Indication Criteria for Genetic Testing
Evaluation of validity and clinical utility

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; quality 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:

<table>
<thead>
<tr>
<th>Diagnostic Setting</th>
<th>Yes.</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. (Differential) diagnostics</td>
<td></td>
<td>✗</td>
</tr>
<tr>
<td>B. Predictive Testing</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>C. Risk assessment in Relatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D. Prenatal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>genotype or disease present</th>
<th>absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>test</td>
<td></td>
</tr>
<tr>
<td>pos.</td>
<td>A</td>
</tr>
<tr>
<td>neg.</td>
<td>C</td>
</tr>
<tr>
<td>B</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
</tr>
</tbody>
</table>

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

sensitivity: \( \frac{A}{A+C} \)
specificity: \( \frac{D}{D+B} \)

pos. predict. value: \( \frac{A}{A+B} \)

neg. predict. value: \( \frac{D}{C+D} \)

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*