

Clinical exome sequencing in structurally normal fetuses: Diagnostic yield and results stratification

Hagit Daum^{1,2*}, Rivka Birenboam^{1*}, Tamar Harel^{1,2}, Vardiella Meiner^{1,2}, Eitan Moses¹, Shlomit Ezer^{1,2}, Hagar Mor-Shaked^{1,2#}, Shiri Shkedi-Rafid^{1,2#}

(*,# contributed equally)

1 Department of Genetics, Hadassah Medical Organization, Israel, 2 Faculty of Medicine, the Hebrew University of Jerusalem, Israel



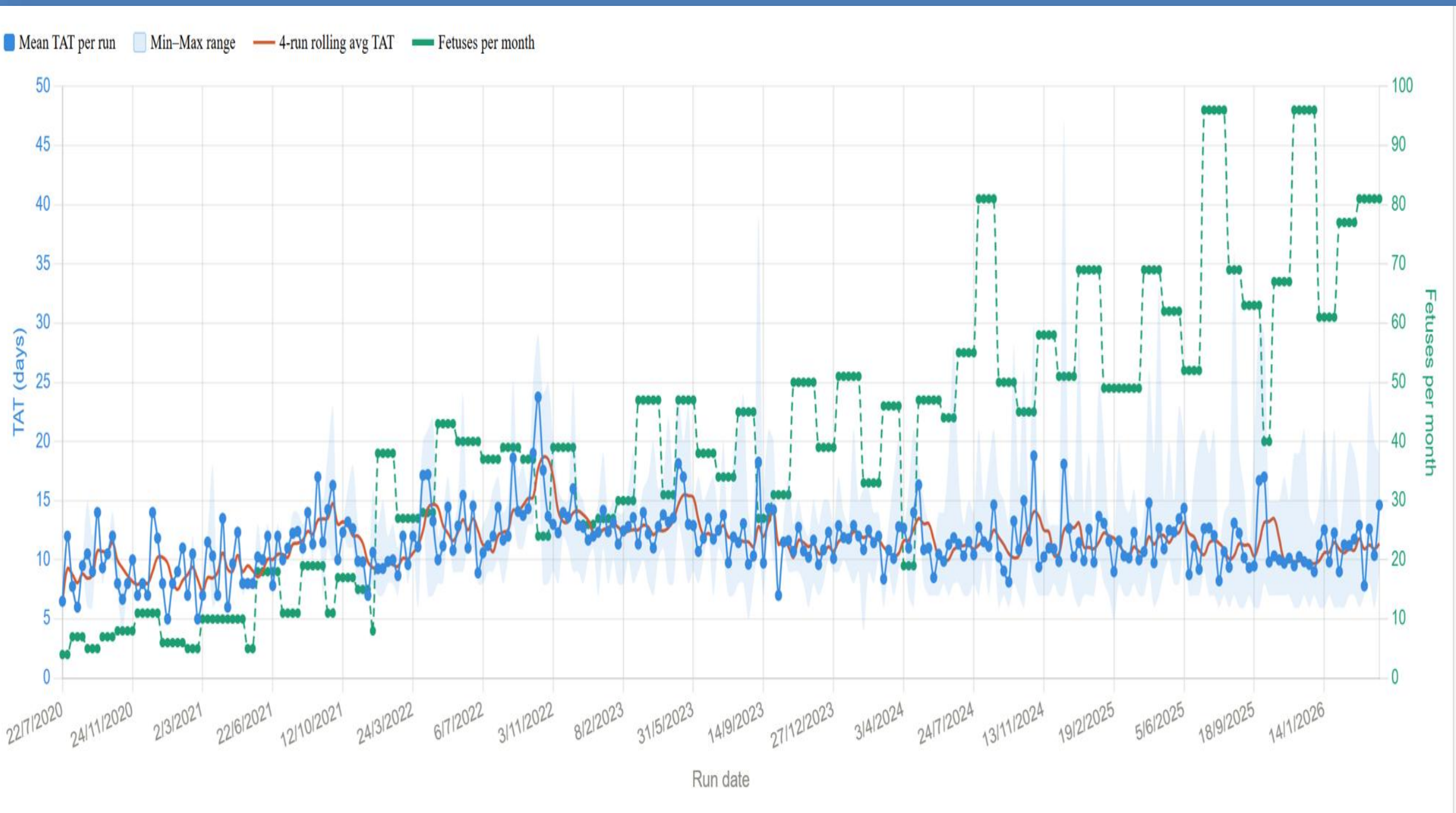
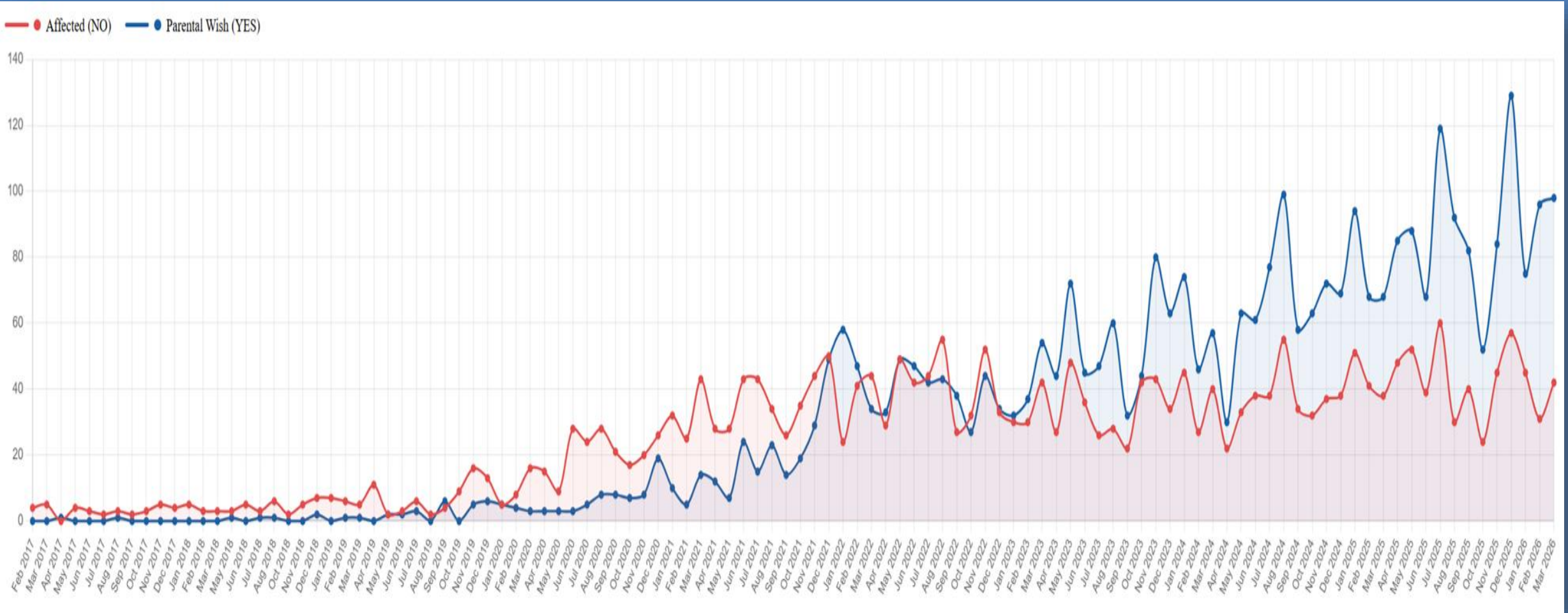
OBJECTIVE: Exome sequencing (ES) is a highly effective and well-established diagnostic tool in pregnancies with structural anomalies. The benefits of ES in structurally normal fetuses are still controversial. This study summarizes our clinical experience with ES in structurally normal fetuses.

CONCLUSION: With restrictive analysis and careful management of the results, prenatal ES might be beneficial and actionable, when offered in adjunct to genetic counseling in structurally normal fetuses.

METHODS: From April 2017 to March 2026, ES was carried out in 2,812 structurally normal fetuses that met our inclusion criteria. A subset of 482 cases has been reported previously. Only American College of Medical Genetics and Genomics (ACMG) pathogenic and likely pathogenic findings were reported. We classified variants into six groups (A1-C2) based on expected disease severity and available management ranging from severe with no treatment, to mild and treatable.

RESULTS: Of the 2,812 structurally normal fetuses, 16 (0.5%) harbored likely pathogenic/pathogenic variants in genes associated with severe and non-treatable conditions. Most of these conditions have a prominent neurodevelopmental phenotype, hence not anatomically-detected during these stages of pregnancy. Another 21 fetuses (0.7%) carried a likely pathogenic/pathogenic variant in genes associated either with severe/moderate conditions for which treatment is available, or moderate conditions without treatment. 73 fetuses (2.6%) were diagnosed with mild genetic conditions. Thirteen of the variants (11%) were de-novo, in genes associated with autosomal dominant inheritance.

dhagit@hadassah.org.il



The Classification Framework

Diagnostic groups are systematically plotted along two primary clinical axes, creating a six-tier gradient from the most severe, untreatable conditions to mild, manageable phenotypes.

		Treatability	
		Without treatment	With treatment
Severity	Severe	A1	A2
	Moderate	B1	B2
	Mild	C1	C2

Diagnostic Groups, Rates, and Examples

Category	Type of condition	Phenotypic characteristics	N (%)	Example (gene)
A1	Severe, without treatment	Neurodevelopmental, shortened life span (infancy)	16 (0.5)	Tubulinopathy (<i>TUB1A1</i>)
A2	Severe, with treatment	Generalized seizures, metabolic treatable diseases	5 (0.2)	Wilson disease Pompe disease, infantile-onset (<i>GAA</i>)
B1	Moderate, without treatment	Impairment in one of the senses	4 (0.1)	Enhanced s-cone syndrome (<i>NR2E3</i>)
B2	Moderate, with treatment	Skeletal anomalies, Impairment in one of the senses	12 (0.4)	X-linked dominant hypophosphatemic rickets (<i>PHEX</i>) Isolated hearing loss (<i>TRIOBP</i>)
C1	Mild, without treatment	Skin diseases	3 (0.1)	Dyschromatosis symmetrica hereditaria (<i>ADAR</i>), Legius disease
C2	Mild, with treatment	Hormone deficiency, premature puberty Incomplete penetrance, treatable/preventable	73 (2.6)	Insulin-like growth factor I, resistance to (<i>IGF1R</i>) Non classical congenital adrenal hyperplasia (<i>CYP21A2</i>) hypogonadotropic hypogonadism