

## Indication Criteria for Genetic Testing *Evaluation of validity and clinical utility*

german society of human genetics  
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### Indication criteria for disease: Mucopolysaccharidosis type II

Ad hoc Committee „Indication Criteria  
for Genetic Testing“

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## 2. Disease characteristics

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

*Mucopolysaccharidosis type II (MPS type II, MPS2, Hunter disease)*

### 2.2 OMIM# of the Disease: 309900

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

*iduronate-2-sulfatase*

### 2.4 OMIM# of the Gene(s): 309900

### 2.5 Mutational Spectrum:

*Majority point mutations (~60%), spread over the 9 exons; ca. 30% smaller rearrangements (< 20 nucleotides); ca. 10% major rearrangements (>21 nucleotides), including a frequent and more complex rearrangement due to homologous non-allelic recombination between the IDS gene and the neighbouring IDS pseudo-gene.*

### 2.6 Analytical Methods:

*Bidirectional sequencing*

### 2.7 Analytical Validation

*Bidirectional sequencing; control of results by parallel use of alternative molecular genetic methods (e.g. restriction analysis, ASO-PCR etc.); simultaneous analysis of family members (as positive and negative controls); comparison with data bases and literature; quality control through sharing samples.*

### 2.8 Estimated Frequency of the Disease in Germany

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

*1.3 per 100,000 male newborns*

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

### 2.10 Diagnostic Setting:

	Yes.	No.
A. (Differential) diagnostics	<input type="checkbox"/>	<input checked="" 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: *Female transmitters are clinically inconspicuous and can be identified by genetic analysis only.*

### 3. Test characteristics

		genotype or disease	
		present	absent
test	pos.	A	B
	neg.	C	D

A: true positives      C: false negatives  
 B: false positives    D: true negatives

sensitivity:             $A/(A+C)$

specificity:             $D/(D+B)$

pos. predict. value:     $A/(A+B)$

neg. predict. value:     $D/(C+D)$

#### 3.1 Analytical Sensitivity

(proportion of positive tests if the genotype is present)

*practically 100%*

#### 3.2 Analytical Specificity

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

*almost 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.

*practically 100%*

#### 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.

*almost 100%*

#### 3.5 Positive clinical predictive value

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

*almost 100%*

#### 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:

*almost 100%*

Index case in that family had not been tested:

*practically 100%*

## 4. Clinical Utility

### 4.1 (Differential) diagnosis: The tested person is 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)

*The activity of iduronate-2-sulfatase is normal in female transmitters, therefore genetic analysis is required for diagnosing the carrier status. Before an enzyme replacement therapy is initiated, the diagnosis should be verified in all patients also by detection of the causal mutation.*

4.1.2 Describe the burden of alternative diagnostic methods to the patient

*small (blood drawing)*

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

*MPS2 is diagnosed primarily by enzyme assay. The results of an enzyme assay, as a rule, are available within 7 days. The biochemical diagnosis presently costs ~30 Euro, significantly less than a molecular genetic diagnosis.*

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

No.

Yes.

Therapy (please describe)

Prognosis (please describe)

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, definitely in female carriers.*

If the test result is positive (please describe)

*Conscious family planning if a carrier status has been diagnosed.*

If the test result is negative (please describe)

*Females may abstain from prenatal diagnosis.*

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)?

*Calculation of the statistical risk for being a carrier, prenatal diagnosis by enzyme assay.*

**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, X-linked inheritance.*

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

*Yes. Family members (possible transmitters) can be typed specifically for the causal mutation if it has been found in the index case.*

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)