Whole-Genome Sequencing for Rare Disease
A Global Patient Advocacy Resource
The Burden of Genetic Disease

- 6% of the population worldwide is affected by a rare disease (RD).\(^{1,2}\)
- Nearly 80% of all RD has a genetic cause; over 7,000 genetic conditions have been identified.\(^{2-5}\)
- Half of RD cases impact children and 30% will not survive beyond the age of 5 years.\(^{3}\)
- The average diagnostic odyssey lasts approximately 7 years.\(^{3}\)

Genetic Testing Approaches

- Current standard of care for RD may include single gene testing, multi-gene panel testing, microarray (CMA) and/or whole-exome sequencing (WES). (Figure 1)
- Whole-genome sequencing (WGS) sequences the entire genome (Figure 1) and is the only test that can nearly detect all types of genetic variants.\(^{10,11}\) (Table 1)

Figure 1
Utility of Whole-Genome Sequencing

Diagnostic Utility

- The likelihood of a diagnosis or diagnostic yield has been shown to be higher in WGS (55-70%) compared to WES (24-33%) and CMA (15-23%).\(^{10,16-18}\)
- Copy number variant detection is greater with WGS compared to CMA.\(^{7,9}\)
- Exome coverage is greater with WGS compared to WES. WES may miss 1-3% of disease-causing mutations in the exomes detectable by WGS.\(^{13-15}\)
- Combined data from 37 studies comprising 20,068 children found an 8.3x increase in diagnostic yield with WES/WGS compared to microarray.\(^{19}\)
- Recent studies demonstrate the diagnostic superiority of WGS compared to standard testing in select patient groups (Table 2).\(^{7,10,12,19-20}\)
  - Critically ill infants.\(^{8,9,21}\)
  - Children with intellectual disability / developmental delay\(^{22-23}\) and pediatric outpatients.\(^{10,12,24}\)
- WGS decreases time to diagnosis compared to standard genetic testing.\(^{7,8}\)
- In a randomized-controlled trial of critically ill NICU and PICU patients, WGS shortened time to diagnosis by 88% (13 days vs. 107 days) compared to standard genetic testing.\(^{8}\)
- In a clinically heterogeneous cohort of pediatric outpatients, WGS provided a diagnosis in an average of 43 days compared to the average diagnostic journey of 77 days prior to study enrollment.\(^{7}\)

Clinical Utility

- Identification of the genetic cause of an individual’s disease has utility and psychosocial benefits for the patient, their family, and society at large as it can:
  - Prevent additional unnecessary testing
  - Lead to the development of new therapies and management strategies
  - Enable informed family-planning
  - Provide opportunities for psychosocial support via disease support groups.\(^{25-27}\)
- A change in management has been reported in 30-72% of critically ill infants and 49-75% of pediatric outpatients who received a diagnosis by WGS.\(^{9,28}\)

Health Economic Utility

- Next-generation sequencing (NGS)-based testing strategies are more cost-effective than multiple, single-gene tests.
- In one study, the cost of tests in children with neurodevelopmental disorders prior to receiving an NGS-based diagnosis was $19,100 (USD).\(^{7}\)
- US-based hospital discharges linked to a genetic disease are associated with higher healthcare utilization, including additional procedures (up to 4 more) longer length of stay (2-18 days) and higher total costs per discharge ($12,000-$77,000) (USD).\(^{6}\)
- Genomic sequencing performed when genetic disease is initially suspected provides an efficient and economical approach to arriving at a diagnosis.\(^{29}\)
### Table 1

**Comparison of Testing Methods**

<table>
<thead>
<tr>
<th>Testing Method</th>
<th>SNVs and Indels</th>
<th>CNVs</th>
<th>Repeat Expansions</th>
<th>Structural Variants</th>
<th>Mitochondrial</th>
<th>Number of loci (regions) evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>WGS</td>
<td>Yes(^1^0)</td>
<td>Yes(^1^0)</td>
<td>Yes(^1^8)</td>
<td>Yes(^{(Emerging)})^(^3^0)</td>
<td>Yes(^1^0)</td>
<td>3 billion</td>
</tr>
<tr>
<td>WES</td>
<td>Yes</td>
<td>Limited</td>
<td>No</td>
<td>Limited</td>
<td>Yes</td>
<td>5 million</td>
</tr>
<tr>
<td>Chromosomal Microarray (CMA)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>~0.05-2 million</td>
</tr>
<tr>
<td>Karyotype</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>~500</td>
</tr>
<tr>
<td>Targeted Gene Panel</td>
<td>Yes</td>
<td>Limited</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Varies based on # of genes</td>
</tr>
<tr>
<td>Sanger (Single Gene)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Average ~27,000 (1,000-2 million)</td>
</tr>
</tbody>
</table>

**Table 2**

**Diagnostic Yield of WGS versus Standard Testing**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Region</th>
<th>Design</th>
<th>N</th>
<th>WGS (%)</th>
<th>Comparator (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Critically Ill Infants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Diemen et al. (2017)^(^2^4)</td>
<td>The Netherlands</td>
<td>Prospective</td>
<td>23</td>
<td>30</td>
<td>4 (standard testing)</td>
</tr>
<tr>
<td>Willig et al. (2015)^(^9)</td>
<td>United States</td>
<td>Retrospective</td>
<td>35</td>
<td>57</td>
<td>9 (standard testing)</td>
</tr>
<tr>
<td>Petrikin et al. (2018)^(^8)</td>
<td>United States</td>
<td>Randomized controlled trial</td>
<td>65</td>
<td>31</td>
<td>22 (standard testing)</td>
</tr>
<tr>
<td><strong>Stable Individuals with an Undiagnosed, Suspected Genetic Condition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lionel et al. (2017)^(^1^0)</td>
<td>Canada</td>
<td>Prospective (children with a suspected genetic condition)</td>
<td>103</td>
<td>41 (diagnostic variants)</td>
<td>24 (standard testing)</td>
</tr>
<tr>
<td>Stavropoulos et al. (2015)^(^1^2)</td>
<td>United States</td>
<td>Prospective (individuals with a suspected genetic disease)</td>
<td>100</td>
<td>41</td>
<td>13 (standard testing)</td>
</tr>
<tr>
<td>Gilissen et al. (2018)^(^2^7)</td>
<td>United States</td>
<td>Prospective (individuals with severe intellectual disability)</td>
<td>50</td>
<td>42</td>
<td>27 (WES)</td>
</tr>
</tbody>
</table>

**Abbreviations:**

- **SNV** – single nucleotide variant
- **Indel** – small insertion/deletion
- **CNV** – copy number variant
- **CMA** – chromosomal microarray
- **WES** – whole-exome sequencing
- **WGS** – whole-genome sequencing
References


3. https://globalgenes.org

4. Illumina manuscript in development


