

Indication criteria for genetic testing
Evaluation of validity and clinical utility

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Indication criteria for disease:
Hereditary hemorrhagic teleangiectasia /
Osler-Rendu-Weber disease (HHT)
[ENG, ACVRL1 (ALK1)]

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2. Disease characteristics

2.1 Name of the Disease (Synonyms):

Osler-Rendu-Weber disease, Hereditary hemorrhagic teleangiectasia (HHT)

2.2 OMIM# of the Disease: *187300*

2.3 Name of the Analysed Genes or DNA/Chromosome Segments:

ENG, ACVRL1 (ALK1)

2.4 OMIM# of the Gene(s): *131195, 601284*

2.5 Mutational Spectrum:

More than 200 mutations are known in each both genes.

2.6 Analytical Methods:

Direct sequencing of both genes. Search for (very rare) deletions or insertions by MLPA or related techniques if necessary.

2.7 Analytical Validation

Internal validation by analysis of known mutations, external validation by exchange of control DNA with other diagnostic institutions (Proficiency test are not offered yet).

2.8 Estimated Frequency of the Disease in Germany

(Incidence at birth ("birth prevalence") or population prevalence):

Prevalence in general population estimated as 1:10,000

2.9 If applicable, prevalence in the ethnic group of investigated person:

Outside Europe more rare.

2.10 Diagnostic Setting:

	yes	no
A. (Differential)diagnostics	<input checked="" type="checkbox"/>	<input type="checkbox"/>
B. Predictive Testing	<input type="checkbox"/>	<input type="checkbox"/>
C. Risk assessment in Relatives	<input checked="" type="checkbox"/>	<input type="checkbox"/>
D. Prenatal	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Comment: *A prenatal test for HHT is very rarely performed, but may be indicated/wanted at times.*

3. Test characteristics

		Genotyp bzw. Krankheit	
		vorhanden	fehlend
Test	pos.	A	B
	neg.	C	D

A: richtig Positive C: falsch Negative
 B: falsch Positive D: richtig Negative

Sensitivität: $A/(A+C)$
Spezifität: $D/(D+B)$
pos. prädikt. Wert: $A/(A+B)$
neg. prädikt. Wert: $D/(C+D)$

3.1 Analytical Sensitivity

(proportion of positive tests if the genotype is present)

nearly 100% with direct sequencing

3.2 Analytical Specificity

(proportion of negative tests if the genotype is not present)

nearly 100%

3.3 Clinical Sensitivity

(proportion of positive tests if the disease is present)

The clinical sensitivity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case.

about 75%

3.4 Clinical Specificity

(proportion of negative tests if the disease is not present)

The clinical specificity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case.

about 100%

3.5 Positive clinical predictive value

(life time risk to develop the disease if the test is positive).

well above 90%

3.6 Negative clinical predictive value

(Probability not to develop the disease if the test is negative).

Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

Index case in that family had been tested:

ca. 100% if mutation in index patient is known

Index case in that family had not been tested:

80%

4. Clinical Utility

4.1 (Differential)diagnosis: The tested person ist clinically affected

(To be answered if in 2.10 "A" was marked)

4.1.1 Can a diagnosis be made other than through a genetic test?

no (continue with 4.1.4)

yes

clinically

imaging

endoscopy

biochemistry

electrophysiology

other (please describe)

4.1.2 Describe the burden of alternative diagnostic methods to the patient

Depends on method:

small (physical examination for cutaneous teleangiectasias, personal history of epistaxis)

to acceptable (imaging techniques and endoscopy in search for organ involvement).

4.1.3 How ist the cost effectiveness of alternative diagnostic methods to be judged?

In clinically affected patients, the alternative diagnostic methods must be applied in order to detect possible complications.

4.1.4 Will disease management be influenced by the result of a genetic test?

no

yes

Therapy (please describe)

Prognosis (please describe)

Patients with ACVRL1 gene mutations have a higher risk of liver involvement than patients with ENG mutations.

Management (please describe)

4.2 Predictive Setting: The tested person is clinically unaffected but carries an increased risk based on family history

(To be answered if in 2.10 "B" was marked)

4.2.1 Will the result of a genetic test influence lifestyle and prevention?

Yes.

If the test result is positive (please describe)

More frequent follow-up investigations for organ manifestations/complications

If the test result is negative (please describe)

The usual follow-up investigations are dispensable

4.2.2 Which options in view of lifestyle and prevention does a person at-risk have if no genetic test has been done (please describe)?

Regular clinical, imaging, and endoscopic follow-up. On conspicuous results, surgical or minimal-invasive (endoscopic) intervention if necessary.

4.3 Genetic risk assessment in family members of a diseased person

(To be answered if in 2.10 "C" was marked)

4.3.1 Does the result of a genetic test resolve the genetic situation in that family?

Yes.

4.3.2 Can a genetic test in the index patient save genetic or other tests in family members?

No.

4.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?

Yes.

4.4 Prenatal diagnosis

(To be answered if in 2.10 "D" was marked)

4.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnostic?

Yes.

5. If applicable, further consequences of testing

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for the patient or his/her relatives? (Please describe)

Yes. Knowledge of the mutation and thereby molecular-genetic confirmation of the diagnosis is beneficial for the patients, e.g. with regard to planning the future.