deutsche gesellschaft für humangenetik e.v.

Indication Criteria for Genetic Testing
Evaluation of validity and clinical utility

Indication criteria for disease:
Marfan syndrome type 2 (MFS2) and Loeys-Dietz syndrome (LDS) [TGFBR1 / TGFBR2]

1. General information on authorship

Name and address of institution:
Name: *Institute of Human Genetics, Medical School Hannover*
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: *06.09.2007*

Reviewer, validation date:
Name: *Prof. Dr. Jörg T. Epplen & Dr. S. Hoffjan*
Tel.: *+49-234-322-3822*
Fax: *+49-234-321-4196*
E-mail: *joerg.t.epplen@rub.de*
Date: *21.09.2007*

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:

Authorized by gfh Ad hoc Committee „Indication Criteria for Genetic Testing“
Date: 20.05.2008

Updated by Jörg Schmidtke
Date: 27.05.2008

german society of human genetics
www.gfhev.de

Ad hoc Committee „Indication Criteria for Genetic Testing“
Ad hoc-Kommission „Indikationskriterien für genetische Diagnostik“

Chairman of the Committee
Prof. Dr. med. Jörg Schmidtke,
Institute of Human Genetics
Hannover Medical School
Carl-Neuberg-Str. 1
30625 Hannover
Tel. 0049 (0)511-532 6538
Fax 0049 (0)511 532 5865
schmidtke.joerg@mh-hannover.de

Members of the Committee
Prof. Dr. med. Gabriele Gillessen-Kaesbach
Prof. Dr. med. Tiemo Grimm
Prof. Dr. med. André Reis
Prof. Dr. med. Eberhard Schwinger
Prof. Dr. med. Peter Wieacker
Prof. Dr. med. Klaus Zerres
Prof. Dr. med. Johannes Zschocke

gfh Council (§26 BGB)
Prof. Dr. med. André Reis, Erlangen
Prof. Dr. med. Olaf Riess, Tübingen
Prof. Dr. med. Evelin Schröck, Dresden

gfh Office
Dipl.-Soz. Christine Scholz
Inselkammerstr. 5
82008 München-Unterhaching
Tel. 0049 (0)89-61 45 69 59
Fax 0049 (0)89-55 02 78 56
organisation@gfhev.de

Banking account
Postbank München
Konto 231 394 805
BLZ 700 100 80
IBAN DE19 7001 0080 0231 3948 05
BIC PBNK DEFF

register of associations Munich
VR 12341

2. Disease characteristics

2.1 Name of the Disease (Synonyms):
Marfan syndrome type 2, MFS2, and Loeys-Dietz syndrome, LDS

2.2 OMIM# of the Disease: *154705 and 609192*

2.3 Name of the Analysed Genes or DNA/Chromosome Segments:
TGFBR2- and TGFBR1-Mutations may cause MFS2 as well as LDS.

2.4 OMIM# of the Gene(s): *190182 and 190181*

2.5 Mutational Spectrum:
Single nucleotide exchanges, PTC, splice mutations. Presently, more than 25 different TGFBR2 and more than 15 different TGFBR1 mutations have been described in MFS2 and LDS.

2.6 Analytical Methods:
Direct sequencing

2.7 Analytical Validation
Sequencing of both strands routinely

2.8 Estimated Frequency of the Disease in Germany
(Incidence at birth ("birth prevalence") or population prevalence):
Prevalence about 1:100,000

2.9 If applicable, prevalence in the ethnic group of investigated person:
about 1:100,000;
about 1:60-80 in patiens with suspected MFS (at least 1 main criterion and involvement of a 2nd organ system); about 1:6 in patient with suspected MFS and exclusion of a fibrillin-1 mutation.

2.10 Diagnostic Setting:

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

Comment:

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)
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.
unknown

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:
66% at a suspected detection rate of 50%.

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

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

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

No. ☐

Yes. ☒

Therapy (please describe)	*Regular and frequent cardiological follow-up and early surgery, and already at a time when diameter of aortic root is still less than in classic MFS.*
Prognosis (please describe)	*In some patients worse than in classic MFS. Some carriers of a TGFBR2 or TGFBR1 mutation suffer an aortic dissection at young age and with a lesser degree of aortic dilatation than in classic MFS.*
Management (please describe)	*Link with an interdisciplinary Marfan center and closely-meshed, particularly cardiological, follow-ups.*

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; drug therapy if needed (e.g. prophylactic use of beta blockers); avoidance of contact sports and sports that produce blood pressure highs; provide medical emergency document

If the test result is negative (please describe)
Follow-up is dispensable and restriction of sports is unnecessary if a familial mutation can be excluded. A negative result does not exclude the disease if the mutation is unknown in the index patients.

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 clinical follow-up including examination with imaging techniques.

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.

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 diagnostics 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.