Whole Exome Sequencing

A guide for patients and families

Blueprint Genetics

Has your doctor or genetic counselor suggested a test called Whole Exome Sequencing (WES) for you or your family member? This booklet will provide you with more information about WES. If you have questions about the information in this booklet, please contact your doctor or genetic counselor.

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General info

Genetics

All humans have about 20,000 genes in almost every cell in their bodies; we inherit half of our genes from our mother and the other half from our father. Genes are the blueprints (or instructions) that control everything in our bodies including our development, growth, and health.
Our genes are made up of DNA (deoxyribonucleic acid) and are organized into exons and introns. The exons are the coding regions of the gene. They contain the information that is used to make proteins required for normal growth, development, and organ function. Introns are the noncoding regions of the gene and often contain important information about when in development (for example, early in pregnancy or in adulthood) and where in the body (for example, in the heart or the brain) a gene should be used.

All of our genetic information, including introns and exons, is referred to as the genome. The exons make up a very small part of our total genetic information (about 1% to 2%). The exons alone are known as the exome.

All humans have some differences in their exome compared to another person's exome. This makes each of us unique! Sometimes, we have genetic differences, or genetic variants, that cause one or more genes to stop working or to work differently than expected. These genetic variants can result in a genetic disease.

What is Whole Exome Sequencing?

Most of the genetic variants that cause genetic diseases are found in the exome. Whole Exome Sequencing (WES) is a test that looks at the genetic information contained in all of our 20,000 genes (and their multiple exons) in a single test. This is different from other genetic tests that might look at only one gene (or a handful of genes) at a time.

WES is done using special technology called next-generation sequencing (NGS). A DNA sample is collected from either a blood or saliva sample given by the patient. The patient's DNA is then compared to a reference sample (a sample that represents the 'normal' sequence of human DNA) in an attempt to find any differences between the patient's DNA and the reference DNA. If there are any differences, they are reviewed by experienced laboratory geneticists and expert doctors.

Who should have WES?

WES can be done in pregnancy, childhood, or adulthood. It is usually done for one or more of the following reasons:

- You are (or your child is) suspected of having a genetic condition
- There are many different genes that can cause your (or your child's) symptoms
- You (or your child) have a complicated medical history that affects many organs and/or body systems
- You (or your child) have had genetic testing in the past but the results were normal.

Who should *not* have WES?

WES may not be the ideal test for you or your child if the condition is:

- Not likely to be genetic
- If you or your child have a genetic condition that is very likely caused by a single gene

Talk to your doctor or genetic counselor about which tests are right for you or your child.

What makes WES at Blueprint Genetics different from WES at other labs?

Many other genetic laboratories offer WES testing. Sometimes, it can be hard to decide why you should choose one lab over another.

Blueprint Genetics stands out because we:

- provide **high coverage and quality** for WES
- our test covers also **>1,500** medically relevant, non-coding deep intronic variants not covered by standard WES tests
- clearly state any limitations the WES may have before and after testing
- report your results in a comprehensive and easy-to-read way
- provide patient-friendly billing

Benefits

What are the benefits of WES?

Genetic testing can help:

- make or confirm a diagnosis
- make informed medical decisions about your, or your child's, current and future health care
- decide on a personalized treatment and care plan
- make decisions about family planning for yourself or for other family members
- give other family members the opportunity to learn their genetic status

How many people get a diagnosis with WES?

The number of patients who receive a diagnosis with WES varies but is estimated to be between **25–50%**. Traditional genetic testing results in a diagnosis less frequently.

Patients are more likely to get a diagnosis with WES if they have a serious condition involving multiple organ systems and the symptoms started at an early age.
A diagnosis is also more likely when parents provide samples along with the patient.

Family members

Do other family members need to give samples?

WES can be performed on the patient alone. Other family members do not have to give samples; however, when WES includes samples from other family members, the chance of finding a diagnosis for the patient is higher.

Does Blueprint Genetics test family members?

Yes, Blueprint Genetics will perform WES on samples from both the patient and their parents. This is called a trio and is the preferred way to perform WES. When WES is performed on a trio, you ensure the most
comprehensive reporting and interpretation in the shortest amount of time. Trio WES also decreases the chance of an uncertain result.

In some cases, it may be helpful to include samples from other family members (for example, siblings). Talk to your doctor or genetic counselor about who should be included.

I am a healthy family member and provided a sample to help with the patient's WES. Why don't I get a WES report?

The purpose of WES is to find an answer for the symptoms in the patient, not to find all of the genetic variants in every family member tested. If samples are received on the patient and one or more family members, all variants relating to the cause of the patient's symptoms, and whether they have been inherited or are de novo, are included in the patient's report.

Secondary findings for family members participating in WES are reported in separate, individual reports if the other family members want to receive this information.

Informed Consent

Informed consent means that:

1) You have enough information to make a decision about whether you would like to have testing, and
2) That you willingly agree to have the test.

Typically, informed consent means that you understand, and have been given the chance to ask questions about:

- what test will be done
- how the test will be done
- what are the benefits of testing
- what are the risks of testing
- what the test results will mean for you and your family members
- who will receive the test results
- what the test can, and cannot, tell you

Informed consent is usually given by adults who are able to make decisions about their own health care. For children or people with intellectual disability or impairment, informed consent can be given by a parent or legal guardian.

Consent for Sample Storage

Blueprint Genetics keeps samples after testing is completed for 1 year. After this time, the sample is destroyed.
You can choose to have your sample stored for a longer period of time. This allows Blueprint Genetics to use your sample for additional tests for yourself or your family members. If you want to have your sample stored for longer than 1 year, please indicate this on the consent form.

Consent for Research Use and Long-Term Storage

You can give consent for your sample to be used in research projects to help understand genetic diseases and to help Blueprint Genetics develop and improve testing for genetic diseases. If you choose to do this, your sample will be kept indefinitely. If your sample is used, all of your identifying information will be removed.

Consent for Future Contact

You can give permission to be contacted regarding further genetic research and/or other genetic services relevant to you in the future. You may withdraw from such contact at any time. Future contact would be via your doctor regarding:

- Patient Organizations and Advocacy Groups involved with the establishment of patient registries to support clinical research, studies, and trials
- Bio-Pharma Companies involved in therapeutic drug development that may benefit individuals with inherited disorders

Can I change my consent?

Yes. If you want to change your consent, talk to your doctor or genetic counselor. You can complete a new consent form with your selections and forward it to our laboratory to update your preferences.

Can I see the Blueprint Genetics Consent form?

Our consent forms for panels and whole exome sequencing are available on our website (www.blueprintgenetics.com/how-to-order).

I have questions about the consent form. Who can I talk to?

If you have any questions about the test that is being offered to you or about the consent form, talk to your doctor or genetic counselor.

Results

What kind of results can I expect?

WES produces four different types of results:

A pathogenic or likely pathogenic variant in a gene that is: 1) known to cause disease or is very likely to cause disease and 2) has been associated with the symptoms in the patient. This result can be used to test other family members to learn whether they may be affected with the same genetic condition.

A variant of uncertain significance (VUS) in a gene known to cause disease. This result means that we have found a change in a gene and this gene has been associated with the symptoms in the patient. However, we do not know enough about the variant found to say if the variant is the actual cause of the disease. Testing other family members for the VUS may be helpful in trying to understand whether the variant is the cause of the disease. We do not recommend using this result to determine whether other family members are at risk to develop the disease.

A variant of uncertain significance (VUS) in a gene not previously known to cause disease. This result means that we have found a change in a gene and the variant type typically causes genetic disease. However, we do not know enough about the gene to say if the gene is associated with human disease. This is called a candidate gene. Additional research is needed to confirm if the gene is related to the patient's symptoms. We do not recommend using this result to determine whether other family members are at risk to develop the disease.

A negative result means that we did not identify any significant changes in any genes related to the reported symptoms/findings of the patient.

A negative result might mean that:

1) the patient does not have a genetic disease,
2) the patient does have a genetic disease but the technology cannot detect the genetic variant,
3) the patient does have a genetic disease but the variant properties and the fact that the gene is not yet known to cause human disease means it is not reported or
4) the patient does have a genetic disease but the genetic variant is in a gene that is not associated with the patient's symptoms as reported by their health care provider.

What is a secondary finding?

A secondary finding is a genetic variant that is likely to cause serious disease, identified by WES, in a gene that is not related to the patient's symptoms. Secondary findings are reported because, if found, there are things you can do, like surgery or screening, that can help reduce the chances of developing the disease. The American College of Medical Genetics and Genomics (ACMG) has recommended that secondary findings be reported for only a subset of genes for all patients undergoing WES.

Blueprint Genetics follows the '**ACMG Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing, 2016 Update**' to look for and report disease-causing genetic variants in these genes if the patient or caregiver has agreed that they want this information. Please see the recommendations for the gene list, related conditions, and our reporting policy. It is not mandatory to have this information if you or your family member is participating in WES.

If parents or other family members are also participating in the WES analysis, they can decide if they want to know if they have any secondary findings. Secondary findings for parents and other family members are not reported in the patient's report. Instead, they are reported in a separate report to ensure privacy and confidentiality for every person who wants secondary findings reported.

How long do results take?

WES testing is complex. Time is needed to perform the test and to review the data and existing scientific literature to help understand and interpret the results. For these reasons, results may take up to **8–10 weeks**.

Where are my results sent?

The results are sent to the doctor or genetic counselor who ordered the testing. It is important for your doctor or genetic counselor to discuss your results with you to help you understand them and to help make a plan about the next steps for your, or your child's, medical care.

Clinical statement

What is included in the patient's WES report?

The WES result includes information about pathogenic variants, likely pathogenic variants, and variants of unknown significance in genes known to cause human disease, as well as in candidate genes related to the patient's symptoms and findings.

If family members were part of the WES analysis, the patient's report will also contain information about whether the variants were inherited from the mother or the father or if the variant is de novo (that is, a new genetic change in the patient that was not inherited).

If the patient (or parents/guardians) opts in, the report will also contain pathogenic or likely pathogenic secondary findings.

Is anything not included in the report?

Although WES allows us to see a large number of genetic variants in every human exome, not all of the variants seen are reported, as this would mean an overwhelming report with thousands of variants and little understanding of their meaning.

The following are NOT included in the WES report:

- Likely benign or benign variants that are considered negative and generally are not reported.
- Variants in genes not related to the patient's symptoms (as reported to the laboratory by the ordering doctor).
- Carrier status for variants in autosomal or X-linked recessive disease genes not related to the reported symptoms in the patient.
- Pharmacogenetic variants (genetic variants that affect how you react to certain medications).
- Family members participating in WES may have a disease-causing variant(s) in a gene(s) unrelated to the patient's features that is not reported.
- If the patient or family member does not want information about secondary findings, a disease-causing variant may be present and not reported.

Limitations

What are the limitations of WES?

WES technology is relatively new. Currently, it is not possible to capture and sequence 100% of the exome with high quality. Blueprint Genetics captures and sequences, on average, >99.4% of the exome with a quality enabling reliable variant call.

In addition, we do not fully understand everything about the human exome; therefore, we may not recognize variants in some genes as the cause of the patient's symptoms. Also, the test may miss variants in other genes due to the limitations of the technology.

For these reasons, it is important to remember that a normal WES result does not rule out a genetic cause for the patient's symptoms.

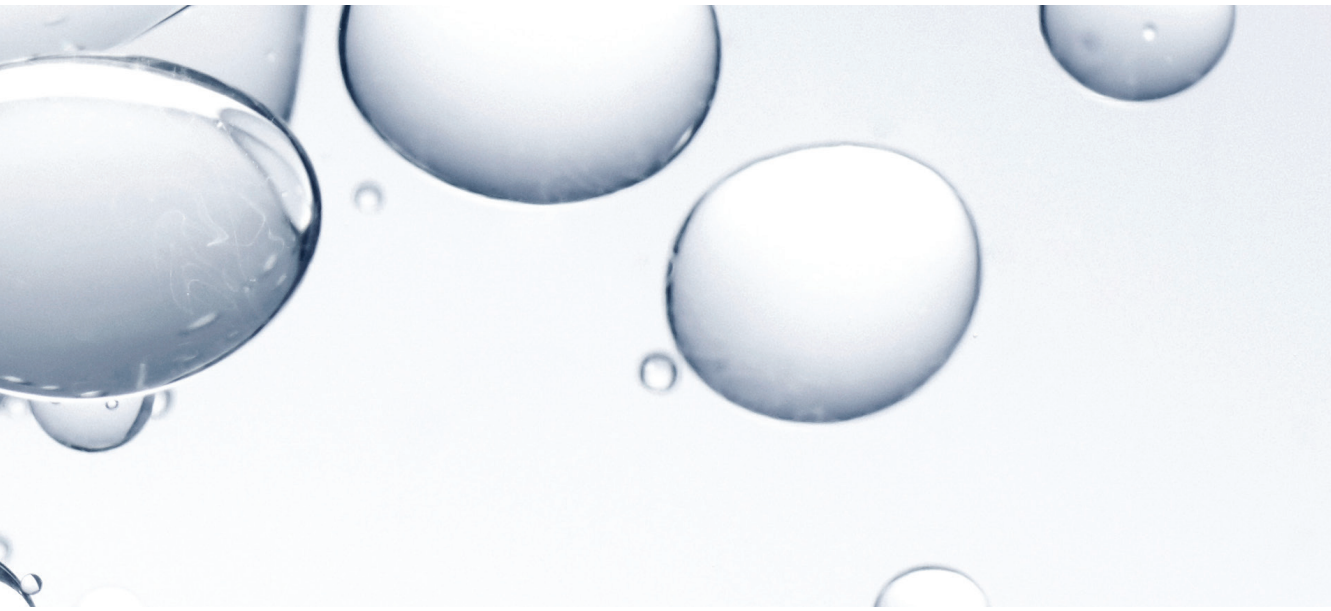
FAQ

How do I order WES for myself or my child?

WES must be ordered by a doctor or a genetic counselor.

Should I see a geneticist or a genetic counselor?

Yes, Blueprint Genetics recommends that you see a geneticist or genetic counselor before and after having WES. Genetic health care providers can help you understand the information this test will provide you, as well as the information the test cannot provide you. Once the results are available, your genetics team can be extremely valuable when it comes to interpreting the results and understanding and planning the next steps.



Will insurance cover WES?

At Blueprint Genetics, we believe that cost should not be a barrier for patients or families who require genetic testing. Our mission is to improve access to genetic testing when it is needed.

Blueprint Genetics will work with all commercial insurers and every patient with active insurance benefits will qualify for Blueprint Genetics diagnostic testing services. The amount the patient will pay for genetic testing depends on their insurance coverage and ability to pay.

When we receive a sample at Blueprint Genetics, we work with the patient and their physicians to obtain the maximum reimbursement from the insurance provider. Our billing specialist will manage the claim process and offer financial assistance and/or a flexible payment plan to eligible patients. Please note, this policy currently does not apply to US patients with Medicare and Medicaid, or patients outside the USA. Please contact our Customer Service team for options if you have Medicare or Medicaid.

Are there drawbacks to WES?

WES has the potential to uncover genetic information that is unexpected or unwanted. This information may be upsetting for some people.

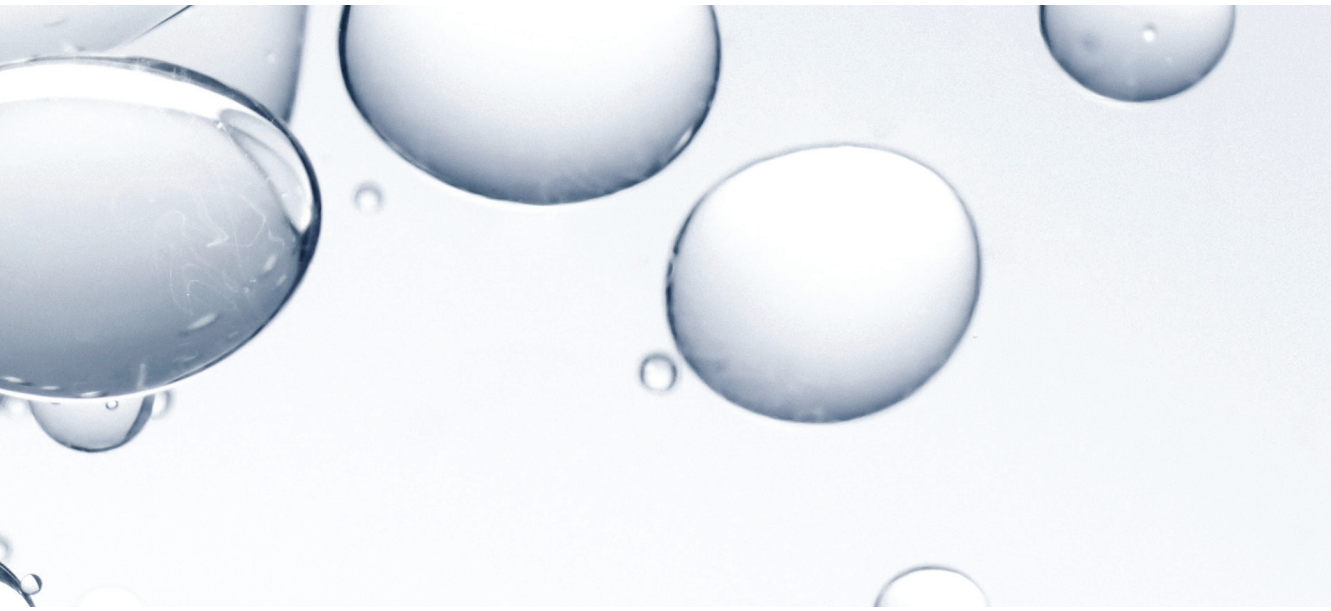
Are there discrimination risks because of this test?

The Genetic Information Non-discrimination Act (GINA) in the United States prevents health 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. Life and long-term insurance companies may withhold services based on genetic test results.

In Canada, Bill S-201 prevents genetic discrimination on the basis of genetic test results.

My result is negative. What are the next steps?

Some people will receive a negative WES result. It is important to remember that this does not guarantee there is no genetic cause for your symptoms. Talk to your doctor or your genetic counselor about whether they recommend more testing. If you have not seen a geneticist or genetic counselor, ask your doctor to make an appointment for you.



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