Knight Diagnostic Laboratories

Fax: (855) 535-1329
Email: KDLClientServices@ohsu.edu
Shipping: 2525 SW 3rd Ave, Ste 350, Portland, OR 97201
Questions? (855) 535-1522

# Exome Requisition for Trio

## Complete Exome Orders Must Include All of the Following:

- ☑ Include completed Requitision Form (pages 1-2) or an Epic Order
- ☑ Clinical and Phenotypic History Form (pages 3-4)
- ☑ Signed Consent Form (pages 7-11)
- ☑ Fax all forms to KDL Client Services: (855) 535-1329

## Exome Tests

| Exome Sequencing and Del/Dup | | |
|---|---|---|
| | **Code** | **Test Name** |
| ☐ | 2850 | Trio |

| Exome Sequencing Only | | |
|---|---|---|
| | **Code** | **Test Name** |
| ☐ | 2890 | Trio |

[1] Trio testing requires blood samples from both parents in addition to the proband.

## Patient Information

Full Name
Street Address
City, State, Zip
Phone DOB / /
Fax ☐ Male ☐ Female
ID/MRN #
Hospital In-Patient ☐ Yes ☐ No

Physician Signature Date

## Ordering Physician Information

Full Name
NPI
Office/Facility Name
Address
City, State, Zip
Phone Fax
Account #
Notes

## Send additional copies of test results to:

Physician Name Physician Phone Fax
Physician Name Physician Phone Fax

## Billing Information - Select One Billing Method

*Billing is done in accordance with the information provided below and OHSU policy. Appropriate areas must be completed or referring laboratory/physician will be billed.*

☐ Self Pay ☐ Bill Insurance
Attach Copy of Insurance Card or Billing Face Sheet

☐ Bill Referring Provider or Institution
Invoice will be sent to Client Account and Address Listed Above

Primary Insurance Name
Primary Policy #
Primary Group #
Preauthorization #

Relation to Insured ☐ Medicaid ☐ Medicare
☐ Self ☐ Child ☐ Spouse ☐ Other_____

Secondary Insurance Name
Secondary Policy #
Secondary Group #
Preauthorization #

Relation to Insured ☐ Medicaid ☐ Medicare
☐ Self ☐ Child ☐ Spouse ☐ Other_____

## Clinical Information

Specimen Type

☐ Saliva
☐ DNA from* _____
☐ Whole Blood
☐ Other _____

Date of Specimen Collection
/ /

Time of Specimen Collection
: :

ICD-10 (required)

* DNA extraction must occur in a CLIA-certified lab or a lab meeting equivalent requirements.

Diagnosis

☐ African American
☐ Alaska Native
☐ Asian
☐ Caucasian / Non-Hispanic
☐ Hispanic American
☐ Jewish, Ashkenazi
☐ Jewish (Other)
☐ Native American Indian
☐ Other:_____

# CLINICAL AND PHENOTYPIC HISTORY FORM

| Indication for Testing | Known Familial Mutations |
|---|---|
| ☐ Family History, Mutation Known: ☐ Yes* ☐ No<br>*If Yes, please complete KNOWN FAMILIAL MUTATIONS<br>☐ Symptomatic<br>☐ Possible Diagnosis<br>☐ Definite Diagnosis<br>☐ Carrier Testing ☐ Presymptomatic Testing<br>☐ Prenatal Testing ☐ Predispositional Testing<br>☐ Other (Please Specify)<br>Pregnancy: LMP:_____<br>GMP:_____ | Please call Client Services at 1-800-KDL-1LAB and provide clinical report if proband testing was performed outside of OHSU.<br>Patient Status: ☐ Symptomatic ☐ Asymptomatic<br>Name of Gene: _____<br>Variants to be tested: _____<br>Name of Proband:_____<br>Relationship to Proband: _____<br>OHSU Sample # of Proband:_____<br>* If proband testing was performed outside of OHSU, please provide clinical report. |

## Family History

Please draw or attach patient's three generation pedigree

Please include any additional relevant family history information:

## Phenotypic History

**Instructions**: Please provide the patient's phenotypic history by filling either Normal or an abnormality in a sub-category. In the space provided below each section, add any additional relevant clinician notes for that category. On the following pages is a list of phenotype terms to assist in completing the requisition form.

| | **Abnormality - Please provide detailed description** | **Normal** |
|---|---|---|
| Nervous system | ☐ | ☐ |
| Voice or speech | ☐ | ☐ |
| Behavioral or neuropsychiatric | ☐ | ☐ |
| Growth and development | ☐ | ☐ |
| Metabolic system | ☐ | ☐ |
| Head, facial, ears or neck | ☐ | ☐ |
| Eye or vision | ☐ | ☐ |
| Skin, nails or hair | ☐ | ☐ |
| Skeletal system or limb extremities | ☐ | ☐ |
| Musculature and soft tissues | ☐ | ☐ |
| Connective or adipose tissues | ☐ | ☐ |
| Genitourinary system | ☐ | ☐ |
| Immune system | ☐ | ☐ |
| Blood and/or bloodforming tissues | ☐ | ☐ |
| Cardiovascular system | ☐ | ☐ |
| Endocrine system | ☐ | ☐ |
| Respiratory system | ☐ | ☐ |
| Abdomen or abdominal organs | ☐ | ☐ |
| Chest or thoracic | ☐ | ☐ |
| Prenatal development or abnormal birth | ☐ | ☐ |
| Neoplasm | ☐ | ☐ |
| Other | ☐ | ☐ |

**Nervous System**

- Behavioral/psychiatric (specify in "description")
- Nervous System Physiology
- Nervous System Morphology
- Seizures/Seizure disorder
- Hypotonia
- Hypertonia
- Spasticity
- Fasciculations
- Abnormal Movements
- Ataxia
- Intellectual Disability
- Structural Brain Malformations

**Skeletal System and Extremities**

- Skeletal Morphology (specify in "description")
- Limb bones (specify in "description")
- Skeletal Physiology
- Abnormal Calcification
- Hemihypertrophy
- Aplasia/hypoplasia of extremities

**Head or Neck**

- Microcephaly
- Macrocephaly
- Facial dysmorphism (specify in "description")
- Hearing abnormality

**Abnormality of the Ear**

- Aplasia/Hypoplasia of the ear
- Abnormality of the Nose
- Oral Cavity or Dental Anomalies
- Abnormality of the Neck

**Metabolism/Homeostasis**

- Electrolyte Abnormality
- Hypoglycemia
- Hyperglycemia
- Mitochondrial Abnormality
- Metabolic Acidosis
- Hyperbilirubinemia
- Hyperammonemia
- Abnormality of Vitamin Metabolism
- Abnormality of Fatty Acid Oxidation
- Abnormality of Amino Acid Metabolism

**Musculature/Soft Tissue**

- Muscle Physiology (specify in "description")
- Muscle Morphology (specify in "description")
- Weakness
- Contracture
- Mitochondrial Muscle Dysfunction
- Calcification of Muscles
- Abnormal Intramuscular Fat

**Genitourinary System**

- Abnormality of the urinary system
- Abnormality of the genital system
- Urogenital fistula
- Cloacal abnormality

**Eye**

- Vision abnormality
- Blindness
- Retinal abnormalities
- Optic nerve abnormalities
- Nystagmus

**Skin or Nails**

- Abnormal pigmentation
- Skin Adnexa
- Abnormal Scarring
- Connective tissue nevi

**Abdomen**

- Abnormality of the abdominal organs
- Abnormality of the abdominal wall
- Abnormality of the diaphragm
- Abnormality of abdominal situs
- Gastroparesis

**Blood or Blood-Forming Tissue**

- Abnormality of bone marrow cell morphology
- Abnormality of leukocytes
- Abnormality of erythrocytes
- Abnormal bleeding, coagulation, or platelets
- Hematological neoplasm
- Abnormal thrombosis
- Extramedullary hematopoiesis
- Abnormality of mast cells

**Cardiovascular System**

- Abnormality of cardiac morphology
- Abnormality of the vasculature
- Abnormality of cardiovascular system physiology
- Abnormality of the fetal cardiovascular system
- Cardiovascular calcification

**Growth and Development**

- Failure to thrive
- Tall stature
- Short stature
- Abnormality of body weight
- Asymmetric growth
- Developmental delay (please specify)
- Developmental regression
- Autistic behavior – autistic spectrum disorders
- Speech articulation difficulties

**Connective Tissues**

- Hyperextensibility
- Abnormality of adipose tissue
- Abnormality of the fascia

**Immune System**

- Abnormality of immune system physiology
- Abnormality of cellular immune system
- Abnormality of the lymphatic system
- Cellulitis

**Neoplasm**

- Neoplasm by anatomical site
- Neoplasm by histology

**Breast**

- Abnormality of the nipple
- Gynecomastia
- Aplasia/Hypoplasia of the breasts
- Galactorrhea
- Hypoplastic areola
- Asymmetry of the breasts
- Breast hypertrophy

**Prenatal Development or Abnormal Birth**

- Abnormality of the amniotic fluid
- Premature birth
- Decreased fetal movement
- Hydrops fetalis
- Fetal ultrasound abnormality
- Abnormalities of placenta or umbilical cord
- Abnormal delivery
- Prenatal maternal abnormality
- Fetal ascites
- Intrauterine Growth Restriction

**Endocrine System**

- Puberty and gonadal disorders
- Abnormality of the thyroid gland
- Diabetes mellitus
- Diabetes insipidus
- Abnormality of the hypothalamus-pituitary axis
- Abnormality of circulating hormone level
- Abnormality of the adrenal glands
- Abnormality of the parathyroid gland
- Abnormality of the thymus
- Abnormality of renin-angiotensin system
- Abnormality of endocrine pancreas physiology
- Abnormality of urine hormone level
- Abnormality of the pineal gland

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# Exome Sequencing Consent Form, Family Trio

Your physician has advised you to undergo the genetic test called the Exome Sequencing test. The purpose of this form is to provide comprehensive information about this test.

## Description of Exome Sequencing

- The patient and their parents' DNA will be analyzed to look for genetic changes that might contribute to the cause of the patient's condition.
- A change in the patient's DNA sequence compared to a reference DNA sequence is called as a variant.
- Every cell in your body contains the genetic code of your DNA. Your genome includes genes that contain exons or short segments of DNA that act as a set of instructions for the creation of proteins. Proteins are the central actors in most of the biological processes in your body. Most disease causing DNA changes, or mutations, are present within the exons.
- A gene can have one or several exons. The term "exome" describes all the exons, or protein-coding regions, in a person. Sequencing the exome targets segments of DNA that are most likely to be associated with medical disorders. The exome accounts for about 1% of the body's genetic code, but 85% of genetic diseases are associated with mutations in the exome.
- The Exome Sequencing test involves sequencing thousands of exons at the same time. Unlike testing one gene at a time, Exome Sequencing testing is a faster and more efficient way of looking for DNA changes contributing to medical disorders.

## Testing of Family Samples

- This test is a family-centered approach to Exome Sequencing and involves the sequencing of three individuals (trio): the patient (proband) and both parents of the proband.
- This approach provides information about which parent contributed to a DNA change in their child. Providing samples for both parents improves the analysis of the test and decreases the likelihood of receiving an inconclusive result.
- As with any family-centered genetic testing, there is a possibility that the family genetic relationships do not align with what is reported. If the results do not confirm the genetic pattern for a biological mother and father as reported, your medical provider will be contacted to determine how to proceed with testing.

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# Exome Sequencing Consent Form, Family Trio

## Indications for Testing

- The test requires a blood or saliva sample from the patient and each of their parents.
- In general, the test is used when your medical history and physical exam findings strongly suggest a genetic cause for your medical issues. The decision to undergo the Exome Sequencing test is made by you and your physician. Your physician will explain the risks and benefits of the test.
- Your genetic information (DNA) will be taken from the sample and put through a machine that reads the genetic information. The patient's genetic information will be compared with their parent's DNA. Genetic information will also be compared to typical and known harmful genetic information to help understand the genetic cause for your medical issue. This will take about 8-16 weeks.
- You will meet with your provider to go over the test results.

## Limitations and Potential Consequences of the Exome Sequencing Test for Trios

- The test may not answer any or all of your health questions for several reasons:
    a. Most of your exome will be examined, but 10-15% of the exome does not have sufficient coverage to accurately determine the presence of a genetic change.
    b. Exome sequencing cannot detect changes that affect the activity or structure of the DNA.
    c. Exome sequencing cannot accurately sequence repetitive regions, such as trinucleotide repeats.
    d. Not all health issues have known genetic causes.
    e. Even when genes increase the risk for a health condition, other factors may play more important roles.
    f. Not all genes in the exome to date have known disease associations; these are genes of unknown significance. Variants in these genes that do not have any diagnostic or phenotypic implications are not reported.
- Results may indicate that additional testing, such as full gene sequencing to fill-in exons with poor coverage, is recommended.
- The meaning of this test may be uncertain. We may not be able to tell you with certainty whether the variant(s) we find are directly related to your medical issue. The interpretation of Exome Sequencing will evolve over time as we learn more about normal and abnormal human variation.

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- This test may find unexpected changes in family tree. Because more than one person in a family is tested, you might learn that family members are not related. The test might show that a child has a different father, that donor eggs or sperm were used for a pregnancy, or that a child has been adopted. This test may show that your mother and father are close relatives or distantly related. This news can cause conflicts in some families. If the results do not confirm the genetic pattern for a biological mother and father as reported, your medical provider will be contacted to determine how to proceed with testing.
- Patients and family members may experience anxiety before, during, and/or after testing.
- This test may affect your ability to get certain types of insurance. Your test results will be in your medical records. Some people worry that genetic information could be used against them. It is against U.S. law to deny someone a job because of genetic testing information. It is against U.S. law to deny or raise the cost of health insurance because of genetic testing information. It is legal to use this information to deny or determine the cost of life insurance, disability insurance, and other supplemental insurance.

### Privacy of Genetic Information

In the U.S., written permission is usually needed before your medical information is shared. The laboratory only shares your results with you and your ordering physician. Your genetic information is protected under H.R. 493, the Genetic Information Nondiscrimination Act of 2008.

### Main Report Results

The main report will contain the following results:

1. Diagnostic findings: Variations in genes interpreted to be responsible for, or contributing to, the patient's condition. This interpretation will be based on information available in the medical literature and scientific databases. In some circumstances, the impact of a genetic change will be unknown due to a lack of scientific information, which will be classified as uncertain significance.

   Only genetic variants classified as pathogenic, likely pathogenic, and uncertain significance will be reported. Every patient (proband) will receive a diagnostic findings report. However, parents will *not* receive a diagnostic findings report.

2. Unexpected findings: In some instances, this test may reveal a clinically relevant genetic change that is not directly related to the patient's symptoms. The lab is obligated to report unexpected findings if it impacts medical care. The lab will not seek findings that are not related to the patient's condition.

However, if a variant is uncovered during analysis, these findings can be reported if requested. Unexpected findings may or may not include genes targeted for analysis for "Optional Results."

Only genetic variants classified as pathogenic and likely pathogenic will be reported. KDL reports unexpected findings for patients and parents. Each parent with incidental findings will be issued a separate report if they opt-in.

Classification of variants into pathogenic, likely pathogenic, uncertain significance, likely benign, and benign categories are based on the American College of Medical Genetics and Genomics and the Association of Molecular Pathology's *Standards and Guidelines for Interpretation of Sequence Variants* (Richards et. al., Genet Med. 2015; 17: 405-423).

Our understanding of genetic changes will improve over time. It is possible that a more certain interpretation of your genetic changes will be possible in the subsequent years following the initial report. For this reason, the lab reviews genetic changes reported as "uncertain significance" annually. If new information is discovered and it is thought to be important to your health and/or the health of your relatives, the patient's healthcare provider will be contacted.

### Optional Results

In addition to the primary test results, the patient and parents can opt-in to receive other findings from the exome analysis. Please read the description below and indicate if you wish these to be reported by opting-in on the signature page.

***Medically Actionable Genes*** (that are not relevant to the reason the testing was done):
You have the option of learning about genetic changes that can make you at higher risk for unrelated, but serious health conditions such as heart disease and certain inherited cancers. If you wish to learn of these conditions (also known as incidental findings), the results reported will be on a limited list of genes based on the American College of Medical Genetics (ACMG) recommendations (Green et. al. Genet Med. 2013 Jul;15(7):565-74). If you choose to opt-in, all the genes on the Incidental Finding List will be analyzed and there is no option to choose the analysis for less than the complete list of genes.

Genetic changes in medically actionable genes might change the way your doctor treats you. Results might show a higher risk for a disease that either may not happen for many years or may not happen at all. Some of these diseases have no treatments but they might change how you plan for the future. These results may also impact other family members, who may wish to know or not know about these conditions.

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If an incidental finding is identified, genetic counseling and/or other medical evaluations may be recommended. These expenses may or may not be covered by your health insurance. This may also impact your ability to get certain types of insurance (see limitation and potential consequences section above).

The patient's "Main Report" will always include results that are thought to be connected to their medical condition. By checking the "Medically Actionable Results" box on the signature page of this consent form, you can also learn about genetic changes not related to the medical symptoms leading to ordering Exome Sequencing. If the parents opt-in, a separate report will be generated for each of them.

### Specimen Retention

The Knight Diagnostic Laboratory does not return the remaining sample to individuals or physicians, and does not guarantee the future availability of isolated DNA. Any requests for additional studies must be ordered by the referring provider and charges will be incurred. Once the test is complete, we will remove your personal information and use the DNA for laboratory quality control or to develop new tests. Any results obtained cannot be related back to the original source.

**DECLINE** the use of your remaining DNA for research purposes by initialing here:

| Proband/Guardian Initials | Mother's Initials | Father's Initials |
|---|---|---|
| _____ | _____ | _____ |

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## Consent for Optional Test Results

Please specify what kinds of results you wish reported for results *not* associated with the reason Exome Sequencing was ordered. Results associated with your condition will be reported, as described in the "Main Report Results" section.

| Report Results if Checked | | | Optional Results Category |
|---|---|---|---|
| Patient | Mother | Father | |
| ☐ | ☐ | ☐ | Medically Actionable Results (not associated with the reason Exome Sequencing was ordered) - *see page 4 for detailed description* |

## Signatures

I hereby authorize the Knight Diagnostic Laboratories to conduct genetic testing for the Exome Sequencing test for family trios, as recommended by my physician. Please note that if the patient (proband) is a child, parents or 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.

| | | |
|---|---|---|
| Patient's Name | Patient or Legal Guardian's Signature | Date |
| Mother's Name | Mother's Signature | Date |
| Father's Name | Father's Signature | Date |

Witness Signature: _____ Date: _____