

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

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### Indication criteria for disease: **MUTYH-associated polyposis (MAP) [MUTYH]**

Ad hoc Committee „Indication Criteria for Genetic Testing“

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## 2. Disease characteristics

2.1 Name of the Disease (Synonyms): *MUTYH-associated polyposis (MAP), autosomal recessive colorectal adenomatous polyposis, multiple colorectal adenomas, multiple adenomatous polyps (MAP)*

2.2 OMIM# of the Disease: *608456*

2.3 Name of the Analysed Genes or DNA/Chromosome Segments: *MUTYH (MYH, outdated name of the gene)*

2.4 OMIM# of the Gene(s): *604933*

2.5 Mutational Spectrum:

*Broad, all types of point mutations (mainly missense and truncating mutations).*

*Because of the two hotspot mutations Y165C in exon 7 and G382D in exon 13, missense mutations generally dominate.*

*Gross genomic deletions have not been described yet.*

*Mutations were described in almost all exons (except exons 1 and 2).*

*In parts ethnicity-specific mutational spectrum.*

2.6 Analytical Methods:

*Direct sequencing of all 16 exons (standard approach in routine diagnostics).*

*Screening the complete gene: DHPLC, SSCP, HD, CSGE.*

*Screening for both hotspot mutations: Restriction digest, ARMS, pyrosequencing.*

*Some procedures start with a screening for both hotspot mutations. If only one of them is detected, the whole gene is searched for a second mutation. By this method a considerable proportion of biallelic mutation carriers is missed.*

2.7 Analytical Validation

*The results of molecular genetic diagnostics can, as a rule, be definitely evaluated.*

2.8 Estimated Frequency of the Disease in Germany

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

*There are no data yet on prevalence.*

*From the proportions of FAP and MAP in our own large group of polyposis patients and assuming an FAP incidence of 1:10.000, the MAP incidence is estimated as about 1:50.000-70.000.*

*From the frequency of MUTYH heterozygotes (~2%) the MAP prevalence (clinical plus subclinical biallelic carriers) can be derived as about 1:10.000.*

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

*There are no reports on prevalence differences among different ethnic groups although some ethnicity-specific mutation pattern suggest such differences.*

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: A prenatal diagnosis is almost never requested and, given a relatively late-manifest and treatable disease, should be performed only exceptionally, in reasonable cases with clear indication and after extensive human genetic counselling*

### 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)

*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.

*About 15-20% (depending on severity of disease and family history: Up to 60% with clear recessive inheritance).*

#### 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% (except causally uncertain variants).*

#### 3.5 Positive clinical predictive value

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

*Penetrance in proven bi-allelic mutation carriers, according to present knowledge, is almost 100%. Due to clinical variability, mildly affected persons may not be diagnosed or will be deceased for other reasons during presymptomatic (subclinical) stage of the disease.*

#### 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% for sibs of index patient; slightly less for obligate heterozygous children because the mutational status of the other parent probably cannot be assessed with 100% certainty. Detection of an uncertain variant in the child of an affected person will not allow in some cases a secure decision whether the test is 'negative' or not.*

Index case in that family had not been tested:

*Probably about 5-10% if index case has not been tested for APC mutation either (locus heterogeneity), but also depending on family history (dominant vs. recessive pedigree pattern).*

*This is not a meaningful approach and should therefore be avoided. Particularly in attenuated courses of adenomatous polyposis more and still unknown genes may be involved.*

## 4. Clinical Utility

### 4.1 (Differential) diagnosis: The tested person is 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) *In some cases by family history. Not rarely*

*however, differentiating MAP from APC-associated familial adenomatous polyposis (FAP) can be achieved by molecular genetic analysis only.*

4.1.2 Describe the burden of alternative diagnostic methods to the patient

*Family history: No strain.*

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

*Family history: Very cost-effective.*

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)

*Yes:*

*Hightened motivation of siblings to participate in specific preventive checkups, eventually colectomy when adenomas etc. are detected.*

*In some cases family planning, choice of profession.*

*To subject children of affected persons to early diagnosis programs appears useful only if, by predictive testing, they were shown to be biallelic carriers.*

If the test result is negative (please describe)

*Yes.*

*Release from preventive program, 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)?

*Same for siblings of index patients as for proven biallelic carriers: Close-meshed early diagnosis programs (particularly complete colonoscopies). Children of affected persons, because of their low disease risk (~1%), should undergo an intensive early diagnosis program only if they are proven biallelic carriers. Whether with the comparatively low a priori disease risk of children predictive diagnostics should be offered at all remains, for the present, a matter of discretion.*

#### **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:

*By securing the primary cause of the disease, extended diagnostic investigations in other symptomatic relatives can be avoided. The low recurrence risk in children and exclusion of carriership by predictive diagnostics in siblings of affected persons allow to avoid superfluous preventive checkups and offer psychological relief.*

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 see the comment in 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)

*For many patients prove of diagnosis is a value in itself - irrespective of a medical benefit - because the disease and its cause can often clearly be named.*

*When a genetic cause is verified, an assumption of 'own fault' as cause of disease (exogenous poisons, 'wrong conduct') often can be lapsed with relief. The main benefits of genetic diagnostics in MAP are the differentiation from FAP, a precise recurrence risk for close relatives, and relief of non-carriers during predictive diagnostics.*