deutsche gesellschaft für humangenetik e.v.

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Indication Criteria for Genetic Testing
Evaluation of validity and clinical utility

Indication criteria for disease:
Spinal muscular atrophy type I-IV [SMN1]

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2. Disease characteristics

2.1 Name of the Disease (Synonyms):
Spinal muscular atrophy type I-IV

spinal muscular atrophy type Werdnig-Hoffmann (SMA I)
intermediate spinal muscular atrophy (SMA II)
spinal muscular atrophy type Kugelberg-Welander (SMA III)
adult proximal spinal muscular atrophy (SMA IV)

2.2 OMIM# of the Disease: *253300, 253550, 253400, 271150*

2.3 Name of the Analysed Genes or DNA/Chromosome Segments: *SMN1*

2.4 OMIM# of the Gene(s): *600354*

2.5 Mutational Spectrum:
>95% homozygous deletions of SMN1
3-4% compound heterozygosity with heterozygous SMN1 deletion and a different SMN1 mutation (mostly point mutation)
<1% homozygous SMN1 point mutation.

2.6 Analytical Methods:
1. Detection of homozygous/heterozygous deletion of the SMN1 gene:
  - PCR and restriction (only homozygosity)
  - MLPA (homo- and heterozygosity)
  - Real time PCR is now replaced by MLPA (only heterozygosity).
2. In special situations (most often search for the second mutation in cases of heterozygous SMN1 deletion), i.e. not as a routine, analysis for SMN1 point mutations by:
  - cDNA sequencing
  - long range PCR and sequencing.

2.7 Analytical Validation
PCR/restriction and MLPA, respectively, were validated by parallel analysis of approx. 50 samples with homozygous SMN1 deletion. The use of MLPA for determination of SMN1 copy number was validated by analysis of approx. 50 DNA samples that had been analysed before by real-time PCR. On analysis of mutation-free probands, all methods yielded identical results within the primer/probe range.

2.8 Estimated Frequency of the Disease in Germany
(Incidence at birth ("birth prevalence") or population prevalence):
Birth prevalence: SMA type I approx. 1:20.000.
Birth prevalence: SMA type II and III (chronic SMA) approx. 1:20.000.
SMA type IV is very rare and heterogenous, reliable epidemiological data are not available.
The total birth prevalence of 5q SMA in middle Europe is slightly higher than 1:10.000.

2.9 If applicable, prevalence in the ethnic group of investigated person:
Birth prevalence is significantly increased in populations with a high rate of consanguineous marriages.

2.10 Diagnostic Setting:

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

Comment: *Predictive diagnostics are not offered in most of the families with SMA type I-III families because the disease is already manifest before adulthood and because predictive testing in childhood has no therapeutic consequences. In exceptional cases with late manifestation predictive diagnosis may be considered in younger siblings.*

3. Test characteristics

	genotype or disease	
	present	absent
test pos.	A	B
test 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)
Depending on the method used almost 100% for homozygous SMN1 deletion, and >95% for heterozygous SMN1 deletion. No data available for homozygous point mutations.

3.2 **Analytical Specificity**
(proportion of negative tests if the genotype is not present)
Depending on the method used almost 100% for homo- and heterozygous deletion, no data available for homozygous point mutations.

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.
>95% for SMA I+II
80-90% for SMA III
<10% for SMA IV

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.
>99.9%

3.5 **Positive clinical predictive value**
(life time risk to develop the disease if the test is positive).
Estimated >99% with homozygous SMN1 deletion, homozygosity of point mutations or compound heterozygosity (systematic studies are missing).

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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:
>95% with homozygous SMN1 deletion detected in the index case, depending on the degree of relationship between index patient and person at risk.

Index case in that family had not been tested:
>95% for clinically unambiguous SMA I+II. Depending on the certainty of clinical diagnosis, on the the type of SMA and on the degree of relationship between index case and risk person, different probabilities must be assumed.

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)	*Knowledge of the genetic diagnosis helps avoiding unnecessary therapies or therapies with possible side effects. This knowledge would be absolutely required if a causal therapy were available one day.*
Prognosis (please describe)	*The individual course in patients with genetically verified SMA can be better related to the published experience and differentiated from other neuromuscular diseases.*
Management (please describe)	*The management of patients with genetically verified SMA is symptomatic and follows international guidelines based on safety and experience.*

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)

If the test result is negative (please describe)

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)?

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, it confirms the genetic transmission and is prerequisite for genetically counseling family members.

4.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
No more tests are required in the patient to secure his diagnosis of an SMA. However, except for the parents, the risk of relatives is uncertain without individual genetic tests.

4.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
Yes (in most cases, however, a predictive test is only performed for diagnosing or excluding heterozygosity).

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)
Genetic diagnosis makes needless invasive neuromuscular diagnostics (e.g. electrophysiology or muscle biopsy which, besides, would not yield a correct diagnosis in each case of SMA) and settles the mode of inheritance in a clinically and genetically heterogeneous group of disorders. Heterozygote tests in relatives, prognostic statements in patients and prenatal diagnosis in pregnancies at risk become possible as a consequence.