deutsche gesellschaft für humangenetik e.v.

Indication Criteria for Genetic Testing
Evaluation of validity and clinical utility

Indication criteria for disease:
HMSN/HNPP HMSN types 1,2,3,6 (CMT1,2,4, DSN, CHN, GAN, CCFDN, HNA); HNPP.
HSAN and HMN not included.
Current state of knowledge, annual revision recommended.

1. General information on authorship

Name and address of institution:
Name: *Institute of Human Genetics, University of Bonn*
Address: *Wilhelmstr. 31*
Postcode: *D-53111*
City: *Bonn*
Tel.: *+49-228-287-22346*
Fax: *+49-228-287-22380*
E-mail: *info@humangenetics.uni-bonn.de*
Internet: *http://bonn.humgen.de*

Head of the institution:
Name: *Prof. Dr. med. Markus M. Nöthen*
Telefon: *0228/287-22346*
Fax: *0228/287-22380*
Email: *markus.noethen@uni-bonn.de*

Author of this text, date:
Name: *Dr. med. Stefan Aretz*
Tel.: *+49-228-287-22391*
Fax: *+49-228-287-22380*
E-mail: *Stefan.Aretz@uni-bonn.de*
Date: *31.05.2007*

Reviewer, validation date:
Name: *Prof. Dr. Bernd Rautenstrauß*
Tel.: *+49-89-30-90-886-0*
Fax: *+49-89-30-90-886-66*
E-mail: *rautenstrauss@mgz-muenchen.de*
Date: *23.07.2008*

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 B. Rautenstrauß
Date: 23.07.2008

2. Disease characteristics

2.1 Name of the Disease (Synonyms):
Hereditary Motor and Sensory Neuropathy types 1, 2, 3, 6, X (HMSN1, HMSN2, HMSN 3, HMSN 6, HMSN X1),
Charcot-Marie-Tooth neuropathy type 1, 2, 4, X1 (CMT1, CMT2, CMT4, CMTX1);
Dejerine-Sottas Neuropathy (DSN);
Congenital Hypomyelinating Neuropathy (CHN)
Giant Axon Neuropathy 1 (GAN1)
Congenital Cataracts, Facial Dysmorphism & Neuropathy Syndrome (CCFDN)
Hereditary Neuralgic Amyotrophy (HNA)
Hereditary Neuropathy with Liability to Pressure Palsies (HNPP).

Current stage of knowledge.

2.2 OMIM# of the Disease:
118220; 118210; 118200; 609260; 162500; 145900; 302800; 607677; 605253, 256850, 162100, 607736

2.3 Name of the Analysed Genes or DNA/Chromosome Segments:
PMP22; MPZ; GJB1 (CX32);MFN2; EGR2; SIMPLE; NEFL; DNM2; RAB7; SH3TC2; GDAP1; GARS; PRX; LMNA; BSCL2; CTDP1; FIG4; MTMR2; SBF2/MTMR13; FGD4, SEPT9.
Current state of knowledge, annual revision recommended.

2.4 OMIM# of the Gene(s):
601097; 159440; 304040; 608507, 129010, 603795, 162280, 602378, 602298, 608206, 606598, 600287, 605725, 150330, 606158, 604927,609390, 603557, 607697, 605379, 611104, 604061. Current state of knowledge, annual revision recommended.

2.5 Mutational Spectrum:
30-50% CMT1A duplication / HNPP deletion in chromosome region 17p11.2 (PMP22);
Remaining patients: private and recurrent mutations in any of the above mentioned and newly identified genes.

2.6 Analytical Methods:
MLPA, microsatellite analysis, qPCR, Southern blot,
FISH for PMP22 duplication/deletion screening, PFGE, dHPLC; high resolution melting, restriction analysis, direct sequencing (Current state of knowledge).

2.7 Analytical Validation
Participation on proficiency tests. For detection of duplication/deletion two different methods are recommended, the results of which verify each other.This is e.g. fulfilled by application of MLPA which uses redundant and multiple probes for the CMT1A/HNPP region, but also for other gene dosage changes (e.g. GJB1/Cx32). 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, in Finnland 1:2500

2.9 If applicable, prevalence in the ethnic group of investigated person:
Not applicable in general. For ethnic subgroups like Roma and e.g. CCFDN (CTDP1 gene) data not yet available.

2.10 Diagnostic Setting:

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

Comment: *A prenatal test is rarely requested.*

3. Test characteristics

		genotype or disease: present	genotype or disease: 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)
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 50%
Mutation in PMP22: about 1%
Mutation/deletion GJB1: up to 10% (depending in clinical manifestation and family history)
Mutation MFN2: about 20%, deletion/duplication not yet described
Mutation MPZ: about 5%, deletion/duplication not yet described
Mutation SH3TC2: about 20% of autosomal recessive HMSN
Mutation other genes: < 1-5% each

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 recommended.

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
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, to verify diagnosis or subtype of disease, differential diagnosis for Friedreich Ataxia, Roussy-Levy syndrome, carpal tunnel syndrome.*
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, ethnic origin, additional symptoms (deafness, pupillary anomalies, scoliosis, visual impairment, cataract, kirly hair etc.) 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)	*Avoidance of unnecessary therapy with undefined diagnosis, e. g. amputation of limbs. Future therapeutical approaches will be mutation-specific, hence a knowledge of the disease causing variant is crucial for inclusion of a patient in these upcoming procedures .*
Prognosis (please describe)	*Not in general, but for selected subtypes possible.*
Management (please describe)	*Prophylactic physical / orthopedic therapy if required, recommendations for avoidance of specific neurotoxic substances, choice of occupation.*

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 and additional recommendations depending on the subtype.

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.