deutsche gesellschaft für humangenetik e.v.

Indication Criteria for Genetic Testing
Evaluation of validity and clinical utility

Indication criteria for disease:
Myotonic dystrophy type 2 (DM2) [ZNF9]

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2. Disease characteristics

2.1 Name of the Disease (Synonyms): *Myotonic dystrophy type 2, DM2, Proximal myotonic myopathy, PROMM, Ricker disease*

2.2 OMIM# of the Disease: *602668*

2.3 Name of the Analysed Genes or DNA/Chromosome Segments: *ZNF9*

2.4 OMIM# of the Gene(s): *116955*

2.5 Mutational Spectrum:
Expansion of a CCTG repeat in intron 1 of the ZNF9 gene. Currently accepted thresholds: Disease at 75 or more CCTG repeats; PROMM excluded with up to 28 repeats; the clinical significance of the 'gray area' in between is still undecided.

2.6 Analytical Methods:
In the lower range of ZNF9 repeat sizes, the best analytical method is PCR followed by sizing of the amplified products directly by capillary electrophoresis. Larger expansions within pathogenic ZNF9 alleles can be detected either by QP-PCR or Southern blotting of genomic DNA or long-range PCR products and oligo-hybridisation. Exact sizing of these in some cases extremely expanded alleles is difficult, and is not routinely performed. As in DM1 analysis, Southern blotting of genomic DNA would be the method of choice when sizing is required. Due to the extreme smearing of the expanded allele in Southern analysis, these alleles could be easily missed, if no precautions are taken, e.g. quantitative determination of the amount of normal-length non-expanded DNA. QP-PCR analysis is a robust alternative, and is considered the first-choice technique for detection of expanded ZNF9 alleles when sizing is not required..

2.7 Analytical Validation
Only the demonstration of an expanded CCTG repeat in intron 1 of the ZNF9 gene is considered diagnostic of DM2. Because there is no alternative test, the method was validated by showing co-segregation of the expanded repeat with the disease in the families originally desribed by K. Ricker. No discrepancy was found between molecular results and clinical phenotype.

2.8 Estimated Frequency of the Disease in Germany
(Incidence at birth ("birth prevalence") or population prevalence):
Prevalence at birth estimated as about 1:20,000. This is about half the German prevalence of DM1.

2.9 If applicable, prevalence in the ethnic group of investigated person:
not applicable

2.10 Diagnostic Setting:

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

Comment: *There is no congenital form of DM2 and symptoms, as a rule, start only beyond 30 years of life with a very variable and often mild course. Therefore prenatal diagnosis is an exceptional and very individual decision.*

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 small expansions in the 'gray zone' may be overlooked.

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.
No quantitative figures can be given. In some cases the clinical phenotype of DM2 can not be differentiated from DM1. (Occasionally there is also a phenotypic overlap with ion channel myotonies.)
Clinical sensitivity is high if, at a given phenotype, tests for both DM1 and DM2 are performed.

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 very mild courses are known.

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:
100%

Index case in that family had not been tested:
see 3.3

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)	*Differentiation from DM1 is important because symptoms usually are milder and because the family has no risk of a congenital form.*
Management (please describe)	*DM2 is a multisystem disorder. Management includes early diagnosis, therapy of internal medical problems like cardiac rhythm disorders, diabetes mellitus and disorders of fat metabolism. In contrast to DM1, risks of general anaethesia have not been reported yet. The risk of cataract necessitates ophthalmologic follow-up.* *Affected women may suffer a progress of the disease during pregnancy. Congenital cases of DM2 have not been observed so far.*

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)
See the preventive measures described above.

If the test result is negative (please describe)
No preventive measures needed.

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)?
Preventive measures and follow-ups are required only when the genetic test uncovered the 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?
With a positive test result, yes.

4.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
No, because very mild courses are possible, e.g. with cataract only, which still may have another cause.

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?
Not applicable, see 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)
not applicable