Dynacare®

Form 1a: Informed Consent to Perform Genetic Testing for Hereditary Hemorrhagic Telangiectasia (HHT) (NY)

By signing below, I acknowledge that:

1. My participation or, as applicable, my child's participation in this DNA testing is voluntary. The decision to consent to, or to refuse the above testing is entirely mine.
2. This testing is done on small biological samples.
3. It is possible that the quantity or quality of sample submitted may be inadequate for testing or that a variant cannot be identified.
4. No tests other than those authorized shall be performed on this biological sample.
5. When DNA testing shows a variant, then the person is a carrier or is affected with that condition or disease. Consulting a doctor or genetic counsellor is recommended to learn the full meaning of the results and to learn if additional testing might be necessary.
6. When the DNA testing does not show a variant, the chance that the person is a carrier or is affected is reduced. There is still a chance to be a carrier or to be affected because the current testing cannot find all the possible variants within a gene.
7. Impact Genetics will only collect, use, and disclose your personal health information as permitted/designated on the requisition/order form or required by applicable laws. For example, if necessary to obtain reimbursement of test fees, Impact Genetics, its agents and legal representatives, may disclose personal health information (including test results) for such purpose.
8. Impact Genetics is not a DNA banking facility and patient DNA samples may not be available for future testing.
9. An error in diagnosis may occur if the true biological relationships of the family members are not as stated in the pedigree submitted with the requisition/order form. It is possible that the test may disclose non-paternity (someone who is not the biological father), or some other previously unknown information about family relationships, such as adoption, and I consent that this finding be reported to the referring specialist designated on the requisition/order form.
10. There is a chance that the test may reveal unexpected abnormalities that may be of medical value in the patient's care. Impact Genetics will inform the referring specialist designated on the requisition/order form.
11. Until the results of this test are reported, the patient and members of the patient's family should still undergo examinations as prescribed by the referring specialist.
12. I have read or have had read to me, the above information and I understand it. I have also read or had explained to me the specific disease or condition tested for, and the specific test(s) I am having, including the test descriptions, principles and limitations. I have had the opportunity to discuss the purposes and possible risks of this testing with my doctor or someone my doctor has designated.

Consent for Storing a Sample

Impact Genetics is not a DNA banking facility and patient DNA samples may not always be available for future testing. However, Impact Genetics has my consent to store any surplus DNA samples indefinitely, for future clinical testing as requested by me. If "No" is checked or if neither box below is checked, the sample will be destroyed within 60 days after test completion.

☐ **Yes** ☐ **No**

Signature of Patient or Consenting Parent/Guardian: _____ Date: _____

Signature of Witness: _____ Date: _____

Statement of Referring Physician

I reviewed this form with my Patient. I offered to answer any questions.

Signature of Referring Physician: _____ Date: _____

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Information about the Hereditary Hemorrhagic Telangiectasia (HHT) Genetic Test

What is Hereditary Hemorrhagic Telangiectasia (HHT)?

Hereditary Hemorrhagic Telangiectasia (HHT) *(hr·eh·duh·teh·ree heh·mr·a·juhk tuh·lang·jee·uhk·tay·zhuh)* is a genetic disorder of the blood vessels which affects about one in 8,000 people. It affects males and females from all racial and ethnic groups. The disorder is also referred to as Osler-Weber-Rendu (OWR) syndrome. It is inherited from parent to child in an autosomal dominant mode of inheritance.

HHT causes malformed blood vessels and can affect multiple organs of the body. HHT can cause bleeding in a number of organs, the most common symptom for individuals with HHT is nosebleeds. Up to 90% of people with HHT live with persistent recurrent nosebleeds that can vary in severity from sporadic "time to time" to nosebleeds that require medical interventions. Other organs at risk for bleeding are the brain, lungs, and gastrointestinal tract.

The diagnosis of HHT can be made based on clinical criteria called "**the Curaçao criteria**".

The HHT diagnosis is classified as **Definite** if three criteria are present, **Possible** or **Suspected** if two criteria are present, and **Unlikely** if fewer than two criteria are present. The Curaçao criteria include the following:

- Epistaxis – Spontaneous, recurrent nosebleeds
- Telangiectases – Multiple at characteristic sites (lips, oral cavity, fingers, nose)
- Visceral lesions – Such as Gastro-Intestinal telangiectasia (with or without bleeding), pulmonary AVM (PAVM), hepatic AVM, cerebral AVM, spinal AVM
- Family history – A first-degree relative with HHT

Purpose and Principle of the Test

Genetic testing for HHT searches for gene variants in DNA from patient blood. Three genes are currently associated with HHT which are *ENG*, *ACVRL1* and *SMAD4*. Variants in the endoglin (*ENG*) gene (HHT type 1) are more often associated with PAVMs. Variants in the *ACVRL1* gene (HHT type 2) lead to a lower frequency of PAVMs than HHT type 1 and show a higher incidence of liver involvement. Clinical features of the disease do not reliably indicate whether the gene mutated is *ENG* or *ACVRL1*. Variants in the *SMAD4* gene (most often in exons 8 through 11) have been associated with Juvenile Polyposis HHT (JP- HHT).

A positive result provides a conclusive answer that the individual is definitively affected with HHT. Most families with HHT have their own unique variant. The position of the variant does not influence the severity of disease, as it is loss of one functional copy of the gene and the consequential deficiency of a key signaling protein (i.e. reduced endoglin) that is believed to lead to the disorder. The spectrum of variants spans all types of pathogenic variants and there are no known "hot spots" on the three genes: *ENG*, *ACVRL1*, and *SMAD4*.

Some individuals with a clinical diagnosis of HHT can have negative genetic testing results. A negative result does not entirely exclude the diagnosis of HHT since it is possible that that individual could be a carrier of a variant not detectable in one of the genes tested or a variant in a gene that is still unknown and not tested for.

Test Method: Impact Genetics' Variant Identification Strategy

Impact Genetics requests a blood sample and isolates DNA from which a series of molecular tests are performed to maximize efficiency in finding *ENG*, *ACVRL1* or *SMAD4* variants. Testing includes screening for large deletions as well as sequencing for single nucleotide changes or small insertions or deletions.

Blood samples from relatives may be required to determine if family members carry the same HHT gene variant as the affected patient. Blood samples from relatives may be required to determine if family members carry the same HHT gene variant as the affected patient.

Impact Genetics is certified under the US Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity clinical laboratory testing. Impact Genetics' tests were developed, and their performance characteristics determined, by Impact Genetics. They have not been cleared or approved by the US Food and Drug Administration, which has determined that such approval is not necessary. Impact Genetics does not perform linkage analysis.