

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

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### Indication criteria for disease: Fabry disease

Ad hoc Committee „Indication Criteria  
for Genetic Testing“

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## 2. Disease characteristics

2.1 Name of the Disease (Synonyms): *Fabry disease*

2.2 OMIM# of the Disease: *301500*

2.3 Name of the Analysed Genes or DNA/Chromosome Segments:  
*alpha-galactosidase A, GLA*

2.4 OMIM# of the Gene(s): *300644*

2.5 Mutational Spectrum:

*Mostly point mutations (~70%) spread over the 7 exons, about 28% smaller rearrangements (<60 nucleotides), and about 2% larger rearrangements (>61 nucleotides)*

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); 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):

*1.5 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	<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:

*A large proportion (~80%) of female carriers manifests disease specific clinical features which are similar in severity to the symptoms of the male patients (this is in contrast to the majority of X-linked metabolic diseases). Nevertheless, in females, a reliable diagnosis can only be made by gene analysis.*

### 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)

*ca. 98% in males and 96% in females*

#### 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.

*ca. 98% in males and 96% in females*

#### 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% in males and 80% in females*

#### 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:

*in practice 100%*

Index case in that family had not been tested:

*depending on age and degree of relationship*

*<2% in males and <3% in females*

## 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 alpha-galactosidase A may be normal in female carriers, therefore a diagnosis of Fabry disease in females can only be made by molecular genetic tests. 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)

*Depending on the mutation, the enzyme replacement therapy may eventually be complemented with other therapeutic options.*

Prognosis (please describe)

*relatively good*

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.*

If the test result is positive (please describe)

*therapeutic options, see 4.1.4;*

*conscious planning of family and life*

If the test result is negative (please describe)

*'relief' from family risk, conscious planning of family and life*

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)?

*see 4.2.1 'if the test result is positive'*

**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. Knowing the causal mutation allows specific analysis of the proband's mutation in relatives whose health problems could not be assigned yet to a medical entity.*

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)

*Gene analysis allows diagnosis in female relatives of probands.*