Can Expanded Carrier Screening Shorten the Diagnostic Odyssey in those with Genetic Disease?

*Presented by: Maysen Mesaros, MS, CGC She/her/hers*
Conflict of Interest Disclosure

- This study was conducted during an internship with Myriad Genetics, Inc.
- Maysen Mesaros had/has no financial interest in Myriad Genetics, Inc.
- Aishwarya Arjunan, Raul Torres, Rotem Ben-Shachar, Katie Johansen Taber were employed by Myriad Genetics, Inc. at the time of the study and received salary and stock options.
Co-authors

- Aishwarya Arjunan, MS, MPH, CGC, CPH
- Raul Torres, PhD
- Rotem Ben-Shachar, PhD
- Katie Johansen Taber, PhD
Background: Whole Exome Sequencing

- Substantial proportion of serious pediatric disease are caused by rare monogenic disorders
- Growing number of pediatric diseases are diagnosed by whole exome sequencing (WES)
  - Analysis of protein-coding region of genes (~20,000)
- WES may be offered after chromosomal microarray, karyotype, multi-gene panel, biochemical testing
- WES Cost
  - Per Tan et. al 2017 WES cost analysis study
    - Cost per patient of the standard diagnostic pathway with WES was $9792
    - WES performed at the first genetics appointment $5347
  - Per Daga et. al 2018
    - Average commercial cost of WES ranges from $1,000-$2,100 per sample in the United States
- Standard Turn Around Time (TAT): 8-10 weeks
Background: Expanded Carrier Screening

- Expanded carrier screening (ECS) identifies reproductive partners who are carriers of autosomal recessive (AR) or X-linked (XL) monogenic disorders
- Screens for severe disorders that typically affect quality of life at an early age
- Regardless of race, ethnicity, ancestry (REA)
- Average of 311 genes on ECS across four commercial laboratories
- Average TAT of 1-2 weeks
Research Question

If the parents of a child diagnosed by WES had undergone ECS, could they have received a diagnosis without needing WES?
Methods

• Literature search reporting WES in pediatric populations from October 2013 to January 2021

• Diagnoses and the associated genes identified were compared to genes on commercially-available ECS panels
  – Myriad Women’s Health, Invitae, Integrated Genetics, and Sema4
Methods

Included studies

- Majority pediatric cohort
- Definitive diagnosis
- > 1 AR or XL diagnosis made
- Global cohorts
- Targeted/small cohorts and large non-targeted

Excluded studies

- Re-analysis
- Genes not previously reported in humans
- Aggregate data only
Results

• 28 cohorts reviewed
• Cohorts of 18 to 2,000 patients
• Previous testing performed in 21 cohorts
  – Microarray, karyotype, metabolic, panel sequencing, single gene tests
• Definitive diagnosis achieved in **40.1%** of patients
  – Autosomal dominant (AD), autosomal recessive (AR) and X-linked (XL)
    • **AD: 61.3%**
    • **AR: 31.4%**
    • **XL: 7.3%**
Results

• Among the AR and XL conditions, **43.4%** are included on commonly ordered commercial ECS panels
• This implies that children whose parents had undergone ECS may have received a diagnosis without needing WES
<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsyndromic hearing loss (MYO15A)</td>
<td>5</td>
</tr>
<tr>
<td>Asphyxiating thoracic dystrophy</td>
<td>5</td>
</tr>
<tr>
<td>ID/Seizures IQSEC</td>
<td>5</td>
</tr>
<tr>
<td>Glycogen storage disease type IV</td>
<td>5</td>
</tr>
<tr>
<td>Bardet-Biedl syndrome</td>
<td>5</td>
</tr>
<tr>
<td>Familial hemophagocytic lymphohistiocytosis</td>
<td>5</td>
</tr>
<tr>
<td>Pendred syndrome</td>
<td>6</td>
</tr>
<tr>
<td>Usher syndrome</td>
<td>6</td>
</tr>
<tr>
<td>Titinopathy</td>
<td>6</td>
</tr>
<tr>
<td>Methylmalonic acidemia with homocystinuria</td>
<td>7</td>
</tr>
<tr>
<td>Oro-facial-digital syndrome</td>
<td>7</td>
</tr>
<tr>
<td>CDKL5 deficiency disorder</td>
<td>7</td>
</tr>
<tr>
<td>POLG-related disorders</td>
<td>9</td>
</tr>
<tr>
<td>Cornelia de Lange SMC1A</td>
<td>9</td>
</tr>
<tr>
<td>Infantile neuroaxonal dystrophy</td>
<td>9</td>
</tr>
<tr>
<td>Alpha thalassemia x-linked disability</td>
<td>10</td>
</tr>
<tr>
<td>Pyruvate dehydrogenase deficiency</td>
<td>11</td>
</tr>
<tr>
<td>Nonsyndromic hearing loss (GJB2)</td>
<td>21</td>
</tr>
<tr>
<td>Rett syndrome</td>
<td>30</td>
</tr>
</tbody>
</table>
All ECS genes were found on >3 of the analyzed panels

- Exception PLA2G6
Tier 3 Carrier Screening

- Total AR and XL diagnoses= 1,042
- 150 are ACMG Tier 3 conditions
  - 14.%
- Tier 3 = > 1/200 carrier frequency
- ACMG Recommends
  - All pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening
Case Example

- 278 infants within the first 100 days of life
- Admitted to Texas Children’s Hospital in Houston
- 190 (68.3%) NICU
- 43 (15.5%) CVICU
- 18 (6.5%) PICU
- Chromosomal microarray analysis (CMA) was completed in 237/278 (85%) infants
Case Example Continued

- 57 AR or XL diagnoses (20.50%)
- 45.09% on ECS

**AR:** NPHP3, HSD17B4, DYNC2H1 (x2), FANCA, UNC13D, ACAD9, LIPT1, KLHL40, SLC4A11, COL12A1, WNT5A, MUT, BRCA2, TRMU (x2), FAT4, ETFDH, ENPP1, GBE1(x2), WDR19, POMT2, GDF1, POMT1, VPS33B, TMEM67, RAG1, ALDH7A1, TTN, ATP8B1, ALG6, EARS2 (x2), SMAD6, BBS1, AGTR1, TBCD, ISPD, OBSL1, PRF1, WNT10B, ASPM

**XL:** CDKL5, SHOX, PDHA1, LAS1L, OCRL, ATP7A, ARX, ABCD1, BCAP31, PLXNB3, MECP2, OFD1 (x3)

= ECS
Familial hemophagocytic lymphohistiocytosis

- **UNC13D** gene, on ECS
- Body makes too many activated immune cells
  - Life threatening
    - Hepatosplenomegaly
    - Fever, rash
    - Lymph node enlargement
    - Kidney, heart, breathing, neurological problems
    - Increased risk for leukemia and lymphoma
- Treat with allogenic hematopoietic stem cell transplant
  - AS EARLY AS POSSIBLE!!
  - Without treatment, median survival <2-6 months after diagnosis
Conclusion/Discussion

A large proportion of genes found by WES as causative of pediatric disease are included on ECS panels.

As WES often is a last resort after many other diagnostic tests, ECS screening, and the knowledge that it provides to parents about risk to their future children, may be useful in targeting and shortening the diagnostic odyssey for affected children.
References


References


