

Indication criteria for genetic testing
Evaluation of validity and clinical utility

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Indication criteria for disease:

HMSN / HNPP

**HMSN type 1, 2, and 3 (CMT1 and 2, DSN); HNPP
[PMP22; MPZ; GJB1 (CX32); MFN2]**

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Date: 20.05.2008

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Updated by

Date:

2. Disease characteristics

2.1 Name of the Disease (Synonyms):

*Hereditary motor and sensory neuropathy type 1 and 2 (HMSN1, HMSN2),
Charcot-Marie-Tooth neuropathy type 1 and 2 (CMT1, CMT2);
Hereditary motor and sensory neuropathy type 3 (HMSN3),
Dejerine-Sottas neuropathy (DSN);
Hereditary neuropathy with liability to pressure palsies (HNPP)*

2.2 OMIM# of the Disease:

118220; 118210; 118200; 609260; 162500; 145900; 302800; 607677; 607736

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

PMP22; MPZ; GJB1 (CX32); MFN2

2.4 OMIM# of the Gene(s):

601097; 159440; 304040; 608507

2.5 Mutational Spectrum:

*70% duplications/deletions in chromosome region 17p11.2 (PMP22);
Rest of cases: private mutations in any of the 4 genes.*

2.6 Analytical Methods:

*MLPA, microsatellite analysis, qPCR, Southern blot,
FISH for PMP22 duplication/deletion screening, direct sequencing of the 4 genes.*

2.7 Analytical Validation

Participation on proficiency tests. For detection of duplication/deletion two different methods are used the results of which verify each other. The results of the molecular genetic diagnostics are unambiguously evaluated, as a rule.

2.8 Estimated Frequency of the Disease in Germany

(Incidence at birth ("birth prevalence") or population prevalence):

Prevalence in the general population 10-40 : 100,000

2.9 If applicable, prevalence in the ethnic group of investigated person:

not applicable

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: *A prenatal test is rarely requested.*

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)

almost 100%

3.2 Analytical Specificity

(proportion of negative tests if the genotype is not present)

almost 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.

Duplication/deletion PMP22: about 70%

Point mutation GJB1: up to 10% (depending in clinical manifestation and family history)

Point mutation MPZ: about 5%

Point mutation PMP22: about 1%

Point mutation MFN2: about 20%.

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.

almost 100%

3.5 Positive clinical predictive value

(life time risk to develop the disease if the test is positive).

The penetrance in verified mutation carriers is almost 100%, according to the literature; because of the wide clinical variability, clinically mildly affected persons may not be diagnosed or they died from other causes in the preclinical stage.

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:

almost 100%

Index case in that family had not been tested:

about 86% (detection rate of mutations). As a rule, however, such an approach is not useful.

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	<input checked="" type="checkbox"/>
imaging	<input type="checkbox"/>
endoscopy	<input type="checkbox"/>
biochemistry	<input type="checkbox"/>
electrophysiology	<input checked="" type="checkbox"/>
other (please describe)	

4.1.2 Describe the burden of alternative diagnostic methods to the patient

NCV/ EMG: acceptable

Nerve biopsy: may be a strain

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

Recommended diagnostic procedure:

1. *Clinical and electrophysiological diagnostics for delineating the type of CMT (demyelinating, axonal or intermediate)*
2. *Search for mutations, if necessary, to verify diagnosis or subtype of disease.*
3. *First step of molecular genetics: Duplication/deletion screening in chromosome region 17p11.2 PMP22 gene) in demyelinating types 1, 3, and HNPP. Mutation analysis in MFN2 in axonal CMT2.*
4. *Economic viability of search for mutations in the other genes can only be assessed individually, in the context of general clinical situation, diagnostic problem, mode of inheritance, and psychological suffering of patients/relatives.*

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

no

yes

Therapy (please describe)	<i>Unnecessary therapy with undefined diagnosis, mostly no influence.</i>
Prognosis (please describe)	<i>No.</i>
Management (please describe)	<i>Prophylactic physical / orthopedic therapy if required, choice of occupation.</i>

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 4.3.1, prophylactic physical therapeutic / orthopedic interventions if required.

If the test result is negative (please describe)

Positive influence on choice of occupation and family planning; psychological relief.

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)?

Choice of occupation depending on risk of disease; avoidance of neurotoxic compounds; avoiding obesity.

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, because specific diagnostics is possible in relatives, else an unspecific differential diagnostic scheme would be applied in symptomatic patients.

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, but is rarely requested.

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)

Verification of the diagnosis is for many patients a value in itself, irrespective of medical benefits: It gives the disease a name and often explains their cause.

Demonstration of a genetic cause eliminates the feeling of guilt and "own faults" (exogenous poisons, "incorrect conduct") which may be relieving.

Knowledge of the individual mutation may enable in the future the access to therapies which are presently in developmental stage. Effects of neurotoxic compounds, e.g. chemotherapeutic agents for treatment of cancer, can be ameliorated or avoided.