Whole Exome Sequencing (WES), or the sequencing all of the exons in a genome, capitalizes on the observation that 85% of disease-causing mutations are found in the coding sequence and regulatory regions of exons\(^1\) (For more information on WES, see *Genovations Volume 1, Issue 3*). In recent years, there have been many published papers that use WES to identify unknown variants in individual patients to identify causal mutations responsible for patient phenotypes. Indeed, Les Biesecker at the National Human Genome Research Institute at NIH and Robert Green of Harvard University have recently published an [interactive video set](#) on the website of the New England Journal of Medicine that is aimed at educating physicians about clinical genome and exome sequencing\(^2\). This sequencing often results in changes in patient care, elimination of unnecessary testing, and future reproductive planning guidance for parents of affected individuals.

One study published recently\(^3\) asked the question on a more global scale “How often does WES identify a causal mutation that makes a difference in the management of patients with genetic disorders?” This study retrospectively analyzed the charts and whole exome sequencing data from 115 patients seen at the Columbia University Medical Center in New York between October 2011 and July 2013. In addition to the clinical genetics patient care applications, this publication also addressed issues of pre-test counseling, consent, insurance coverage, and updating of test results based on new scientific evidence. The results indicated that WES is “feasible, has clinical utility and allows timely medical interventions, informed reproductive choices, and avoidance of additional testing.” Furthermore, in 4 cases, the results identified new phenotype ranges associated with particular genetic variants and found new candidate disease genes that would not have been identified otherwise. The clinical use of WES for diagnostic purposes in these 115 patients resulted in a definitive genetic etiology in 37/115 or 32.1% of the cases. Within a subset grouping of patients with developmental delay/intellectual disability, this number rose to 7/18 or 34% of patients receiving a definitive diagnosis by WES.

WES is a powerful tool that can be incorporated into routine clinical use to diagnose genetic disease, identify incomplete penetrance, and predict future risk. However, the clinical utility of 32-34% as published in the Columbia study may not seem remarkable. Despite the enormous capability of WES to impact our diagnostic capacity and patient care, an understanding of the limitations of WES is critical:
1. All exons, regulatory regions, splice sites and UTRs are not necessarily covered. For example, genes that are located within or very near repeats at the ends or middle of chromosomes are infrequently represented in the exome capture libraries. The Genomics Core is working with excellent partner companies such as Personalis, who have generated an exome capture library that includes all genes, regulatory regions, splice sites and UTRs, to minimize this limitation and provide the most informative WES data to our clinical colleagues.

2. A small subset of genetic disorders is the result of variants in the mitochondrial genome and not the nuclear genome. These variants are typically not present within exome capture libraries.

3. Structural variants, meaning chromosomal translocations and inversions are not going to be detected by WES. These structural changes must be identified by other means (karyotyping, G-banding) but do not alter the nucleotide sequence and are undetectable by WES.

4. Copy number variations, meaning changes in the number of copies of any given gene, also do not alter the nucleotide sequence and will go undetected by WES.

5. Repeat expansions such as those present in Huntington’s Disease, Friedreich ataxia and Fragile X syndrome also do not change the nucleotide sequence. These diseases result from expanded DNA repeats rendering them undetectable by WES.

6. Uniparental disomy – meaning two mutations inherited from one parent instead of a single mutation from each parent will appear the same in WES. The affected child will still have two mutations. This has implications for future reproductive planning for the parents and will impact the disease risk of future siblings.

7. Epigenetic changes, including alterations in chromatin methylation, phosphorylation, ubiquitination, etc. all impact gene expression, but do not change the underlying gene sequence and will not be detected by WES. Furthermore, the genes for small, 19-22 nucleotide microRNAs are typically found in introns of other genes and therefore, not found in exome capture libraries.

8. Gene-gene (epistatic) interactions where one gene affects the expression of another can explain why diseases present with a varied spectrum of severity. Two siblings can inherit the same single-gene disease variant, but one sibling also inherits a variant in another gene that counteracts the first and results in a less severe disease phenotype

References:

