Claritas Clinical Exome Informed Consent Guide

How to Use This Guide

Your physician or genetic counselor (hereafter, "provider") has recommended that you or your child (hereafter, "you") submit a DNA sample for exome testing, called the Claritas Clinical Exome. This guide is designed to provide background information on the test and should be used to supplement discussions with your provider. Your provider may use this document to guide the conversation about the risks, limitations, benefits, methodologies, and what to expect of the test.

Review the information in this document, which describes the Claritas Clinical Exome. Then read the Informed Consent signatures page of the test order form—also called the requisition form—and sign your name, which indicates that you have given your consent to have this test, that you have discussed this test with your provider, and that you have had the opportunity to have your questions answered.

Review the information on secondary findings in this document. After reviewing the information about secondary findings, discuss with your provider whether you want to place your signature on the secondary findings page of the test order form.

You may want to ask your provider for a copy of these documents for your records.

What is the Claritas Clinical Exome?

A person's genes are like a recipe or blueprint for how their body will develop and function over time. We get our genes from our parents. Most of our genes come in sets of two: one from our father and one from our mother. Each gene determines a specific protein in the body. Antibodies, enzymes, and hormones are all examples of proteins. Genes are made of a molecule called deoxyribonucleic acid, referred to as DNA. DNA has an "alphabet" of 4 letters- A, C, T, and G. These letters are combined into a very long "sentence", which is our DNA. Genetic diseases are caused by "spelling" changes in the DNA sentence. Some of these changes are inherited and others occur for the first time in an individual. There are many types of changes in DNA that cause genetic disorders, from a single change in a gene to larger changes that involve many genes. All humans have variations in their DNA that cause one person to be different from another person. Genetic testing helps to identify variation that causes a genetic disease; this allows you and your provider to learn more about the condition and what to expect.

In the past, most genetic testing focused on testing just one gene at a time. The Claritas Clinical Exome (the "CCE") is different because it looks at all human genes at one time. This means that nearly 20,000 genes are analyzed simultaneously, looking for differences—also called variants, or changes—that may be associated with disease. Specifically, exome testing focuses on the parts of the genes called exons. Genes have many parts, but it is the exons that contain the DNA sequence that determine what protein is made. An exome test looks only at the DNA that codes for proteins because changes — or variants— in these regions are the most likely to cause the medical symptoms of a genetic disease.

Why is My Doctor Ordering this Test?

Your provider is recommending the CCE because they think that there is a genetic reason for your medical symptoms, rather than an acquired reason such as environmental factors or a virus. Additionally, the CCE is a more efficient test when compared to ordering testing one gene at a time. Exome-based testing analyzes many genes at the same time and so it may reduce both the cost of testing and the time spent obtaining a diagnosis.

How is the Test Performed?

1. Your provider draws 5-10cc (2-4 teaspoons) of your blood and sends it to Claritas Genomics.
2. Your provider completes the test order form, which includes information about your medical and family history. This information is sent to Claritas Genomics and is a critical part of the interpretation of the results.
3. A team of highly trained medical geneticists and genetic counselors at Claritas Genomics look at the sequence of your DNA to identify variants that may be the cause of your medical symptoms.
4. Variants that may cause your medical symptoms or may be associated with your medical symptoms are reported to your provider in a written report that becomes a part of your medical record.

More details on our methodologies are available at www.claritasgenomics.com.

What are the Possible Outcomes of this Test?

REPORTING TEST RESULTS

We expect to see many variants in your DNA because individuals differ greatly from each other. Scientists at Claritas Genomics must go through the process of determining which variants are part of normal individuality and which cause the medical symptoms related to genetic disease. This can take some time and is reliant on specially trained experts.

A report is sent to your provider within 12-14 weeks of when your sample is received by Claritas Genomics. Any variants reported by Claritas Genomics have been "confirmed," which means they have been identified by two separate laboratory techniques.

The CCE clinical report will contain any variants in genes known to be or expected to be associated with your medical symptoms. These variants are classified using the following system:

a. Pathogenic variant: known to cause genetic disease.
b. Likely pathogenic variant: evidence suggests that the variant is likely to cause genetic disease.
c. Variant of uncertain clinical significance: there is currently insufficient evidence to determine if the variant is causative of a genetic disease.
d. A negative result does not mean variants were not identified, but rather based on the judgment of trained experts, there were no variants determined to be related to your medical symptoms at this time.

Optional: ***It is Claritas Genomics' policy to include analysis of a specific list of genes as recommended by the American College of Medical Genetics and Genomics (ACMG). This list of genes is also known as secondary findings. You may choose not to receive this information.***

The ACMG recommends that variants in a specific set of genes be analyzed for all individuals who receive whole exome testing because variants in these genes lead to conditions that are "medically actionable" or sometimes treatable. Sometimes these conditions may cause symptoms that do not appear until later in life. With this information in hand, you and your provider may be able to make clear and immediate treatment or management decisions to avoid or minimize serious illness. Several examples of these genes are listed below. The most up-to-date list is available by contacting our client services team.

- ***BRCA1, BRCA2 —*** *Hereditary Breast and Ovarian Cancer*
- ***COL3A1 —*** *Ehlers Danlos Syndrome — vascular type*
- ***TSC1, TSC2 —*** *Tuberous Sclerosis Complex*
- ***MYBPC3 —*** *Hypertrophic cardiomyopathy*

A patient whose provider orders the Claritas Clinical Exome has the option to choose not to receive information on these genes. This is called "opting out". You can communicate this choice to us by signing your name on the secondary findings page of the test order form.

- ***If the patient opts out of receiving information on the genes recommended by the ACMG, any parental samples received by Claritas Genomics will automatically be opted out also.***
- ***If the patient chooses to receive information on the genes recommended by the ACMG, the parents may choose not to receive the information ("opt-out").***
- ***If both parental samples are sent, both parents must make the same choice to either receive or not receive the information.***
- ***Only those variants found in the patient's sample will be investigated in the parental sample(s). Therefore, if no variants in these genes as recommended by the ACMG are reported in the patient, these genes will not be investigated in the parental sample(s).***

CLARITAS CLINICAL EXOME REPORTS DO NOT INCLUDE THE FOLLOWING TYPES OF VARIANTS:

- Benign and likely benign variants. However, these are available upon request.
- Pathogenic or likely pathogenic variants not expected to be related to the patient's medical symptoms, except for the the genes as recommended by ACMG.
- Variants that are associated with increased or decreased risk of common disease, such as high blood pressure.
- Variants that are associated with adult-onset disease and unrelated to the patient's phenotype for which there is no prevention or cure, such as Alzheimer's disease.
- Pharmacogenetic variants such as those related to drug metabolism.
- Carrier status of autosomal recessive diseases that are unrelated to the patient's phenotype, unless the gene is recommended by the ACMG.
- Findings in the genes recommended by the ACMG in parents that are not observed in the patient.

Who in My Family Might Need to Be Tested?

Family members are sometimes asked to give samples because knowing their DNA sequence can help with the interpretation of the patient's DNA. For example, consider a situation in which the medical literature and the experts aren't sure whether a variant is causing the medical symptom (this is a variant "of unclear clinical significance"): if the patient's mother or father does not have the same medical symptoms as the patient, but has the same DNA variant as the patient, that is a piece of evidence that this particular variant is not causing the medical symptoms.

It is difficult to make general statements about which family members might need to be tested. It depends on your family history (whether anyone else has the same medical symptoms that you do) or whether biological relatives are available to give samples; sometimes a person is adopted, egg or sperms donors are used, or a parent is not available to submit a sample or is no longer living.

Claritas Genomics recommends that samples from both biological parents be sent with the patient's sample, as this may help with the interpretation of the patient's DNA. Results will be included in the patient's report; a separate report will not be issued for the parents. Providers are asked to contact Claritas Genomics if samples from family members other than biological parents are sent.

What are the Limitations, Potential Benefits, and Risks of Testing?

LIMITATIONS OF THIS TEST

- There is no single test that tests for all genetic conditions; with that in mind, this may not be the only test that your provider orders.
- Exome testing does not analyze all three billion letters of your DNA, so your DNA may have a variant that causes your medical symptoms that this test does not detect.
- No exome test covers 100% of the exome; some regions cannot be covered, usually because of technological challenges involving the structure of DNA.
- Even though a variant explaining your medical symptoms may be identified, it may not affect medical management or treatment.
- Exome testing does not report on some types of genetic variations, such as structural changes, deletions/duplications, trinucleotide repeat expansions or other expansion mutations, or abnormal methylation.

POTENTIAL BENEFITS

Data shows that approximately 25-30% (1 in 4 or higher) of patients receive a diagnosis after having an exome performed on their DNA. This percentage may be higher or lower for you depending on your specific medical symptoms.

When compared with traditional genetic testing strategies in which one gene is tested at a time, the cost of exome-based testing may be lower and it may take less time to get a genetic diagnosis. Your provider has determined that this is the best test for you at this time. This may be for one or several reasons, including reasons related to medical management, health insurance, cost, timing, sample type available, and/or genes analyzed by this test.

POTENTIAL RISKS

There are no physical risks related to this test. However, there may be psychological risks related to genetic testing in addition to those listed under the "Limitations" section of this document. For example, some people are frustrated, angry, disappointed, or depressed if no definitive diagnosis is made; they may have felt confident that this test would give them a diagnosis. Your provider can talk with you about these possibilities and how you can prepare yourself. On the other hand, some people experience negative emotions upon receiving a diagnosis. Your provider can discuss this with you in more detail.

Some patients are concerned about the impact of genetic testing on their insurance rates. The Genetic Information Nondiscrimination Act, also known as GINA, was passed in 2008 and prohibits discrimination on the basis of genetic information in health insurance and in employment. If you have concerns about this or want more details, ask your provider.

When parental testing is performed, this test may find a genetic disorder in other family members that is unexpected. Your provider should discuss this possibility with you.

When parental samples are included in the analysis of data, it is possible that the laboratory may identify non-paternity or non-maternity, which means that the person identified as the father or mother on the test order form is not the biological parent. Claritas Genomics is obligated to note this finding in the test report.

You always have the right to access your data and control its use; you can inquire about who has accessed it, or you may request to have it removed it from the laboratory at Claritas Genomics. At any point in time, you also have the right to request the report associated with your genetic testing. Contact Claritas Genomics Client Services toll-free at 855-373-9003.

Research Policies:
Specimen Retention and De-identified Scientific and Medical Research

DNA samples are not returned to individuals or to health care providers. De-identified samples and de-identified test results may be stored in a repository and used for internal validation, educational, and/or research purposes or presented in scientific presentations or papers. In addition, de-identified information may be submitted in a HIPAA-compliant manner to research databases.

Any such research with such de-identified samples and test data that results in medical advances, including new products, tests or discoveries, may have potential commercial value and may be developed and owned by Claritas Genomics or the researchers who analyze the data. If any individuals or corporations benefit financially from studying your de-identified genetic material, no compensation will be provided to you or your heirs.

Claritas Genomics has no obligation to retain your sample indefinitely and may destroy it once it no longer has a legal duty to retain it. By consenting to this agreement, you authorize for Claritas Genomics and its partners to use your de-identified sample and test results for such purposes as mentioned above. New York state residents must specifically give permission to Claritas Genomics to retain any remaining sample longer than 60 days after completion of testing and to use de-identified data for scientific and medical research purposes. Such authorization is optional and is not required for testing. Review the Informed Consent page on the requisition form for signatures and opt-out options.

Research studies that are specific to your condition or variant can benefit you individually as knowledge is gained in the fast-moving field of genetics. As part of our service, Claritas Genomics may alert ordering providers to research opportunities that could be beneficial. If your provider is contacted, he or she will choose whether to pass that information on to you. At that time, you would learn more and have the opportunity to decide whether you are interested in participating. Claritas Genomics may also contact you in the future regarding the opportunity to participate in research opportunities, including treatment for the condition in your family. You may choose to opt out of being contacted; review the Informed Consent page on the requisition form for opt-out options.

You always have the right to access your data and control its use; you can inquire about who has accessed it, or you may request to have it removed from the laboratory at Clariats Genomics. At any point in time, you also have the right to request the report associated with your genetic testing. Contact Client Services at 855-373-9003 to make this request.

Return of Raw Data

At Claritas Genomics, our criteria for reporting of variants include stringent review of the evidence that suggest a variant is medically relevant depending on the information about your symptoms that your provider includes on the test order form. This high standard of review is established by teams of experts, and includes guidelines recommended by the ACMG.

In some instances your provider may want to look at your raw data, which can be beneficial in some cases. Raw data are the A, T, G, C “letters” that make up the very long “sentence” that is your DNA. This is called raw data because it does not include any interpretation by experts. We can provide your raw data to your provider as a benefit of our testing service. Claritas Genomics takes no responsibility for what your provider finds or does not find outside of our established reporting criteria and process. More information about this program is available on our website. This service is not available to providers in New York State.

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