Disclosure Slide

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Milen Velinov, MD, PhD

Head, Department of Human Genetics

NYS Institute for Basic Research in Developmental Disabilities

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Advanced Genetic Testing for Underserved Developmentally Disabled Patients

Milen Velinov[1], Andrea Haworth[2], Louisa Ive[2], Elaine Marchi[1], Maureen Gavin[1], Karen Amble[1], Ricardo Madrid[1], Mohammed Arif [1]and Gholson Lyon[1]

1. *NYS Institute for Basic Research in Developmental Disabilities, Staten island, NY 10314, USA*
2. *Congenica Limited, Biodata Innovation Centre, Wellcome Genome Campus, Hinxton, CB10 1DR, UK*

Abstract Background: Many families cannot afford next generation sequencing (NGS) based advanced genomic testing, as they are denied insurance coverage. These underserved families represent more than 50% of our patient population and include infants & children with developmental disabilities.

Methods We have developed a research-to-clinical testing system for genomic evaluation of individuals/families for which the insurance coverage is denied. This approach includes research-based exome sequencing using an accredited third-party provider (Novogene Ltd) with sequence data analysis undertaken using the Congenica clinical decision support platform (Congenica Ltd) where clinicians and data analysis specialists collaborate to identify causal DNA variants. Variant classification is undertaken in accordance with ACMG guidelines and variants are confirmed in a clinically accredited laboratory. After clinical confirmation, the families receive appropriate post-test counseling.

Family N°	Age at diagnosis (years)	Sex	Proband phenotype	Family structure	Findings	Clinical impact
17	12	F	progressive ataxia, developmental delay and hypotonia	Duo (mother/son)	MFN2: c.314C>T p.(Thr105Met) , Heterozygous, Pathogenic, Absent in mother	helped address co-morbidities; hearing loss, vision loss, scoliosis
23	30	M	ataxia, dysarthria, cataract, spastic diplegia	Hextet (3 affected siblings, 1 unaffected sibling, 2 unaffected parents)	ITPR1:c.800C>T p.(Thr267Met), Heterozygous, Pathogenic, Present in three affected siblings; absent from rest of family.? Parental Mosaicism	helped address co-morbidities
6	7	M	global developmental delay, astigmatism, hypotonia, microcephaly	Trio	GABRB2:c.911C>T; p.(Ala304Val) Heterozygous, Likely pathogenic, de-novo	visual impairment, seizure precautions
12	7	F	Hearing loss, global developmental delay, IUGR, agenesis of corpus callosum, chronic kidney disease, microcephaly	Trio	SLC30A9: c.[40delA+c.86_87dupCC] ; p.[p.Ser14AlafsTer28+Cys30Profs] , Compound heterozygous, Likely pathogenic Biparental inheritance	helped address kidney failure
13	11	M	white forelock, skin hypopigmented lesions, speech delay	Trio (father similar symptoms)	KIT: c.1342C>T p.(Gln448Ter) Heterozygous, Likely pathogenic. Paternal inheritance. Note: does not explain speech delay	provided unifying diagnosis
15	22	F	progressive ataxia, dysarthria	Singleton	SETX: c.1589_1590delCT p.(Ser530Cysfs) Apparent Homozygous, Likely pathogenic	provided unifying diagnosis
35	7.5	M	autism	Duo (mother/son)	KIF2A: c.949A>C p.(Ser317Arg). Heterozygous, Likely pathogenic. Absent in mother	provided unifying diagnosis
34	4	M	global developmental delay, retinal detachment, cataract	Trio	NHS: c.742C>T p.(Arg248Ter). Hemizygous, Pathogenic, Maternal inheritance	provided unifying diagnosis

Table 1: Clinical details of families with pathogenic or likely pathogenic variants identified as part of this study

Results Using this approach to date we have evaluated 28 probands. The studied individuals were 1-56 years old and had some form of neuro-developmental disability suggestive of genetic etiology. One or more close relatives for all but one of the participants were included in this study. We identified 8 actionable pathogenic or likely pathogenic sequence variants in genes *MFN2*, *ITPR1*, *GABRB2*, *SLC30A9*, *KIT*, *SETX*, *KIF2A and NHS (Table 1)*. This testing approach helped provide etiological diagnosis for about one third of our cohort. The diagnosis helped address actionable co-morbidities in three patients and provide better informed family planning for three families. The average cost of our testing was $1600. For comparison, the cost of clinical genomic testing done in a CLIA certified laboratory in the US ranges from $4,000 to $6,000 (Table 2)

Conclusions

The current unequal insurance coverage in the US creates a two-class system where some families have the resources and insurance policies to cover testing and other families are simply denied testing. Our approach allowed for the denied individuals to have in-house testing at a fraction of the commercial service cost. In addition, the analysis of the test findings was done with active participation of the referring clinicians. This approach contributed for more efficient symptom driven approach for the genomic analyses

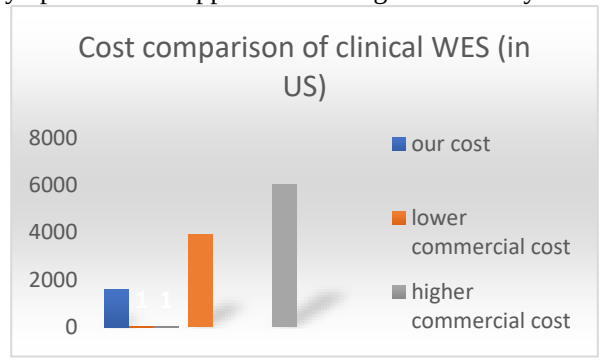

Table 2: Cost comparator between our study and typical commercial providers

References:

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