Whole-Genome Sequencing for Rare Disease

A Global Patient Advocacy Resource

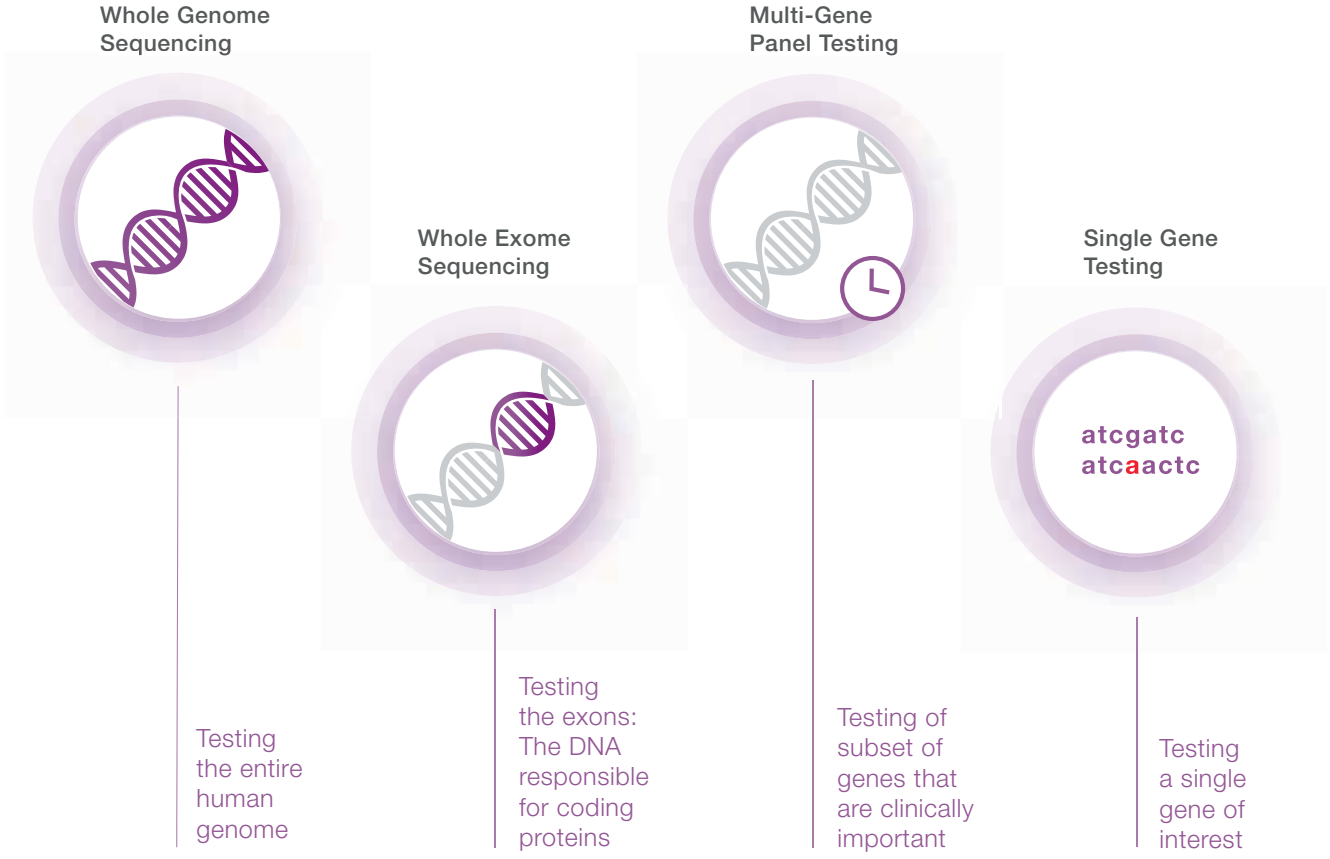
The Burden of Genetic Disease

- 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)

References

1. Ferreira CR. The Burden of Rare Diseases. *American Journal of Medical Genetics.* 2018
2. https://www.eurordis.org/content/what-rare-diseaseGlobal Genes. https://globalgenes.org/rare-diseases-facts-statistics/
3. https://globalgenes.org
4. Illumina manuscript in development
5. https://www.omim.org/statistics/geneMap
6. Gonzaludo N, Belmont JW, Gainullin VG, Taft RJ. Estimating the burden and economic impact of pediatric genetic disease. *Gen Med.* 2018;
7. Soden SE, Saunders CJ, Willig LK, et al. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. *Sci Transl Med.* 2014;6(265): 265ra168.
8. Petrikin JE, Cakici JA, Clark MM, et al. The NSIGHT1-randomized controlled trial: rapid whole-genome sequencing for accelerated etiologic diagnosis in critically ill infants. *NPJ Genom Med.* 2018 Feb 9;3:6. doi: 10.1038/s41525-018-0045-8.
9. Willig LK, Petrikin JE, Smith LD, et al. Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings. *Lancet Respir Med.* 2015;3(5): 377–387. doi:10.1016/S2213-2600(15)00139-3.
10. Lionel AC, Costain G, Monfared N, et al. Improved diagnostic yield compared with targeted gene sequencing panels suggests a role for whole-genome sequencing as a first-tier genetic test. *Genet Med.* 2017; Aug 3. doi: 10.1038/gim.2017.119.
11. Sanghvi RV,Buhay CJ, Powell, V et al. Characterizing reduced coverage regions through comparison of exome and genome sequencing data across 10 centers. *Genet Med.* 2017; doi:http://doi.org/10.1038/gim.2017.192.
12. Stavropoulos DJ, Merico D, Jobling R, et al. Whole-genome sequencing expands diagnostic utility and improves clinical management in pediatric medicine. *NPJ genomic medicine*, 2016;1.
13. Meienberg J, Bruggmann R, Oexle K, Matyas G. Clinical sequencing: is WGS the better WES? *Hum Genet.* 2016;135(3):359-362.
14. Belkadi A, Bolze A, Itan Y, et al. Whole-genome sequencing is more powerful than whole-exome sequencing for detecting exome variants. *Proc Natl Acad Sci U S A.* 2015 Apr 28;112(17):5473-8. doi: 10.1073/pnas.1418631112
15. Ostrander BEP, Butterfield RJ, Pedersen BS, et al. Whole-genome analysis for effective clinical diagnosis and gene discovery in early infantile epileptic encephalopathy. *NPJ Genom Med.* 2018;3:22.
16. Vissers LE, Gilissen C, Veltman JA. Genetic studies in intellectual disability and related disorders. *Nat Rev Genet* 2016;17:9-18.
17. Wilfert AB, Sulovari A., Turner TN, et al. Recurrent de novo mutations in neurodevelopmental disorders: Properties and clinical implications. *Genome Medicine,* 2017; 9(1), 1–16. http://doi.org/10.1186/s13073-017-0498-x
18. Dolzhenko E, van Vugt JJ, Shaw RJ, Bekritsky, et al. Detection of long repeat expansions from PCR-free whole-genome sequence data. *Genome Res.* 2017; Sep 8. doi: 10.1101/gr.225672.117
19. Clark MM, Stark Z, Farnaes L, et al. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected diseases. *NPJ Genom Med.* 2018 Jul 9;3:16. doi: 10.1038/s41525-018-0053-8.
20. Farnaes L, Hildreth A, Sweeney NM, et al. Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization. *NPJ Genom Med.* 2018;3:10.
21. Mestek-Boukhibar L, Clement E, Jones WD, et al. Rapid Paediatric Sequencing (RaPS): comprehensive real-life workflow for rapid diagnosis of critically ill children. *J Med Genet.* 2018;55(11):721-728.
22. Bick D, Fraser PC, Gutzeit MF, et al. Successful Application of Whole-Genome Sequencing in a Medical Genetics Clinic. *J Pediatr Genet.* 2016;6(2):61-76.
23. Saunders CJ, Miller NA, Soden SE, et al. Rapid whole-genome sequencing for genetic disease diagnosis in neonatal intensive care units. *Sci Transl Med.* 2012;4(154):154ra135.
24. van Diemen CC, Kerstjens-Frederikse WS, Bergman KA, et al. Rapid Targeted Genomics in Critically Ill Newborns. *Pediatrics.* 2017;140(4).
25. Hayeems R, Scherer S, Ungar W et al. Care and cost consequences of pediatric whole-genome sequencing compared to chromosome microarray. *Euro J Hum Gen.* 2017; doi:10.1038/s41431-017-0020-3
26. Costain G, Jobling R, Walker S, et al. Periodic reanalysis of whole-genome sequencing data enhances the diagnostic advantage over standard clinical genetic testing. *Eur J Hum Genet.* 2018;26(5):740-744.
27. Gilissen C, Hehir-Kwa JY, Thung, DT et al. Genome sequencing identifies major causes off severe intellectual disability. *Nature.* 2014; 511:344-7.
28. Scocchia A et al. Clinical whole-genome sequencing as a first-tier test at a resource-limited dysmorphology clinic in Mexico. *NPJ Genom Med.* 2019 Feb 14;4:5. doi: 10.1038/s41525-018-0076-1. eCollection 2019.
29. Sabatini LM, Mathews C, Ptak D, et al. Genomic sequencing procedure microcosting analysis and health economic cost-impact analysis: A report of the Association for Molecular Pathology. *J Molecular Diagnostics.*
30. Chen, X., Schulz-Trieglaff, O., Shaw, R., et al. Manta: Rapid detection of structural variants and indels for germline and cancer sequencing applications. *Bioinformatics,* 2016;32(8):1220–1222. http://doi.org/10.1093/bioinformatics/btv710

Brought to you by the Illumina Corporate Foundation