Prenatal Whole Exome Sequencing

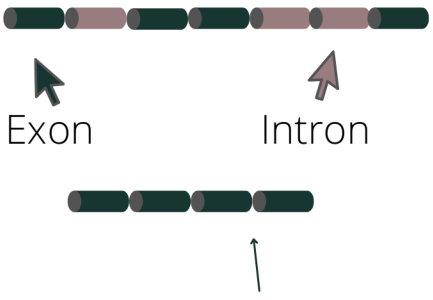
Prenatal whole exome sequencing (WES) is a relatively new test available in the prenatal setting. Whole exome sequencing is usually ordered for young children, who are suspected to have a genetic condition. However, there are some studies that have found this test can be helpful for pregnancies in which there is a suspected genetic condition or for unexplained stillbirth. WES is usually ordered after all other testing has come back negative, but this may not be the case for everyone. Other testing would include the microarray test which is able to identify chromosomal conditions such as microdeletions or microduplications. Gene panels may also have been offered before WES. A gene panel assesses multiple genes which are well studied and selected because they are most likely to be the underlying cause of certain birth defects.

WES analyzes multiple genes simultaneously to identify mutations or pathogenic variants that could explain birth defects. However, it does not assess all genetic conditions. It focuses on the "exons" or important protein-coding regions of genes.

Our genes instruct our bodies to make proteins. The gene will be "read" like an instruction manual. Some of the information from the gene is more important than other information. The exon is the most important information of the gene whereas the intron is the information that can be left out in the protein instructions. Whole exome sequencing will evaluate the exons from the genes but not the introns.

WES has some limitations. Insurance coverage for WES may not be guaranteed, and prior authorization may be necessary to assess costs. Results can take a few weeks, potentially limiting reproductive options. Additionally, the test is interpreted using the description of birth defects found on the ultrasound. An ultrasound cannot predict developmental delay or other future health complications, so the whole exome sequence results may be interpreted with limited information. Therefore, it may need to be reanalyzed once the baby is a little older.

Pathogenic variant = Also known as a mutation, is a change in a gene that disrupts its normal function, leading to incorrect instructions for the body or the protein it produces. This variant can result in a genetic condition, causing health problems or abnormalities.



Only the "exons" or protein instructions are assessed with WES

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The results of prenatal WES fall into three main categories: Negative, Positive, and Variants of Uncertain Significance (VUS).

A positive result indicates the presence of a pathogenic variant in a gene associated with the ultrasound findings, providing a likely cause for the observed features.

A negative result means no pathogenic variants were found, but it doesn't rule out the possibility of an underlying genetic condition. Reanalysis of data in the future may be considered for negative results.

A variant of uncertain significance (VUS) means there was a variant identified in a gene, but it is unknown if the variant causes the gene not to work in the way it is supposed to. Essentially, it is not clear if the VUS is normal variation or disease causing. More information may be available later.

In some cases, whole exome sequencing (WES) may not provide a definitive answer for the findings observed on ultrasound or other medical history. Reanalysis of WES data can be done after a year or so, as more genes and data become available, which may offer additional insights.

When undergoing WES, there is an option to include assessment for "clinically actionable" conditions, even if they are not directly related to the initial reason for pursuing WES. Clinically actionable conditions are those for which healthcare management recommendations may be available later in life. Examples include Hereditary Breast and Ovarian Cancer syndrome caused by pathogenic variants in the BRCA1 or BRCA2 genes. However, the decision to include these conditions is a personal one, as it may not be relevant to the initial purpose of WES, may not have childhood treatment options, and may cause anxiety or reveal risks for parents. The option to include additional conditions is discussed during the consent process prior to proceeding with WES.

This handout discusses what whole exome sequencing is, its limitations, and possible results. It is important to review this information with your healthcare provider.

Resources:

- Jelin AC, Vora N. Whole Exome Sequencing: Applications in Prenatal Genetics. Obstet Gynecol Clin North Am. 2018;45(1):69-81. doi:10.1016/j.ogc.2017.10.003
- Wapner RPs, Brennan K, Bier L, Wou K, Goldstein D. Whole exome sequencing in the evaluation of fetal structural anomalies: A prospective study of sequential patients. Am J Obstet Gynecol. 2017;216:S5–6.
- https://www.ncbi.nlm.nih.gov/clinvar/docs/acmg/

For more information, please speak to a healthcare provider.