

Indication criteria for genetic testing
Evaluation of validity and clinical utility

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

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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	<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: -

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)

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.