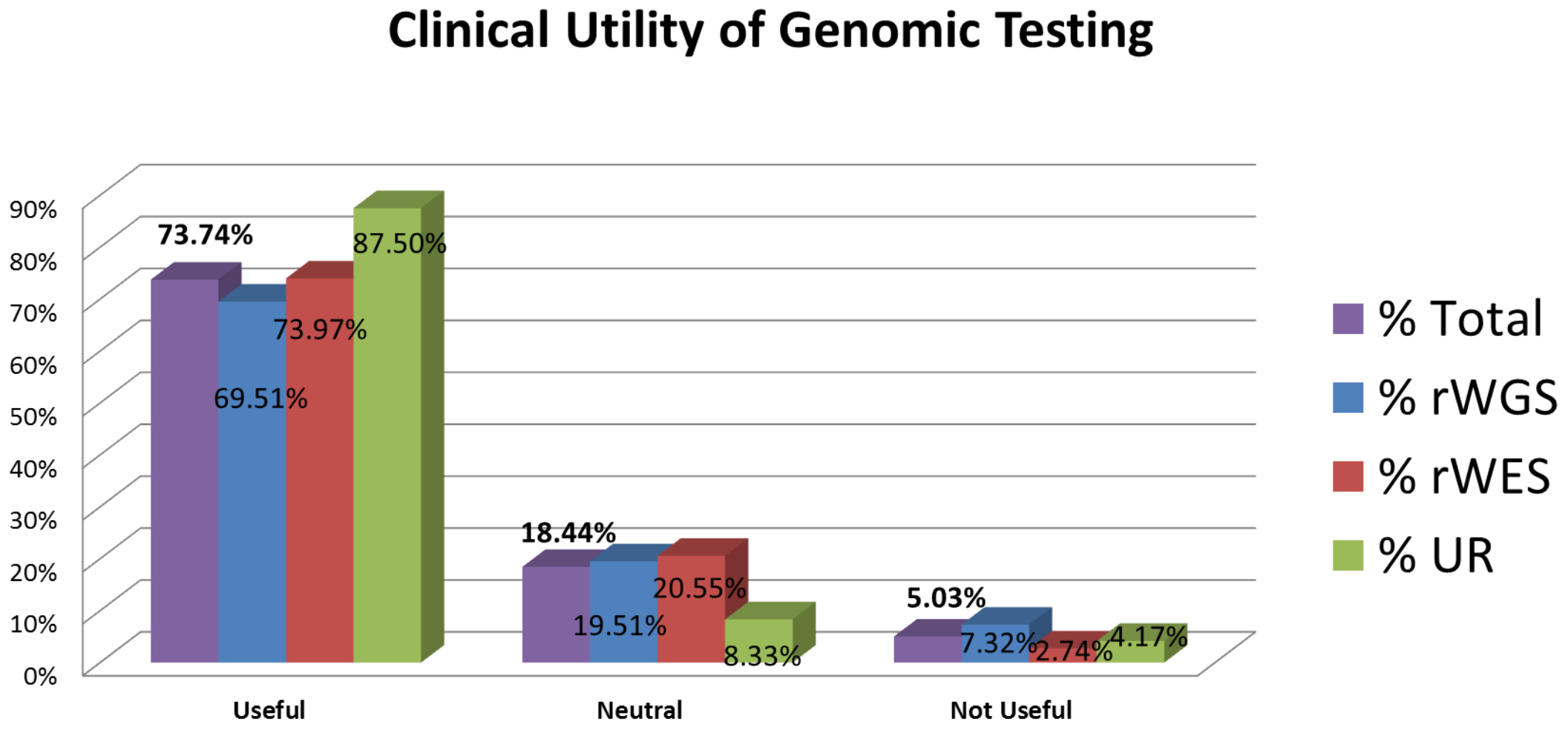

Clinician Survey Post- Results

Rady Children's Institute Genomic Medicine

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

Rady Children's Institute

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

Rady Children's Institute Genomic Medicine

Other care changes (select all that apply):	Total	rWGS	rWES	Ultra-Rapid WGS
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

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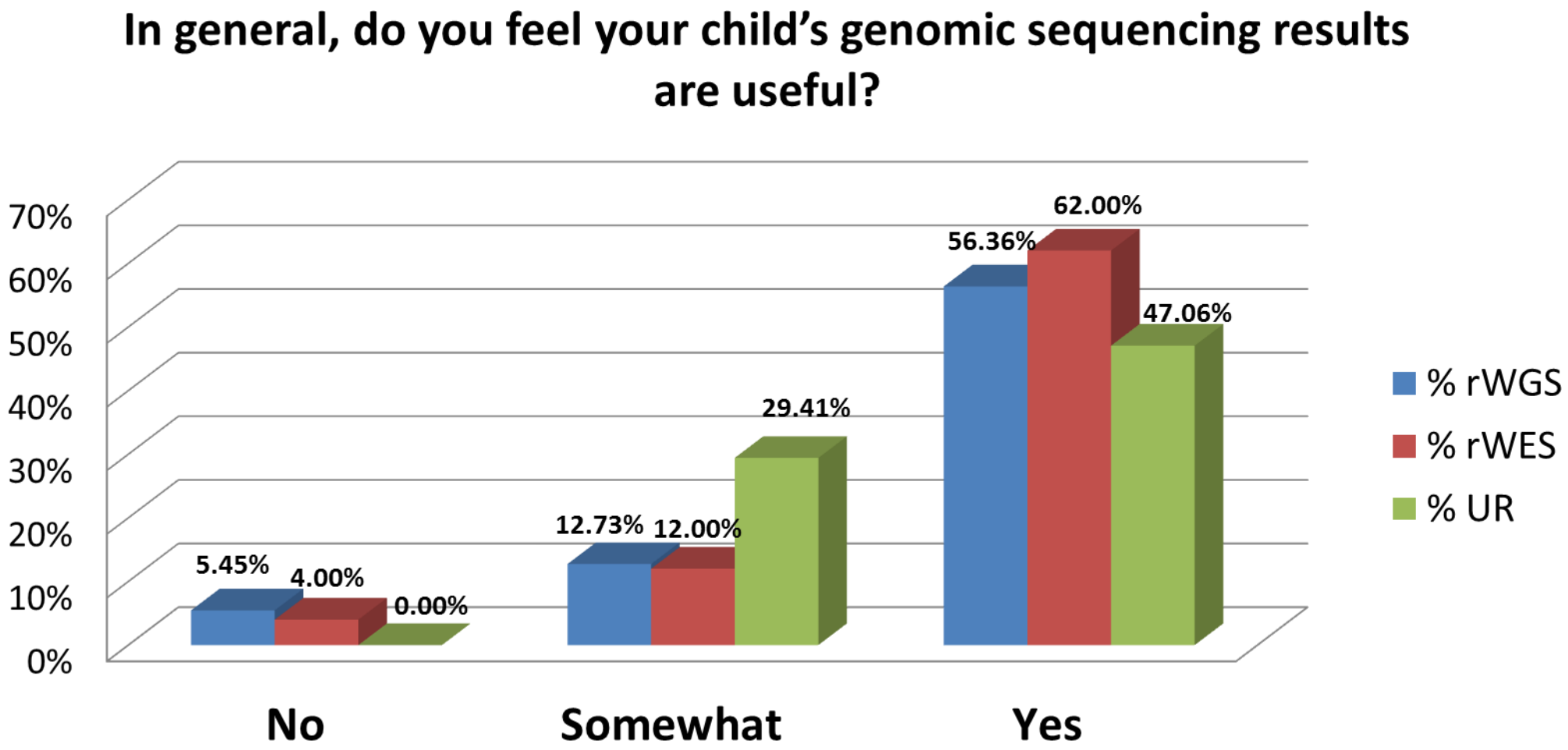

Parent Post-Results

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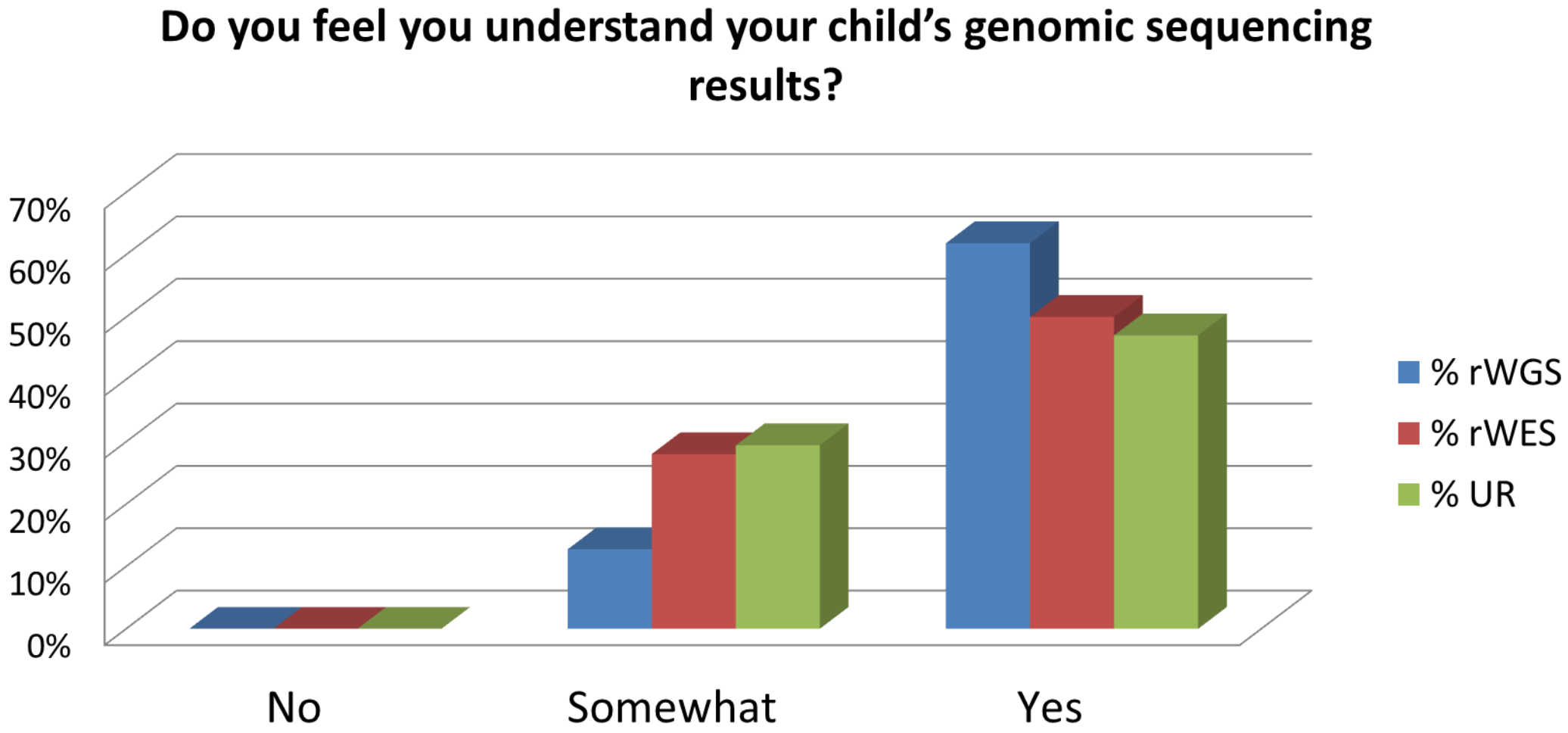
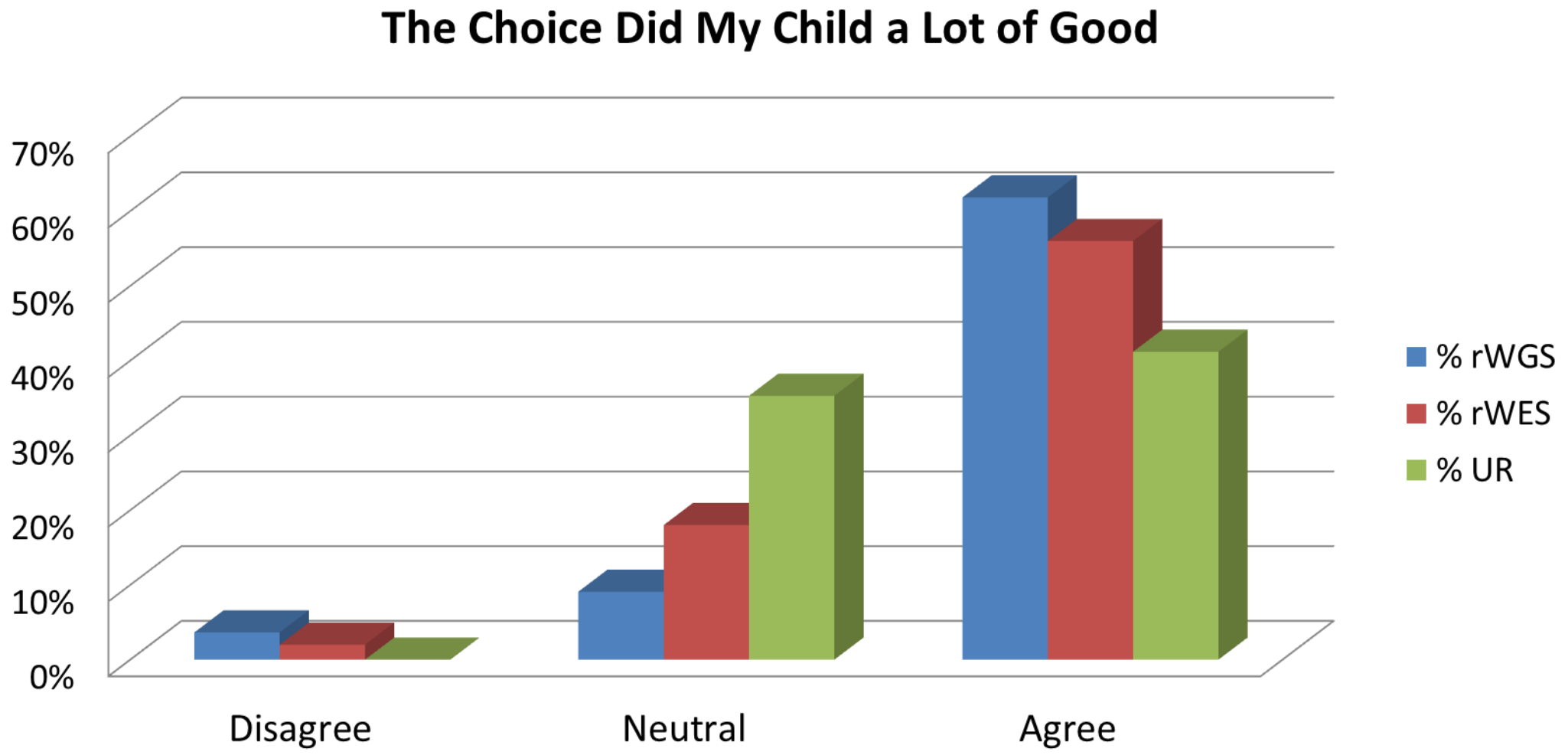
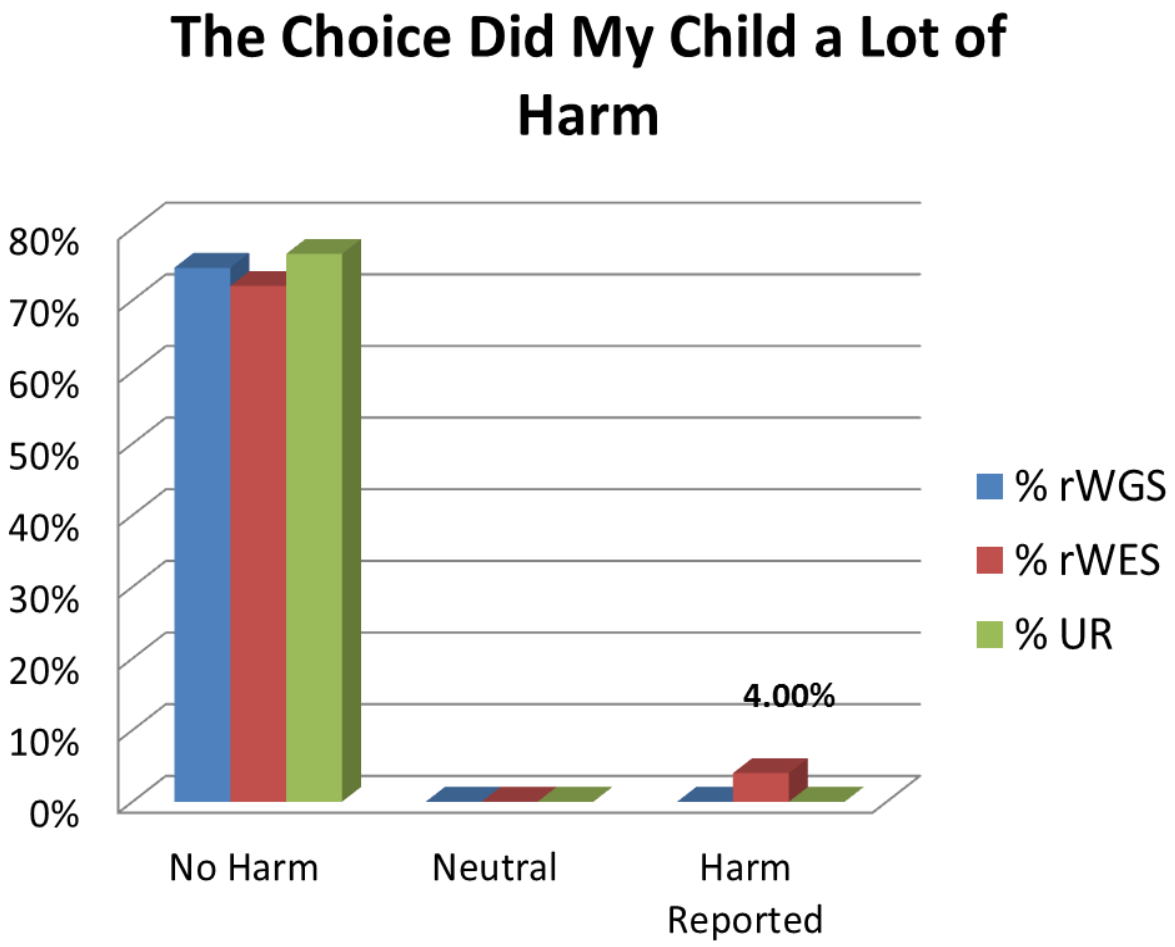


Parent Post-Results

Rady Children's Institute Genomic Medicine



Parent Post-Results



	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?

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- 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

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The Near Future

project baby bear

Rady Children's Hospital - San Diego

DHCS

California Department of Health Care Services

Rady Children's Institute Genomic Medicine

- **$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

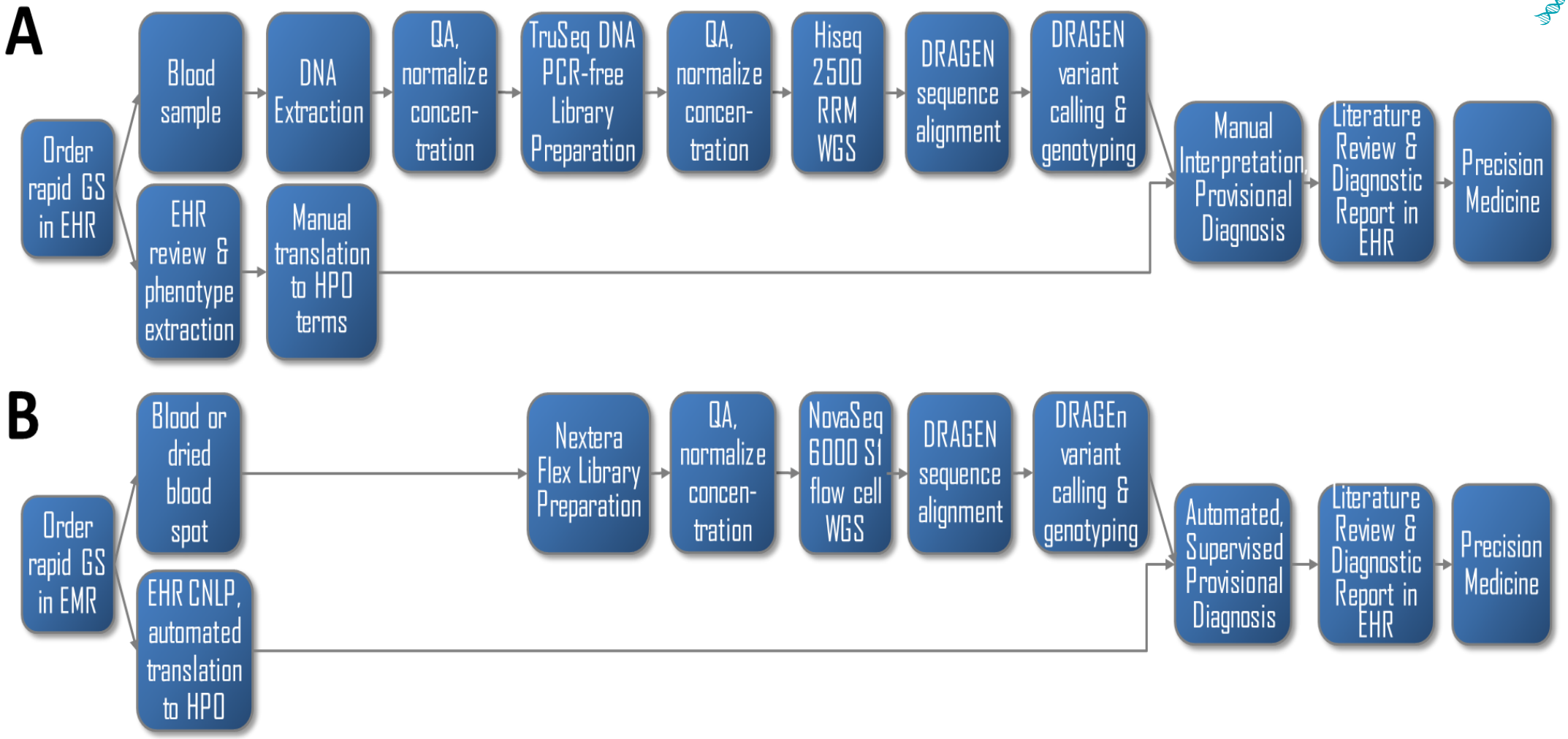
Rady Children's Institute Genomic Medicine

- 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

Genomics england

NHS England

Rady Children's Institute Genomic Medicine



Phenotyping automated by Natural Language Processing of EMR: 20 sec

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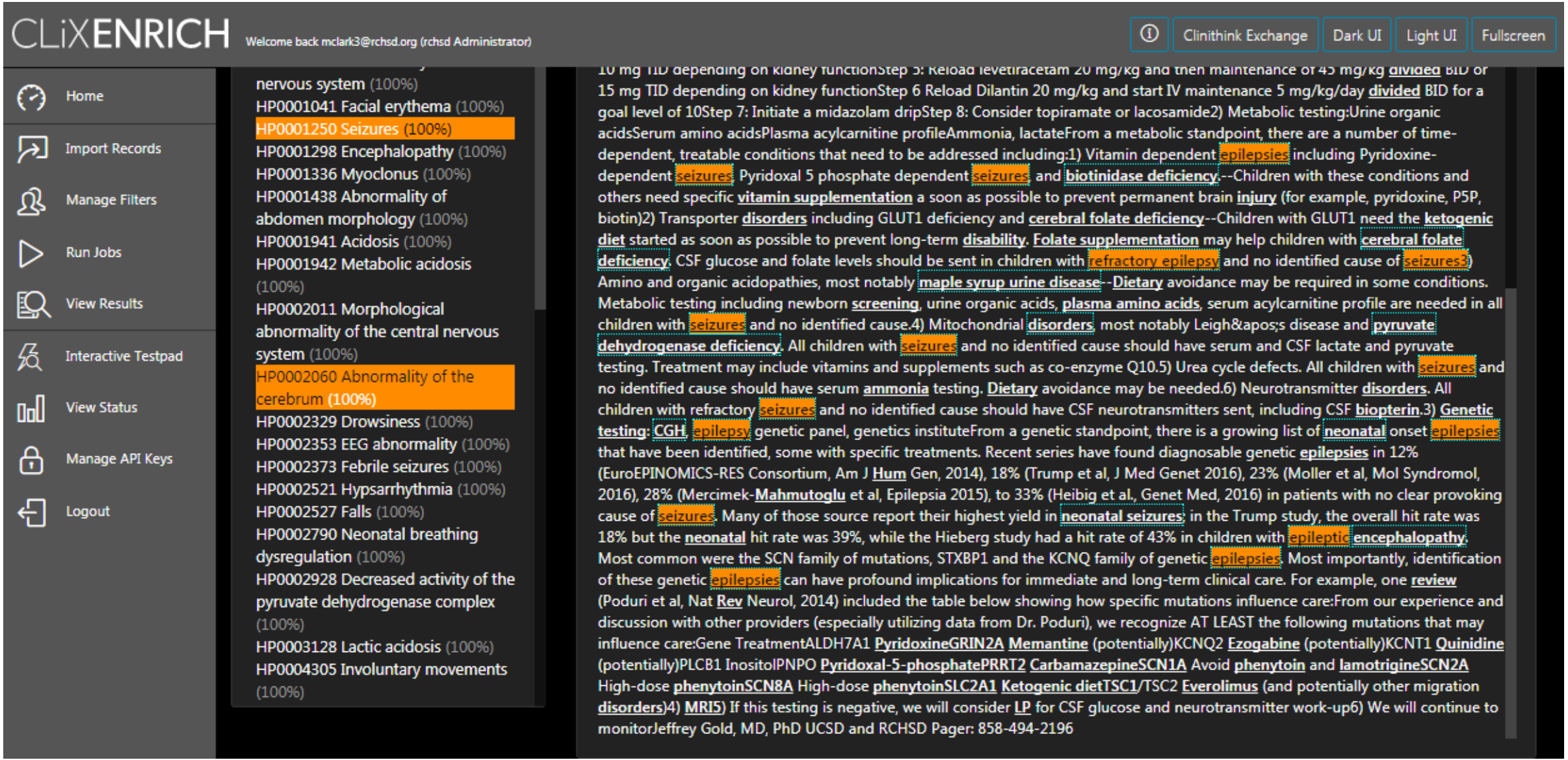

In most NICU patients, there is little overlap between the observed clinical features and the classical textbook description of that disease

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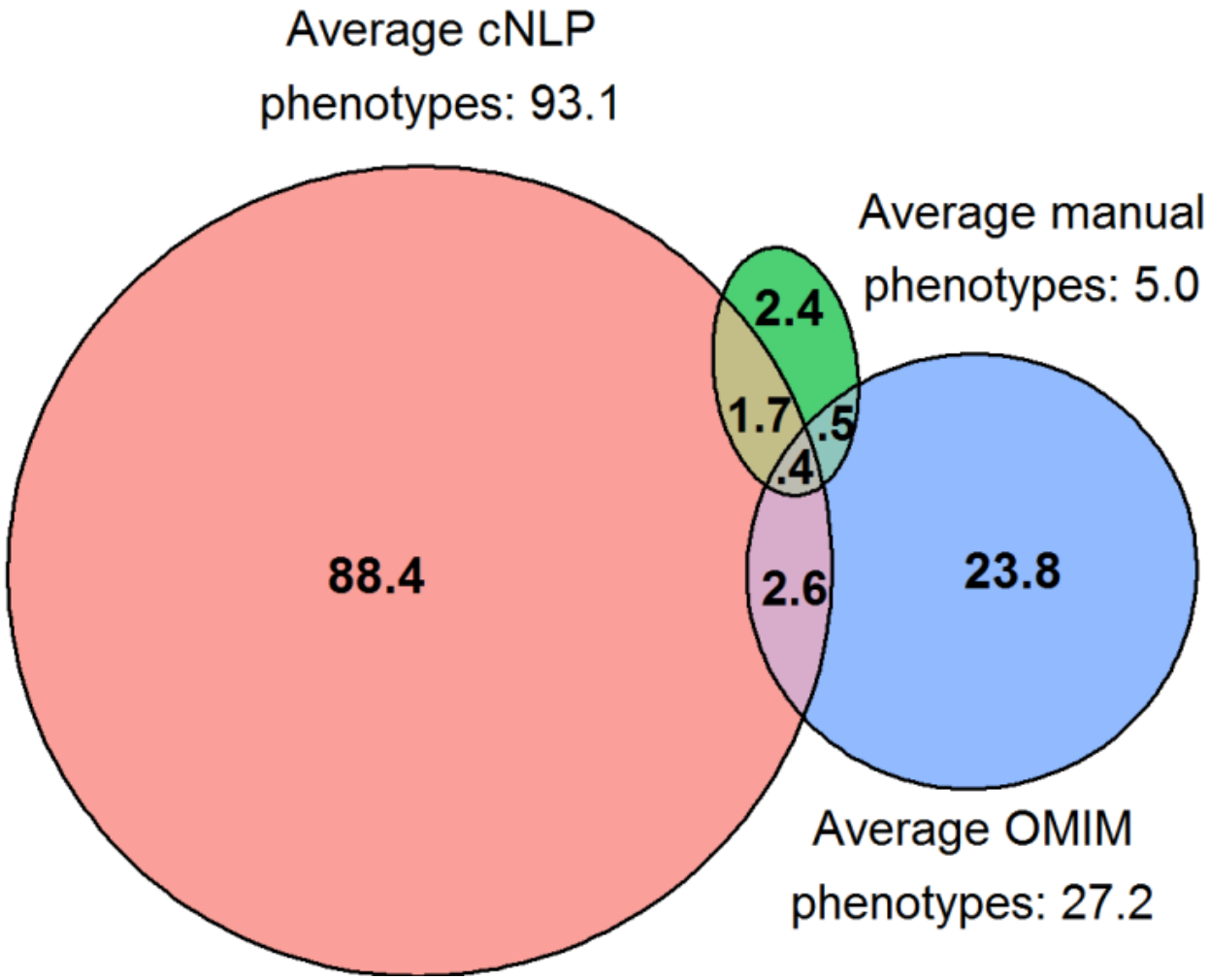

76 children with genetic diseases; cNLP: natural language processing of EMR; OMIM: Mendelian Inheritance in Man

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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**

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?