UAGC Clinical Services Laboratory
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Information about Clinical Exome Sequencing for patients

I, (name) _____, voluntarily request clinical exome sequencing (CES) to be performed by the **University of Arizona Genetics Core - Clinical Services (UAGC-CS)** for myself and/or my child_____ (child's name). Given the complexity of exome sequence analysis, **genetic counseling and informed consent by a trained medical geneticist or genetic counselor is required before and after undergoing this testing**. Informed consent is a process that provides education about genetics, and the options, benefits, limitations, and consequences of genetic testing. Genetic counseling provides the patient with informed consent prior to the decision to undergo testing and with the opportunity to review the results of the test in detail.

What is genetic testing?

Our DNA is organized in the form of chromosomes. Genes are distinct sequences of DNA. The sequence of a gene contains instructions for making proteins, which can be structural and determine traits like the shape of our nose or the color of our eyes, or have specific function such as enzymes. Genetic disorders occur when a defect happens in the sequence of a gene that has an essential function and this function is compromised by the defect. Genetic defects can be small or very large and can affect multiple genes. Genetic testing is a laboratory test that tries to identify the gene defects in chromosomes or the DNA. Genetic testing can be a diagnostic test, which is used to identify or rule out a specific genetic condition when a specific gene is being tested. Genomic testing such as the exome sequencing test is a test that examines all genes that are known to code for proteins.

The purpose of this test is to see if I, or my child, may have a genetic variant causing a genetic disorder or to determine the chance that I, or my child, will develop or pass on a genetic disorder in the future. 'My child' can also mean my unborn child, for the purposes of this consent.

If {I/my child} already know the specific gene variant(s) or chromosome rearrangement that causes the genetic disorder in my family, I will inform the laboratory of this information.

What are the benefits of the Clinical Exome Sequencing (CES) test?

The CES test is used to identify the genetic cause of a disease or disability in an individual. It is estimated that we have about 20,000 genes in the cells in our body. The total amount of DNA in the typical cell of an individual is called the genome. The functional parts of the genes that make up the entire genome and 'encode' proteins are called exons. The word 'exome' refers to all exons in the genome. This test will analyze about 93-97% of all exons at the same time and compare them to those of healthy people to identify DNA changes that are related to a particular medical condition in question. The results that are expected to come out of exome sequencing can be as follows:

1) Positive: A positive result indicates that a genetic variant has been identified that explains the cause of {my/my child's} genetic disorder or indicates that {I/my child} am at increased risk to develop the disorder in the future. It is possible to test positive for more than one genetic variant. Such variants are typically called "pathogenic variants".

2) Negative: A negative result indicates that no disease-causing genetic variant was identified for the test performed. However, since the current exome sequencing covers only 93-97% of coding exons and some exons may not been satisfactorily sequenced, there is a chance that genetic defects could be present in regions that are not sequenced or poorly sequenced and therefore those changes were not detected. Additional consideration is that this test examines only one type of genetic defects called single nucleotide variations or short deletions/insertions. Exome sequencing cannot detect other types of genetic defects such as large deletions or insertions and structural rearrangements such as translocations or inversions, nor can it detect repeat expansion. These defects can also cause genetic disorders. A negative result does not guarantee that {I/my child} will be healthy or free from genetic disorders or medical conditions. If {I/my child} test negative for a variant known to cause the genetic disorder in other members of {my/my child's} family, this result rules out a diagnosis of the same genetic disorder in {me/my child} due to this specific change.

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3) Inconclusive/Variant of Uncertain Significance (VUS): A finding of a variant of uncertain significance indicates that a genetic change was detected, but it is currently unknown whether that change is associated with a genetic disorder either now or in the future. A variant of uncertain significance is not the same as a positive result and does not clarify whether {I/my child} is at increased risk to develop a genetic disorder. The change could be a normal genetic variant or it could be disease-causing. Further analysis may be recommended, including testing both parents and other family members. Detailed medical records or information from other family members also may be needed to help clarify results. Supporting information for pathogenicity from medical literature would also be important in clarifying about a potential pathogenicity of such variants.

4) Unexpected results: In rare instances, this test may reveal an important genetic change that is not directly related to the reason for ordering this test. For example, this test may inform me about the risk for another genetic condition {I/my child} is not aware. This information may be disclosed to me if I consented to.

Why are parental samples needed?

Depending on the family history of the disorder and which members are available for testing, it may be suggested that other family members also undergo CES or targeted testing in order to better interpret your results. UAGC–CS, in consultation with your ordering physician, can recommend which other family members need to be tested.

How is the Clinical Exome Sequencing performed?

This test requires 2 ml of blood for infants and 3-7 ml of blood for children/adults, which DNA will be extracted. Blood draw can have risks associated with it, such as minor bruising or bleeding. CES is performed using next generation sequencing (NGS) technology. Using a computational filtering algorithm, a list of variants identified from the sequencing is generated and analyzed to identify the variants that might explain the patient's medical condition.

How long will it take to get the results?

It will take approximately 3-6 months to obtain results. The results will be sent to your physician.

What are the limitations and risks of the Clinical Exome Sequencing test?

1. The CES test analyzes 93-97% of all exons. Around 10% of genes have suboptimal sequencing coverage that may affect the sensitivity of mutation detection. Therefore, pathogenic variants may not be detected in these DNA regions even though one exists.
2. CES cannot detect all types of variants that can cause disease. For example, it cannot detect large deletions, duplication, or structural rearrangements such as translocations or inversion, nor can it detect copy number variations or repeat expansion. These types of variants can also cause genetic disorders.
3. CES test will not detect disease-causing variants that occur outside of the exons.
4. Results from CES may indicate that additional testing maybe necessary, such as full gene sequencing to fill-in exons with poor coverage or deletion/duplication analysis.
5. The methods are reliable, but as with any laboratory test, there is the small chance that an error may occur. The interpretation of test results will be based on our current information. As medical knowledge advances and new discoveries are made, the interpretation of your results may change. It is possible that re-interpretation of your results based on new medical findings could lead to new information about your medical condition. Such re-interpretation must be requested by your physician and will involve additional costs. However, it may not be possible to re-interpret your data at a future date, and it may instead require retesting with a new sample.

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Potential risks associated with Clinical Exome Sequencing:

1. Pathogenic variants in genes that lead to conditions for which the patient currently has no symptoms may be discovered (such as cancer, neuromuscular and adult onset disorders). For some conditions (adult onset), the option of knowing if pathogenic variants are present is provided (see the list of the 56 genes recommended by the American College of Medical Genetic and Genomics (ACMGG)).
2. Uncertainty – For some findings, we may not be able to inform you with certainty whether these finding(s) are directly related to the patient's clinical condition. The interpretation of CES will evolve over time as we learn more about human DNA variation.
3. Anxiety - Patients and family members may experience anxiety before, during, and/or after testing. In some instances, we might need to test other family members to be able to better interpret the test results.
4. Diseases unrelated to the primary reason for ordering the CES test. There is a risk that you may learn about genetic variants that are not related to the medical concern for which this test was ordered. Learning about this information might cause anxiety and psychological stress.
5. Testing can potentially lead to the knowledge that the reported relationship of a family member is not consistent with the genetic relationship of that family member (examples are non-paternity, undisclosed adoption and non-maternity in the context of IVF).

Privacy

The Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, is a federal law that protects people from being treated unfairly because of differences in their DNA that may affect their health, and prevents discrimination by health insurers and employers based on genetic information. Before the federal law was passed, many states had passed laws against genetic discrimination. The degree of protection from these state laws varies widely. The federal law sets a minimum standard of protection that must be met in all states. It does not weaken the protections provided by any state law.

The federal law is intended to ease concerns about discrimination that might keep some people from getting genetic tests that could benefit their health, and enable people to take part in research studies without fear that their DNA information might be used against them in health insurance or the workplace. Additional information can be found at http://www.genome.gov/10002328.

Your privacy is very important to us, and we will use many safety measures to protect your privacy. However, in spite of those safety measures, we cannot guarantee that your identity will never become known. It may be possible for someone who gained illegal access to your genetic information and to protected genetic databases to determine your identity by matching your genetic information against the database. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other relatives. Consequently, it may be possible that by gaining illegal access to your genetic information, someone could guess your identity based on other genetic information that they might know about your relatives. Similarly, it may be possible that genetic information from you could be used to help identify your relatives. Because the DNA sequence of each individual is unique (with the exception of identical twins), it is likely that if your complete DNA sequence were publicly disclosed, it could be used to determine your identity.

There also may be other privacy risks that we have not foreseen. While we believe that the risks to you and your family are very low, we are unable to tell you exactly what all of the risks are. We believe that the benefits of this genetic test to your health outweigh these potential risks.

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WES Secondary Findings & Opt-Out

As many different genes and conditions are analyzed in the exome test, the test may reveal some findings not directly related to the reason for ordering WES. Such findings are called "incidental" or "secondary" and can provide information that was not anticipated.

The American College of Medical Genetics and Genomics (ACMG) has recommended that patients undergoing exome sequencing be offered the option to receive or not receive information about secondary findings identified in a specific subset of medically actionable genes (total 56 genes) associated with various inherited disorders(Genet Med. 2015 Jan;17(1):68-9.) A list of the 56 genes can be found in the reference (Green RC et al. Genet Med. 2013 Jul;15(7):565-74.).

- **What will be reported for the proband**

All known and/or expected pathogenic variants that are related to patient's phenotype(s) identified in the coding exons of the genes (for which a minimum of 10X coverage was achieved by the exome sequencing test), as recommended by the ACMG.

- **What will be reported for relatives (if tested with the exome sequencing).**

If the family members opted in for receiving information on the secondary findings, the presence or absence for any secondary findings reported for the proband will be provided for all relatives tested by the exome sequencing test.

Limitations

- Pathogenic variants may be present in a portion of the gene not covered by this test and therefore are not identified and reported. **The absence of reportable secondary findings for any particular gene does not mean there are no pathogenic variants in that gene**.
- Pathogenic variants that may be present in a relative, but are not present in the proband, will not be identified, or reported.
- Only changes at the sequence level will be reported in the secondary findings report. Larger deletions/duplications, abnormal methylation, triplet repeat or other expansion variants, or other variants not routinely identified by whole exome sequencing will not be reported.

Mandatory Disclosures (for both minors and adult patients):

Diagnostic findings related to phenotype - pathogenic variant(s), likely pathogenic variants(s), and variant(s) of uncertain significance in genes interpreted to be responsible for, or contributing to the patient's phenotype will be reported to all patients.

The risks, benefits, and limitation of the CES test have been explained to me and I have had an opportunity to have my questions answered. I have read and will receive a copy of this consent form.

_____	_____	_____	_____
Patient Signature	Date	Parent/Guardian Signature	Date

Physician/Counselor/Clinician Statement:

I have provided genetic counseling and have explained the CES test to the patient/parent/guardian. The consent form and limitations of genetic testing have been reviewed with the patient/guardian. I accept responsibility for pre- and post-test genetic counseling.

Note to Ordering Clinician:

The University of Arizona Genetic Core for Clinical Services laboratory encourages the discussion of the limitations and utility of a genomic test with the patient prior to specimen collection. This form is provided to address pertinent issues regarding this test. Specific information describing indications, methodology and detection can be found on the UAGC – CS website.

_____	_____
Clinician Signature	Date