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]
- Average healthcare cost per discharge is significantly higher ($12,000-$77,000) in patients with a genetic diagnosis vs. those without.[6]
- For critically ill infants with a RD, a fast diagnosis can be critical for timely and appropriate medical intervention. For pediatric outpatients, it can put an end to the long expensive diagnostic journey. [7-9]

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

Likelihood of Finding a Diagnosis: High → Low

Current Testing Options	SNVs and Indels	CNVs	Repeat Expansions	Structural Variants	Mitochondrial	Number of loci (regions) evaluated
WGS	Yes[10]	Yes[10]	Yes[18]	Yes (Emerging)[30]	Yes[10]	3 billion
WES	Yes	Limited	No	Limited	Yes	5 million
Chromosomal Microarray (CMA)	No	Yes	No	No	No	~0.05-2 million
Karyotype	No	No	No	Yes	No	~500
Targeted Gene Panel	Yes	Limited	No	No	Yes	Varies based on # of genes
Sanger (Single Gene)	Yes	No	No	No	Yes	Average ~27,000 (1,000-2 million)

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

Table 2

Diagnostic Yield of WGS versus Standard Testing

Reference	Region	Design	N	WGS (%)	Comparator (%)
Critically Ill Infants					
Van Diemen et al. (2017)[24]	The Netherlands	Prospective	23	30	4 (standard testing)
Willig et al. (2015)[9]	United States	Retrospective	35	57 (rapid WGS)	9 (standard testing)
Petrikin et al. (2018)[8]	United States	Randomized controlled trial	65	31	22 (standard testing)
Stable Individuals with an Undiagnosed, Suspected Genetic Condition					
Lionel et al. (2017)[10]	Canada	Prospective (children with a suspected genetic condition)	103	41 (diagnostic variants)	24 (standard testing)
Stavropoulos et al. (2015)[12]	United States	Prospective (individuals with a suspected genetic disease)	100	41	13 (standard testing)
Gilissen et al. (2018)[27]	United States	Prospective (individuals with severe intellectual disability)	50	42	27 (WES)

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