

Rapid Whole Genome Sequencing in Neonates: Treatable Diagnoses Beyond the New York State Newborn Screening Panel

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Background

- Newborn screening (NBS) is a critical public health tool used to identify treatable conditions and improve health outcomes.¹
- However, many newborns in the neonatal intensive care unit (NICU) remain critically ill and undiagnosed, with normal NBS results.
- Rapid whole genome sequencing (rWGS) has emerged as a useful tool to broaden the spectrum of conditions diagnosed in neonates, some of which are treatable.²
- As more treatments become available for genetic conditions diagnosed in the neonatal period, rWGS has an increasingly important role in the NICU.

Results

- Average turnaround time: 5.5 days.
- Average age at the time of diagnosis was 16.5 days.
- rWGS yielded a single genetic diagnosis in 178 patients, two diagnoses in 9 patients (4.7%), and three diagnoses in 1 patient (0.5%).
- 48 patients had diagnoses with specific available medical management, including 3 with FDA-approved gene therapy.
- 83% of single-gene conditions with available treatment or intervention would not have been detected by NYS NBS.³

Figure 1. Reported Clinical Features

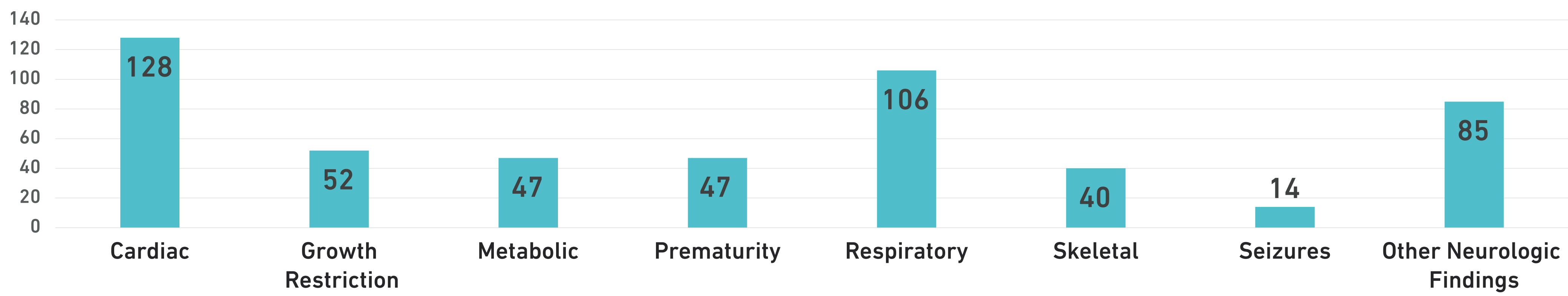


Figure 2. Single Genes with Two or More Positive Cases

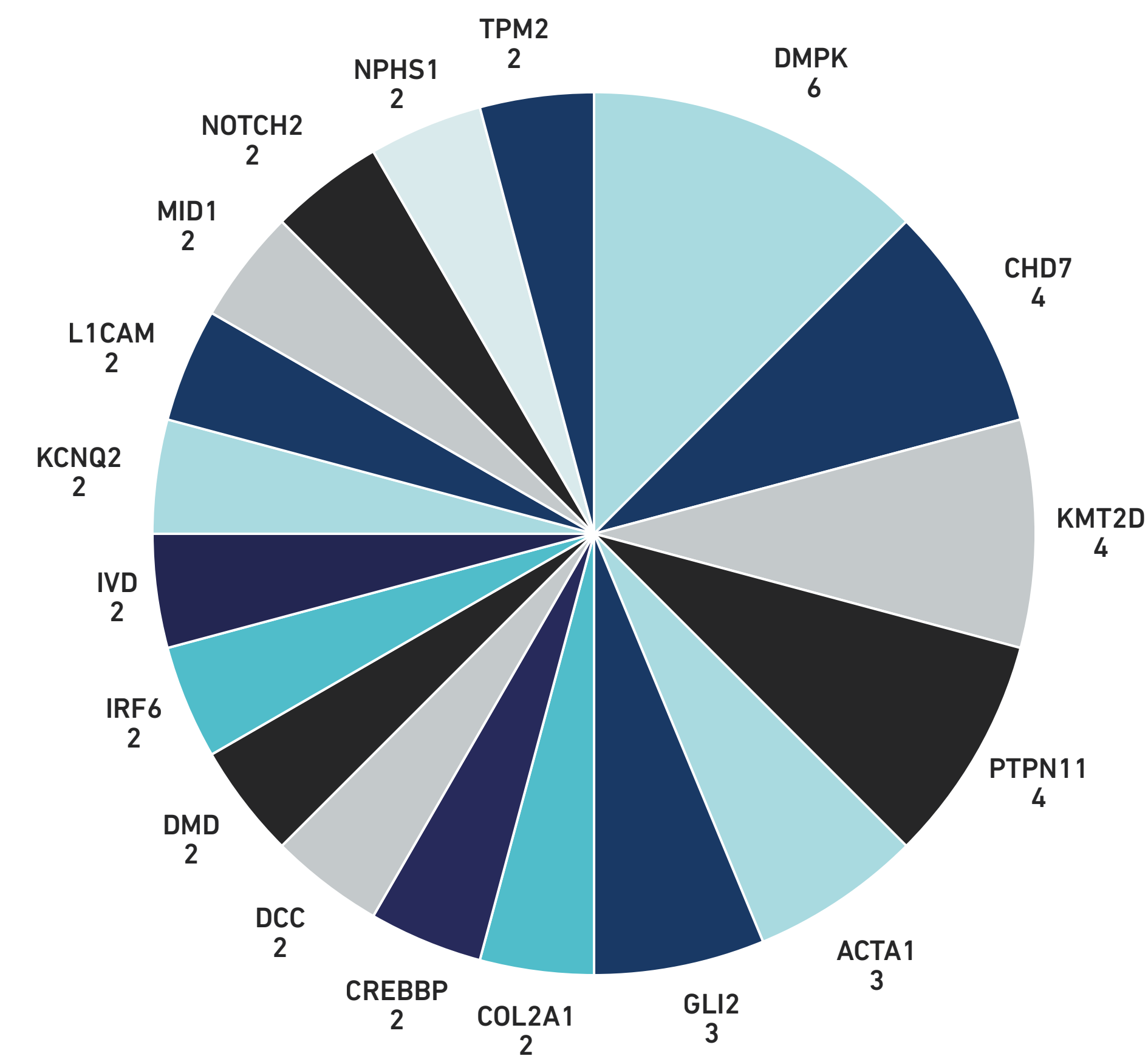
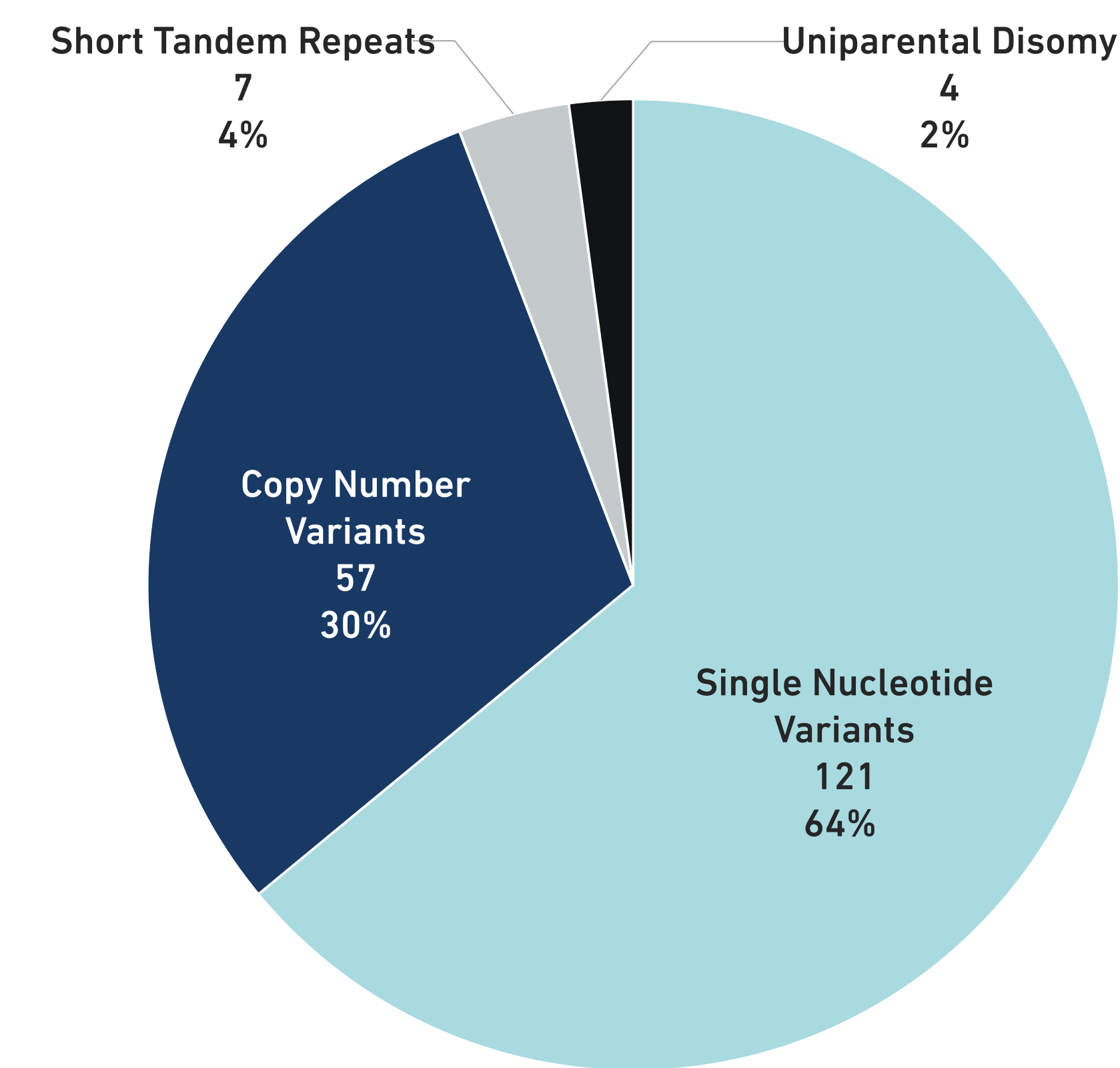


Figure 3. Variant Types Associated with Diagnoses



Methods

- Study Design: retrospective analysis of rWGS results at our clinical diagnostic laboratory was conducted.
- Inclusion Criteria: Neonatal patients (<28 days of age) who were inpatients at the time of referral and had a positive rWGS result.
- Analysis: Reviewed clinical indications and genetic results for 189 consecutive positive cases, assessed medical intervention availability for each identified condition, compared positive results with conditions detected by the New York State (NYS) NBS panel.

Medical Intervention



Medication: 15.3% (29/189)



Monitoring: 3.7% (7/189)



FDA-approved Gene Therapy: 1.6% (3/189)



Dietary: 5.3% (10/189)



Surgery: 0.5% (1/189)

Table 1. Comparison of Conditions with Available Intervention vs. NYS NBS Panel

Intervention	Identifiable by NYS NBS (9/189)	Not Identifiable by NYS NBS (45/189)
Dietary	Carnitine-acylcarnitine translocase deficiency	<i>ATAD3</i> duplication syndrome
	Citrullinemia type I	Combined oxidative phosphorylation deficiency 10
FDA-Approved Gene Therapy	Glutaric acidemia IIC	Diarrhea 1, secretory chloride, congenital
	Isovaleric acidemia(2)	Glucose/galactose malabsorption
Medication Changes	Spinal muscular atrophy	Ornithine transcarbamylase deficiency
		Duchenne muscular dystrophy (2)
Monitoring		6q24-related Transient Neonatal Diabetes Mellitus (2)
		Myoclonus, familial (2)
Surgery		Achondroplasia
		Alagille Syndrome 1
		Cardiac valvular dysplasia (2)
		<i>COL1A1</i> -related disorders
		Congenital nephrotic syndrome, Finnish type (2)
		<i>DEPDC5</i> -related epilepsy disorder
		Epilepsy, early-onset, 4, vitamin B6-dependent
		Familial focal epilepsy with variable foci 3
		<i>GATA6</i> -related disorders
		<i>GLI2</i> -related disorders (3)
		<i>KCNQ2</i> -related disorders (2)
		Loeys-Dietz syndrome 3
		Malignant hyperthermia susceptibility 1
		Neonatal diabetes mellitus (2)
		Neurofibromatosis, type 1
		<i>NOTCH2</i> -related disorders (2)
		Renal tubular dysgenesis
		<i>SCN8A</i> -related disorders
		<i>SMAD2</i> -related disorders
		<i>TNNT2</i> -related cardiac disorders
		Cardiomyopathy, familial hypertrophic (2)
		<i>COL4A1</i> -related disorders
		Hereditary hemorrhagic telangiectasia type 2
		Split-hand/foot malformation 1 with sensorineural hearing loss
		<i>TAB2</i> -related disorders
		Tuberous sclerosis-2
		<i>WT1</i> -related disorders
		Primary macronodular adrenal hyperplasia

Conclusions

- Rapid WGS in neonatal patients provides substantial diagnostic yield beyond traditional NBS, identifying conditions with meaningful implications for both patient care and family management.
- Patients may have multiple molecular findings which can be missed by targeted testing approaches.
- Some variants, such as copy number variants and short tandem repeats, may be missed by traditional sequencing approaches.
- Incorporating genomic sequencing alongside conventional NBS may strengthen public health efforts by enabling earlier, more comprehensive detection of genetic disorders.