

Indication Criteria for Genetic Testing *Evaluation of validity and clinical utility*

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Indication criteria for disease: **HNPCC [MLH1, MSH2, MSH6, PMS2]**

Ad hoc Committee „Indication Criteria for Genetic Testing“

Ad hoc-Kommission „Indikationskriterien für genetische Diagnostik“

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2. Disease characteristics

2.1 Name of the Disease (Synonyms): *HNPCC / Lynch syndrome*

2.2 OMIM# of the Disease: *120435*

2.3 Name of the Analysed Genes or DNA/Chromosome Segments:
MLH1, MSH2, MSH6, PMS2

2.4 OMIM# of the Gene(s):
MLH1 (120436), MSH2 (609309), MSH6 (600678), PMS2 (600259)

2.5 Mutational Spectrum:
Point mutations, large deletions and duplications

2.6 Analytical Methods:
Stepwise analyses:

- 1. Clinical Amsterdam-II-Criteria, Bethesda or revised Bethesda Criteria have to be fulfilled.*
- 2. Immuno-histochemical study of tumor samples for expression of the mismatch repair proteins MLH1, MSH2, MSH6 and PMS2.*
- 3. Microsatellite analysis of tumorous and normal tissue.*

In case the Amsterdam-II-Criteria are fulfilled and/or tumor tissue shows HNPCC characteristics:

- 4. MLPA on genomic DNA of the index patient.*
- 5. DHPLC and sequencing of the conspicuous exons or direct sequencing of all coding exons.*

2.7 Analytical Validation
HNPCC proficiency test; confirmation of mutations in positive control samples (if possible in families); repeat analysis and confirmation by another diagnostic technique if necessary (in case of deletions of single exons).

2.8 Estimated Frequency of the Disease in Germany
(Incidence at birth ("birth prevalence") or population prevalence):
Prevalence in population about 1:500

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 type="checkbox"/>	<input checked="" type="checkbox"/>

Comment:

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%

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.

44-74%, depending on criteria of inclusion.

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).

about 80%

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:

This is an unusual approach. The interpretation of the test depends on many factors, e.g. on personal history (age, sex, previous preventive checkups) and family history (Amsterdam criteria fulfilled?), a risk estimate can therefore not be given.



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)

Prognosis (please describe)

Management (please describe)

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)

Recommendation of the yearly colorectal cancer screening described below (see 4.2.2).

If the test result is negative (please describe)

Intensified screening (see 4.3.2) is not required; screening as recommended for the general population (according to the DGVS guideline)

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)?

Recommendation of yearly colorectal cancer screening from age 25 on (or beginning 5 years before the earliest age of manifestation in the family): complete endoscopic examination of colon, physical examination; trans-vaginal sonography in women; yearly endoscopic examination of stomach starting at age 35.

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, *autosomal-dominant inheritance.*

4.3.2 Can a genetic test in the index patient save genetic or other tests in family members?

Yes, *recommendation for screening only applies to mutation carriers and persons at risk.*

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?

In principal yes, but is neither requested nor offered.

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 a value in itself for many patients, irrespective of medical benefits: It is because the disease and its origin can often be named and explained then. A definite diagnosis helps the relatives to estimate the personal risk of disease; it helps to reduce feelings of guilt, and it influences the planning of family and future life. A definite diagnosis of HNPCC leaves no doubt about the necessity of cancer screening.