Shodair Children's Hospital
Genetics Laboratory
2620 Shodair Dr. Helena, MT 59601
Phone (406) 444-7532 Fax (406) 444-1022

Family Member Whole Exome Sequencing Informed Consent

Family Member First and Last Name: _____ Date of Birth: _____ Sex: _____

What is the informed consent process?

Whole exome sequencing (WES*)* can be used to help diagnose one or more hereditary conditions. The risks and benefits of this test are explained in this consent form so that the patient can make an informed decision about whether to proceed with this test. Participation in WES is voluntary. Genetic counseling is required prior to, as well as following, this complex test.

What is whole exome sequencing (WES)?

Whole exome sequencing (WES) is a test that analyzes most of our approximately 20,000 genes and is designed to identify genetic changes (variants) in the DNA that may cause disease or are important to the patient's health in other ways. Through WES, thousands of DNA variants are detected. Some variants are disease-causing while others are harmless or have an uncertain effect. This process involves analyzing genes that have been previously associated with human disease, known as characterized genes. Additionally, many human genes have *not* been associated with an underlying genetic condition; these are known as novel genes.

Most changes that cause disease affect the portions of our genes called exons. The exons of a gene contain the genetic information the body uses to make proteins, which are molecules that carry out all the essential functions in the body. The DNA within the exons of all the genes is collectively called the exome. WES is a test that looks for disease-causing changes in any gene that may be related to the patient's underlying clinical presentation.

How is testing performed?

Acceptable sample types for WES are blood, extracted DNA, or saliva/buccal cells. Once collected, the sample will be sent to Shodair for testing. Shodair Genetics Laboratory will perform WES on the patient's sample.

Samples from other family members may be studied to help interpret the results. In the case of duos and trios, results are only reported on the patient's sample. Family members' results are *not* analyzed separately from the patient's, with the exception of secondary findings described on the next page. Shodair performs this analysis with the expectation that family members are not affected; if a family member is suspected of also sharing the condition, then Shodair Genetics Laboratory should be notified. WES interpretation and analysis is significantly enhanced by a complete clinical history. For informative results and the highest likelihood of a conclusive diagnosis, it is critical that the ordering provider includes all relevant clinical and family history.

What are possible results from whole exome sequencing (WES)?

WES is performed to identify a potential genetic basis for the health condition(s) in consideration. Shodair will report results that may help answer that question. The results of this test could be:

1. **Positive:** This may (1) Identify a likely diagnosis of a genetic condition; (2) Identify a predisposition/increased risk for developing a genetic disease in the future; and/or (3) Have implications for other family members.
2. **Negative:** This may (1) Reduce but not eliminate the possibility that the condition in consideration has a genetic basis; (2) Reduce but not eliminate a predisposition/risk for developing a genetic disease in the future; (3) Not remove the need for additional testing; and/or (4) Be uninformative.
3. **Of Uncertain Significance:** This may (1) Result in the recommendation of additional testing for the patient or the genetic testing of additional family members; (2) Remain uncertain for the foreseeable future; (3) Be resolved over time if additional information becomes available regarding the identified sequence variant; (4) Lead to the recommendation of additional studies to clarify the findings, such as muscle or skin biopsy, or imaging to obtain more information about the significance of the genetic change.

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What are the risks and limitations of whole exome sequencing (WES)?

Exome sequencing has technical limitations that may prevent the detection of certain changes in the DNA. Although genetic test results are usually accurate, several sources of error are possible, including: trace contamination, rare technical error in the laboratory, DNA changes that compromise data analysis, inconsistent scientific classification systems, inaccurate reporting of family relationships, and/or inaccurate or incomplete description of clinical findings.

There is a possibility that, if multiple family members are tested, this test may find that family relationships are not what they are believed to be. For example, this test may detect non-paternity, revealing that the stated father of the patient is not the biological father; or consanguinity, revealing a close blood relationship between the biological parents. If identified, it may be necessary to report these findings to the healthcare provider who ordered testing.

Often, exome sequencing is not able to identify the cause of a patient's medical issues. This does not exclude the possibility that the patient has a genetic condition. Some disease-causing variants are in genes with unknown function while others are in areas not tested (between genes or within the non-coding regions of genes). Still others are in genes that are not possible to analyze with this testing method.

Although this test will analyze and detect changes in the nuclear genes associated with mitochondrial function, it does *not* sequence the DNA within the mitochondria. As a result sequence changes, deletions, and duplications in mitochondrial DNA are not evaluated with this test.

What will be included in the whole exome sequencing (WES) report?

Variants related to the patient's underlying clinical presentation are reported. *De novo* variants (not inherited from either parent) or variants inherited from both parents in the same gene may be reported even if the function of the gene is unknown. Variants unrelated to the patient's medical condition are *not* reported, except for known disease-causing variants in the genes recommended for testing by the American College of Medical Genetics and Genomics (ACMG), referred to as secondary findings.

Professional organizations, including the ACMG, have recommended that all patients and family members undergoing exome testing have the option to have a particular group of medically actionable genes analyzed to identify disease-causing changes. These genes were chosen because the associated conditions are considered medically treatable or avoidable. WES may also predict that another family member has / is at risk for / is a carrier of a genetic condition. The patient and/or family members may or may not want to be informed of these potential secondary findings.

Because changes in these genes represent an additional analysis beyond what is being performed for the primary indication for testing, it is the patient's and family members' decision to be informed about any secondary findings. The patient, as well as any family members sequenced as part of the duo/trio, must mark their selection below indicating whether or not they would like secondary findings reported. Each duo/trio family member choosing to receive secondary findings results will undergo an individual, secondary findings analysis and report. Please note, pathogenic variants that may be present in a family member, but not in the patient, may be detected and reported.

Please mark your selection and sign below.

☐ **YES,** please report secondary findings

☐ **NO,** please do ***not*** report secondary findings

Signature of patient/parent/legal guardian: _____

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What about reanalysis and sample/data storage and use?

The field of genetics is discovering new information at a rapid rate. Over time, variants that currently have no association with disease may ultimately prove important for the health of the patient. Reanalysis of this testing may be performed on request or as a routine laboratory practice when relevant new gene/disease associations are described in OMIM or other medical literature sources.

Data from this testing will be maintained indefinitely. Extracted DNA samples are maintained in the laboratory for a minimum of 2 years. This minimizes the need for additional sample collection for future studies. DNA samples are only utilized for additional requested testing or authorized family studies. Our laboratory does *not* provide data or samples to third parties, except on specific request from patients or legal guardians/representatives. Please contact our laboratory if the patient and/or family member would prefer to have their sample discarded once testing is completed.

I Consent to Whole Exome Sequencing

The ACMG and the American Academy of Pediatrics (AAP) offer the following precautions when performing genetic testing in minors: (1) Parents/legal guardians may authorize predictive genetic testing for asymptomatic children at risk of childhood-onset conditions. Ideally, the assent of the child should be obtained; (2) Predictive genetic testing for adult-onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality; (3) For ethical and legal reasons, health care providers should be cautious about providing predictive genetic testing to minors without the involvement of their parents/legal guardians, even if a minor is mature. Results of such tests may have significant medical, psychological, and social implications, not only for the minor but also for other family members.

BY SIGNING BELOW, I CONFIRM THAT: (1) I have read (or had read to me) and I understand the information provided in this consent; (2) I understand that genetic testing is voluntary, and I may choose not to have my sample tested; (3) I have received a copy of this consent form; (4) All my questions have been satisfactorily answered; and (5) I hereby consent to genetic testing and to the retention, use, and sharing of my data and sample as described in this form.

Signature: _____ **Date:** _____

Printed Name: _____ **Relationship to Patient:** _____

Healthcare Provider Statement

By signing below, I attest that: (1) I am the referring physician or authorized healthcare provider; (2) I have explained the purpose of the test described above; (3) The patient has had the opportunity to ask questions regarding this test and the retention, use, and sharing of their data and sample, and to seek genetic counseling; and (4) The patient has voluntarily decided to have this test performed by Shodair Genetics Laboratory.

Healthcare Provider Signature: _____ **Date:** _____