deutsche gesellschaft für humangenetik e.v.

Indication Criteria for Genetic Testing
Evaluation of validity and clinical utility

german society of human genetics
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Ad hoc-Kommission „Indikationskriterien für genetische Diagnostik“

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Indication criteria for disease:
Mucopolysaccharidosis type VI

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2. Disease characteristics

2.1 Name of the Disease (Synonyms):
Mucopolysaccharidosis type VI
(MPS type VI, MPS6, Maroteaux-Lamy disease)

2.2 OMIM# of the Disease: *253200*

2.3 Name of the Analysed Genes or DNA/Chromosome Segments:
arylsulfatase B (ARSB, 4S)

2.4 OMIM# of the Gene(s): *611542*

2.5 Mutational Spectrum:
Majority point mutations (~80%); ca. 20% smaller rearrangements (<20 nucleotides); both types spread over the 8 Exons.

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; qualitty control through sharing samples.

2.8 Estimated Frequency of the Disease in Germany
(Incidence at birth ("birth prevalence") or population prevalence):
0.23 per 100,000 births

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

2.10 Diagnostic Setting:

	Yes.	No.
A. (Differential) diagnostics	☐	☒
B. Predictive Testing	☒	☐
C. Risk assessment in Relatives	☒	☐
D. Prenatal	☒	☐

Comment:
ad B: The earlier an enzyme replacement therapy (ERT) is started, the better the results of treatment appear to be. For this reason,also pre-symptomatic DNA diagnostics may be considered.

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)
almost 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:
almost 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)

In heterozygous carriers the ARSB activity may be normal; thus genetic analysis is required for diagnosing heterozygosity. Before an enzyme replacement therapy is initiated, the diagnosis should be verified in all patients 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?
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.

If the test result is positive (please describe)
Start of enzyme replacement therapy.

If the test result is negative (please describe)
An enzyme replacement therapy is not required.

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)?
biochemical diagnostics (assay of ARSB activity),
regular clinical monitoring

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 (see comment 2.10).

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)
not applicable