

MY HHT DIAGNOSIS CARE CHECKLIST

USING THE HHT GUIDELINES

The HHT Diagnosis Guidelines are detailed on the next pages

Date: _____

Name: _____

Please check all that apply

I THINK I MIGHT HAVE HHT, BUT I HAVE NOT BEEN FORMALLY DIAGNOSED.

- I assume I have HHT until the diagnosis is ruled out.
- Check with my doctor to confirm if I meet the criteria for a definite clinical diagnosis of HHT (using the Curaçao Criteria).
- Ask my relatives if they have been diagnosed with HHT or have typical symptoms.
- Check with family to find out if an HHT mutation has been identified in our family.
- I am still unsure if I have HHT and my family's mutation is known: Ask my doctor to refer me for genetic testing to determine if I carry the family mutation.
- I am still unsure if I have HHT but my family's mutation is not known: Ask my doctor to refer me for genetic testing, to determine if I have a typical HHT mutation.

I HAVE A DEFINITE CLINICAL DIAGNOSIS OF HHT. DO I ALSO NEED GENETIC TESTING?

- I don't require genetic testing for my own personal HHT care.
- If no one else in the family has had genetic testing or if results are unclear, I can ask for HHT genetic testing, so that my results can help sort out my relatives' diagnoses.

I HAVE NO SYMPTOMS OF HHT, BUT MY RELATIVES HAVE IT.

- I assume I have HHT until the diagnosis is ruled out.
- Check with my doctor to confirm if I meet the criteria for a definite clinical diagnosis of HHT (using the Curaçao Criteria).
- Check with family to find out if an HHT mutation has been identified in our family.
- If the family's genetic mutation is known: Ask my doctor to refer me for genetic testing to determine if I carry the family mutation.
- If my family's mutation is not known or available: Ask my doctor to refer me for genetic testing, to determine if I have a typical HHT mutation.



WHAT ARE THE HHT GUIDELINES AND WHY ARE THEY IMPORTANT?

- The HHT Guidelines are recommendations for care based on evidence and expertise from HHT experts from around the world.
- The HHT Guidelines help ensure that people living with HHT get the best care possible.

WHAT IS MY ROLE AS SOMEONE LIVING WITH HHT?

- Be aware of the Guidelines. Share them with your care team. Ideally you should be seen at an HHT Center of Excellence or your care team may want to consult with one.
- Read up on your condition and know what care is available for HHT.
- **Prepare ahead of time for your appointments:** Bring your HHT Care Checklists and a family member or friend. They can help you communicate your questions and priorities, as well as act as a second set of ears. Share your experiences, worries and priorities to help your care team better understand your needs and provide individualized care.

DIAGNOSIS OF HHT

Making the diagnosis of HHT 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 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" (Table) and are based on the typical symptoms, 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.



HHT GUIDELINES RECOMMENDATIONS

DIAGNOSIS OF HHT

Making the diagnosis of HHT 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 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” (Table) and are based on the typical symptoms, 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.

The expert panel recommends that:
(all recommendations are from the First HHT Guidelines)

G1 CLINICIANS DIAGNOSE HHT USING THE CURAÇAO CRITERIA (TABLE) OR BY IDENTIFICATION OF A CAUSATIVE MUTATION.

Clinical Considerations: Applying the Curaçao Criteria for clinical diagnosis of HHT requires a targeted, multigeneration family history for HHT, given that most individuals with HHT will have an affected parent, grandparent and other close relatives. When applying the Curaçao Criteria, the clinician should consider the patient’s age, given the frequently delayed appearance of the signs and symptoms of HHT. At least 90% of patients with HHT meet the clinical criteria by age 40, but few do in the first decade of life. If a patient has clinical features suggestive of HHT, but no family history, it is possible that patient has a new mutation and therefore the diagnosis of HHT remains possible.

G2 CLINICIANS CONSIDER THE DIAGNOSIS OF HHT IN PATIENTS WITH ONE OR MORE CURAÇAO CRITERIA (TABLE).

Clinical Considerations: When applying the Curaçao Criteria for clinical diagnosis, identifying 2 or less of the criteria after clinical examination and history should not be considered sufficient evidence to rule out the diagnosis, particularly in the first few decades of life.

G3 ASYMPTOMATIC CHILDREN OF A PARENT WITH HHT BE CONSIDERED TO HAVE POSSIBLE HHT, UNLESS EXCLUDED BY GENETIC TESTING.

Clinical Considerations: Given the expected poor sensitivity of the Curaçao Criteria for clinical diagnosis in children, the clinician can clarify the diagnosis using genetic testing, if a familial mutation has been identified. If genetic testing is not possible, the clinician should proceed as if the child has HHT and consider appropriate screening for visceral AVMs.



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CLINICIANS REFER PATIENTS FOR DIAGNOSTIC GENETIC TESTING FOR HHT:

- » To identify the causative mutation in a family with clinically confirmed HHT
- » To establish a diagnosis in relatives of a person with a known causative mutation, including:
 - a. Individuals who are asymptomatic or minimally symptomatic
 - b. Individuals who desire prenatal testing
- » To assist in establishing a diagnosis of HHT in individuals who do not meet clinical diagnostic criteria

Clinical Considerations: Genetic testing for HHT is a multistep process. In an experienced lab, the index case is generally tested by sequence and deletions/duplications analysis of both the ENG and ACVRL1 genes. It is reasonable to perform the deletion/duplication analysis either simultaneously with the sequence analysis or only in cases in which the sequence analysis is negative or equivocal. If an HHT causing mutation is identified in the index case (test is positive), diagnostic genetic testing for HHT can be offered to all at risk relatives. These relatives would have “family specific” mutation testing by targeted sequencing. If no mutation is identified (test is negative) in the index case, diagnostic genetic testing can not be offered to other family members. Such families should be advised that, in the future, currently undetectable HHT mutations will become detectable as new genes and testing methods are discovered. In the meantime, diagnosis and medical management of at risk family members will rely on clinical findings and knowledge of the natural history of HHT. If a genetic variant of uncertain significance is identified (test is equivocal) in the index case, additional confirmatory testing may be available, or additional interpretive information may become available in the future, to clarify whether the genetic variant in question is in fact a benign variant or a disease causing mutation.

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FOR INDIVIDUALS WHO TEST NEGATIVE FOR ENG AND ACVRL1 CODING SEQUENCE MUTATIONS, SMAD4 TESTING SHOULD BE CONSIDERED TO IDENTIFY THE CAUSATIVE MUTATION.

Table: Curaçao Criteria for Clinical Diagnosis of HHT: Using these criteria, a diagnosis of HHT is considered ‘definite’ if three or more Curaçao criteria are present, ‘possible or suspected’ if two criteria are present, and ‘unlikely’ if 0 or 1 criterion is present.

Criteria	Description
Epistaxis	Spontaneous and recurrent
Telangiectases	Multiple, at characteristic sites: lips, oral cavity, fingers, nose
Visceral lesions	Such as gastrointestinal telangiectasia, pulmonary, hepatic, cerebral or spinal AVMs
Family history	A first degree relative with HHT according to these criteria

(Shovlin C. et al. AJMG 2000)