

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

**Indication criteria for disease:**  
**Marfan-syndrome (Type 1) [FBN1]**

**1. General information on authorship**

**Name and address of institution:**

Name: *Medizinische Hochschule Hannover, Institut für Humangenetik*  
Address: *Carl-Neuberg-Str. 1*  
Postcode: *D-30625*  
City: *Hannover*  
Tel.: *+49-511-532-6538*  
Fax: *+49-511-532-5865*  
e-mail: *Humangenetik@mh-hannover.de*  
Internet: *www.mh-hannover.de/humangenetik.html*

**Head of the institution:**

Name: *Prof. Dr. Jörg Schmidtke*  
Tel.: *+49-511-532-6538*  
Fax: *+49-511-532-5865*  
e-mail: *schmidtke.joerg@mh-hannover.de*

**Author of this text, date:**

Name: *Dr. Mine Arslan-Kirchner*  
Tel.: *+49-511-532-6532*  
Fax: *+49-511-532-8533*  
e-mail: *arslan.mine@mh-hannover.de*  
Date: *06.06.2007*

**Reviewer, validation date:**

Name: *Prof. Dr. Jörg T. Epplen*  
Tel.: *+49-234-322-3822*  
Fax: *+49-234-321-4196*  
e-mail: *joerg.t.epplen@rub.de*  
Date: *15.06.2007*

**Translator, translation date:**

Name: *Prof. Dr. Ulrich Langenbeck*  
E-mail: *Ulrich.Langenbeck@gmx.net*  
Date: *10.03.2008*

**Re-editor, date:**

Name:  
Tel.:  
Fax:  
e-mail:  
Date:

german society of human  
genetics  
www.gfhev.de

**Chairman**

Prof. Dr. med. André Reis, Erlangen

**Vice Chairman**

Prof. Dr. med. Olaf Riess, Tübingen  
Prof. Dr. med. Evelin Schröck,  
Dresden

**Treasurer**

PD Dr. rer. nat. Iris Bartels,  
Göttingen

**Secretary**

Prof. Dr. rer. nat. Christine Zühlke,  
Lübeck

**Scientific Advisory Board**

Prof. Dr. rer. nat. Gudrun Rappold,  
Heidelberg

Prof. Dr. med. Jürgen Kohlhase,  
Freiburg

Prof. Dr. med. Michael Speicher,  
Graz

Prof. Dr. med. Jörg Schmidtke,  
Hannover

(conference president 2008)

Prof. Dr. med. Klaus Zerres,  
Aachen

(conference president 2009)

Prof. Dr. med. Uwe Claussen, Jena  
(conference president 2010)

**Address of chairman**

Institut für Humangenetik  
Universität Erlangen-Nürnberg  
Schwabachanlage 10  
91054 Erlangen  
Tel 0049 (0)9131-852 2318  
Fax 0049 (0)9131-209297  
reis@humgenet.uni-erlangen.de

**GfH-Office**

Dipl.-Soz. Christine Scholz  
Inselkammerstr. 4  
82008 München-Unterhaching  
Telefon+49 (089) 614 56 95 9  
Telefax +49 (089) 55 02 78 56  
organisation@gfhev.de

**Bank Details**

Postbank München  
Konto 231 394 805  
BLZ 700 100 80

**IBAN**

DE19 7001 0080 0231 3948 05

**BIC**

PBNK DEFF

**Vereinsregister München**

VR 12341

## 2. Disease characteristics

2.1 Name of the Disease (Synonyms): *Marfan-Syndrome Type 1*

2.2 OMIM# of the Disease: *154700*

2.3 Name of the Analysed Genes or DNA/Chromosome Segments: *FBN1*

2.4 OMIM# of the Gene(s): *134797*

2.5 Mutational Spectrum:

*Single nucleotide exchanges, PTC, splice mutations, deletions, insertions; over 600 different disease-causing mutations have been described*

2.6 Analytical Methods:

*Direct sequencing*

2.7 Analytical Validation: *Sequencing of both strands.*

2.8 Estimated Frequency of the Disease in Germany

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

*Prevalence about. 1:4.000*

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. Pränatal	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Comment: *A prenatal test for Marfan-Syndrom is very rarely requested.*

### 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)

*practically 100%*

#### 3.2 Analytical Specificity

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

*practically 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.

*highly variable expressivity; in full-blown cases (Ghent criteria fulfilled) 70-90%*

#### 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%, but no data available for this measure*

#### 3.5 Positive clinical predictive value

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

*nearly 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:

*nearly 100%*

Index case in that family had not been tested:

*83% if the detection rate is 80% (see above)*

*This question arises almost only in children, carriers or non-carriers, below the age of clinical manifestation.*

## 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)

4.1.2 Describe the burden of alternative diagnostic methods to the patient

*Cardiological, orthopaedic, and ophthalmologic investigations can establish a diagnosis (but not always), they are necessary for follow-up even if a FBN1-mutation has been identified. MRT to diagnose/exclude dural ectasia is occasionally necessary only to establish the diagnosis.*

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)

*Early and ample replacement of dilated aortic segments, drug therapy*

Prognose (bitte beschreiben)

*Presence of FBN1 mutation is generally associated with worsening the prognosis and requiring earlier intervention*

Management (please describe)

*regular clinical follow-up, integration of all cases in a multidisciplinary clinic*

#### 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)

*More frequent follow-up, antihypertensive drug therapy, avoidance of contact sports, provide medical emergency document*

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)?

*Regular follow-up.*

#### 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, but see commentary to 2.10.*

#### 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)

*Yes. Other differential diagnostic tests are unnecessary. Patients and parents of affected children are usually relieved that the disease has been identified ("received a name"). They can seek contact to other persons affected by this disease through patient organisations, which is usually seen as an enormous help in coping with the condition.*