

**Indication criteria for genetic testing**  
Evaluation of validity and clinical utility

**Indication criteria for disease:**  
***Ehlers-Danlos syndrome types I-VII***

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## 2. Disease characteristics

### 2.1 Name of the Disease (Synonyms):

*Ehlers-Danlos syndrome type I/II, III, IV, VI, VIIA/B, VIIC; or, according to the Villefranche classification (Beighton et al., 1998): Classic type (EDS I and II), hypermotility type (EDS III), vascular type (EDS IV), kyphoscoliotic type (EDS VI), arthrochalasia type (EDS VIIA and VIIB), dermatosparaxis type (EDS VIIC); varia and unspecified types.*

### 2.2 OMIM# of the Disease:

*130000, 130010, 130020, 130050, 225400, 130060, 225410*

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

*COL5A1, COL5A2, TNXB, COL3A1, PLOD1, COL1A1, COL1A2, ADAMTS2*

### 2.4 OMIM# of the Gene(s):

*120215, 120190, 600985, 120180, 153454, 120150, 120160, 604539*

### 2.5 Mutational Spectrum:

*missense mutations, nonsense mutations, splice mutations, insertions, deletions, genomic rearrangements.*

*Presently, more than 270 mutations are known for all 8 genes together. The majority of them (about 170) are in the COL3A1 gene.*

### 2.6 Analytical Methods:

*genomic sequencing of coding regions, eventually MLPA (multiple ligation dependent analysis) for detection of genomic rearrangements*

### 2.7 Analytical Validation

*direct sequencing of both DNA strands; verification of sequence and MLPA results with second DNA extraction or second PCR or hybridisation (MLPA)*

### 2.8 Estimated Frequency of the Disease in Germany

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

*Prevalence about. 1:5,000-1:100,000 depending on EDS type*

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

*not applicable*

### 2.10 Diagnostic Setting:

|                                 | yes                                 | no                       |
|---------------------------------|-------------------------------------|--------------------------|
| A. (Differential)diagnostics    | <input checked="" type="checkbox"/> | <input type="checkbox"/> |
| B. Predictive Testing           | <input checked="" 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: *Prenatal diagnosis is rarely requested for Ehlers-Danlos syndrome.*

### 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%, if a deletion/duplication diagnostic test has been made for genes with the possibility of a rearrangement.*

#### 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.

*5% (TNXB; EDS type III) – 50% (COL5A1, COL5A2; EDS type I/II) in genetically heterogeneous EDS types with additional, still unknown gene loci.*

*Up to 95% (COL3A1; EDS type IV); (COL1A1, COL1A2; EDS type VIIA/B); not known in EDS type VI (PLOD1) and EDS type VIIC (ADAMTS2).*

*Highly dependent on fulfilment of the clinical criteria as well as of the biochemical and ultrastructural dermal findings documented in the Villefranche nosology.*

#### 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.

*probably 100%*

#### 3.5 Positive clinical predictive value

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

*100% penetrance with, depending on EDS type, extremely variable clinical expressivity.*

#### 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:

*nearly 100%*

Index case in that family had not been tested:

*5%-95%, corresponding to the detection rate in the genes of the different EDS types. This question arises quite often in EDS type IV if the index patient has died already.*

## 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) *ultrastructural analysis of skin biopsy*

*Because EDS comprises a group of different entities, each with highly variable clinical expressivity, a primary molecular genetic analysis for differential diagnostics is indicated only in exceptional cases with classical clinical features and known associated mutations (e.g. EDS VII). Histological/ultrastructural and biochemical/biophysical (electrophoretic mobility of collagen from cell culture) investigations should be performed initially, if ever possible.*

4.1.2 Describe the burden of alternative diagnostic methods to the patient

*Initial clinical, imaging, biochemical and ultrastructural investigations complement the molecular genetic analysis which, however, cannot replace the former. Patients with predominantly dermal symptoms experience skin biopsy as particularly stressful, because wound healing may be complicated.*

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

*unknown*

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

no

yes

Therapy (please describe)

*Specific supportive therapy of joints and musculature in patients with EDS type I/II, III, VI. Scrutiny for eventually developing aneurysms, special caution during surgery, scrutiny of pregnancy in EDS type IV. Early surgical-orthopedic measures in EDS type VIIA/B.*

Prognosis (please describe)

*The genetic diagnosis essentially contributes to classification of cases with indistinct clinical, biochemical or ultrastructural features. This is the basis for prognostic statements.*

Management (please describe)

*Frequent interdisciplinary clinical follow-up, depending on EDS type.*

#### 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)

*Frequent interdisciplinary follow-up, depending on EDS type.  
Specific therapeutic support of joints and musculature. Avoidance of sports with physical contacts in EDS types with predominant involvement of joints.  
Scrutiny for eventually developing aneurysms, special caution during surgery, tight follow-up of pregnancy, emergency card in EDS types with vascular involvement.  
Trauma protection in EDS types with involvement of skin and a tendency to hematomas.*

If the test result is negative (please describe)

*Follow-up dispensable, if a familial mutation can be excluded.*

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)?

*Interdisciplinary follow-up considering all possible EDS types if the index patient had not been analysed genetically.  
Regular and specific follow-up if the index patient's EDS type is known.*

#### 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. In many cases, the genetic diagnostics contributes substantially to classification of EDS type if clinical, biochemical and ultrastructural findings are not fully informative. Recognizing clinical symptoms as belonging to the Ehlers-Danlos syndrome and classifying them as a given EDS type is prerequisite for clinical prognosis, specific therapy and official acceptance as severe handicap. In children with a tendency to hematomas, a suspicion of child abuse may be alleviated through the correct diagnosis of EDS type. For adults, the correct diagnosis will end a diagnostic odyssey and the unwarranted suspicion of hypochondria. And the 'correct' patient organisation can now be approached.*

### 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)