Demonstrating the Value of Genome Sequencing in a Pediatric Neurology Cohort: A Successful Partnership Between a Patient Organization and Industry

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INTRODUCTION

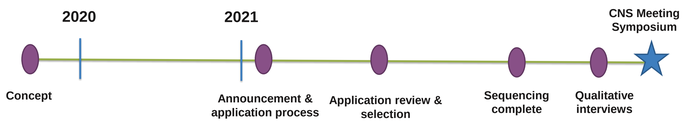
Approximately 2-6% of the population have a rare disease.[1,2] Up to 80% of rare diseases have a genetic etiology and a majority have an associated neurological phenotype.[3] Genome sequencing (GS) can be a powerful diagnostic tool for pediatric rare disease. Evidence demonstrating clinical utility of GS is also growing as the American College of Genetics and Genomics recently published evidence-based guidelines recommending exome sequencing (ES)/GS as a first- or second-tier test in individuals with ≥1 congenital anomaly prior to one year of age or individuals with intellectual disability and/or developmental delay with onset <18 years.[4]

OBJECTIVES

The Child Neurology Foundation (CNF) is an advocacy organization that serves as a collaborative center of education, resources and support for children and families living with neurological conditions. In 2020, CNF adopted an educational initiative focused on shortening the diagnostic odyssey. The objectives of this project were to:

- Identify strategy for how industry and advocacy organizations can work together towards similar goals
- Provide no-cost GS to pediatric patients with a neurologic condition who remain undiagnosed
- Apply case-based learning to improve awareness and comfort with GS among child neurologists

TIMELINE



METHODS

- Project was promoted through the CNF provider network
- An expert panel of child neurologists selected by CNF developed the inclusion criteria:
  - Neurology clinic based in the U.S.
  - Access to genetic counseling
  - Able to submit 5 cases that would benefit from GS
  - Clinician complete laboratory onboarding
  - Clinician agreement to interview with CNF
- Five sites selected with cases representing neurological conditions with unknown and suspected genetic etiology
- Consideration given to severity of phenotype or potential for treatment modification
- Clinical GS performed by one of two CAP/CLIA approved laboratories:
  - Illumina Clinical Services Laboratory (n=20)
  - Rady Children's Institute of Genomic Medicine (n=5)
- Clinical reports sent directly to ordering provider
- IRB exemption obtained retrospectively through WCG IRB

RESULTS

Cohort

- 104 applications received from 39 sites
- 25 cases from 5 clinical sites selected
  - University of Rochester Medical Center
  - Children's Hospital of Philadelphia
  - Children's Hospital Colorado
  - Marshfield Clinic
  - Kennedy Krieger Institute
- Significant diversity across geography, age, prior testing and phenotype
- Referrals to genetic counseling, philanthropic GS programs and research programs were provided to all referring sites not accepted to this program

PRIOR GENETIC TESTING (N=25)

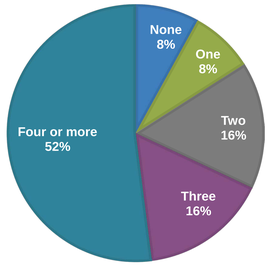


Figure 1: Number of prior genetic tests (ES, CMA, single gene, panel testing, mt DNA, methylation) (n=25)

Genome Sequencing Results

- 24% (6/25) of probands received a diagnosis through GS
- 92% (23/25) had at least one previous genetic test and 76% (19/25) had previous ES
- 40% (10/25) of probands received either a variant of uncertain significance (VUS) or incidental finding
  - 2 probands with incidental finding (IF) (G6PD; CLCN1)
  - 1 proband with G6PD IF and VUS
  - 2 probands with VUS in a gene of uncertain significance (GUS)
- 100% (6/6) of probands with positive GS result had ≥4 prior genetic tests

Demographics	N=25
Gender (Male; Female)	12;13
Average Age (Range)	9.04 yrs (1.6-21.7)
Ethnicity (N;%)	
White	20 (80%)
African Am.	1 (4%)
Asian Am./Pacific Islander	1 (4%)
Middle Eastern	1 (4%)
Not reported	1 (4%)
Sequencing structure	
Duo	1
Trio	20
Quad (1 with 2 affected probands)	3
Phenotype	Probands (n)
Epilepsy/seizures	18
Global developmental delay	17
Cognitive impairment	12
Hypotonia	13
Absent/delayed speech	10
Facial dysmorphia	9
Visual impairment/ocular abnormalities	8
Brain malformation	8
Feeding difficulties/G-tube	7
Autism spectrum disorder	6

Table 1: Cohort demographics; Phenotypes listed include top 10 reported across cohort

FREQUENCY OF PRIOR GENETIC TESTS IN TOTAL COHORT AND POSITIVE GS CASES

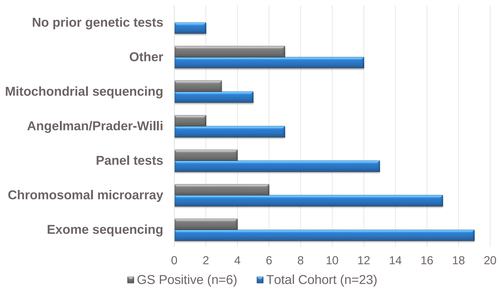
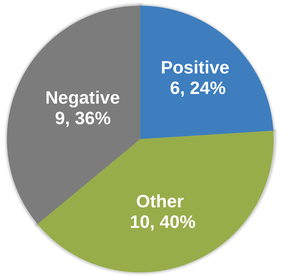


Figure 2: Comparison of frequency of genetic tests performed in probands prior to GS for the entire cohort (blue) and probands with a positive GS finding (gray). Other tests include karyotype, Fragile X syndrome, single gene testing. Three patients had no prior genetic tests.

PRIMARY FINDINGS (N=25)



OTHER (N=10)

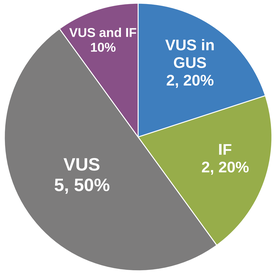


Figure 3: GS results categorized by positive (molecular finding explaining phenotype), negative (no molecular findings and other (VUS and/or IF).

Figure 4: Further classification of "other" results in 10 patients. Includes one case with both an IF & VUS. IF

Provider feedback

- *"GS can change care in meaningful ways"*
- *"GS changed the child's prognosis"*
- *"We know GS is a better test than ES or any other testing. Would love it to be standard of care."*

CASE EXAMPLE

- **Proband**: 16-year-old male, symptom onset at one year including, leukoencephalopathy, retinitis pigmentosa, bilateral progressive sensorineural hearing loss, mild intellectual disability, spastic diplegia, global delay, and short stature.
- **Prior genetic testing:** All negative, including ES
- **GS result:** Pathogenic SNV in MORC2 c/w MORC2-related neurodevelopmental disorder
  - Autosomal dominant, axonal Charcot-Marie-Tooth disease type 2
  - SNV missed on ES as MORC2 was not implicated in disease at that time
- **Clinical management impact:** Psychosocial and family counseling implications, limits need for recurrent brain MRI, initiate nerve conduction studies, thyroid screening

CONCLUSIONS & FUTURE THOUGHTS

- Diagnostic yield in diverse child neurology patient population was 24%
- Referring providers perceive value in GS for their patients
- Industry and patient advocacy groups should find innovative ways to partner to reach similar goals for education, evidence generation and access to care
- High level details about the project presented at the 2021 Child Neurology Society Annual Meeting as an educational initiative for neurology providers
- Continued follow up on the impact of results is indicated

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