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Informed Consent for Clinical Exome Sequencing (CES)

Patient Name: _____
DOB (MM/DD/YYYY): _____

I, _____ (*patient or patient's legal representative*) authorize the Center for Personalized Medicine at Children's Hospital Los Angeles to conduct Clinical Exome Sequencing (CES) as ordered by my/my child's healthcare provider. I understand that I have the right to refuse genetic testing and that participation is completely voluntary.
It has been explained to me and I understand the following statements:

About the Clinical Exome Sequencing Test

The test that is being pursued is the Clinical Exome Sequencing test. This test will be used in an attempt to identify a genetic cause for my/my child's medical condition. Genes carry information about heredity that determines how a body functions and develops. It is estimated that humans have about 20,000 genes. Half of an individual's genetic material comes from the biological mother and the other half from the biological father. The collection of the entire set of genes is called the genome and consists of exons and introns. Exons are the functional parts of the genome that make proteins. "Exome" refers to the parts of the genome formed by all the exons. The CES test will analyze approximately 95% of an exome in order to find a change in the DNA that is causing an individual's medical condition.

I understand that the CES test is not 100% sensitive and does not identify every DNA change. The comprehensiveness of a CES result will depend on the accuracy of family history and the amount of relevant clinical information an individual and their ordering healthcare provider are able to provide.

Test Samples

- I understand that a blood specimen will be obtained from the patient and members of the patient's family. CES will be performed on the patient's specimen for the purpose of determining if a change in the DNA is causing a medical condition. Blood specimens from the patient's family members will be used to help interpret the result of the patient's exome sequencing.

- Approximately 5ml (1 teaspoon) of blood will be collected for this test. The minimum amount needed is 0.5ml.

Genetic Counseling

- Genetic counseling prior to consenting to CES is recommended to fully understand the benefits, risks, and limitations of exome sequencing.

- Post-test genetic counseling should be provided by a genetic counselor, physician, or other authorized healthcare provider to give information about clinically relevant results and available interventions or resources. Continued follow-up at a genetics clinic may be recommended.

Benefits

- CES may identify a DNA change resulting in a molecular diagnosis for a medical condition. In some cases, a molecular diagnosis provides additional information about a medical condition that may modify the healthcare management and/or treatment an individual is currently receiving.

- A molecular diagnosis may be used for family planning purposes and to help identify family members who may be “at-risk” of developing a similar medical condition.

Risks and Limitations

- There is a possibility that an individual has a genetic condition even though the CES result may be negative. Due to limitations in technology, some types of DNA changes will not be detected by this test. In addition, some disease-causing variants that do not occur in an exon will not be detected. A healthcare provider may decide that additional genetic testing is needed to obtain a molecular diagnosis.

- Due to incomplete knowledge of some DNA changes, there is a possibility that the test result may be a variant of unknown significance (VUS). This means that a DNA change was identified; however, it is unknown whether the variant is responsible for an individual’s medical condition.

- Genetic knowledge is constantly changing. The interpretation of an exome sequencing test will be based on the most currently available information. As further discoveries are made this interpretation may change. A re-interpretation of a CES result at a future date may lead to a molecular diagnosis that may impact an individual's healthcare management. A request for a re-interpretation of a CES result may be submitted by a healthcare provider.

- The accuracy of the test depends on correct family history. An error in diagnosis may occur if the true biological relationships of the family members involved in this study are not as they have been stated. In addition, testing may inadvertently reveal non-paternity or non-

maternity. This means that the biological father or biological mother of an individual is not the person stated to be the father or mother. It may be necessary to disclose this finding to the ordering healthcare provider. This is due to the fact that an erroneous diagnosis in a family member can lead to an incorrect diagnosis for other related individuals.

Additional Medically Actionable Results

- Exome sequencing may identify a previously undiagnosed genetic condition that is not related to the symptoms for which the CES was initially ordered. For example, a result may indicate that an individual has a hereditary predisposition to develop cancer or cardiomyopathy. The symptoms of these conditions may not be apparent at the time of testing and they may or may not occur in the future. These findings are called medically actionable results because a physician may modify an individual's healthcare management based on these results. In 2013, the American College of Medical Genetics and Genomics (ACMG) released an updated guideline of genes to be included in a medically actionable findings report. A list of these genes can be found on the ACMG website www.acmg.net/docs/IF_Statement_Final_7.24.13.pdf). Variants in these genes, or other reportable genes as indicated by recent clinical literature and publications, will be reported as a medically actionable result only if they are known to be disease-causing or expected to be disease-causing. Variants of unknown significance will not be reported.

- A medically actionable finding will be reported for relatives (i.e.: parents, siblings) who have submitted a sample only if the variant has been detected in the patient. Variants that have been identified in relatives but are not detected in the patient will not be reported. I understand that the medically actionable findings report is optional and I have the ability to "opt out" of receiving these results. Please initial one of the following options (adult patient or parent/legal representative of minor child must initial)

Option I: Initialing here indicates that I wish to receive the "additional medically actionable findings" results. Initial here _____.

Option II: Initialing here indicates that I do **not** wish to receive the "additional medically actionable findings" results. Initial here _____.

Results Reporting & Confidentiality

- The expected turn-around-time for the Clinical Exome Sequencing result is approximately 3 months. The CES report will be sent to the ordering healthcare provider.

- There are autosomal recessive conditions in which an individual must inherit two disease-causing variants on the same gene in order for symptoms to occur. One variant is inherited from the mother and the other from the father. An individual who has only one disease-causing variant on an autosomal recessive gene is an unaffected carrier. The CES result will not include the carrier status for autosomal recessive conditions unless it is a gene

associated with an individual's medical condition or a gene on the ACMG "medically actionable" guideline list.

- Because of the complexity of genetic testing and the important implications of the test, results should be reported only through a geneticist, genetic counselor, or other authorized healthcare provider. The results are confidential to the extent allowed by law. Those with legal access include, but are not limited to, healthcare providers involved in the patient's care and the patient's health insurance provider. The results will be included in my/my child's electronic medical record at Children's Hospital Los Angeles and will only be released to other medical professionals from an outside institution, family members, or other parties with a written consent or as otherwise allowed by law.

- Interpretation of genetic results for this CES test relies on databases that have been developed by experts in the field of genetics. In order to help us continue to improve the quality of genetic testing and result interpretation for families like yours, the Center for Personalized Medicine may contribute your data to such databases. This data sharing will allow geneticists to gather information from a large number of people so they can find causes of childhood diseases, help prevent diseases, and find new treatment for childhood diseases. Any data that is shared will be anonymized and your name or other personal identifying information will not be used. The anonymized data contributed to the database may be used for research on any condition.

By initialing here I give my consent to anonymized data sharing. Initial here _____.

- I understand that this is not a specimen banking facility and my/my child's sample may not be available for future clinical studies. I understand that my/my child's specimen will be used for the CES test as authorized by my consent. At the end of the testing process, my/my child's specimen and data results may be retained by Children's Hospital Los Angeles for activities necessary to support its healthcare operations, such as improving the quality of its tests. My/my child's sample and results will not be used in any identifiable fashion for research purposes without my consent.

Signatures

My signature below acknowledges my voluntary participation in this test. I acknowledge that I have discussed the benefits, risks, and limitations of the Clinical Exome Sequencing test with my physician or genetic counselor. All of the above information has been explained to me, to my satisfaction, and my signature below attests to the same. I have been given the opportunity to ask questions and my questions have been answered to my satisfaction. I understand that the genetic analysis performed by the Children's Hospital Los Angeles Center for Personalized Medicine is specific only for the personal and family health histories provided and in no way guarantees my/my child's health, the health of an unborn child, or the health of other family

members. I am the patient, the patient's legal representative, or otherwise duly authorized by the patient to sign and provide consent to the CES test on the patient's behalf.

_____ _____

Patient or Legal Representative Name (Please Print) Birth Date (MM/DD/YYYY)

If signed by someone other than patient, indicate relationship: _____

_____ _____

Patient or Legal Representative Signature Signature Date (MM/DD/YYYY) and Time (AM/PM)

_____ _____

Witness Name (Please Print) Birth Date (MM/DD/YYYY)

_____ _____

Witness Signature Signature Date (MM/DD/YYYY) and Time (AM/PM)

Family Member Consents

I understand that I am submitting my blood sample to help in the interpretation of the Clinical Exome Sequencing analysis of the person being tested. The results obtained from my sample will be used solely for this purpose and I will not receive a separate report for the DNA analysis performed on my blood. The physician or the genetic counselor has discussed the information about this test with me. I have been given an opportunity to ask questions and all of my questions have been answered about this test. By signing this form, I willingly agree to participate in the CES test.

_____ _____

Name of Family Member (Please Print) Relationship to Patient

_____ _____

Family Member Signature Signature Date (MM/DD/YYYY) and Time (AM/PM)

Patient Name: _____

DOB (MM/DD/YYYY): _____

_____ _____

Name of Family Member (Please Print) Relationship to Patient

_____ _____

Family Member Signature Signature Date (MM/DD/YYYY) and Time (AM/PM)

Physician's or Genetic Counselor's Statement

I have explained the Clinical Exome Sequencing test (including the risks, benefits, and alternatives, if any) to the patient or the patient's legal representative and each family member submitting a specimen. I have addressed the limitations outlined above and given each of these individuals an opportunity to ask questions and seek genetic counseling. I have answered their questions to the best of my ability and the patient or the patient's legal representative has received a copy of this consent. I have disclosed to the patient or the patient's legal representative any research or economic interest I may have regarding this test.

_____ _____

Physician/ Counselor Signature Signature Date (MM/DD/YYYY) and Time (AM/PM)

Interpreter's Statement (Where Applicable)

I have accurately and completely read the foregoing document to (*patient or patient's legal representative and each family member submitting a sample)* _____ in their primary language (*identify language)* _____. Each individual understood all of the terms and conditions and acknowledged his/her agreement by signing the document in my presence.

_____ _____

Interpreter Name (Please Print) Signature Date (MM/DD/YYYY) and Time (AM/PM)

_____

Interpreter Signature