ExomeSeq Whole Exome Sequencing
A Guide for Families
**ExomeSeq** is a test that looks at most genes. This test may be useful for patients whose medical and family histories suggest a genetic cause for their signs and symptoms. Most patients who have whole exome sequencing (WES) have had other genetic testing that did not find a genetic cause of their condition.

**Genes**

Genes are chemical instructions that tell a cell what job to perform. A gene is like a recipe for making a particular protein. Proteins do important jobs in every cell of the body.

Genes are written in code, with four chemicals (represented by the letters A, T, C, and G) that spell out the instructions to make a protein. People generally have two copies of most genes, one copy from each parent.
Parts of a Gene

Most genes are made up of *introns* and *exons*. Exons are the parts of the gene that contain the information used to make a protein. They are the “coding” part of the gene. Introns are regions of DNA in between exons and do not code for proteins.

The exons are the parts of the gene that make the protein.
**Genome and Exome**

Your DNA is your own personal blueprint for life. The *genome* includes a person’s entire DNA, both the introns and the exons. The *exome* includes only the exons (the parts used to make proteins). The introns and other non-coding sequences of DNA are not part of the exome. If you think of the genome as all of the action in a football game, the exome is like the game highlights with many of the important plays.

**Genome vs. Exome**

<table>
<thead>
<tr>
<th>Genome</th>
<th>Exome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A genome is like watching a football game from beginning to end.</td>
<td>An exome is like reading about the game highlights the next day.</td>
</tr>
</tbody>
</table>

**Genetic Testing**

There are several types of genetic tests. Some genetic tests “read” the genetic code of a single gene to see if that gene has any changes. Other genetic tests look for extra or missing pieces of DNA. Whole exome sequencing reads through the exons of most of the genes all at once.
Mutations

A mutation is a change in the DNA. Mutations may cause proteins to work poorly or to not be made at all. If you think of a gene as a recipe for making a protein, a mutation is like a mistake in the recipe that causes the protein to not work normally.

<table>
<thead>
<tr>
<th>Genetic Mutations: An Error in the Recipe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal Recipe</strong></td>
</tr>
<tr>
<td>Chocolate Chip Cookies</td>
</tr>
<tr>
<td>2 1/4 c. all-purpose flour</td>
</tr>
<tr>
<td>1 tsp. baking soda</td>
</tr>
<tr>
<td>1 tsp. salt</td>
</tr>
<tr>
<td>1 c. butter, softened</td>
</tr>
<tr>
<td>3/4 c. granulated sugar</td>
</tr>
<tr>
<td>1 tsp. vanilla extract</td>
</tr>
<tr>
<td>2 large eggs</td>
</tr>
<tr>
<td>2 c. semi-sweet chocolate chips</td>
</tr>
<tr>
<td>1 c. chopped nuts</td>
</tr>
<tr>
<td><strong>Addition to Recipe</strong></td>
</tr>
<tr>
<td>Chocolate Chip Cookies</td>
</tr>
<tr>
<td>3 c. butter, softened</td>
</tr>
<tr>
<td>3 c. granulated sugar</td>
</tr>
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</table>

Chocolate Chip Cookies

Normal gene

Working protein

Insertion

Non-working protein

Too much butter
Mutations, continued

Mutations may be “misspellings” where the wrong letter is included in the gene, or they may be deletions or duplications where there is missing or extra DNA in a gene. Genetic mutations are random. People cannot do anything to cause mutations or to stop them from happening.

Genetic Mutations: An Error in the Recipe

<table>
<thead>
<tr>
<th>Deletion from Recipe</th>
<th>Substitution in Recipe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chocolate Chip Cookies</strong></td>
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<tr>
<td><strong>0 c. flour</strong></td>
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</tr>
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Deletion

- Not enough flour

Substitution

- Too much salt

Deletion Point Mutation

A mistake in a cookie recipe makes unappetizing cookies. A mistake in a gene (a genetic mutation) may make a non-working protein.
What is the purpose of whole exome sequencing?

The purpose of whole exome sequencing is to try to find a genetic cause of your or your child’s signs and symptoms. Most people who have WES have already had some genetic testing. WES is one of the most extensive genetic tests available. Because WES looks at more genes than most genetic tests, it may find a genetic cause for your or your child’s signs and symptoms even if previous genetic testing did not.

What is whole exome sequencing not used for?

Cincinnati Children’s Hospital Molecular Genetics Laboratory does not recommend WES for healthy people. WES is not usually the best test for finding out if someone is at risk of having a child with a genetic condition. WES does not help diagnose non-genetic conditions.

How is whole exome sequencing performed?

This test requires 3 mLs (about 1 teaspoon) of blood from the patient having WES. Sometimes blood samples from parents or other family members are also tested. The laboratory will isolate DNA from the blood sample. The exons (coding parts) of most genes will be examined. This is done for both the person having exome sequencing and for any family members that give DNA for comparison.

How is whole exome sequencing interpreted?

Your or your child’s DNA will be compared to a normal “reference” DNA sequence and (if applicable) to family members’ DNA. WES will identify some changes in the DNA that differ from the normal sequence. The laboratory will use information from your doctor or genetic counselor, as well as many different scientific tools in the laboratory, to decide which genetic changes are likely to be responsible for your or your child’s signs and symptoms. The genetic changes that are likely to cause these signs and symptoms will be reported to your doctor.
How many patients get a diagnosis from whole exome sequencing?

WES determines a genetic diagnosis in about one in every four patients (25%) who has the test.

What are the benefits of whole exome sequencing?

WES may find a genetic cause for your or your child’s signs and symptoms. This may help guide medical care. A genetic diagnosis may give your family information about the chance that you could have other children affected with the same condition. This information may also be useful for other family members.

What are the limitations of whole exome sequencing?

It is possible that this test will not find a reason for your or your child’s signs and symptoms. About 3 out of 4 patients tested (75%) do not receive a diagnosis from WES.

WES is not a perfect test. Our current understanding of the human exome is limited. This technology is new. Some parts of the exome are not examined. In addition, WES does not detect certain types of mutations. For any of these reasons, it is possible that WES will not find some mutations that are actually present in the DNA.

WES may reveal information that is unexpected or unwanted. This information might upset some people. See page 10 for more information and talk with your doctor or genetic counselor about this possibility.
What kinds of results can I expect from whole exome sequencing?

Positive Results
It is possible that WES will find a genetic cause of your or your child’s condition. Identifying the genetic cause of your or your child’s symptoms may change your medical treatment, but may or may not help predict the outcome of the condition.

Negative Results
It is possible that WES will not find a genetic cause of your or your child’s condition. A negative result does not mean that this condition is not genetic. The result may be negative because:

• your or your child’s condition may not have a genetic cause
• WES may not detect the type of genetic change that is causing your or your child’s signs and symptoms
• our ability to interpret test results is limited by the current understanding of the exome.

Uncertain Results
The test may detect a change in the DNA, called a variant of uncertain clinical significance (VUCS). A VUCS may or may not be related to disease. Your doctor will tell you if additional testing is needed to help understand these results.
What is included in the report?

Primary Result
Genetic changes in genes that are likely related to your or your child’s condition will be discussed in detail in the report. Genetic changes identified in family members and related to your or your child’s primary result will also be included in the patient’s report. Family members will not receive separate written reports.

Other important results (secondary findings)
Genetic changes in genes that are not associated with your or your child’s current disease, but which may have an important impact on health, will be included in the patient’s report, unless you tell us that you do not want this information. See page 11 for more information on secondary findings.

What information is not included in the report?

• Variants in genes which are not thought to affect one’s health
• Variants identified in research studies and whose relationship with disease is unclear
• Variants that predict an increased risk of common diseases, but do not cause a disease by themselves.
What kind of information, other than results related to your child’s condition, might be revealed by this test?

• Whole exome sequencing may reveal information about family relationships. For example, a test could show that a father may not be the biological father of a child. This test could also reveal that a couple may be related by blood.

• WES results may reveal that a parent of a symptomatic child is actually also affected with the same genetic condition, which may have medical consequences for the parent (even if he/she is currently healthy) and his or her family members.

• Results may show that family members are at risk of having a child with the same genetic disorder.

• Unexpected medical information (secondary findings) will be reported to you, unless you choose not to receive this information. Please see the section on secondary findings below.
What are secondary findings?

A secondary finding is a test result that is not expected and is not related to the reason for doing the test. For example, a genetic mutation in a gene that is not related to the patient’s condition is considered a secondary finding. Secondary findings may have important implications for your or your child’s health.

For example, the American College of Medical Genetics and Genomics has recommended that all laboratories that perform WES report mutations in 57 specific genes generally unrelated to the patient’s present signs or symptoms. Mutations in these genes may lead to serious health problems, but these problems can be monitored or treated if your doctor knows about them. These disorders include some inherited cancer syndromes, connective tissue disorders associated with sudden cardiac events, certain types of heart disease, high cholesterol and susceptibility to complications from anesthesia. If a mutation in one or more of these 57 genes is identified, it will be included in the secondary findings section of your or your child’s report. Some other genetic disorders do not have any effective treatment and may lead to death or lifelong disability. These types of results are also included for you or your child and any family members whose DNA is used for testing in the secondary findings section of the report. Family members will not receive a separate report with their results.
Can I choose NOT to receive secondary findings in my or my child’s report?

Yes. The Cincinnati Children’s Hospital Molecular Genetics Laboratory will report secondary findings unless you tell us in writing at the time of consent that you do not want this information. If you decide not to receive secondary findings at the time of testing, you may not be able to request those results later.

If a secondary finding is identified in a child, how does this affect a parent’s health?

If a child has a genetic mutation, one of the parents may have the same genetic mutation. For example, if a child is found to have a BRCA1 mutation (which can cause breast, ovarian, and other cancers), one of the parents is likely to have the same mutation. This information is very important for that parent’s clinical care. Secondary findings may lead to more medical screening, procedures and testing for your child, you, and possibly other family members.
Will my health insurance company know if a secondary finding is found in my or my child’s DNA?

If you choose to receive the report including secondary findings, this report does become part of your or your child’s medical chart. Your health insurance company has access to information in your or your child’s medical record. Your or your child’s medical record may also be reviewed when applying for life or disability insurance.

If you choose not to receive the report including any secondary findings, this information does not become part of your or your child’s record and would not be accessible by your health insurance company.

Can my health insurance company or employer discriminate against me or my child based on my or my child’s genetic test results?

No. The Genetic Information Non-discrimination Act (GINA) prevents insurance companies from denying health insurance coverage based on a person’s genetic test results. GINA also prevents employers from discriminating against employees based on their genetic test results. However, this law does not apply to life insurance or long-term care insurance companies that may withhold services based on genetic tests.
How long will Cincinnati Children’s Hospital Molecular Genetics Laboratory store the information from a WES test?

The laboratory will keep left over DNA for WES for two years, and may discard those samples after two years. The laboratory will store the information from this test for 20 years. The data will be stored on a protected computer and will be kept safe.

Will my health insurance cover the cost of whole exome sequencing?

WES is a new and expensive genetic test. Not all health insurance companies will pay for the cost of the test. All WES tests will be discussed with your insurance company before testing.

You will be responsible for all copays and deductibles. Some insurance companies may charge a premium if Cincinnati Children’s Hospital is not part of your network. It is important that you follow the steps outlined by your insurance company in order to reduce your cost for the test.
How do I schedule an appointment with a geneticist or genetic counselor?

An appointment with a geneticist and genetic counselor is an important part of WES. We recommend that you meet with a geneticist and genetic counselor before having WES. They will help you understand what information you can get from this test and will help with the payment precertification process. They will also help you to decide if you want to know about secondary findings. A referral from a doctor is required to schedule an appointment in the Genomic Medicine Clinic.

It is also important to meet with a geneticist and genetic counselor after the results of the test are known, so that you can understand what these results mean for you or your child. Patients at Cincinnati Children’s Hospital with a physician referral may schedule an appointment for genetic evaluation and counseling by calling the Division of Human Genetics (513-636-4760) and asking to speak with the Genomic Medicine Clinic coordinator.

If you are outside of the Cincinnati Children’s Hospital area and would like to find a geneticist or genetic counselor near you, please ask your doctor for a referral, or visit www.acmg.net (for a geneticist) or www.nsgc.org (for a genetic counselor).
You can find additional information about whole exome sequencing on our website:

www.cincinnatichildrens.org/exome