Supplementary Table 2. Select references demonstrating that GS can provide a molecular diagnosis where ES did not.

Reference	Pathogenic variant category/allelic class where ES did not provide a diagnosis	Condition	Notes
Lionel et al. 2017[1]	deep intronic variants	1. ocular albinism, type 1, Nettleship-Falls Type 2. Ornithine transcarbamylase deficiency	
	small CNVs	1. thiamine metabolism dysfunction syndrome 2. early infantile epileptic encephalopathy, 4	
	SNVs in a noncoding RNA	Roifman syndrome	
	mitochondrial DNA variants	Leigh syndrome	
	exonic SNVs in regions with poor coverage on WES	1. Congenital disorder of glycosylation Type Iq 2. early infantile epileptic encephalopathy, 2	
Alfares et al. 2017[2]	repeat expansion (+25)	Congenital central hypoventilation syndrome	
	large deletion	Nemaline myopathy 1	
	intronic	Tuberous sclerosis type 2	
Zepeda-Mendoza et al. 2018[3]	complex chromosomal rearrangement (8 pairs of breakpoints mapped, translocation more complex rearrangement than initially thought)	severe global developmental delay, features of Rett syndrome and FOXG1 syndrome	
Carss et al. 2017[4]	structural variant	Inherited retinal disease	heterozygous (~55 kb) deletion spanning at least three other exons missed by ES
	Variants in GC-rich regions	Inherited retinal disease	GS had higher coverage in dataset bins with GC < 30% or > 70%
	Variants in noncoding regions	Inherited retinal disease	ES did not detect deep intronic variants in 3 cases
Ostrander et al. 2018[5]	Structural variants	Early infantile epileptic encephalopathy	ES unable to detect tandem duplication of

			CDKL5 or reciprocal translocation

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