

Learn more about...

Hereditary Hemorrhagic Telangiectasia (HHT)

(Osler-Weber-Rendu Syndrome)





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The information (in particular, the medical and scientific information) contained in this brochure is provided with the understanding that the HHTFI is a voluntary health organization and is not engaged in rendering medical advice or recommendations on diagnosis or treatment of the HHT syndrome. The material provided is designed for educational and informational purposes only and as a benefit and service in furtherance of the HHTFI mission. The HHT syndrome is a complex, multi-organ disorder that can only be properly diagnosed and managed by skilled and trained health care professionals. The information contained in this brochure should not replace necessary consultations with qualified health care professionals.

PRIVACY STATEMENT

Your personal information is private and is not shared with a third party outside of the HHT Foundation.



WELCOME TO THE HHT FOUNDATION

Hereditary Hemorrhagic Telangiectasia (HHT), also known as Osler-Weber-Rendu Syndrome, is a genetic blood vessel disorder that affects about 1 in 5,000 people worldwide. HHT does not discriminate... it impacts males and females, regardless of age, from all racial and ethnic groups.

You have been affected by HHT in some way. Whether you have known that generations of HHT exists in your family or you are newly diagnosed – **we are here for you!** Whether you are a health care professional or a parent of an individual with HHT – **we are here for you!** Maybe you have a friend with HHT and you want to understand how this disease will impact their life – **we are here for you!**



Any medical diagnosis can be scary but the HHT Foundation, along with our partnering medical institutions known as HHT Treatment Centers of Excellence, are here to relieve your anxiety. You are one of the lucky ones.... It is believed that 90% of those who have HHT don't know that they have the disease. These people are at great risk of experiencing a catastrophic event. You, however, have been diagnosed and there are physicians specializing in HHT that are waiting to take care of you and other members of your family affected by this disease.



The **HHT Foundation International, Inc.** is the only organization in the world that advocates for advancements in research, treatment and funding for HHT.

Each year, we host medical and scientific conferences to educate patients and physicians about the latest research and treatment protocols, we publish a newsletter three times annually that informs our members about the initiatives of the Foundation, we refer hundreds of people to HHT specialists, we train and certify new HHT Treatment Centers of Excellence across North America, we produce educational materials like this brochure, and we fund HHT research.

Now that you know HHT runs in your family, consider becoming a member of the HHT Foundation so that you can be kept current in the latest developments of a disease that affects you and the ones you love. Your support allows us to continue dedicating our time and resources to the important work necessary to identify the remaining 90% of people who don't know they have HHT and fund research breakthroughs. It is through our partnership with you, that great advances and a cure are within our reach.

Marianne S. Clancy
Executive Director
HHT Foundation International, Inc.

It is our mission to find a cure for HHT while saving lives and improving the well-being of individuals and families affected by HHT. To achieve this mission, we will:

- Educate patients and medical professionals
- Fund research
- Provide linkages between people affected by HHT
- Collaborate with multidisciplinary HHT Treatment Centers worldwide
- Advocate for and support those with HHT
- Engage the scientific and medical community



The earliest symptom of HHT is usually nosebleeds, often developing in adolescence.

DIAGNOSTIC CRITERIA FOR HHT

The four diagnostic criteria for HHT are listed below. A person has **definite HHT** if they meet at least three criteria and **possible HHT** if they meet two. Persons with less than two criteria are unlikely to have HHT.

- Recurrent and spontaneous nosebleeds, which may be mild to severe.
- Multiple telangiectasias on the skin of the hands, lips or face, or inside of the nose or mouth. Telangiectasias are small red spots that disappear when pressed upon.
- Arteriovenous Malformations (AVMs) or telangiectasias in an organ including the lungs, brain, liver, intestines, stomach, and spinal cord.
- A first-degree relative (brother, sister, parent or child) who meets these same criteria for definite HHT or has been diagnosed through genetic testing.

What is HHT?

HHT is a hereditary disorder (passed down through generations) that is characterized by abnormal blood vessels. A person with HHT has a tendency to form blood vessels that lack normal capillaries between an artery and vein. This means that arterial

blood under high pressure flows directly into a vein without first having to squeeze through very small capillaries. This place where an artery is connected directly to a vein tends to be a fragile site that can rupture and bleed.

We usually call a blood vessel that is abnormal in this way a telangiectasia (tel-AN-jee-eck-TAZE-ee-ya) if it involves small blood vessels. The **telangiectasias** most commonly occur on the skin of the face and hands and the lining of the nose and mouth. The telangiectasias on the lining of the nose cause recurrent nosebleeds, the most common symptom of HHT. Telangiectasias can also occur in the digestive tract, particularly in the stomach and small bowel. There are a number of different treatments available for bleeding from telangiectasias in the nose and digestive tract.

When the abnormal artery to vein connection occurs in a larger blood vessel, it is called an **arteriovenous malformation (AVM)**. Some people with HHT will also have AVMs in one or more organs. AVMs occurring in the lungs and brain and

can lead to serious complications. Everyone with HHT should undergo screening for lung and brain AVMs because if these are detected, they can be treated. The HHT Foundation recommends that all patients and families with HHT be assessed at an HHT Treatment Center for proper screening and treatment.

SIGNS and SYMPTOMS of HHT

About 95% of people with the gene for HHT will eventually develop signs or symptoms of HHT, usually by the age of 40. However, just because a person reaches the age of 50 without symptoms of HHT does not mean that they are not affected. They may have subtle signs on physical exam and lab testing that only a doctor familiar with HHT might detect. The earliest symptom of HHT is usually nosebleeds, often developing in adolescence. Patients also start to develop small red spots, or telangiectasias, on the face, mouth, and fingers. **Other common symptoms include** shortness of breath, exercise intolerance, fatigue, migraine headaches, seizures, abdominal pain, leg swelling, and intestinal bleeding.

How does HHT affect a person?

Telangiectasias in the **nose**, along with the nosebleeds they cause, are the most common sign of HHT. About **90%** of people with HHT **will ultimately develop recurring nosebleeds** by the time they reach their forties. The average age at which nosebleeds begin is 12, but they can begin as early as infancy, or as late as adulthood. The nosebleeds can be as infrequent as a few times a year or can occur daily. When a nosebleed occurs it can last anywhere from seconds to hours. The amount of blood lost may be one or two drops, or enough to require an emergency blood transfusion.

The Epistaxis Severity Score (ESS) is a way to monitor the severity of your nosebleeds and their response to treatment. This is a simple score that is calculated automatically when you answer six simple questions about your nosebleeds. You can access the ESS tool through the HHT Foundation website at www.hht.org.

Telangiectasias on the **skin** of the hands, face and mouth are also found in about **95%** of all people with HHT. However, these often do not become apparent until the 30s or 40s. They appear as small red to purplish spots, usually pinpoint to pinhead size. In some individuals with HHT they become quite prominent by late adulthood; in others they are more subtle. These telangiectasias on the hands, face or in the mouth can bleed, but they are less likely to bleed than those in the nose. Both telangiectasias of the skin and nose have a tendency to become more numerous with increased age. However, not all red spots are telangiectasias. Red spots on the chest, belly or upper arms are common in people without HHT and are usually called cherry angiomas.

About **80%** of those with HHT have telangiectasias in their **stomach or intestines**, but only **20%** develop obvious **gastrointestinal bleeding**. Again, it can range from mild to severe. Telangiectasias can be found anywhere in the gastrointestinal system, including the esophagus, stomach, small intestines, and

colon (large intestines), but most commonly, the stomach and the upper part of the small intestines are involved. Telangiectasias in the GI tract do not cause pain or discomfort. Symptoms of GI bleeding are black or bloody stools and/or anemia; often patients don't notice any change in the stool but instead are found anemic through blood work. Anemia can cause fatigue, shortness of breath, chest pain or lightheaded feelings.



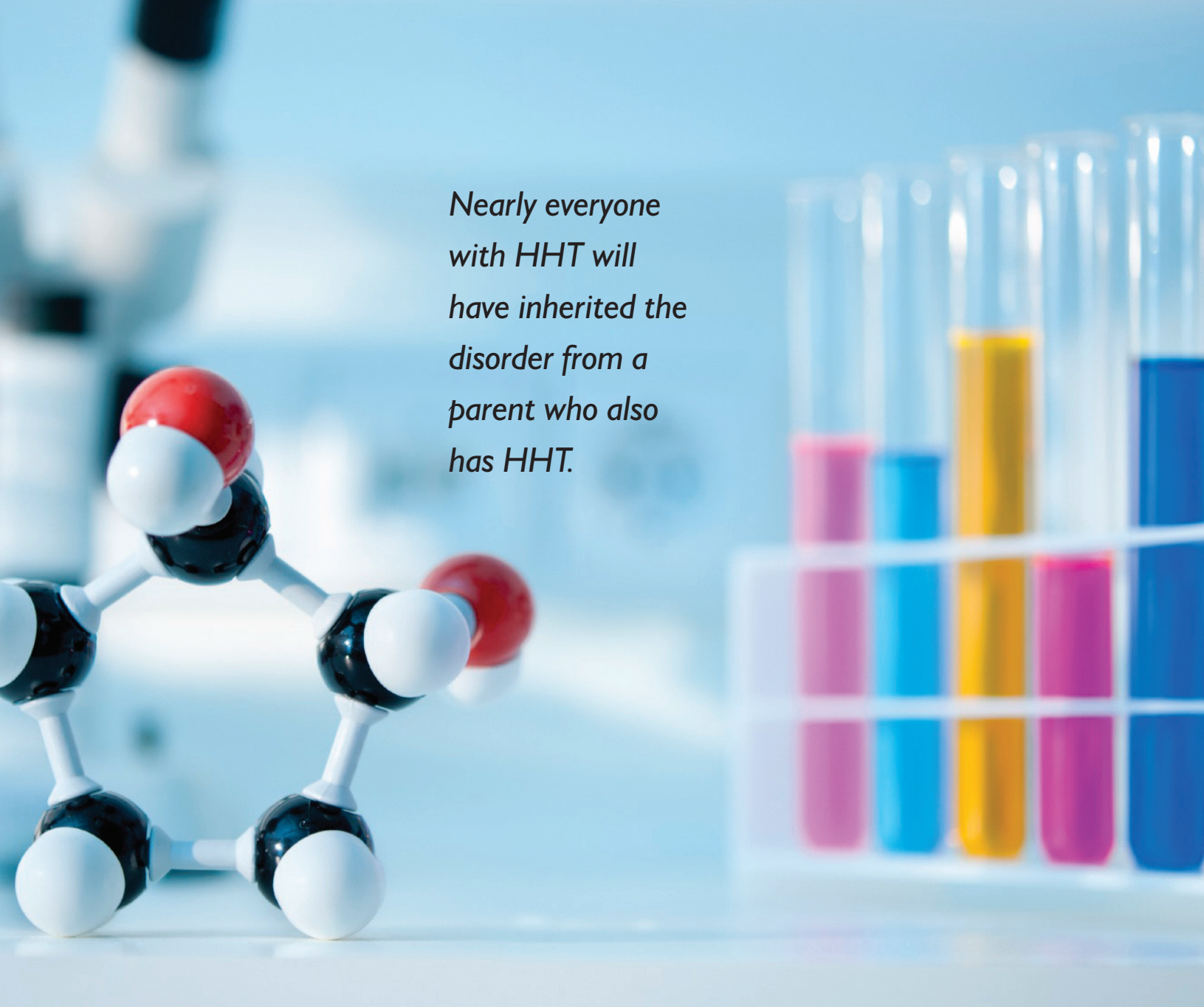
Approximately **40%** of people with HHT have AVMs in the **lungs** (pulmonary AVM or PAVM). People with HHT1 (ENG) are 5-10 times more likely to have PAVMs than people with HHT2 (ACVRL1). PAVMs, particularly during pregnancy, have a risk of rupturing when blood volume tends to increase. This can be life-threatening. However, there are additional concerns about untreated PAVMs. Normally, the lung arteries get smaller and smaller as they go deeper into the lungs, similar to the branches of a tree. At the ends of these artery branches, hair-like blood vessels called capillaries join the arteries and veins. These capillaries perform many important functions including allowing passage of oxygen into the blood as well as filtering the blood of impuri-

ties (clots, bacteria, air bubbles) before the blood circulates to the brain. With a PAVM, these capillaries are missing and the artery connects directly to the vein. If the artery leading into the PAVM is larger than 2-3 mm in diameter, small blood clots can travel through the PAVM and go to the brain causing a stroke. Bacteria can travel through even smaller PAVMs and result in brain abscesses (a brain infection). Stroke and brain abscess can be life-threatening or disabling. Fortunately, PAVMs are almost always easily treatable.

Brain AVMs are found in about **5-20%** of people with HHT and can also be successfully treated in most cases. They can be life-threatening or disabling if they bleed. Since they often do not cause warning symptoms prior to bleeding, we recommend screening for them in all people with HHT, even infants. Other types of brain vascular malformations may be seen in HHT patients, such as telangiectasias and venous malformations. It is not clear if these malformations are seen any more commonly in HHT patients, but they are usually harmless and most do not require treatment.

Spinal AVMs are more rare, **less than 1%**, but can also be treated. They can cause pain in the area of the back over the spine, or loss of feeling or function in an arm or leg.

Liver AVMs are found in **32-74%** of people with HHT, but only cause symptoms in an estimated 8%. AVMs in the liver occasionally cause heart failure, usually later in life. Heart failure can occur if the heart has been overworked for years, pumping extra blood through the low resistance pathway of a liver AVM (shunt), as well as through all the normal vessels of the body. There are several other even more rare and complex complications that can result when HHT affects the liver. Few physicians outside of clinics that specialize in HHT are familiar with these complications.



*Nearly everyone
with HHT will
have inherited the
disorder from a
parent who also
has HHT.*

What causes HHT?

HHT is caused by a change (a “mutation”) in one of several HHT-associated genes. Changes in one of two of the genes, endoglin (ENG-HHT 1) and activin receptor-like kinase 1 (ACVRL1-HHT 2) are responsible for most cases of HHT. Changes in another gene, SMAD-related protein 4 (SMAD4), cause a combined syndrome of juvenile polyps of the gastrointestinal tract and HHT. At least two other unidentified genes also appear to cause HHT in a smaller number of individuals. There are hundreds of different mutations in each of the three known

genes that can cause HHT. Having a mutation in an HHT-associated gene causes some blood vessels to form improperly leading to symptoms of HHT.

How is HHT inherited?

Each child born to an HHT parent has a 50% chance of inheriting the HHT gene mutation. One copy of each gene is inherited from the father and the other copy from the mother. People with HHT have one normal copy of the HHT gene and one mutated copy. When a person with HHT has a child, he or she will either pass on the normal copy of the gene, or

the copy with the mutation. A child who inherits the gene with the mutation will have HHT. A child who inherits the normal copy of the gene will not have inherited HHT. Therefore, each time a person with HHT has a child, there is a 1 in 2 chance (50%) that the child will have HHT.

Nearly everyone with HHT will have inherited the disorder from a parent who also has HHT. In rare cases, a change in an HHT gene occurs in only an egg or sperm cell of someone who does not have HHT themselves. In these cases, the resulting child will have HHT, although the parents are unaffected.

WHY IS IT IMPORTANT TO SCREEN FOR MANIFESTATIONS OF HHT?

The recommended screening guidelines for each organ impacted by HHT are outlined in the *Clinical Guidelines*, published in the *Journal of Medical Genetics*, located in the resource section of the HHT Foundation website, www.hht.org.

Nosebleeds and skin telangiectasia are the most obvious signs of HHT but there are many hidden manifestations that can contribute to life-threatening events. Therefore, it is important to gain an understanding of how HHT impacts the internal organs. There are several tests that everyone who is known or suspected to have HHT should have. These are called **screening tests** since the abnormality is looked for prior to its causing a problem. Lung and brain AVMs

Although there is not yet a way to prevent the telangiectasias or AVMs from occurring, most can be treated once they occur

are the only problems associated with HHT for which we recommend pre-symptomatic, preventive screening. **A screening test will:** 1) determine whether you meet the criteria for a diagnosis of HHT and 2) look for pulmonary (lung) AVMs and cerebral (brain) AVMs since these can cause serious life-threatening events without warning.

Screening for **Pulmonary AVMs** (PAVM) is dependent on the age of the individual, and to a lesser degree, their symptoms. Preferably, individuals with HHT will have had screening for PAVMs by the time of their early teens. If a pregnant woman has not had a recent evaluation for PAVM, it is imperative for her to do so as soon as pregnancy is recognized. In many cases, an HHT Treatment Center will be able to use tests performed by another facility unless the

original tests are too old, the old test is not of high enough quality, or the old test was performed a little differently.

- **Contrast Echocardiogram** (bubble echo): The recommended test of choice



for PAVM screening in adults and also used in older children and adolescents. This test uses sound waves (ultrasound) to determine if injected saline bubbles can get through the lung circulation and be seen back in the heart, on the left side. This is called a shunt. It is a very sensitive test but not everyone with a “positive” or “abnormal” bubble echo test has a Pulmonary AVM large enough to require treatment by embolization. To determine if treatment is necessary, a chest CT scan should be done if the bubble echo is more than minimally abnormal.

- **Chest X-ray:** A standard X-ray of the lungs to look at the size of your heart and the condition of your lungs.
- **Shunt test:** During this test you breathe pure oxygen for 15 minutes with a nose clip on, and then a small sample of arterial blood is collected from an artery in your wrist. This is not a routine screening test but rather is used to assess a

patient before and after treatment for PAVMs.

- **CT scan of the lungs:** This is like a 3-dimensional high-resolution X-ray of your lungs. If “X-ray dye” is used, an IV will need to be started.
- **Pulmonary Angiogram:** A catheter is inserted through a large vein in either your leg or neck, and is passed up into the arteries of the lungs. This involves one or more injections of “X-ray dye” into the arteries to expose the AVM.

PAVMs larger than a certain size should be embolized to prevent complications like brain abscesses and strokes. For smaller PAVMs, antibiotics prior to most dental work and certain other non-sterile invasive procedures, like colonoscopy, are recommended.

Until PAVMs are excluded by testing, a person over the age of 10 with known or suspected HHT should take antibiotics before all dental cleanings, work and other medical procedures which have a risk of introducing bacteria into the bloodstream.

To screen for **Brain AVMs** an MRI with and without gadolinium dye is recommended. Since brain AVMs have been known to cause brain hemorrhage even in infants, a brain MRI early in life is recommended.

Other than in the brain and lungs, HHT can be screened as the symptoms warrant. With this in mind, a yearly evaluation by a physician familiar with the wide spectrum of symptoms associated with HHT is recommended, along with an annual check of ferritin levels, hematocrit, and hemoglobin. Without periodic check-ups with an HHT expert, HHT related medical problems are often missed, misdiagnosed or mismanaged which can lead to catastrophic events.



CAN HHT BE TREATED?

Yes. Although there is not yet a way to prevent the telangiectasias or AVMs from occurring, most can be treated once they occur. They should be treated if they are either causing a significant problem (as in the case of frequent nosebleeds) or if they have a high risk to cause a problem (such as a stroke from a lung AVM or brain AVM). The current recommended treatment for a telangiectasia or AVM depends on both its size and location in the body.

Treatment of Recurring Nosebleeds

The Epistaxis Severity Score (ESS) is a way to monitor the severity of your nosebleeds and their response to treatment. This is a simple score that is calculated automatically when you answer six simple questions about your nosebleeds. You can access the ESS tool through the HHT Foundation website at www.hht.org.

Home Treatment: Through one or more treatments, an Otolaryngologist (ENT) can significantly improve the severity of nosebleeds for almost everyone, although it is rare for these treatments to permanently cure one's nosebleeds. Nosebleeds sometimes respond satisfactorily to simple treatments that can be implemented at home. It is very important to avoid any injury to the nose such as picking or blowing hard. Humidification of the air and lubrication of the nose (with saline spray) can reduce nosebleeds. If home treatments do not result in a satisfactory reduction in nosebleed frequency or severity, the next

treatment that is usually considered is some type of medicated spray/ointment or some type of coagulation therapy.

Medical Treatment: Coagulation therapy is often the quickest way to stop nosebleeds, but there is some controversy as to the best way to do this. Many experts believe that laser coagulation therapy is preferable to electric and chemical cautery because it causes less damage to the inside of the nose. However, some experts have reported good success with bipolar electric cautery. Regardless of the method used, it is important to have coagulation therapy by someone who has expertise in treatment of HHT patients. Most patients who undergo coagulation therapy see significant improvement for a period of time, but it usually needs to be repeated periodically. Sprays and ointments containing medicines like estrogen, bevacizumab (Avastin), and tranexamic acid have been used in small numbers of patients and are currently being studied in clinical trials.

Several small research studies have suggested that various oral therapies can help some patients for whom the local therapies (i.e. home moisturizing care and laser therapy) have not been successful. Birth control pills have been used the most, and while they do seem to help some patients, they have significant side effects. Drugs that affect either the formation of clots or blood vessels are being investigated (i.e., estrogens, tamoxifen, n-acetylcysteine, bevcizumab (Avastin), and others) to examine the effectiveness

and safety of these drugs. We encourage patients to participate in these research studies if they have permission from their doctor.

Surgical Treatment: Septal Dermoplasty and Young's Nasal Closure Procedure are surgical treatment options for nosebleeds, but are usually only considered when nosebleeds are severe, significantly affecting one's quality of life and coagulation therapy has repeatedly failed to help. Septal dermoplasty replaces the thin lining of the nose with a graft of thicker skin from somewhere else on the body. When performed by an ENT experienced with treating HHT patients, it can significantly reduce or stop nosebleeds, often for two or more years. Daily care of the nose is required after septal dermoplasty to keep the nose moist and clean. Also new vessels can grow around the graft and nosebleeds may return. In the Young's procedure, the nostrils are sewn closed so a person no longer breathes through their nose. This therapy is quite effective but the downside is that taste and smell are affected.

Embolization: This procedure blocks an artery which, in most cases, stops severe nosebleeds that have been unresponsive to other treatments. This procedure is usually only effective for 6-8 weeks; other arteries enlarge and cause recurrence. This therapy for the nose should be used only on an emergency basis until more durable therapies can be started.

Treatment of Pulmonary (Lung) AVM

Pulmonary AVM (PAVM) are seen in about 40% of patients, and are especially common if someone else in your family has them. However, about 30-40% of patients have PAVM large enough to require treatment. PAVM are potentially one of the most serious complications of HHT because they can result in strokes or brain abscesses. The good news is that these complications can be prevented in almost all cases.

Embolization: A tiny metal coil or a small balloon is inserted to block off the artery that leads into or “feeds” the PAVM. This stops the blood flow to the PAVM which eliminates the occurrence of a potentially life-threatening complication. This is accomplished by passing a small catheter through a vein in the leg and then passing it up to the arteries of the lungs. This procedure is usually performed under conscious sedation.

Surgical Removal: A surgical procedure to remove the part of the lung that contains the PAVM. Because of the success of embolization, surgery is rarely necessary.

If you have a known PAVM or if you have not been screened to determine if you have a PAVM, you should take the following precautions:

- Take antibiotics before any invasive procedures like dental cleaning, surgical procedure, or colonoscopy.
- A .22 micron IV filter is recommended to keep air out of the IV line (does not apply to blood transfusions) *see full disclosure on p.13.
- Avoid blood thinners or nonsteroidal anti-inflammatory medicines like aspirin and ibuprofen as they can worsen bleeding tendencies.
- Return to your HHT Treatment center every 3-5 years so that you can be monitored for development of new PAVM.

Treatment of Cerebral (Brain) AVM

It is thought that 5-20% of HHT patients have at least one Brain AVM (BAVM). Without treatment, BAVM are a com-

mon cause of hemorrhagic stroke in HHT families. Research is currently being conducted to determine what genetic and clinical factors signal high risk hemorrhage from brain AVMs in HHT patients. It is recommended that all children of HHT families be screened for brain AVMs as early as birth and throughout adolescence (until post-puberty) to monitor the development of new BAVM.

Embolization: A small catheter is passed through an artery in the leg and then into the arteries of the brain. A small balloon or glue is inserted which stops the blood flow into the AVM and lessens the risk of stroke. Typically, this procedure is successful more than 95% of the time and has a relatively low complication rate.

Surgical Removal: A surgical procedure to place a clip on the AVM or to remove the AVM. This procedure is fully curative, but has a higher complication rate than embolization.

Gamma Knife: A type of focused radiation that destroys the AVM tissue. This is often done after embolization to ensure that the AVM is cured.

Treatment of Intestinal AVM

A large percentage of patients with HHT have intestinal AVM, but only 20% of HHT patients develop significant stomach or intestinal bleeding. Bleeding usually does not occur before age 50. These AVM can usually be detected by endoscopy, which involves inserting a flexible tube with a camera on the end through your mouth or rectum to look inside the intestines, and treated with a laser. Other treatments include oral hormone pills (estrogen and danazol) and tranexamic acid (Amicar). Research has not proven the effectiveness or potential risks of these treatments.

The biggest problem with intestinal bleeding is that it leads to anemia. Anemia is generally treated by a hematologist. Common remedies include oral or intravenous iron therapy and blood transfusion.

Treatment of Symptomatic Liver Involvement

Liver AVMs are currently treated only if a patient shows signs of heart failure or other significant problems. Embolization of liver AVM has led to severe complications in several patients and therefore is not usually first line treatment.

Current treatment options for liver AVM include standard heart failure treatment, liver transplantation, and possibly medications like bevacizumab (Avastin). Decisions regarding treatment of liver AVM are made on a case-by-case basis and should be managed by an HHT Treatment Center physician who is very familiar with the liver manifestations of HHT.

Abnormal blood vessels in the liver (AVM) are common in HHT but usually require no treatment. **When liver abnormalities are detected by X-rays or blood tests, it is vitally important that the following procedures NOT BE DONE without seeking the opinion of an HHT Treatment Center physician:**

- LIVER EMBOLIZATION (blocking the hepatic artery with particles);
- LIVER BIOPSY (sampling the liver tissue with a small needle);
- ERCP (endoscopic retrograde cholangiopancreatography—which is passing a tube through the mouth into stomach, duodenum, and biliary ducts).

The invasive procedures listed above can potentially make an HHT patient much worse if not done in consultation with an HHT specialist. Similarly, routine screening for liver abnormalities is not recommended by most HHT Centers at this time. Sudden events leading to serious disability, such as those that occur from lung and brain AVMs in HHT patients, do not occur from liver involvement in HHT.

SCREENING CHILDREN FROM AN HHT FAMILY

Not all children show signs of HHT (i.e., nosebleeds and “red spots” on the skin). Children without nosebleeds or other symptoms of HHT can have AVMs in their lungs or brain that require intervention.³ In fact, potentially life-threatening manifestations of HHT have been identified in asymptomatic children under 12 years of age.¹

- If a family has had genetic testing, then all children in the family should be tested against the identified gene mutation.
- If the family gene has not been identified, then a clinical evaluation will be required.

All children diagnosed with HHT should receive a pediatric screening for HHT. A screening appointment consists of a thorough history, a physical examination, pulse oximetry, a contrast (or bubble) echocardiogram (CE), and brain magnetic resonance imaging (MRI) with and without contrast.¹ If a child's initial screening is not conducted at an HHT Center, it would be recommended that all patients with a positive MRI or an abnormal echobubble test consult an HHT Treatment Center for consideration of more invasive testing and further treatment.

According to the Clinical Guidelines², there is not consensus on the recurring tests of children with HHT. However, it is recommended by most HHT Centers that:

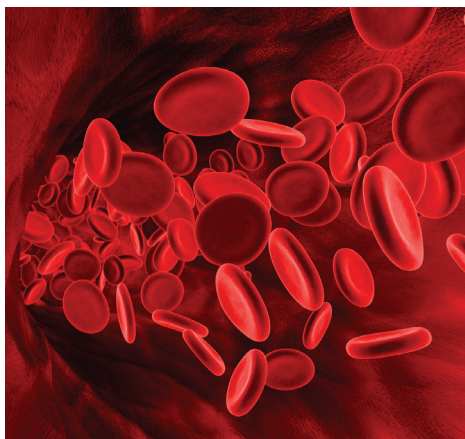
- Children with possible or confirmed HHT should be screened for **Brain AVM** in the first year of life (or at the time of diagnosis) and at least one follow-up MRI at puberty since brain AVM development appears to correlate with times of growth.
- **Lung AVM** screening is recommended every 3-5 years, if a pulse oximetry test result is 97% or higher. If a pulse oximetry result is lower than 97%, or a child is short of breath, additional tests or treatment may be required.



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Based on the fact that some children did have complications from PAVMs, we currently advocate screening for all children of a parent with HHT.

Should your Child be Screened for Lung AVM?

Since the 1980's we have learned a great deal about pulmonary (lung) arteriovenous malformations (PAVMs) in adults. We know that they frequently cause neurological complications, such as stroke or brain abscess. Multiple studies have shown that treatment of PAVMs is safe and effective. For this reason we recommend screening for PAVMs in all adults.

However, it is less clear what constitutes optimal screening and treatment of PAVMs in children. The largest study of PAVM in children reported on 42 children who underwent embolization of PAVM from 3 HHT Centers of Excellence. Neurological complications such as stroke were less common in children compared with adults. The children that did have neurological complications tended to have low oxygen levels in the blood or felt short of breath when exercising. Embolization techniques were similar to those used for adults except that general anesthesia or heavy sedation were more commonly required for children. Embolization was effective and well tolerated by children and about 15% required repeat embolization at some time in the future. In some children the repeat embolizations were required because blood flow returned through an embolized PAVM – so called re-perfusion. Although it is not clear-cut, some experts believe that children have more

re-perfusion after embolization than adults. This may be due to the fact that they are growing and thus their blood vessels are growing too. This means that children need to be followed closely after embolization to make sure that their PAVMs remain closed.

Based on the fact that some children did have complications from PAVMs, HHT medical professionals currently advocate screening for PAVM in all children of a parent who has HHT. Bubble echo is the recommended screening test for symptomatic children who have low oxygen levels, complain of shortness of breath, have a hard time keeping up in sports, or have had prior neurologic complications. However, the best screening test for asymptomatic children is controversial: some HHT Treatment Centers perform pulse oximetry before the age of 10 followed by bubble echo after the age of 10-14; other HHT Treatment Centers perform bubble echo at all ages. The optimal management of children who are diagnosed with PAVM is complicated and should be done in consultation with HHT Center of Excellence.



IRON DEFICIENCY & HHT

Iron deficiency is common among people with HHT and is primarily a consequence of bleeding from telangiectasias in the lining of the nose and intestinal tract. Iron deficiency tends to be both under-diagnosed and under-treated in HHT patients and can lead to decreased exercise tolerance, chronic fatigue, and poor quality of life.

Why do we need iron?

Iron is required for the production of hemoglobin in red blood cells and the protein myoglobin in muscle cells. Iron is also a component of many proteins and enzymes in the body and plays important roles in energy metabolism and immunity. The total amount of iron in an adult is about 3-4 grams. The majority of this (about 2.5 grams) is present in hemoglobin within circulating and developing red blood cells. About a gram of iron is present as 'stored iron' mostly in the bone marrow, liver and spleen. Of note, women of child-bearing age usually have lesser amounts of stored iron, as they use more iron to make up for menstrual blood loss and iron requirements during pregnancy, childbirth and nursing.

How much iron do we need?

The amount of iron in the body is tightly regulated. As the body cannot make iron,

the amount of iron absorbed from the diet needs to equal the amount of iron lost on a daily basis. This is about 1mg of iron per day. The daily requirement is slightly higher in adult women (2mg/day) secondary to menstrual loss. The iron requirements are higher during adolescent years due to growth and development. Iron requirements also increase during pregnancy and the total amount of iron utilized during pregnancy, childbirth and nursing is about 1 gram. **Foods that are rich in iron** include red meats, liver, egg yolk, salmon, tuna and oysters (iron in these foods are in the form of hemoglobin and myoglobin, referred to as heme-iron). Iron is also present in vegetables, fruits and grains, but this iron (referred to as non-heme iron) is harder for the body to absorb.

Causes of iron deficiency

The overwhelming cause of iron deficiency in developed countries is blood loss. Less likely causes include decreased intestinal absorption (e.g. Celiac disease, following gastric bypass surgery), and decreased iron intake (in extreme diets). Unless an individual experiences sudden and massive blood loss, iron deficiency tends to develop slowly over time. At first, the body progressively uses up its' iron stores due to an imbalance between the supply and demand for iron in the body. In this early stage people do not yet have anemia, as there is sufficient iron available for hemoglobin

synthesis. However, if the imbalance persists (such as with continued bleeding as can happen in HHT), over time the iron stores become exhausted resulting in iron deficiency anemia. ***It is important to realize that iron deficiency can occur in the absence of anemia.*** This state can be diagnosed using routine laboratory tests.

Clinical features of iron deficiency

The clinical features of iron deficiency are mainly related to anemia and include fatigue, weakness, headaches, irritability, and decreased exercise tolerance. Rarely, affected individuals can develop dry mouth, hair loss, and brittle fingernails. In children and adolescents, iron deficiency (with or without anemia) can also cause poor cognitive function (difficulty with concentration and learning, memory, school performance, etc.) and poor physical performance (running, endurance). Further, studies have shown improvement in performance with correction of the iron deficiency. A classic but uncommon finding in individuals with iron deficiency anemia is a craving for ice or substances like clay (referred to as 'pica'). Iron deficiency has also been associated with Restless Leg Syndrome, a condition causing an urge to repeatedly move the legs or arms because of an uncomfortable feeling in the affect body part.

How do we diagnose iron deficiency?

Iron deficiency should be suspected in any person with HHT who develops one or more of the above mentioned clinical features. Further evaluation should consist of doing the following blood work: a complete blood count (CBC), reticulocyte count, and an iron panel (serum iron, iron saturation, total iron binding capacity, ferritin). These together provide information on a person's iron stores and whether or not an individual is iron deficient/anemic.

How do we treat iron deficiency?

Once a person has been diagnosed with iron deficiency, this should be corrected by replacing the iron stores. The goal is to correct the iron deficiency as well as replenish the body iron stores. This can be achieved by taking iron by mouth in the form of iron supplements (tablets, liquid, suspension or elixir) or by replacing iron directly into the vein (intravenous or IV). Generally, the initial approach is to pursue oral iron replacement. A number of oral iron

People with HHT should be treated by medical professionals at an HHT Treatment Center of Excellence.

preparations are available; consult your HHT Treatment Center physician for recommended products and dosage. It is important to note that oral iron supplements can be associated with gastrointestinal side effects such as nausea, bloating, and constipation that frequently limit their use. The side effects appear to be related to the amount of elemental iron and, therefore, preparations that contain less elemental iron tend to be better tolerated. Once the hemoglobin becomes normal, there is still a deficiency in the total amount of iron in the body, and it is recommended that iron treatment be continued for an additional 6 months to replace the missing iron stores in the body. In individuals with severe iron deficiency anemia or frequent/severe bleeding, oral iron may be inadequate to treat the iron deficiency. In such cases, and in individuals who do not tolerate oral iron, treatment with intravenous iron should be considered. A number of intravenous iron preparations are currently available. The number of doses of intravenous iron necessary to correct a person's iron deficiency will vary depend-

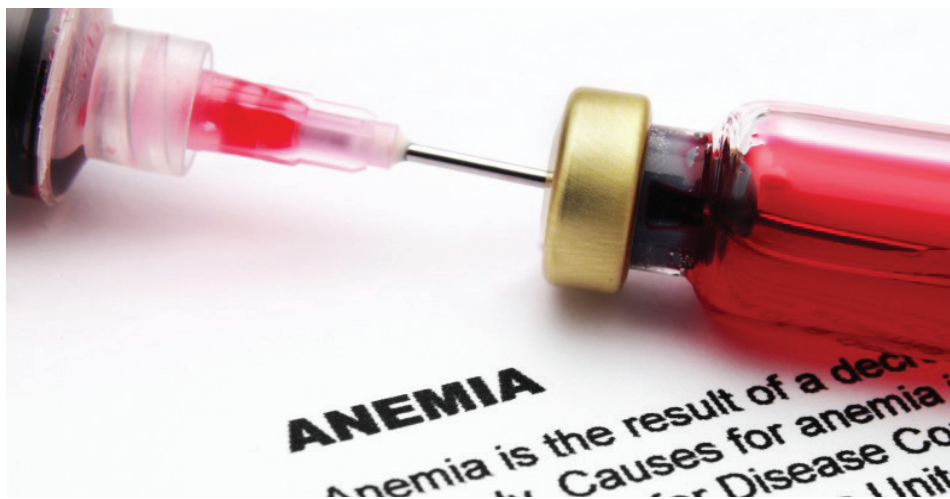
ing on the preparation being used. Of note, preparations that contain less iron (Ferrlecit and Venofer) have the advantage of quicker infusions. On the other hand, the iron dextran preparations (INFeD and Dexferum) take a few hours to administer but offer the option of replacing the entire iron deficit in a single infusion. Regardless of the preparation used, intravenous iron can be associated with allergic reactions. Some preparations require the use of a small test dose and pre-treatment with antihistamines (e.g. Benadryl) for this reason.

Following iron replacement, one can begin to see a rise in the hemoglobin in 2-4 weeks. It is important to realize that treatment with iron, either oral or intravenous, will not immediately correct the anemia. Therefore, individuals with symptomatic anemia may need to receive an initial blood transfusion to improve their symptoms. While transfused red blood cells contain iron (about 250mg/unit of blood), this alone is inadequate to correct the iron deficiency.

It is essential in individuals with HHT who have frequent nose bleeds or intestinal bleeding to continue to aggressively treat/prevent iron deficiency. Once treatment with iron is started, it is important to repeat a CBC and iron panel in 2-3 months to assess response to treatment. Individuals with chronic nose or GI bleeding who tolerate oral iron should continue to take this long term. Individuals that require treatment with intravenous iron may require repeated treatments based on the severity of bleeding.

Key points

- Iron deficiency is an important and under-appreciated cause of symptoms and poor quality of life among individuals with HHT.
- People with HHT who suffer from bleeding should be routinely screened for iron deficiency. The appropriate blood tests for the physician to order are: CBC, reticulocyte count, and iron panel.
- If iron deficiency is found, this should be treated aggressively.
- If oral iron preparations are poorly tolerated or the iron deficiency is very pronounced, iron can be given intravenously in easy to give preparations.
- People with HHT should be treated by medical professionals at an HHT Treatment Center of Excellence.
- Care should be taken to avoid air in intravenous (IV) lines. This is to prevent large air bubbles from getting into the blood stream and causing problems (such as TIAs). This is most effectively done by using a filter in the IV line as close to the patient as possible. A 0.22 micron filter is best if available, but a blood filter is also acceptable (about 260 microns) and will stop all large air bubbles (which are the most dangerous ones). During a blood transfusion, a standard blood filter is all that is needed. Please note that filters cannot be used for IV contrast injections like you might get for CT or MRI scans.





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. **“Targeted Sequencing”** looks to see if one particular mutation that was previously identified in another family member is present or absent. **“Deletion and Duplication”** testing looks to see if there is a piece of the gene that is missing or duplicated.

For a person who meets clinical diagnostic criteria for HHT, genetic testing by sequencing and deletion and duplication testing of ENG (HHT1) and ACVRL1 (HHT2) will detect a mutation in approximately 87% of those tested. If testing of ENG and 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 known HHT genes.

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 lung 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 in 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 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-\$400 (2013). 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.



The HHT Foundation strongly encourages individuals and families to arrange genetic testing through health care providers who understand all of the complexities and limitations of genetic testing for HHT.



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 not, a family member, who clearly has HHT, 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.



WHAT IS THE IMPACT OF HHT ON PREGNANCY?

Most women with HHT can have a normal pregnancy and delivery with no more risk for complications than women in the general population. HHT pregnancies are sometimes considered “high-risk”, but this is not necessarily always the case...some women with HHT can benefit from a “high-risk” clinic approach, but others don’t really need this. **The key is information and consultation with an HHT expert**, to help the pregnant woman make the best decisions for herself and her baby.

This means being aware of the extent of the HHT in the Mother (her “HHT footprint”) and planning accordingly, rather than simply assuming that HHT is not a problem, or conversely assuming that the pregnancy is high-risk due to the simple presence of HHT. By the “HHT footprint”, we mean a conceptual map of the abnormal vessels in someone with HHT, including everything from telangiectasia in the nose to AVMs in the organs. The HHT footprint is personalized, different in each woman with HHT, and can change over her lifetime. Knowing the **specific HHT footprint** in a woman should help guide pregnancy planning and care. For example, if a woman’s HHT footprint includes only telangiectasia in the nose

and she has no abnormal blood vessels in the organs, then there is no reason to think that her pregnancy or delivery is high-risk. On the other hand, if a woman’s HHT footprint includes lung AVMs, then several steps and precautions need to be taken to minimize risk, and in some cases this may be considered a high-risk pregnancy.

What does the term high-risk pregnancy really mean?

First, it doesn’t necessarily mean that the risks are extraordinary, but rather that they are higher than in the general population. A high-risk pregnancy is one in which some condition puts the mother or the developing fetus, or both, at an increased risk for complications during or after pregnancy and birth. These women may benefit from additional monitoring and specialized care during pregnancy and delivery, to reduce the risk of complications. This can be also very reassuring for the mother and the family, when there is higher risk.

As typical for rare diseases, there are not many studies published about pregnancy and delivery in HHT. As such, there are no clear guidelines for physicians to follow for care of

pregnant women with HHT. However, the published experience in the last few years has been reassuring and can help dispel some of the myths and concerns about risks for pregnancy in women with HHT.

Myth #1: Women with HHT are at risk of excessive bleeding (from the uterus) during or after delivery.

There is no evidence of this. In fact, the experience is that women with HHT are no more likely to bleed excessively at delivery or after delivery than women in the general population.

Here’s why: People with HHT don’t have a clotting disorder. So, they are not more likely to bleed with an injury, trauma or cut. People with HHT bleed from parts of the body where they have abnormal blood vessels (AVMs and telangiectasia). The uterus is not a typical place for AVMs to occur in HHT, so there is no reason to expect women with HHT to bleed with delivery.

Myth #2: Women with HHT can’t have an epidural.

NO, this is not the case. In fact most

women with HHT decide to have an epidural, or at least to have the option of having one. There is no evidence of increased risk of complications.

Why is there concern? Many anesthesiologists and other doctors are worried about the risks of epidural anesthesia in women with HHT. Specifically, they are worried about puncturing a spinal AVM when they insert the epidural needle into the women's lower spine. This worry stems from the knowledge that approximately 1% of HHT patients can have AVMs in the spinal canal. BUT, the vast majority of spinal AVMs in HHT are much higher in the spinal canal than where the epidural needle is usually inserted. ALSO, complications of spinal AVMs are exceedingly rare in adults (most have come to attention during childhood). In fact screening for spinal AVMs hasn't been routinely recommended in adults with HHT (unlike screening for lung and brain AVMs) given how very rare they are in adults. FINALLY, no case has ever been reported in the medical literature of an epidural causing spinal bleeding in HHT. In other words, if there is a risk, it is so low that no one has been able to document a case or quantify the risk. On the other hand, there is no study that has "ruled out" any risk of epidural in HHT. For all of these reasons, we call it a "theoretical" risk.

If a pregnant woman with HHT wants the option of an epidural, she should meet with the anesthesiologist prior to delivery and have a discussion about all the risks, including the "theoretical" risk related to HHT. Many anesthesiologists will agree to proceed if the woman understands the risks.

Myth #3: Women with HHT should have a cesarean section to avoid bleeding and other HHT-related complications with labor and delivery.

There is no evidence to support this as a routine approach. There are three main concerns that have led some doctors to recommend cesarean section for women with HHT.

The first concern is that women with HHT might be likely to bleed during or after delivery. This is addressed in Myth #1.

The second concern is that a brain AVM might be more likely to rupture when "pushing" at delivery. There is no evidence that this is the case, or that cesarean section is a safer alternative to normal vaginal delivery in people with brain AVMs. This situation needs to be handled on an individual basis. Screening for brain AVMs can be performed in early third trimester with an unenhanced MRI of the brain. If the MRI is negative (i.e. no brain AVMs), then this is no longer a concern (90% of women with HHT will have a negative MRI of the brain). If the woman does have a brain AVM then her case needs to be discussed in detail with a brain AVM expert and an obstetrician, and likely should be considered a high risk pregnancy and delivery. There may be some discussion about assisting the delivery to reduced pushing or about a cesarean section, though there is no good evidence that this is the safer approach. These decisions will need to be made on a case by case basis, with all the experts involved. If a brain AVM is diagnosed, the usual recommendation is to treat within two or three months after delivery. As such, since treatment will be delayed anyway, some women opt to postpone the brain MRI till after delivery. This is not unreasonable, but may leave the woman and her physicians unnecessarily worrying about the possibility of brain AVMs, and therefore considering it a "high-risk" pregnancy, whereas an MRI would dispel this worry in 90% of women.

The third concern is that lung AVMs might be more likely to rupture and bleed when "pushing" at delivery. There is no evidence of this. However, lung AVMs do seem to be more likely to rupture during pregnancy if untreated. Screening and preventative treatment for lung AVMs should be done prior to pregnancy, when possible. If lung screening is negative, then lung AVMs are no longer a concern for pregnancy and delivery. If the woman has lung AVMs and these have been successfully treated (and recently reassessed), then lung AVMs are not a concern

for pregnancy and delivery, and the pregnancy need not be considered high risk, though some precautions should be followed. If a pregnant woman has untreated lung AVMs, treatment during Trimester 2 or Trimester 3, with embolization should be considered, but only at an expert HHT center. Once treated, the lung AVMs are no longer a significant concern for pregnancy and delivery. If lung AVMs are present but not treated, then the pregnancy should be considered high-risk.

Summary

For most women with HHT, the main problem is nosebleeds, and though bothersome, this is not often a major concern during pregnancy. Some women with HHT have a more extensive HHT footprint, with AVMs in the brain or lungs, which may be more concerning. However, with the right screening, treatment and surveillance, most women with HHT can have normal pregnancy and delivery, with no more risk than women without HHT. Any patient with lung AVMs (treated or untreated) should follow pulmonary AVM precautions, including antibiotics before any procedures that can cause bacteria in the blood as well as an air filter (bubble trap) any time they have an intravenous access.

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THANK YOU FOR YOUR CONTRIBUTION TO THE LEARN ABOUT HHT BROCHURE

The HHT Foundation International would like to acknowledge the individuals who contributed to the medical information presented in this brochure. Although the HHT Treatment Centers and the HHT Foundation are independent institutions, it is through partnerships like this that extraordinary outcomes are accomplished.

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Join Our Community!

We hope that you find this information helpful and we encourage you to share it with your extended family members.

The HHT Foundation International, Inc. provides the primary source of information about HHT throughout the world. As the only HHT patient advocacy organization, we strive to find a cure for this disease while funding HHT research and educating patients and healthcare professionals.

Your donation to the HHT Foundation will fund important HHT specific initiatives:

- Research
- International Guidelines Conference
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Your contribution will ensure that the HHT Foundation continues to provide you with the most current information.

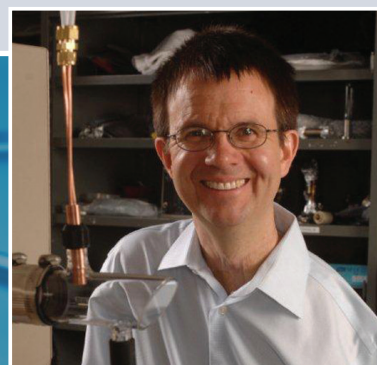
Please consider making a contribution or becoming a member of the HHT Foundation.

Your support is greatly appreciated.

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"I think of the Foundation as the power plant for HHT families - creating knowledge through research, collating the knowledge through sponsored conferences, and spreading that knowledge around through outreach. The HHT Foundation is the source of power we need to hold this troublesome condition at bay while we all go on to do the stuff in life we care about."

ERIC CORNELL
Staff Scientist, National Institute of Science and Technology
Physics Professor, University of Colorado
2001 Nobel Prize Recipient
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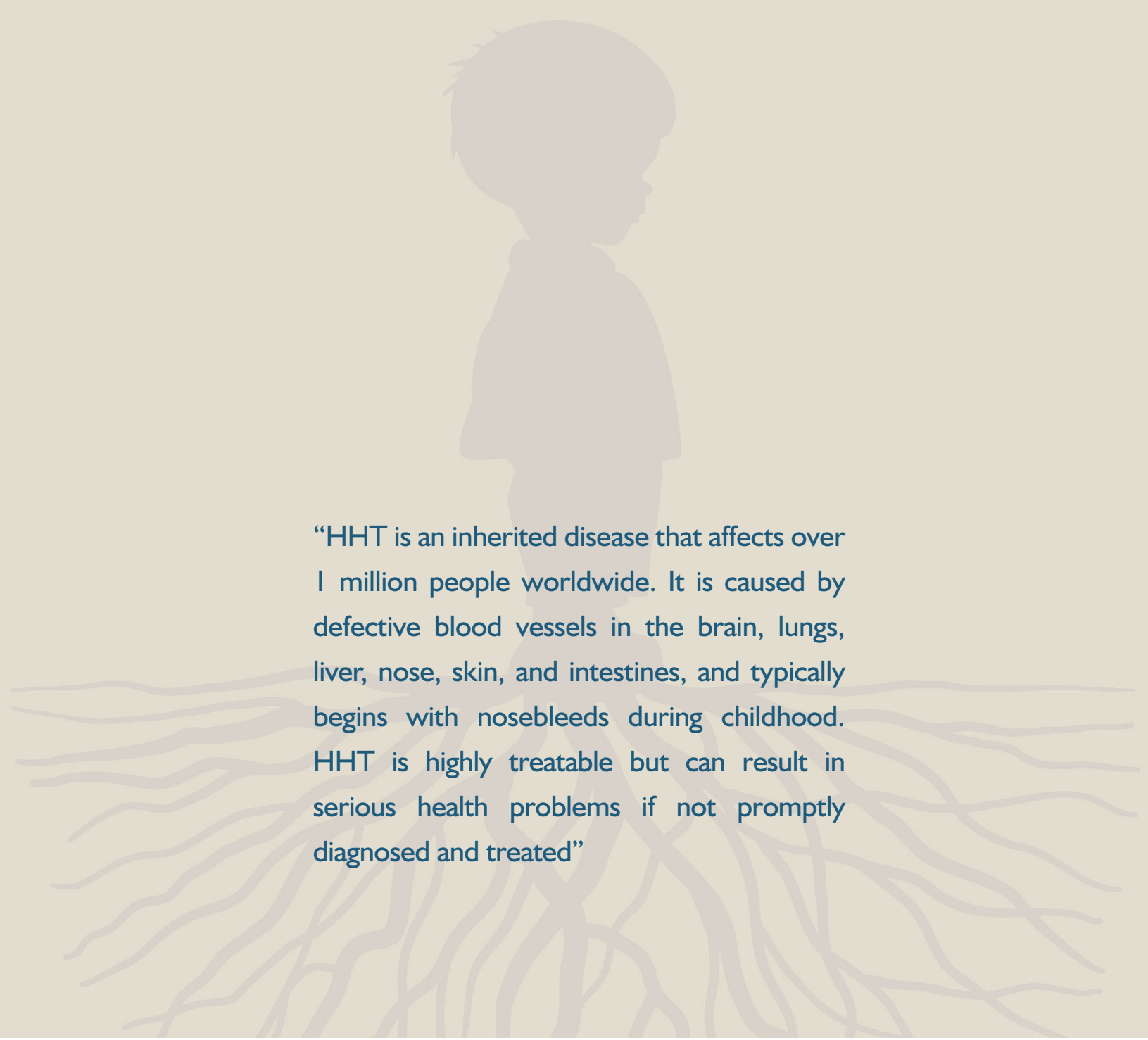
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A light beige background featuring a faint silhouette of a child's head and shoulders in profile, facing right. Below the silhouette, a network of thin, wavy lines resembling roots or blood vessels spreads across the width of the page. Centered over this graphic is a block of text in a dark blue, sans-serif font.

“HHT is an inherited disease that affects over 1 million people worldwide. It is caused by defective blood vessels in the brain, lungs, liver, nose, skin, and intestines, and typically begins with nosebleeds during childhood. HHT is highly treatable but can result in serious health problems if not promptly diagnosed and treated”



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