GENETIC TESTING for HHT

What is genetic testing for HHT?

Genetic testing for HHT consists of analyzing DNA (the genetic material carried in cells) of the HHT-associated genes in a laboratory. Genetic testing is usually done on a small sample of blood, but can be done on a sample of saliva in certain cases. In a given family, genetic testing should start with someone who clearly has HHT.

Three different kinds of genetic tests for HHT are available. "Sequencing" of the genes involves looking at the precise sequence of building blocks in the sample of DNA to see if there is any abnormality. "Deletion and duplication" testing looks to see if there is a piece of the gene that is missing or duplicated. Single mutation analysis (often referred to as targeted sequencing) looks to see if one particular mutation that was previously identified in another family member is present or absent.

For a person who meets clinical diagnostic criteria for HHT, genetic testing by sequencing and deletion and duplication testing of *ENG* and *ACVRL1* will detect a mutation in approximately 87% of those tested. If testing of *ENG/ACVRL1* is negative, sequencing of *SMAD4* identifies a mutation in an additional 2% of people diagnosed with HHT. For about 10-15% of people with HHT, the laboratory will not find a mutation in one of the HHT genes. Therefore, someone with HHT can get normal results from genetic testing.

Why would genetic testing for HHT be done?

Genetic testing for HHT is done for several reasons. First, it may be useful in confirming a diagnosis of HHT in someone who is suspicious for HHT, but who does not meet established clinical diagnostic criteria based on their observable symptoms alone. In such a person, finding a mutation in one of the HHT associated genes can confirm that the person has HHT.

Second, genetic testing might be done in a person who definitely has HHT in order to identify the family's HHT-associated mutation. Third, genetic testing might be done on people in an HHT family who have minimal or no symptoms of HHT but have a close relative who has HHT. In this case, testing would be done for the familial mutation to determine whether or not the person has HHT.

Because the most easily identified features of HHT such as telangiectasias and nosebleeds often do not appear until adolescence or later, it is particularly difficult to determine whether young "at-risk" individuals have inherited HHT from an affected parent. Anyone with a parent or sibling with HHT would be considered "at-risk". If genetic testing is not used, all at-risk children should be screened for brain and pulmonary AVMs using procedures that will require sedation, or general anesthesia, in young children. If an HHT mutation has already been identified in a family, genetic testing of at-risk family members for this known mutation will allow identification of which

family members carry the mutation and need to be screened for AVMs, and which do not carry the mutation and therefore do not need further screening. This could potentially eliminate the need for procedures which require sedation or anesthesia in children.

What are possible results from genetic testing for HHT?

Possible results from HHT genetic testing depends of the type of genetic test done. Typically "full" gene analysis for the HHT genes is done in the first person tested within a family, and "single mutation" analysis for those subsequently tested.

When full **gene** analysis is performed, there are three possible results:

- **Positive for a "deleterious" (HHT-causing) mutation.** This result means that the laboratory found a mutation in one of the HHT associated genes, and the mutation is thought to cause HHT. This result would confirm that the person tested has HHT. A positive result would also make it possible to test other people in the family for the precise mutation found in order to determine if they have or do not have HHT.

- **Negative.** This result means that the laboratory did not find a mutation in one of the HHT-associated genes. There are several reasons for a negative result. First, the person tested might not have HHT. Second, the person tested does have HHT, but carries a mutation in an HHT-associated gene that hasn't yet been identified and therefore was not tested. Third, the person might have a mutation in one of the HHT genes that was tested, but the current techniques used for testing were not able to pick up the person's HHT mutation.

- **Variant of uncertain significance.** This result means that the laboratory found a change in one of the HHT –associated genes, but it is not possible to predict whether or not it causes HHT.

When **single mutation analysis** for the HHT-associated mutation that has already been identified in the family, there are two possible results.

- **Positive.** This result means that the person carries the HHT gene mutation present in the family. This person does have HHT.
- **Negative.** This result means that the person does not carry the HHT gene mutation present in the family. This person therefore did not inherit HHT.

How much does genetic testing for HHT cost, and will my insurance pay for it?

The cost of genetic testing varies among laboratories and according to type of testing needed. Testing to initially determine which mutation is present in a family can potentially cost $2,000 or more. Once a mutation has been identified in the family,

testing of other family members for that mutation typically costs $200-$300. Genetic testing is usually covered by insurance, including Medicare and some state Medical Assistance Programs. Several of the laboratories performing genetic testing will assist patients and providers with obtaining verification of insurance coverage. Although a letter of medical necessity may sometimes be requested, genetic testing is generally covered as a regular laboratory test. Rarely, insurance policies will specifically exclude genetic testing.

Does testing positive for a mutation in an HHT gene lead to discrimination?

There is no evidence that testing positive for a mutation in an HHT-associated gene results in discrimination in obtaining medical insurance. Some people are worried that if they test positive, they will have trouble obtaining or keeping health insurance coverage. The possibility of genetic discrimination in employment and health insurance is reduced with the passage of the federal Genetic Information Nondiscrimination Act of 2008 (GINA). GINA prohibits a health insurer or employer from discriminating against an individual based on that person's genetic risk for future disease. Genetic test results cannot be used by health insurers as a basis for determining eligibility or premiums, nor can they be used by employers as a basis for hiring, firing or other terms of employment. Nearly all states also have laws prohibiting various forms of discrimination based on genetic test results. Protections through GINA and various state laws should lessen the risk of the misuse of genetic information. These protections do not extend to life insurance coverage, however.

I have HHT and want to know if my children have HHT. What do I do?

First, you should find out if anyone in your family with HHT has had genetic testing. If someone has, and the familial HHT-causing mutation has been identified, your children can be tested for that mutation to find out if they have HHT. If no family member has had genetic testing, you should have genetic testing by genetic sequencing followed by deletion duplication analysis if sequencing is negative to determine what mutation is causing the HHT in your family. There is currently about an 87% probability that such testing will identify your HHT-associated mutation. Your children can then be tested for that specific mutation to determine whether or not they have HHT. Children who do not carry the mutation do not have HHT and do not need further follow-up. Children who carry the mutation would then be screened for complications of HHT, particularly for AVMs in the brain and lungs.

How do I go about arranging for genetic testing?

Genetic testing can be arranged through an HHT Center of Excellence, through a medical genetics clinic, or sometimes through a primary care provider or specialty physician. The laboratories offering genetic testing for HHT employ genetic counselors who can assist providers with test ordering, facilitate sample collection and shipping, and help with interpretation of results. Providers can also call one of the HHT Centers

of Excellence and ask to speak with a genetic counselor about genetic testing. The testing labs (which can be identified through www.hht.org and www.genetests.org) also include information on their websites that addresses many common questions about genetic testing.

If the family cannot travel to an HHT Center and their healthcare provider is unable to order HHT genetic testing him or herself, genetic testing can often be obtained through a genetic counselor (who can be identified through National Society of Genetic Counselors (www.nsgc.org), or through a genetics clinic (which are listed on the website www.geneclinics.org).

What happens if my family is one of those where it is not possible to find a mutation in one of the HHT genes?

In such a family, genetic testing cannot be used to figure out who does and who does not have HHT. . At-risk members of HHT families without detectable mutations should have a focused clinical evaluation for HHT by a physician very familiar with the signs and symptoms of the disorder. Physicians who don't regularly see HHT patients often miss the signs, and don't understand the risk of HHT to young children in the family, even those without obvious nosebleeds or telangiectasias. HHT experts generally recommend that children born to parents with HHT have screening for brain AVMs as early in life as possible, unless HHT can specifically be ruled out by mutation testing.

Important Note!!

New HHT-associated genes will be identified in the future, and genetic testing technologies will change and improve in the future. Therefore, people from HHT families in which a mutation has not been identified should periodically check back with the testing laboratory or a genetics professional to find out if additional testing would be useful.