



Baby Badger Network ECHO

Evidence and Recommendations for Genomic (ES/GS) Testing in Critically Ill Neonates

—
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Learning Objectives

- Describe evidence regarding diagnostic yield of ES/GS in CIN
- Describe evidence for clinical utility of ES/GS in CIN
- Describe literature supporting the cost efficiency of ES/GS utilization in CIN
- Discuss challenges and solutions to implementing genomic medicine in a NICU setting



Genomic Testing



- Diagnostic Yield

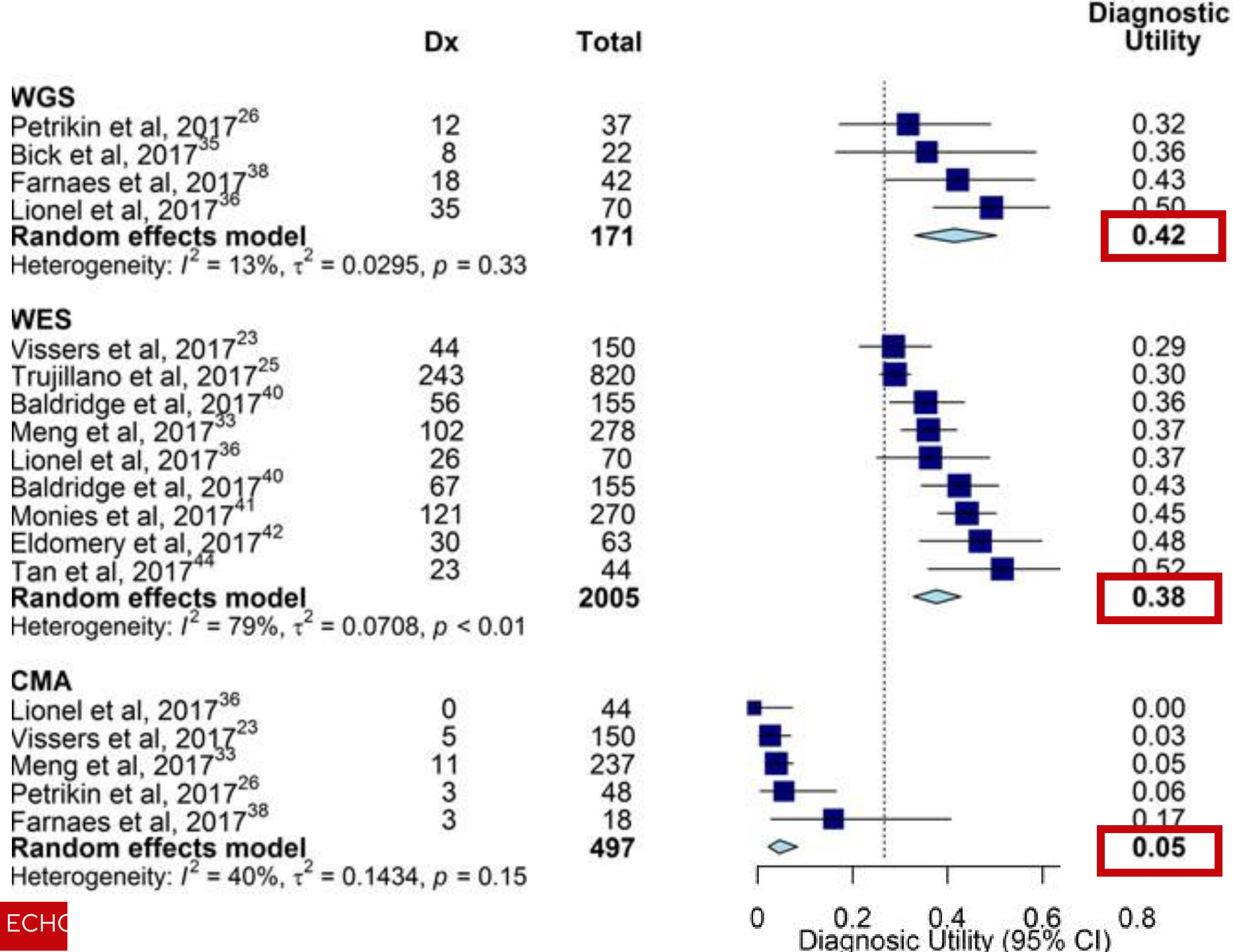


- Clinical Utility

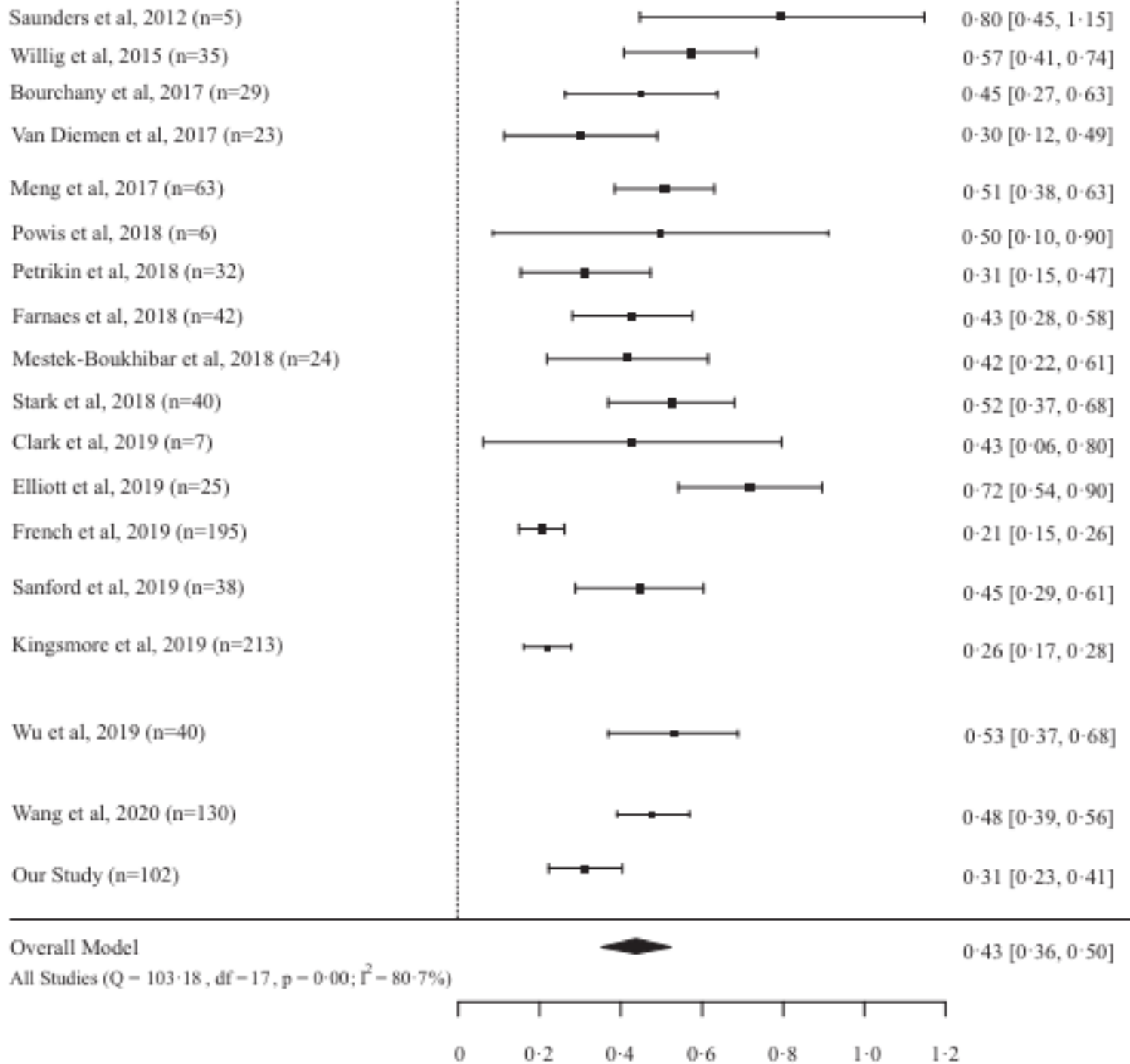


- Cost Efficiency

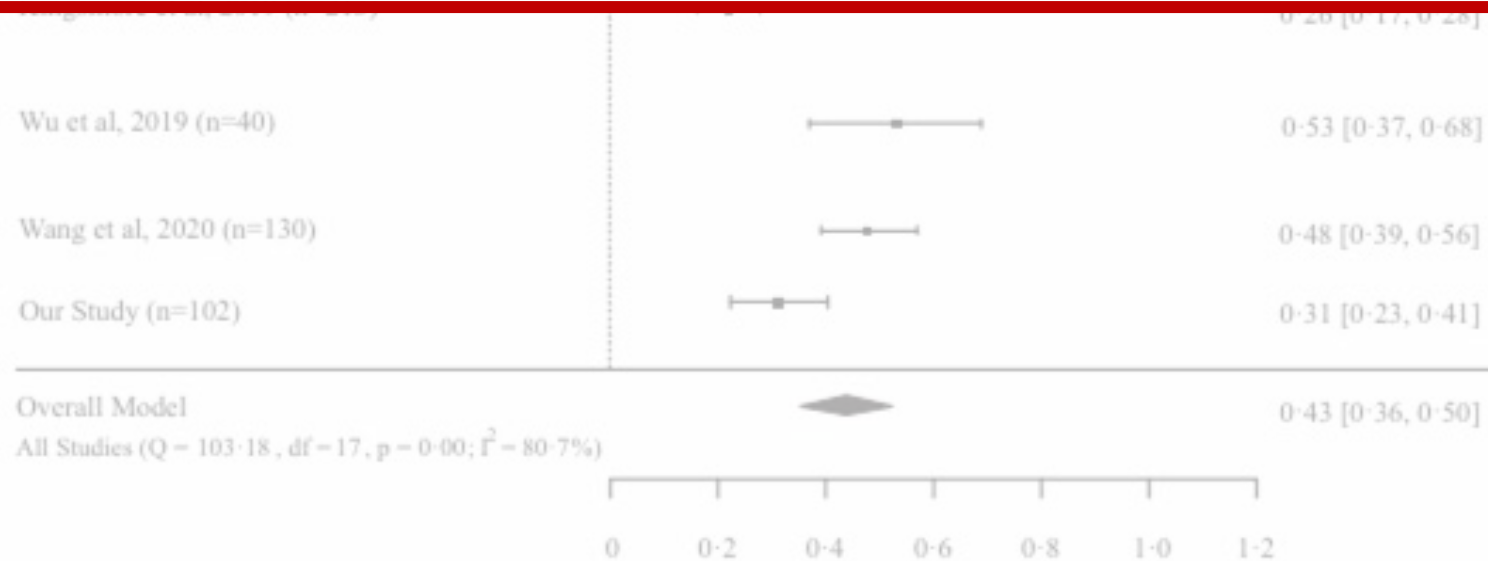
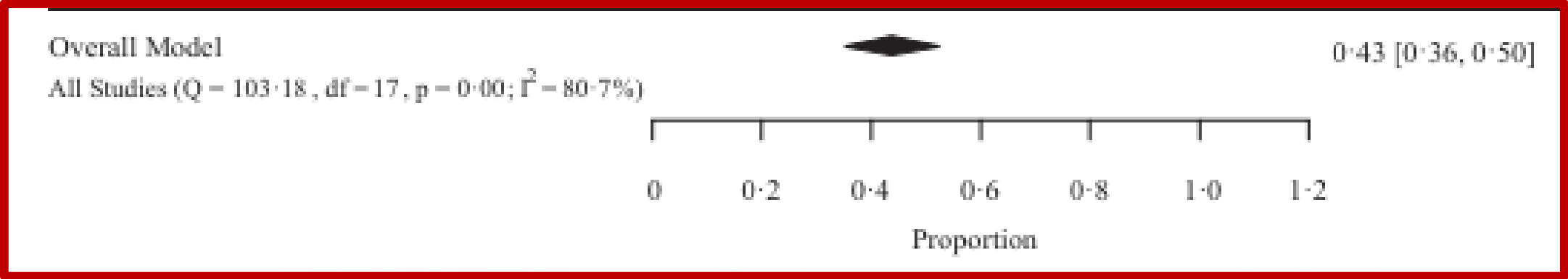
Diagnostic Yield



Diagnostic Yield



Diagnostic Yield



Diagnostic Yield



Publication (First Author, Ref#), Year	Study Population ^a	Study Type	Test ^b	Turnaround Time	Diagnostic Rate
Studies with all patients located in NICU					
Clark et al, ¹⁴ 2019	n = 7, neonates; NICU	Prospective	GS (trio)	20 h (median)	43%
Elliot et al, ²² 2019	n = 25, neonates; NICU	Prospective	ES (trio)	7 d (mean)	60%
Freed et al, ²³ 2020	n = 46, neonates; NICU	Prospective	ES (trio)	9 d (mean)	43%

Muriello M. Exome and Whole Genome Sequencing in the Neonatal Intensive Care Unit. Clin Perinatol. 2022 Mar;49(1):167-179.

Ref.	Year	Country	Number of probands	Dx rate
53	2018	USA	42	43%
73	2021	USA	184	40%
6	2022	USA	61	33%
93	2022	USA	38	45%
80	2022	USA	65	40%
94	2022	Australia	40	53%
82	2023	USA	89	39%
95	2023	USA	184	40%
83	2023	USA	400	49%
Median				40%



Clinical Utility

Publication (First Author, Ref#), Year	Study Population ^a	Study Type	Test ^b	Turnaround Time	Diagnostic Rate	Change in Management ^c
Studies with all patients located in NICU						
Clark et al, ¹⁴ 2019	n = 7, neonates; NICU	Prospective	GS (trio)	20 h (median)	43%	100% of diagnosed (43% of tested)
Elliot et al, ²² 2019	n = 25, neonates; NICU	Prospective	ES (trio)	7 d (mean)	60%	83% of diagnosed (60% of tested)
Freed et al, ²³ 2020	n = 46, neonates; NICU	Prospective	ES (trio)	9 d (mean)	43%	95% of diagnosed (52% of tested)

Ref.	Year	Country	Number of probands	Dx rate	Δ Mx
⁵³	2018	USA	42	43%	33%
⁷³	2021	USA	184	40%	32%
⁶	2022	USA	61	33%	n.d.
⁹³	2022	USA	38	45%	34%
⁸⁰	2022	USA	65	40%	n.d.
⁹⁴	2022	Australia	40	53%	39%
⁸²	2023	USA	89	39%	27%
⁹⁵	2023	USA	184	40%	32%
⁸³	2023	USA	400	49%	n.d.
Median				40%	33%

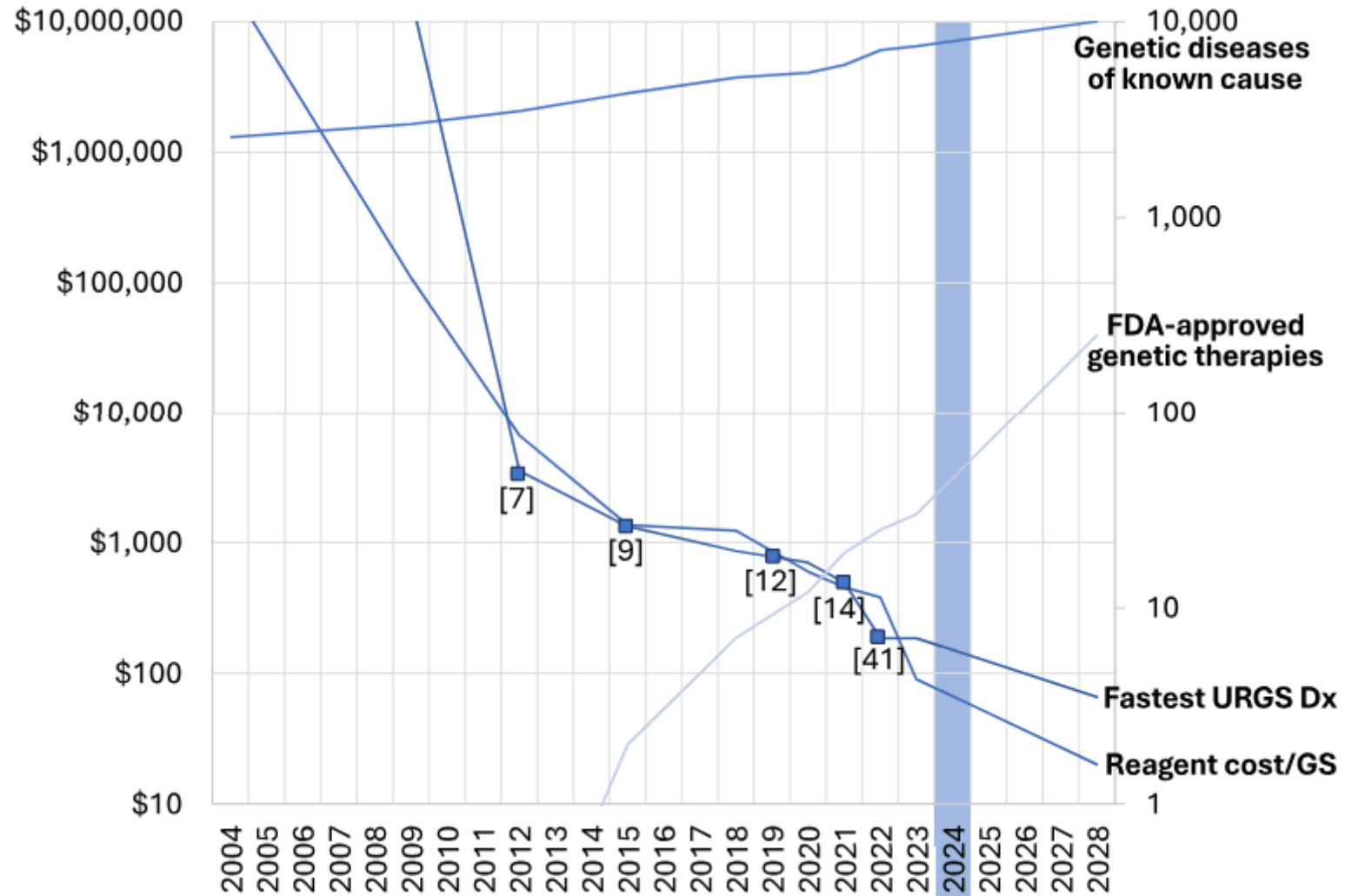


Patient	Ward	Diagnosis (OMIM)	Gene	R	D	P	S	M	L	O
RAP005	Genetics clinic	Neurofibromatosis, type 1 (OMIM: 162200)	<i>NF1</i>							
RAP006	NICU	Primary coenzyme Q10 deficiency-7 (OMIM: 616276)	<i>COQ4</i>							
RAP009	NICU	Polycystic kidney disease 4 (OMIM: 263200)	<i>PKHD1</i>							
RAP014	Non-ICU	Alagille syndrome 1 (OMIM: 118450)	<i>JAG1</i>							
RAP022	NICU	Nemaline myopathy (OMIM: 161800)	<i>ACTA1</i>							
RAP026	NICU	Osteogenesis imperfecta Type I-IV (OMIM: 166200, 166210, 259420, 166220)	<i>COL1A1</i>							
RAP031	Non-ICU	Histiocytosis-lymphadenopathy plus syndrome (OMIM: 602782)	<i>SLC29A3</i>							
RAP036	PICU	PCWH syndrome (Peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome, Hirschprung's disease) (OMIM: 609136)	<i>SOX10</i>							
RAP038	NICU	Autosomal-Recessive Nemaline Myopathy (OMIM: 615348)	<i>KLHL40</i>							
RAP042	Non-ICU	Glycogen storage disease Ia (OMIM: 232200)	<i>G6PC</i>							
RAP043	Non-ICU	Neurodevelopmental disorder with spastic diplegia and visual defects (NEDSDV) (OMIM: 615075)	<i>CTNNA1</i>							
RAP045	NICU	CHARGE syndrome (OMIM: 214800)	<i>CHD7</i>							
RAP047	Non-ICU	Tuberous sclerosis-2 (OMIM: 613254)	<i>TSC2</i>							
RAP048	Non-ICU	Dilated cardiomyopathy-1DD (OMIM: 613172)	<i>RBM20</i>							
RAP051	Genetics clinic	Hereditary angioedema type 1 (OMIM: 106100)	<i>SERPING1</i>							
RAP053	Non-ICU	Multiple types of congenital heart defects (OMIM: 614980)	<i>TAB2</i>							
RAP061	PICU	Fatal Infantile Cardioencephalomyopathy (OMIM: 604377)	<i>SCO2</i>							
RAP064	NICU	Early infantile epileptic encephalopathy-11 (OMIM: 613721)	<i>SCN2A</i>							
RAP066	Genetics clinic	Spastic paraplegia 11 (OMIM: 604360)	<i>SPG11</i>							
RAP068	NICU	{Thiopurines, poor metabolism of, 2} (OMIM: 616903)	<i>NUDT15</i>							
RAP075	Non-ICU	Coffin-Siris syndrome 1 (OMIM: 135900)	<i>ARID1B</i>							
RAP078	PICU	Wilson disease (OMIM: 277900)	<i>ATP7B</i>							
RAP080	Non-ICU	Wilson disease (OMIM: 277900)	<i>ATP7B</i>							
RAP085	Non-ICU	Noonan syndrome 1 (OMIM: 163950)	<i>PTPN11</i>							
RAP096	NICU	Wiedmann Steiner syndrome (OMIM: 605130)	<i>KMT2A</i>							
RAP098	Genetics clinic	Juvenile-onset dystonia (OMIM: 607371)	<i>ACTB</i>							
RAP102	NICU	Spectrum of overlapping neonatal epileptic phenotypes, ranging from the milder form of seizures, benign neonatal, 1 (OMIM: 121200) to severe form of epileptic encephalopathy, early infantile, 7 (OMIM: 613720)	<i>KCNQ2</i>							
RAP106	PICU	Epileptic encephalopathy, early infantile, 17 (OMIM: 615473) and neurodevelopmental disorder with involuntary movements (OMIM: 617493)	<i>GNAO1</i>							
RAP114	PICU	Noonan Syndrome 5 (OMIM: 611553)	<i>RAF1</i>							
RAP118	PICU	Noonan Syndrome 7 (OMIM: 164757)	<i>BRAF</i>							
RAP119	Genetics clinic	Pseudohypoaldosteronism, type IIB (OMIM: 614491)	<i>WNK4</i>							
RAP125	PICU	Severe combined immunodeficiency, T-cell/negative, B-cell/natural killer cell-positive type (OMIM: 608971)	<i>IL7R</i>							
Total (%)				9 (28)	5 (16)	11 (34)	10 (31)	10 (31)	5 (16)	2 (6)

Clinical Utility



	rWES	rWGS	rWES versus rWGS p Value	urWGS	urWGS versus rWES+ rWGS P value	Positive Tests	Negative Tests	Pos versus Neg Tests p Value
Infants enrolled ^a	95	94	N/A	24	N/A	51	162	N/A
Clinician Perception								
Surveys completed, n (%)	90 (95%)	93 (99%)	N/D	24 (100%)	N/D	49 (96%)	158 (98%)	N/D
Test was useful or very useful, n (%)	66 (76%)	66 (73%)	0.73	22 (92%)	0.07	42 (93%)	112 (72%)	0.002
Test changed management, n (%)	19 (21%)	23 (25%)	0.6	15 (63%)	0.0001	31 (63%)	26 (16%)	<0.00001
Test changed an outcome, n (%)	17 (19%)	9 (10%)	0.09	6 (25%)	0.22	19 (39%)	13 (8%)	<0.00001
Test improved communication, n (%)	34 (38%)	34 (37%)	0.88	16 (67%)	0.008	34 (69%)	50 (32%)	<0.00001
Test increased stress or confusion, n (%)	3 (35)	1 (1%)	0.36	2 (8%)	0.14	4 (8%)	2 (1%)	0.14
Test led to other changes in management, n (%)	20 (22%)	21 (23%)	1	10 (42%)	0.047	40 (82%)	11 (7%)	<0.00001
Test led to another test being cancelled, n (%)	16 (19%)	20 (22%)	1	8 (32%)	0.18	13 (27%)	31 (20%)	0.32
Test led to another test being ordered, n (%)	11 (12%)	15 (16%)	0.53	5 (21%)	0.37	19 (39%)	9 (6%)	<0.00001





	sWES infant cohort 2014–2015 Usual care + conventional sequencing tests, AU\$ N = 40	sWES infant cohort 2014–2015 Usual care + sWES, AU\$ N = 40	rWES cohort 2016–2017 AU\$ N = 40
Clinical assessments			
<i>Clinical geneticist</i>	22,239.24	32,452.97	6,681.54
<i>Genetic counselor</i>	0	14,914.07	1,527.60
<i>Subspecialist (OP)</i>	9,187.73	9,187.73	240.00
Pathology			
<i>Anatomical pathology</i>	14,409.32	14,409.32	3,277.81
<i>Basic biochemistry</i>	4,289.12	4,289.12	2,204.81
<i>Complex biochemistry</i>	9,437.04	9,437.04	17,767.52
<i>Serology/immunology</i>	1,520.72	1,520.72	2,145.41
Imaging	50,165.45	50,165.45	35,198.15
Electrophysiology	22,027.97	22,027.97	20,886.90
Genetic tests			
<i>SNP microarray</i>	23,880.00	23,880.00	23,880.00
<i>Nonsequencing tests (e.g., methylation)</i>	2,663.40	3,863.40	6,403.20
<i>Single-gene and panel sequencing</i>	22,488.39	0	0
<i>WES</i>	0	80,000.00	157,960.00
Other			
<i>Medical photography</i>	809.62	809.62	0
<i>DNA extraction/ sample shipping</i>	2,541.00	440.00	1,710.00
<i>OT/anesthesia costs</i>	3,693.53	3,693.53	1,260.00
Total cost	189,352.53	271,090.94	281,142.94
Patients diagnosed	7	25	21
Cost per diagnosis 95% CI	27,050.36 (15,365.51–68,529.77)	10,843.60 (7,487.62–14,090.02)	13,387.76 (9,268.68–17,506.84)



Cost Efficiency

Ref.	Year	Country	Number of probands	Dx rate	Δ Mx	RGS cost per proband	Cost per Dx	TAT	Net savings per proband
53	2018	USA	42	43%	33%	\$16,063	\$37,480	23	\$18,741
73	2021	USA	184	40%	32%	\$9239	\$23,602	3	\$6294
6	2022	USA	61	33%	n.d.	\$9758	\$29,570	n.d.	\$11,286
93	2022	USA	38	45%	34%	\$6300	\$14,082	14	(\$1436)
80	2022	USA	65	40%	n.d.	\$11,029	\$27,573	12	\$100,440
94	2022	Australia	40	53%	39%	\$8088	\$15,406	3	\$17,243
82	2023	USA	89	39%	27%	\$7564	\$19,395	n.d.	\$4155
95	2023	USA	184	40%	32%	\$14,450	\$36,125	3	\$22,395
83	2023	USA	400	49%	n.d.	\$8000	\$16,326	6	n.d.
Median				40%	33%	\$9239	\$25,588	\$6	\$14,265



Cost Efficiency

Table 3. Effect of rWGS-based precision medicine on acute healthcare utilization in six infants and three matched controls

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 admission for etiologic Dx	<i>NPC1</i>	7 (G)	8	15 (35%)	\$ 25,278	\$ 27,004
	Cholestasis. 2nd admission for etiologic Dx			15		\$ 27,004	
6012	Palliative care started DOL 250	<i>ARID1B</i>	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	<i>NEB1</i>	7 (G)	45	2 (6%)	\$ 156,914	\$ 9900
Control 1	Electromyogram, GA, muscle biopsy					\$ 9900	
6026	Cholestasis and congenital heart disease. Avoided hepatopertoenterostomy	<i>JAG1</i>	3 (G)	11	3 (18%)	\$ 50,327	\$ 131,795
Control 2	Kasai hepatopertoenterostomy					\$ 44,451	
Avg cost	Cost of liver transplant x 43% occurrence					\$ 87,344	
6041	Seizures. Diagnosis DOL 4	<i>KCNQ2</i>	4 (G)	18	41 (69%)	\$ 79,675	\$ 181,481
	Seizures. Diagnosis DOL 42		42 (S)	59		\$ 261,156	
6053	Hypoglycemia. Diagnosis DOL 12	<i>ABCC8</i>	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



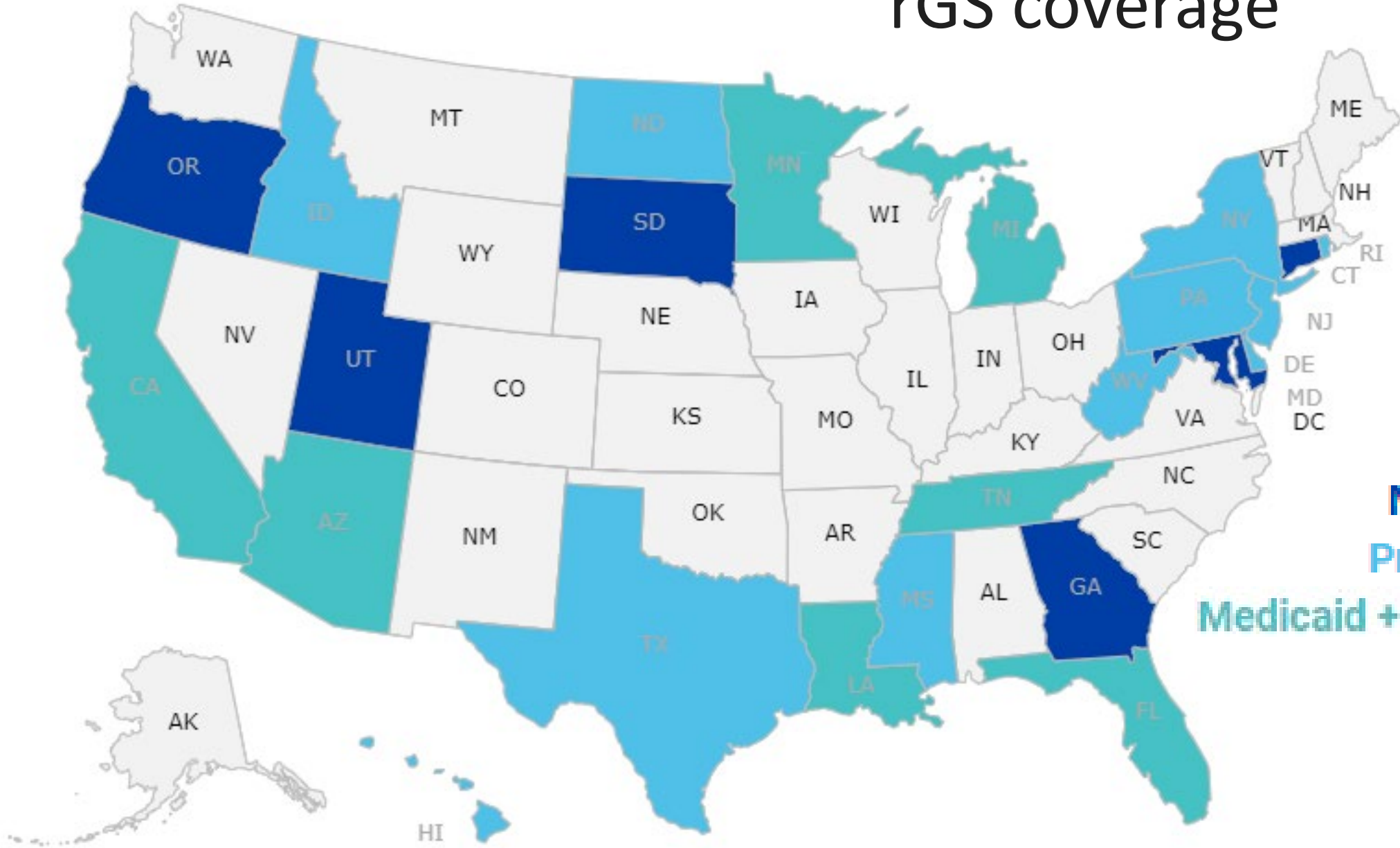
What challenges do you see in implementing genomic sequencing in the NICU?



Challenges and Solutions

- Funding
 - Hospital/Institution Support
 - Insurance Authorization and Reimbursement
 - Test may not affect immediate inpatient care – deferred to outpatient
- Pre-test counseling
 - Consent
 - Obtaining samples from both parents
- Post-test counseling
 - Variants of Uncertain clinical significance
 - Secondary findings
- Patient and provider education
- Complicated workflows and test ordering processes

rGS coverage



Medicaid
Private Payer(s)
Medicaid + Private Payer(s)



NICU

\$3,000 - \$8,000 per day



Rapid Genome Sequence

- Test for things too rare and/or heterogeneous to be considered
- Identification of genotype before phenotype fully manifests
- Diagnose or rule out known mutations
- Reduce unnecessary tests & empiric therapies
- Improve prognostic assessment, genetic counseling
- Unique opportunity to intervene before irreversible disease processes manifests with irreversible symptoms