Why are parental samples important?

Using the parents' exome data significantly improves the analysis of the patient's exome and increases the chance of identifying a diagnosis. Having the parents' information also helps decrease the number of VUSs. Comparing the exome of the patient to the parents' exomes can determine if a mutation or VUS was inherited or is new to the patient. If both biological parents are not available, we may request samples from other appropriate family members, such as unaffected siblings. We will only use the parents' exome data to help determine which changes identified in the patient are most likely to cause disease. Therefore, parents (or other family members) will not receive a separate report.

Since we will be using the parents' exome data, WES could reveal a potential blood relationship between the parents and could also detect mistaken parentage of the patient. These types of findings will typically not be reported unless it is necessary for the understanding of the patient's results.

What are secondary findings?

Secondary findings are changes in genes that are not related or not thought to be related to the patient's concerns. WES includes analysis of essentially every gene, including genes known to be associated with adult onset conditions such as cancer. The purpose of WES is not to analyze these genes but rather to identify the cause of the patient's current condition. However, the American College of Medical Genetics and Genomics (ACMG) recommends that laboratories report mutations identified in a specific set of genes for every patient undergoing WES, regardless of the indication for testing or the age of the patient. ACMG chose this set of genes because they are considered "medically actionable", meaning that there are specific medical guidelines for prevention, intervention, and/or medical management. These genes were also chosen because abnormalities in them can be associated with a significant risk for life threatening conditions. These genes can be grouped into the following categories:

Cancer predisposition genes – some of the genes are associated with a significantly increased risk for malignant or cancerous tumors. Some of these genes are only associated with adult onset tumors but many can cause tumors in childhood.

Heart and/or vascular conditions – some of the genes are associated with a significantly increased risk for heart and blood vessel related conditions such as aneurysms, aortic dissections, and arrhythmias, which can cause sudden death.

Other – there are other genes, including one that causes a specific type of high cholesterol, and another that is associated with malignant hyperthermia. Malignant hyperthermia is a genetic condition that can cause significant complications and even death while under anesthesia for surgery.

Knowing about mutations in these genes can provide important information for an individual's health. ACMG recommends the reporting of mutations in these genes but also recognizes the importance for families to have a choice of whether or not they want this type of information. Our laboratory may also feel compelled to report secondary findings in additional genes not included in the set of genes recommended by ACMG. You will have the option to "opt out" of learning about secondary findings. If you choose to "opt out," the results report will only include changes in genes known or thought to be related to the patient's condition. Secondary findings will not be reported for parents or any other family members that have been included in WES to help understand the patient's concerns.

We will not report secondary findings in genes that cause certain types of conditions that occur in adulthood and/or cannot be prevented. For example, there are genes associated with adult onset conditions such as Alzheimer disease and Parkinson disease. There are currently no preventions for these types of conditions. These conditions also occur in adulthood and most healthcare professionals consider it unethical to test children for a genetic predisposition to one of these types of conditions. Please talk to your physician or genetic counselor if you have questions about secondary findings.

Whole Exome Sequencing

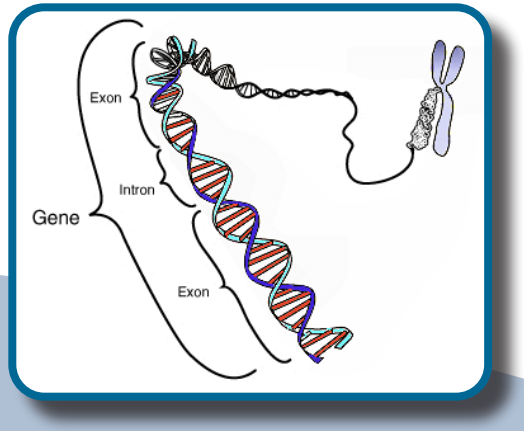
Information for Patients

Greenwood Genetic Center

www.GGC.org

What is an exome?

The human body is made of cells that contain chromosomes. The chromosomes are made of DNA and carry the genetic information that we pass down from one generation to the next. Genes are units of DNA and provide the instructions that our bodies use to grow, develop, and function properly. Only about 2% of our entire amount of DNA consists of genes. When changes happen in DNA leading to disease or disability, they occur most often within a gene. Genes are made up of different sections called exons and introns. The exons are the sections that code for specific proteins. These proteins perform the jobs in our cells that allow our bodies to work properly. The exome is the entire set of exons from every gene.



What is whole exome sequencing (WES)?

Whole exome sequencing is a technology that reads the DNA of the most important parts (the exons) of essentially every gene. The goal of WES is to look for misspellings in the DNA that could provide an explanation for the concerns a person is having. WES is currently one of the most comprehensive genetic tests available. WES is performed using DNA usually isolated from a blood sample. The patient's DNA sequence is compared to the sequences of healthy people to look for differences that could harm the function of a gene and cause the patient's concerns.

How long does it take to complete WES?

Once the laboratory receives the sample, it will take several months to complete the WES test.

What type of results can be expected?

The analysis of the entire exome is a very complicated process and results can be complex. There are typically four types of results when analyzing the exome. Most results will fit into one of the following categories:

- A **mutation** in a gene that has been associated with the symptoms or concerns of the patient. A mutation is a change or misspelling in the DNA that is known or predicted to harm the function of the gene and cause disease. This type of result is typically the most helpful since it usually leads to a diagnosis for the patient.
- A **variant of uncertain significance (VUS)** in a gene known to be associated with the patient's condition. A VUS is a change in a gene, but we do not know enough to say for sure that it harms the function of the gene. Not every misspelling in a gene leads to disease. Calling a change a VUS means that we cannot determine whether it is the cause of the patient's concerns or is just a benign or normal variation. Testing the biological parents for any VUS found in the patient may help us understand the significance of the VUS. This is one reason why we request samples from each parent when performing WES.
- A **mutation or VUS in a candidate gene**. A candidate gene is a gene that has not been previously proven to cause a disease or disability, but there is good evidence to believe that it might. Additional research would be needed to determine whether the candidate gene is associated with a medical condition. A change in a candidate gene would not be an immediate diagnosis for the patient.
- **Normal**, meaning no mutations or VUSs were detected in the areas of the exome that were tested. This does not mean that the patient does not have a genetic condition. There could be a change in an untested region since WES does NOT look at EVERY part of EVERY gene. There may also be a change in a gene that cannot be detected by WES technology (see limitations). Information about genes and their association with disease can change and therefore an analysis of WES done today could be different if done several years from now. You should check back with us in the future about new information or re-analysis of your/your child's WES data.

We will only report mutations and VUSs in genes that are known or thought to be associated with the patient's symptoms and features. There is a potential to find changes in genes that are unrelated to the patient's current concerns. We call these types of changes secondary findings. You will have the option to learn about secondary findings associated with a subset of particular conditions. Please see the section on secondary findings for more information.

What are the limitations of WES?

WES does not detect all possible causes of genetic conditions. It does not detect changes outside of the exome and it cannot detect certain types of changes such as large deletions (missing pieces) or duplications (extra pieces) within the genes or chromosomes. WES will also not detect abnormal repeat expansions (which cause certain diseases like Fragile X syndrome, myotonic dystrophy, and Huntington disease). This test may not detect changes in the mitochondrial DNA, which is separate from the chromosomal DNA.