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 family 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

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
  - Submit 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, the Rady Children's Institute of Genomic Medicine

Results

Prior genetic testing

- 104 applications received from 39 sites
- 25 cases from 5 clinical sites selected
  - University of Rochester Medical Center
  - Children's Hospital of Philadelphia
  - 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

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 (IP): GSDP and CLCN1
  - 1 proband with GPD IP and VUS
  - 2 probands with VUS in a gene of uncertain significance (UGS)
- 100% (6/6) of probands with positive GS result had >4 prior genetic tests

Demographics

- 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 4 (16%)

Sequencing structure

- Duo 1
- Trio (F 1 with 2 affected probands) 20
- Quad (F 1 with 2 affected probands) 6

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

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N=25</th>
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<tbody>
<tr>
<td>Brain malformation</td>
<td>8</td>
</tr>
<tr>
<td>Retinal abnormalities</td>
<td>8</td>
</tr>
<tr>
<td>Facial dysmorphia</td>
<td>9</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>12</td>
</tr>
<tr>
<td>Language deficit</td>
<td>8</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>13</td>
</tr>
<tr>
<td>Global developmental delay</td>
<td>17</td>
</tr>
<tr>
<td>Epilepsy/seizures</td>
<td>13</td>
</tr>
<tr>
<td>Seizure disorder</td>
<td>13</td>
</tr>
<tr>
<td>Congenital heart defect</td>
<td>11</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>PRIMARY FINDINGS (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>Negative</td>
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<tr>
<td>Other</td>
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</tbody>
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Case Example

- Probands: 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
- 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

- Referring providers perceive value in GS for their patients
- Industry and patient advocacy groups should find innovative ways to partner to reach similar goals
- Continued follow up on the impact of results is indicated

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References


CONCLUSIONS & FUTURE THOUGHTS

- Diagnostic yield in diverse childhood 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 detail 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