deutsche gesellschaft für humangenetik e.v.

Indication Criteria for Genetic Testing
Evaluation of validity and clinical utility

Indication criteria for disease:
Myotonic dystrophy type 1 (DM1) [DMPK]

1. General information on authorship

Name and address of institution:
Name: *Institute of Human Genetics, University Hospital Münster*
Address: *Vesaliusweg 12-14*
Postcode: *D-48149*
City: *Münster*
Tel.: *+49-251-83-55401*
Fax: *+49-251-83-55431*
E-mail: *humangenetik@uni-muenster.de*
Internet: *http://humangenetik.klinikum.uni-muenster.de*

Head of the institution:
Name: *Prof. Dr. med. Peter Wieacker*
Tel.: *+49-251-83-55401*
Fax: *+49-251-83-55431*
E-mail: *wieacker@uni-muenster.de*

Author of this text, date:
Name: *Prof. Dr. med. Peter Wieacker*
Tel.: *+49-251-83-55401*
Fax: *+49-251-83-55431*
E-mail: *wieacker@uni-muenster.de*
Date: *01.06.2007*

Reviewer, validation date:
Name: *Prof. Dr. med. Manuela Koch*
Tel.: *+49-6421-28-66269*
Fax: *+49-6421-28-68920*
E-mail: *koch2@staff.uni-marburg.de*
Date: *23.06.2007*

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

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

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

Updated by
Date:

2. Disease characteristics

2.1 Name of the Disease (Synonyms):
Myotonic dystrophy type 1, Curschmann-Steinert disease, DM1

2.2 OMIM# of the Disease: *160900*

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

2.4 OMIM# of the Gene(s): *605377*

2.5 Mutational Spectrum:
CTG-repeat expansion in the 3' untranslated region; currently accepted threshold: diseased with 50 and more CTG repeats

2.6 Analytical Methods:
Southern blot analysis, PCR

2.7 Analytical Validation
Up to now, CTG-repeat expansions in the 3' region of the DMPK gene are the only known cause of DM1. These expansions are very reliably detected by Southern blot analysis. Only very rarely, an expansion may remain undetected if it is highly heterogeneous. By conventional PCR, only the normal allele is amplified. PCR may therefore be used as 'screening' before Southern blot analysis.

2.8 Estimated Frequency of the Disease in Germany
(Incidence at birth ("birth prevalence") or population prevalence):
Prevalence about. 1:8,000

2.9 If applicable, prevalence in the ethnic group of investigated person:
none

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)
Nearly 100%.
In rare cases a highly heterogeneous expansion may remain undetected

3.2 **Analytical Specificity**
(proportion of negative tests if the genotype is not present)
nearly 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.
Nearly 100%, if clinically similar diseases like DM2/PROMM and other entities are not considered. DM2 is about half as prevalent as DM1 and difficult to differentiate clinically from DM1.

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.
nearly 100%

3.5 **Positive clinical predictive value**
(life time risk to develop the disease if the test is positive).
nearly 100%, but variable expressivity

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:
nearly 100%

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)	*see below*
Prognosis (please describe)	*The genetic diagnosis of DM1 allows differentiation from diseases with similar clinical manifestatations, like DM2. Features of DM1 and DM2 are similar, but some are divergent. A gene test therefore enables more detailed prognostic statements.*
Management (please describe)	*DM1 is a multisystem disorder. Management entails early recognition and if possible therapy of cardiac arrhythmias, diabetes mellitus, and hypogonadism (in male as well as in female patients).* *Special precaution is recommended during general anaesthesia. With inheritance through the mother, there is the risk of congenital myotonic dystrophy, which is characterized by severe generalized muscular hypotony already during intra-uterine life. It includes disordered swallowing thus causing polyhydramnion. Often, an artificial ventilation cannot be suspended because of continuing muscular hypotony. Overall prognosis therefore is poor. Women with DM1 have an increased rate of abortions.*

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?

If the test result is positive (please describe)
see above

If the test result is negative (please describe)
see above

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)?
The preventive measures mentioned in 4.1.4, particularly during surgery, are useful only with with proven mutation.

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?
Yes.

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)
Not applicable.