DIAGNOSIS OF HHT

COMPANION FACTSHEET TO
MY HHT CARE CHECKLISTS

DIAGNOSING HHT

GENETIC TESTING

CLINICAL DIAGNOSTIC CRITERIA (OR "CURAÇAO CRITERIA")

FACTSHEET **FS**

SOME IMPORTANT FACTS TO REMEMBER ABOUT HHT ARE:

Making the diagnosis of **HHT (Hereditary Hemorrhagic Telangiectasia)** in a patient allows for the appropriate screening and preventative treatment to be undertaken in the patient and their affected family members. The cornerstone of an HHT diagnosis is the clinical diagnosis, but HHT can now also be diagnosed using genetic testing. The clinical diagnostic criteria are called the "Curaçao Criteria" and are based on the typical signs and organ involvement in HHT, as well as the family history. The goal of genetic testing for HHT is to clarify the specific HHT mutation in an HHT family, allowing diagnosis among those relatives (often children and young adults) who do not meet clinical diagnostic criteria.

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HOW HHT IS DIAGNOSED

> Genetic testing for HHT:

HHT (Hereditary Hemorrhagic Telangiectasia) is caused by a mutation (change) in one of several HHT-associated genes. There are hundreds of different mutations in each of the three known genes that can cause HHT. HHT is an autosomal dominant genetic disease (it does not skip a generation), and each child born to an HHT parent has a 50% chance of inheriting the genetic change. Once genetic testing has established the gene mutation which causes HHT within a particular family, this information can be used to help diagnose other members of the family.

- 80% of people who meet the clinical diagnostic criteria for HHT are found to have a mutation in either the **ENG (HHT type 1)** or **ACVRL1 (HHT type 2)** gene.
- **Endoglin (ENG)** - A mutation in the ENG gene causes HHT1. Pulmonary and brain AVMs are more common in patients with HHT1.
- **Activin Receptor-like Kinase 1 (ACVRL1 or ALK1)** - A mutation in ALK1 causes HHT2. Liver VMs are more common in people with HHT2.
- **SMAD-related Protein 4 (SMAD4)** - 3-5% of HHT cases are caused by a mutation in SMAD4. A mutation in SMAD4 causes a combined syndrome of juvenile polyps of the GI tract and HHT, also known as JP-HHT.
- About **10-15% of patients will not have a mutation detected** in a known HHT gene, and in these cases a diagnosis is made based on clinical evaluation alone. Therefore, negative genetic testing does not necessarily mean that a person does not have HHT.
- Although a handful of people in the world with HHT have been reported to have a mutation in the **BMP9/GDF2 gene**, it is so rare (<1%) that it is not typically a part of routine genetic testing for HHT.
- Cure HHT strongly encourages individuals and families to arrange genetic testing through a health care provider who understands all of the complexities and limitations of genetic testing for HHT. In most cases this means having an appointment with a medical geneticist or genetic counselor.

HERE ARE SOME THINGS TO DISCUSS WITH YOUR PHYSICIAN:

Whether you meet the criteria for a definite clinical diagnosis of HHT *(using the Curaçao Criteria)*.

If you have a family history of HHT and/or a HHT mutation has been identified in your family.

A referral for genetic testing to determine if you carry the family mutation if a HHT mutation has been identified in your family.

A referral for genetic counseling and genetic testing if a HHT mutation has not been identified in your family.

Clinical evaluation and/or genetic testing for your children.

Getting screening and/or treatment at an HHT Center of Excellence.

> Diagnosis with clinical diagnostic criteria, or "Curaçao Criteria":

The four Curaçao Criteria that HHT physicians use to determine if a person has 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 **epistaxis** (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 pressure is placed on them.
- **Arteriovenous malformations (AVMs)** or telangiectasias in one or more of the internal organs, including the lungs, brain, liver, intestines, stomach, and spinal cord.
- A **family history** of HHT (i.e. first-degree relative such as brother, sister, parent or child who meets these same criteria for definite HHT or has been genetically diagnosed).

ANEMIA, IRON DEFICIENCY & HHT

COMPANION FACTSHEET TO
MY HHT CARE CHECKLISTS

SIGNS AND SYMPTOMS

- WEAKNESS AND FATIGUE
- SHORTNESS OF BREATH
- DECREASED EXERCISE TOLERANCE
- LIGHTHEADEDNESS
- POOR MEMORY OR DIFFICULTY CONCENTRATING
- FAST HEARTBEAT (PALPITATIONS)
- LOW BLOOD PRESSURE
- FAINTING
- RESTLESS LEGS
- POOR SLEEP

FACTSHEET **FS**

SOME IMPORTANT FACTS TO REMEMBER ABOUT HHT ARE:

Approximately 50% of patients with HHT develop anemia.

Iron deficiency without anemia is important and should be treated.

Anemia is most common in adulthood and only rarely in childhood.

Anticoagulant and antiplatelet therapy is not absolutely contraindicated in HHT patients and individualized patient bleeding risks should be considered.

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HERE ARE SOME THINGS TO DISCUSS WITH YOUR PHYSICIAN:

If you have been previously diagnosed with and/or treated for anemia or iron deficiency.

If you have a medical condition for which anticoagulation is recommended.

If you have any of the listed signs and symptoms.

Blood work for anemia (complete blood count, iron panel and ferritin).

Additional testing you might need for other causes of anemia.

Whether referral to a hematologist is indicated.

Getting screening and/or treatment at a HHT Center of Excellence.

Anemia is a decrease in the number of **red blood cells (RBCs)** or hemoglobin in the blood. **Hemoglobin** is the compound that allows RBCs to carry oxygen throughout your body. Anemia leads to reduced oxygen flow to the body's organs.

Anemia is a common complication in people with **HHT (Hereditary Hemorrhagic Telangiectasia)**, occurring in approximately 50%, typically diagnosed in adulthood and only rarely in children with HHT. The primary cause of anemia is iron deficiency secondary to chronic mucocutaneous bleeding (nosebleeds and/or GI bleeding from telangiectasias). **Iron deficiency** by itself is also a common and important manifestation of HHT. Lack of iron makes it harder to produce RBCs, is associated with symptoms similar to anemia and makes anemia more likely to occur if active bleeding occurs as the body will not have the needed iron available to produce the lost RBCs.

Patients with HHT should be screened for iron deficiency and anemia, and then supported with **iron replacement** and red blood cell **transfusion** when indicated. Anticoagulation is not absolutely contraindicated in HHT patients. When there is an indication for **anticoagulant** or **antiplatelet therapy**, individualized patient bleeding risks should be considered.

HOW IT IS DIAGNOSED

- **Complete blood count (CBC)** and **ferritin**.
- **Iron panel** (serum iron, total binding capacity, and transferrin saturation).

TREATMENT

- **Oral iron supplements:** This is the initial recommended therapy and should include a healthy diet that is rich in iron containing foods. It should be noted that it is unlikely that changes to diet will have a significant impact on those people who are significantly iron deficient.
- **IV (intravenous) iron replacement:** Recommended for patients who do not respond, or can not tolerate, oral iron.
- **Red blood cell (RBC) transfusions:** This should be utilized for patients who are **severely anemic** and who have other factors that increase their risk for complications related to their anemia (i.e. underlying **heart conditions**).

AFFILIATED ISSUES

- GI bleeding
- Nosebleeds

CONNECT WITH US

BRAIN *(Cerebral)* VASCULAR MALFORMATIONS & HHT

COMPANION FACTSHEET TO
MY HHT CARE CHECKLISTS

SIGNS AND SYMPTOMS

- PERSISTENT HEADACHES
- SEIZURES
- WEAKNESS
- NUMBNESS IN THE BODY
- VISION CHANGES
- SPEECH PROBLEMS

FACTSHEET **FS**

SOME IMPORTANT FACTS TO REMEMBER ABOUT HHT ARE:

At least 10% of people with HHT have brain VMs.

Brain VMs can be life-threatening or disabling if they bleed.

Since brain VMs often do not cause warning symptoms prior to bleeding, screening is recommended in all people with HHT, even infants.

Brain VMs can be successfully treated in most cases.

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Brain (cerebral) vascular malformations (VMs), are abnormal vessels with direct artery to vein connections in the brain. At least 10% of people with **HHT (Hereditary Hemorrhagic Telangiectasia)** have VMs in the brain (cerebral) blood vessels. They are generally thought to arise during embryonic or fetal development. Without treatment, brain VMs are a common cause of **hemorrhagic stroke** (bleeding in the brain) in HHT families. People are often unaware that they have brain VMs until they develop a life-threatening complication, such as **stroke** or **seizure**.

With the right screening and treatment, these life-threatening complications can be prevented, however, there is no single 'standard treatment' that can be recommended for all brain VMs in HHT at the current time.

HERE ARE SOME THINGS TO DISCUSS WITH YOUR PHYSICIAN:

Whether you are due for routine screening for brain VMs.

If you have been previously diagnosed with and/or treated for brain VMs.

If you have any of the listed signs and symptoms.

Getting screening and/or treatment at a HHT Center of Excellence.

HOW IT IS DIAGNOSED

- **Magnetic Resonance Imaging (MRI):** The recommended test for identifying **brain VMs**. This test utilizes strong magnetic fields to form images of the body. No radiation is used during this study. An **IV** will need to be started for contrast (dye) to be given. The scanner resembles a large tube and the patient is required to lie still during the actual MRI scanning. If the patient has **claustrophobia**, the doctor may prescribe an oral medication to take prior to the MRI. This typically requires **sedation** or anesthesia in young children.
- **Brain (cerebral) angiogram**: May be recommended if a **brain VM** is identified on MRI. It is a minimally invasive procedure performed by a **neurointerventional radiologist** in an angiography suite. The patient is given **sedation** or general anesthesia for this procedure. A **catheter** (a small tube) is inserted into an **artery** in the top of the thigh and directed through the blood vessels in the body to arteries in the neck or the brain. After the procedure, the patient is observed for several hours or overnight before being discharged home.
- **Screening** should be performed at the time of initial clinical evaluation for HHT.
- Patients with **brain VMs** should be referred to a center with neurovascular expertise to be considered for further testing and individualized management.

TREATMENT

- **Brain (cerebral) embolization:** A procedure performed to block the blood flow to the abnormal vessels. The patient is given **sedation** or general anesthesia for this procedure. In an angiography suite, a **catheter** (a small tube) is inserted into an **artery** in the top of the thigh and directed through the blood vessels in the body to arteries in the brain. An **agent** is then inserted to block off blood flow into the VM and lessen the risk of stroke. After the procedure, the patient is observed overnight before being discharged home.
- **Surgical Removal:** A surgical procedure to place a clip on the VM or to remove the VM. This procedure is fully curative, but has a higher complication rate than embolization.
- **Stereotactic Radiosurgery (Gamma Knife):** A type of **focused radiation** that destroys the AVM tissue. This is often done after embolization to ensure that the VM is cured.
- Oftentimes, treatment requires a combination of the above procedures.
- Treatment should be performed by a clinician with neurovascular expertise.

AFFILIATED ISSUES

- Brain hemorrhage
- Seizures

CHILDREN & HHT

COMPANION FACTSHEET TO
MY HHT CARE CHECKLISTS

FACTSHEET **FS**

SOME IMPORTANT FACTS TO REMEMBER ABOUT HHT ARE:

Life-threatening complications of lung AVMs and brain VMs can occur at any age.

The clinical diagnostic criteria (Curacao Criteria) for HHT are less reliable for young children as many symptoms do not present until late childhood or adulthood.

Screening should be performed at the time of diagnosis/ presentation.

Screening can be performed in newborns.

Genetic testing can identify asymptomatic HHT or rule-out HHT in children of HHT families with a known mutation.

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HHT (Hereditary Hemorrhagic Telangiectasia) is autosomal dominant genetic disease (it does not skip a generation), and each **child** born has a 50% chance of inheriting the genetic change. While some manifestations of HHT, such as **telangiectasia** and **epistaxis (nosebleeds)**, are age dependent and may be absent in young children with HHT, potentially serious and even life-threatening complications of **pulmonary (lung) arteriovenous malformations (AVMs)** and **brain vascular malformations (VMs)** can occur at any age. The pediatric HHT guidelines focus therefore on screening and management of pulmonary AVMs and brain VMs in children.

HERE ARE SOME THINGS TO DISCUSS WITH YOUR CHILD'S PHYSICIAN:

Genetic testing for your child.

Screening for pulmonary AVMs for your child.

Screening for brain VMs for your child.

If your child has pulmonary AVMs or brain VMs.

If your child has nosebleeds.

Getting screening and/or treatment at an HHT Center of Excellence.

Talk to your child's dentist and other health care professionals about the need for pulmonary AVM precautions, lifelong.

RECOMMENDATIONS

- Genetic testing should be offered for **asymptomatic children** of a parent with HHT. The affected family member should be tested first to determine the mutation, prior to testing an asymptomatic child.
- Screening for **brain VMs** should be performed in **asymptomatic children** with HHT or at risk for HHT at the time of diagnosis/presentation.
- Children with HHT who have **brain VMs** should be referred to a center with multidisciplinary expertise in neurovascular disease management.
- Screening for **pulmonary AVMs** should be performed in **asymptomatic children** with HHT or at risk for HHT at the time of diagnosis/presentation and should be repeated every 5 years if negative.

TREATMENT

- Large **pulmonary AVMs** and those associated with reduced oxygen saturation should be treated in children to avoid complications.
- **Brain VMs** with high-risk features should be treated in children and treated brain VMs require close follow-up.

SCREENING STUDIES

- **Magnetic Resonance Imaging (MRI)**: The recommended test for identifying **brain VMs**. This may also be performed to evaluate for **liver VMs**. This test utilizes strong magnetic fields to form images of the body. No radiation is used during this study. An **IV** will need to be started for contrast (dye) to be given. The scanner resembles a large tube and the patient is required to lie still during the actual MRI scanning. If the patient has **claustrophobia**, the doctor may prescribe an oral medication to take prior to the MRI. This typically requires **sedation** or anesthesia in young children.
- **Contrast echocardiography (echo bubble study)**: The recommended study for initial screening. 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**. An **IV** will need to be started for saline bubbles to be given. No radiation is used during this study.
- **CT (computed tomography) scan**: If the echo bubble study is positive, diagnosis should be confirmed with a CT scan. This is a high-resolution X-ray of the lungs. If contrast (dye) is used, an **IV** will need to be started.
- Screening for **pulmonary AVMs** in children may be performed with either chest X-ray and pulse oximetry OR contrast echocardiography.

NOSEBLEEDS *(Epistaxis)* & HHT

COMPANION FACTSHEET TO
MY HHT CARE CHECKLISTS

SIGNS AND SYMPTOMS

- NOSEBLEEDS
- TASTING BLOOD IN BACK OF THROAT OR MOUTH
- VOMITING BRIGHT RED OR BLACK FROM SWALLOWING BLOOD
- ANEMIA (LOW BLOOD COUNT)
- IRON DEFICIENCY (LOW AMOUNTS OF IRON IN BLOOD)
- SIGNS AND SYMPTOMS OF ANEMIA AND IRON DEFICIENCY *(SEE ANEMIA AND ANTICOAGULATION FACTSHEET)*

FACTSHEET **FS**

SOME IMPORTANT FACTS TO REMEMBER ABOUT HHT ARE:

Nosebleeds occur in approximately 90% of adults with HHT.

Nosebleeds can significantly impact quality of life.

Nosebleeds often lead to iron deficiency and anemia.

Nosebleeds can be life-threatening if severe.

Moisturizing topical therapies are the initial mainstay of nosebleed care.

The expertise of an ENT doctor is often required to treat nosebleeds.

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HERE ARE SOME THINGS TO DISCUSS WITH YOUR PHYSICIAN:

Nosebleeds or any of the listed signs and symptoms that bother you and impact your quality of life.

Moisturizing topical therapies for my nose.

Treatment with tranexamic acid tablets.

Getting an HHT-experienced ENT doctor for ablative therapies.

Referral to a hematologist to discuss the use of bevacizumab if indicated.

Ask for packing that won't likely make your nose rebleed, such as liquid packing, dissolvable packing or lubricated low-pressure packing.

Blood work to evaluate for anemia and iron deficiency (complete blood count, ferritin levels, iron panel).

Getting an expert opinion from an HHT-experienced ENT doctor and/or at an HHT Center of Excellence.

Nosebleeds (epistaxis) are the most common sign of **HHT (Hereditary Hemorrhagic Telangiectasia)**, developing in 90% of adults with the disease, affecting quality of life and often leading to iron deficiency and anemia. Typically, turbulent nasal airflow with breathing leads to mucosal dryness and bleeding from telangiectasias of the nasal mucosa.

Topical moisturizing may help to prevent the telangiectasias from cracking and bleeding and is a initial mainstay of epistaxis care. When nosebleeds do not respond to moisturizing, other therapies are considered, including oral antifibrinolytics, ablative therapies, systemic antiangiogenic therapy and surgical management. The expertise of an ear, nose, and throat (ENT) doctor, also called an **otolaryngologist**, is often required for management of epistaxis.

HOW IT IS DIAGNOSED

- **Clinical history** and **physical examination**.
- **Blood work** to evaluate for anemia and iron deficiency (complete blood count, ferritin levels, iron panel).

AFFILIATED ISSUES

- Anemia and iron deficiency

TREATMENT

- **Moisturizing topical therapies**: Topical moisturizers (spray or gel) are typically used during the day.
- **Oral antifibrinolytics (tranexamic acid)**: An oral medication that can be used for patients that do not respond to moisturizing topical therapies.
- **Ablative therapies for nasal telangiectasias**: These are procedures performed by an **ENT** doctor for patients that do not respond to moisturizing topical therapies. Treatments include laser treatment, radiofrequency ablation, electrosurgery, and sclerotherapy.
- **Nasal packing**: Can be used for epistaxis that is difficult to stop. Packing unlikely to make the nose rebleed should be used, such as **liquid packing**, **dissolvable packing** or **lubricated low-pressure packing**.
- **Bevacizumab (Avastin)**: A medication used to treat a number of types of cancer. Although not a chemotherapy drug, it slows the growth of blood vessels and has been shown to help reduce nosebleeds. Bevacizumab is available as a nasal injection or Intravenous (IV) treatment for HHT. There are potential side effects which should be considered prior to treatment.
- **Septodermoplasty surgery and nasal closure surgery (Young's procedure)**: Reserved for patients who have failed other treatments and should be discussed with an HHT-experienced **ENT** doctor.

GASTROINTESTINAL *(GI)* BLEEDING & HHT

COMPANION FACTSHEET TO
MY HHT CARE CHECKLISTS

SIGNS AND SYMPTOMS

- BLOODY STOOL OR BLACK (TARRY LOOKING) STOOL
- VOMITING BRIGHT RED OR BLACK
- ANEMIA (LOW BLOOD COUNT)
- IRON DEFICIENCY (LOW AMOUNTS OF IRON IN BLOOD)
- SIGNS AND SYMPTOMS OF ANEMIA AND IRON DEFICIENCY *(SEE ANEMIA AND IRON DEFICIENCY FACTSHEET)*

FACTSHEET **FS**

SOME IMPORTANT FACTS TO REMEMBER ABOUT HHT ARE:

Approximately 30% of people with HHT develop symptomatic GI bleeding.

GI bleeding is most common after age 40.

Bleeding telangiectasias are most common in the stomach and small bowel and are less common in the colon and esophagus.

GI bleeding should be considered if patient has chronic anemia or iron deficiency.

The SMAD4 gene causes Juvenile Polyposis Syndrome (JPS) and can also be associated with HHT.

Patients with the SMAD4 gene have an increased risk of developing non-cancerous GI polyps, as well as colorectal cancer and stomach cancer and will require additional routine screening.

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Gastrointestinal (GI) bleeding is all forms of bleeding from the gastrointestinal tract, from the mouth to the rectum. About 80% of those with **HHT (Hereditary Hemorrhagic Telangiectasia)** have **telangiectasias**, dilated small blood vessels, in their stomach or intestines. Only 30% develop obvious gastrointestinal (GI) bleeding. The bleeding can range from mild to severe.

Telangiectasias can be found anywhere in the gastrointestinal system, including the esophagus, stomach, small intestine, and colon (large intestine). Telangiectasias in the GI tract do not cause pain or discomfort. Signs of GI bleeding are black or bloody stools and/or **anemia**. Symptoms of GI bleeding are usually due to anemia and may include fatigue, shortness of breath, chest pain, light headedness, etc. Often patients do not notice any change in the stool but instead are found to be anemic through blood work.

HERE ARE SOME THINGS TO DISCUSS WITH YOUR PHYSICIAN:

If you have been previously diagnosed with and/or treated for GI bleeding.

If you or your family members have the SMAD4 gene and/or Juvenile Polyposis Syndrome (JPS).

If you have any of the listed signs and symptoms.

Blood work to evaluate for anemia and iron deficiency (complete blood count, ferritin levels, iron panel).

Whether you are due for a colonoscopy for colon cancer screening.

Getting screening and/or treatment at a HHT Center of Excellence.

HOW IT IS DIAGNOSED

- **Esophagogastroduodenoscopy (EGD)**: If GI bleeding is suspected. This is a procedure that examines the **esophagus**, **stomach**, and first portion of the **duodenum** (small intestine) using a flexible tube with a camera at the end of it. The scope is inserted into the mouth and advanced to the small intestine. The patient is given **sedation** for this procedure.
- **Capsule endoscopy (camera pill)**: If EGD does not show any significant telangiectasia. This is a procedure that uses a tiny wireless camera to take pictures of your **digestive tract.** A camera sits inside a vitamin-size capsule you swallow. As the capsule travels through your digestive tract, the camera takes thousands of pictures that are transmitted to a recorder you wear on a belt around your waist.
- **Colonoscopy**: This is a procedure that examines the **large intestine** (colon) using a flexible tube with a camera at the end of it. The scope is inserted into the rectum and advanced to the large intestine. The patient is given **sedation** for this procedure.
- **Blood work** to evaluate for **anemia** and **iron deficiency** (complete blood count, ferritin levels, iron panel).
- Patients with **SMAD4-HHT** should undergo **screening colonoscopy** at age 15 AND every 3 years thereafter if no polyps are found OR every year along with EGD if colonic polyps are found.

TREATMENT

- **Argon Plasma Coagulation (APC)**: Should only be used sparingly for **bleeding lesions** and significant (1-3 mm) **non-bleeding lesions**. This procedure is done under EGD and uses a jet of argon gas and high-frequency electric current to seal the irregular or bleeding areas. The patient is given **sedation** for this procedure.
- **Oral antifibrinolytics (tranexamic acid)**: An oral medication that can be used for patients with **mild GI bleeding**.
- **IV bevacizumab or other systemic anti-angiogenic therapy**: An IV medication used to treat a number of types of cancers. There is growing evidence of the benefits of this medication for patients with **moderate to severe GI bleeding**. This may be considered for patients who have failed other types of medical management. There are potential serious side effects which should be considered prior to treatment.
- **Management of anemia and iron deficiency** *(see Anemia and Iron Deficiency Factsheet)*.

AFFILIATED ISSUES

- Anemia and Iron deficiency
- Juvenile Polyposis Syndrome (JPS) if the SMAD4 gene is present

IMAGING & HHT

COMPANION FACTSHEET TO
MY HHT CARE CHECKLISTS

UTILIZED IMAGING

- MAGNETIC RESONANCE IMAGING (MRI)
- CT (COMPUTED TOMOGRAPHY) SCAN
- DOPPLER ULTRASOUND
- CONTRAST ECHOCARDIOGRAPHY (ECHO BUBBLE STUDY)
- ECHOCARDIOGRAM
- BRAIN (CEREBRAL) ANGIOGRAM
- BRAIN (CEREBRAL) EMBOLIZATION
- PULMONARY EMBOLIZATION

FACTSHEET **FS**

SOME IMPORTANT FACTS TO REMEMBER ABOUT HHT ARE:

Some manifestations of HHT can be asymptomatic (no visible symptoms), can occur at any age, and can result in serious and life-threatening complications.

Imaging is used to identify these manifestations and is an important part of screening and management for HHT patients.

Imaging is used to treat pulmonary AVMs and brain VMs.

Screening imaging studies are essential in the disease management and prevention of catastrophic events in HHT.

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HHT (Hereditary Hemorrhagic Telangiectasia) is a hereditary disorder (meaning it is passed down through generations) that is characterized by abnormal blood vessel formation. A person with HHT has a tendency to form blood vessels that lack normal capillaries between an artery and vein.

Some manifestations of HHT, such as **telangiectasia** and **epistaxis** (nosebleeds) present with symptoms or can be seen on physical examination. Other manifestations, like **pulmonary (lung) arteriovenous malformations (AVMs)**, **brain vascular malformations (VMs)**, and **liver VMs**, can be asymptomatic, can occur at any age, and can result in serious and life-threatening complications. **Imaging** is used to identify these manifestations and is an important part of screening and management for HHT patients. Imaging is also used to treat pulmonary AVMs and brain VMs.

Screening imaging studies are essential in the disease management and prevention of catastrophic events in HHT.

TYPES OF IMAGING UTILIZED FOR SCREENING AND TREATMENT:

- **Magnetic Resonance Imaging (MRI)**: The recommended test for identifying **brain VMs**. This may also be performed to evaluate for **liver VMs**. This test utilizes strong magnetic fields to form images of the body. No radiation is used during this study. An **IV** will need to be started for contrast (dye) to be given. The scanner resembles a large tube and the patient is required to lie still during the actual MRI scanning. If the patient has **claustrophobia**, the doctor may prescribe an oral medication to take prior to the MRI. This typically requires **sedation** or anesthesia in young children.
- **CT (Computed Tomography) scan**: Used to evaluate for **pulmonary AVMs** if the echo bubble study is positive. This may also be performed to evaluate for **liver VMs**. This a high-resolution X-ray. If contrast (dye) is used, an **IV** will need to be started.
- **Doppler ultrasound**: The imaging of choice for screening for **liver VMs**. This test uses sound waves to produce a picture of the organs in the abdomen. No radiation is used during this study.
- **Contrast echocardiography (echo bubble study)**: The recommended study for initial screening for **pulmonary AVMs**. 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**. An **IV** will need to be started for saline bubbles to be given. No radiation is used during this study.
- **Echocardiogram**: Used to assess for cardiac effects of **liver VMs**. This test uses sound waves (ultrasound) to determine how the heart muscle and valves are working. No radiation is used during this study. It is recommended at the time of liver VM diagnosis.
- **Brain (cerebral) angiogram**: May be recommended if a **brain VM** is identified on MRI. It is a minimally invasive procedure performed by a **neurointerventional radiologist** in an angiography suite. The patient is given **sedation** or general anesthesia for this procedure. A **catheter** (a small tube) is inserted into an **artery** in the top of the thigh and directed through the blood vessels in the body to arteries in the neck or the brain. After the procedure, the patient is observed for several hours or overnight before being discharged home.
- **Brain (cerebral) embolization**: A procedure performed to block the blood flow to the abnormal vessels. The patient is given **sedation** or general anesthesia for this procedure. In an angiography suite, a **catheter** (a small tube) is inserted into an **artery** in the top of the thigh and directed through the blood vessels in the body to arteries in the brain. An **agent** is then inserted to block off blood flow into the VM and lessen the risk of stroke. After the procedure, the patient is observed overnight before being discharged home.
- **Pulmonary embolization**: A procedure performed to block the blood flow to the abnormal vessels. The patient is given **sedation** or general anesthesia for this procedure. In an angiography suite, a **catheter** (small tube) is inserted into a **vein** in the top of the thigh and directed through the blood vessels in the body to the pulmonary arteries. A small **coil** or plug is then inserted to block off the artery that leads into or "feeds" the **pulmonary AVM**. This stops the blood flow to the pulmonary AVM which eliminates the occurrence of a potentially life-threatening complication. After the procedure, the patient is observed for several hours or overnight before being discharged home.

LIVER VASCULAR MALFORMATIONS & HHT

COMPANION FACTSHEET TO
MY HHT CARE CHECKLISTS

SIGNS AND SYMPTOMS

- CHRONIC LIVER PAIN
- ELEVATED LIVER FUNCTION TESTS (LFTS)
- YELLOWING OF THE SKIN AND EYES
- SHORTNESS OF BREATH
- FATIGUE
- LOSS OF APPETITE
- DECREASED EXERCISE TOLERANCE
- SWOLLEN LEGS AND FEET
- CHEST PAIN

FACTSHEET **FS**

SOME IMPORTANT FACTS TO REMEMBER ABOUT HHT ARE:

- Liver VMs occur in approximately 75% of HHT patients.
- Liver VMs are typically more severe in patients with ACVRL1 mutation (HHT2).
- Screening for liver VMs should be offered to adults with definite or suspected HHT.
- Liver VMs are most often asymptomatic but can result in heart failure and other complications.
- Echocardiogram is recommended at the time of liver VM diagnosis.
- Patients with symptomatic liver VMs should be managed by an expert team at an HHT Center of Excellence, with at least annual follow-up.
- Liver biopsy should be avoided in patients with definite or suspected VMs.
- Hepatic artery embolization should be avoided in patients with liver VMs.
- MRI and CT scan findings of Liver VMs are often confused with cirrhosis when viewed by physicians who may not have expertise in HHT.

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Liver vascular malformations (VMs) are abnormal vascular connections in the liver. They occur in approximately 75% of **HHT (Hereditary Hemorrhagic Telangiectasia)** patients, more commonly in women and often presenting in the 5th decade. The clinical presentation is typically more severe in patients with **ACVRL1 mutation (HHT2)**. Liver VMs in HHT typically present as **diffuse small lesions (telangiectasias)** throughout the liver, and rarely as discrete large **arteriovenous malformations (AVMs)**. Clinicians should offer screening for liver VMs and be aware of possible symptoms or complications and prognostic factors. First-line management depends on symptoms.

HERE ARE SOME THINGS TO DISCUSS WITH YOUR PHYSICIAN:

About diagnostic imaging for liver VMs.

If you have been previously diagnosed with and/or treated for liver VMs.

If you have any of the listed signs and symptoms.

Getting an expert opinion at a HHT Center of Excellence.

Getting diagnostic imaging for liver VMs, using specialized Doppler ultrasound, CT or MRI with special contrast (dye) protocols.

Getting an echocardiogram to look for cardiac effects of liver VMs.

HOW IT IS DIAGNOSED

- Clinical history, physical examination and bloodwork (LFTs).
- **Doppler ultrasound**: The imaging of choice for screening. This test uses sound waves to produce a picture of the organs in the abdomen. No radiation is used during this study.
- **CT (computed tomography) scan**: May also be performed to evaluate for liver VMs. This a high-resolution X-ray of the abdomen. An IV will need to be started for contrast (X-ray dye) to be given.
- **Magnetic resonance imaging (MRI)**: May also be performed to evaluate for liver VMs. This test utilizes strong magnetic fields to form images of the body. No radiation is used during this study. An IV will need to be started for contrast (dye) to be given. The scanner resembles a large tube and the patient is required to lie still during the actual MRI scanning. If the patient has claustrophobia, the doctor may prescribe an oral medication to take prior to the MRI.
- **Echocardiogram**: Used to assess for cardiac effects of liver VMs. This test uses sound waves (ultrasound) to determine how the heart muscle and valves are working. No radiation is used during this study. It is recommended at the time of liver VM diagnosis.
- The type of imaging should be performed based on the risk/benefit balance, local expertise, and availability/cost
- These tests will be most informative when performed in a center with HHT expertise, in the context of a clinical assessment at an HHT Center of Excellence.

TREATMENT

- No treatment recommended for asymptomatic liver VMs.
- Treatment is reserved only for patients with complications and/or symptomatic liver VMs.
- Patients with heart failure and pulmonary hypertension should be co-managed by an HHT Center of Excellence and an HHT cardiologist or a pulmonary hypertension specialty clinic.
- **Bevacizumab**: An IV medication used to treat a number of types of cancers. Although not a chemotherapy drug, it slows the growth of blood vessels and has been shown to help patients with severe liver VMs and heart failure who have failed other types of medical management.
- **Liver transplant**: Considered for patients with symptomatic liver VMs, specifically those with refractory heart failure, biliary ischemia, or complicated portal hypertension.

AFFILIATED ISSUES

- Heart failure
- Pulmonary hypertension
- Biliary ischemia
- Cirrhosis
- Portal hypertension

CONNECT WITH US

LUNG *(Pulmonary)* ARTERIOVENOUS MALFORMATIONS & HHT

COMPANION FACTSHEET TO
MY HHT CARE CHECKLISTS

SIGNS AND SYMPTOMS

- SHORTNESS OF BREATH
- LOW OXYGEN SATURATION OR DECREASED OXYGEN IN BLOOD
- DECREASED EXERCISE TOLERANCE
- MIGRAINES
- BLUISH OR PALE LIPS OR FINGERS
- COUGHING UP BLOOD

AFFILIATED ISSUES

- MIGRAINES
- STROKE
- BRAIN ABSCESS
- LUNG HEMORRHAGE

FACTSHEET **FS**

SOME IMPORTANT FACTS TO REMEMBER ABOUT HHT ARE:

At least 40% of people with **HHT (Hereditary Hemorrhagic Telangiectasia)** have pulmonary AVMs (about 50% with HHT1 and about 10% with HHT2).

Pulmonary AVMs often present early in life and are found in children of all ages with all types of HHT.

People are often unaware that they have pulmonary AVMs until they develop a life-threatening complication, such as stroke, brain abscess or lung hemorrhage.

With the right screening and treatment, these life-threatening complications can be prevented.

During pregnancy pulmonary AVMs can be especially dangerous as the volume of blood flowing through the body significantly increases and make complications more likely.

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Pulmonary (lung) arteriovenous malformations (AVMs) are direct artery to vein connections in the pulmonary circulation. 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 **impurities (clots, bacteria, air bubbles)** before the blood circulates to the brain and other organs. With a pulmonary AVM, these capillaries are missing, and the artery connects directly to the vein. If the artery leading to the pulmonary AVM is larger than two to three millimeters in diameter, small **blood clots** can travel through the pulmonary AVM and go into the brain, causing a **stroke**. **Bacteria** can also travel through AVMs and result in **brain abscesses (a brain infection)**. Stroke and brain abscess can be life-threatening.

HERE ARE SOME THINGS TO DISCUSS WITH YOUR PHYSICIAN:

Whether you are due for routine screening for pulmonary AVMs.

If you have been previously diagnosed with and/or treated for pulmonary AVMs.

If you have any of the listed signs and symptoms.

Getting screening and/or treatment at an HHT Center of Excellence.

Talk to your dentist and other health care professionals about the need for pulmonary AVM precautions, such as prophylactic antibiotics.

HOW IT IS DIAGNOSED

- **Transthoracic contrast echocardiography (echo bubble study)**: The recommended study for initial screening. 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**. An **IV** will need to be started for saline bubbles to be given. No radiation is used during this study.
- **CT (computed tomography) scan**: If the echo bubble study is positive, diagnosis should be confirmed with a CT scan. This a high-resolution X-ray of your lungs. If **contrast** (dye) is used, an IV will need to be started.
- **Screening** should be performed at the time of initial clinical evaluation for HHT.
- **Repeat screening** should be performed every 5-10 years AND after puberty, after pregnancy, within 5 years preceding planned pregnancy.

TREATMENT

- **Pulmonary embolization**: A procedure performed to block the blood flow to the abnormal vessels. The patient is given **sedation** or general anesthesia for this procedure. In an angiography suite, a **catheter** (small tube) is inserted into a **vein** in the top of the thigh and directed through the blood vessels in the body to the pulmonary arteries. A small **coil** or plug is then inserted to block off the artery that leads into or "feeds" the **pulmonary AVM**. This stops the blood flow to the pulmonary AVM which eliminates the occurrence of a potentially life-threatening complication. After the procedure, the patient is observed for several hours or overnight before being discharged home.
- **Surgical Removal**: A surgical procedure to remove the part of the lung that contains the pulmonary AVM. Because of the success of embolization, surgery is rarely necessary.
- Pulmonary AVMs of a certain size should be treated (those feeding an artery diameter of **2-3 mm or greater**).

IMPORTANT PRECAUTIONS FOR PATIENTS WHO HAVE BEEN DIAGNOSED WITH A PULMONARY AVM OR WHO HAVE NOT YET BEEN SCREENED FOR THEM:

- **Antibiotic Prophylaxis**: Recommended for **dental** and other procedures that can introduce **bacteria** in the blood.
- **IV Filter**: An **IV air filter (bubble trap)** should be used when possible, if a patient has an intravenous **(IV)** line. This is to prevent any large air bubble from entering the bloodstream, going through a **lung AVM**, and then causing a temporary **stroke**. 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. During a **blood transfusion**, a standard blood filter is all that is needed. Please note that filters often cannot be used for IV contrast injections like you might get for CT or MRI scans.
- Avoidance of **SCUBA diving** is recommended.

CONNECT WITH US

PREGNANCY & HHT

COMPANION FACTSHEET TO
MY HHT CARE CHECKLISTS

FACTSHEET **FS**

SOME IMPORTANT FACTS TO REMEMBER ABOUT HHT ARE:

Nosebleeds commonly worsen during pregnancy.

Pulmonary AVMs can grow during pregnancy.

Your pregnancy may be considered high-risk.

During pregnancy pulmonary AVMs can be especially dangerous as the volume of blood flowing through the body significantly increases and make complications more likely.

Any HHT patient with lung AVMs (treated or untreated) should follow pulmonary AVM precautions, including antibiotics before any procedures that can cause bacteria in the blood. This is also true for HHT patients that have not yet been screened for lung AVMs.

Each child born to an HHT parent has a 50% chance of inheriting the HHT gene mutation. Genetic testing can be done on the child at birth if the familial mutation is known.

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A **pregnant woman** with HHT should be assessed for their risk of pregnancy and delivery-related complications and have access to, as needed, a multidisciplinary maternal-fetal medicine team that includes HHT experts. Screening for **pulmonary (lung) arteriovenous malformations (AVMs)** and **brain vascular malformations (VMs)** should be considered, and unscreened patients may need to be considered high-risk. In addition, since offspring are at 50% risk of inheriting the pathogenic mutation, pre-pregnancy consultation with an **obstetrician** is recommended, for consideration of options for genetic diagnosis. Some families have pursued **pre-implantation genetic testing** which involves screening cells from embryos for HHT and is performed with **in-vitro fertilization (IVF)** prior to embryo transfer, before a pregnancy is established.

HERE ARE SOME THINGS TO DISCUSS WITH YOUR PHYSICIAN:

If you have HHT or a family history of HHT and are planning a pregnancy.

Options for pre-implantation genetic testing (PGT).

Genetic testing for you and your child.

If you have pulmonary AVMs and are pregnant.

If you have brain VMs or a prior brain hemorrhage and are pregnant.

Referral to a center with high-risk pregnancy care and HHT expertise.

RECOMMENDATIONS

- Discuss **diagnostic options** including genetic testing for HHT during **pregnancy planning**. Once the causative familial mutation is identified in an affected parent, then it can be used to screen future off-spring.
- **Magnetic Resonance Imaging (MRI),** without gadolinium, should be planned in **second trimester,** for symptomatic patients including patients with previous **cerebral (brain) hemorrhage**. Asymptomatic patients do not require routine screening for brain VMs during pregnancy.
- Pregnant women with HHT who have not been recently screened and/or treated for **pulmonary AVMs** should be screened using either **contrast echocardiography (echo bubble study)** or low-dose non-contrast **chest CT**, depending on local expertise. Chest CT, when performed, should be done early in the **second trimester**.
- In patients with symptoms suggestive of **pulmonary AVMs**, diagnostic testing should be performed using low-dose non-contrast **chest CT**. This testing can be performed at **any gestational age**, as clinically indicated.
- **Pulmonary AVMs** should be treated starting in the **second trimester** unless otherwise clinically indicated.
- Pregnant women with untreated **pulmonary AVMs** or **brain VMs**, and those who have not been screened, should be considered high risk for **hemorrhagic and neurologic complications**, and should be managed accordingly by a high-risk team with HHT expertise.
- Patients with HHT may get an **epidural** and screening for **spinal VMs** is not required.
- Patients without **high-risk brain VMs** can labor and proceed with **vaginal delivery**.
- Patients with **brain VMs** should be considered for **Cesarean Section** and talk to an expert multidisciplinary neurovascular team about the brain VMs and risk of bleeding, to decide if they can proceed with vaginal delivery.