

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

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Indication criteria for disease: Familial adenomatous polyposis (FAP) and Attenuated FAP (AFAP) [APC]

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for Genetic Testing“

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für genetische Diagnostik“

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2. Disease characteristics

2.1 Name of the Disease (Synonyms): *Familial adenomatous polyposis (FAP), adenomatous polyposis of the colon (APC), familial polyposis of the colon (FPC), attenuated adenomatous polyposis coli (AAPCI)*

2.2 OMIM# of the Disease: 175100

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

2.4 OMIM# of the Gene(s): 611731

2.5 Mutational Spectrum:

*About 10-15% gross deletions (typical, classical FAP).
Very rarely large duplications.
85-90% point mutations, more than 90% of them truncating mutations (stop and frameshift, more rarely splice mutations).
A few hotspot mutations (codons 1061, 1068, 1309), else private mutations.
The vast majority of mutations is located in the APC gene's 5' half.
Rather high number of mosaics (10 - 15%) among new APC mutations.*

2.6 Analytical Methods:

*MLPA (large genomic deletions and duplications).
Screening: Protein truncation test (PTT): Complete gene on the RNA level, on genomic level exon 15 only.
Screening: DHPLC (all exons or exons 1 - 14 and first 500 bp of exon 15).
Sequencing of exons / sections that were conspicuous on screening.
Direct sequencing the whole gene.
Rarely: Indirect diagnostics (linkage by haplotype analysis)*

2.7 Analytical Validation

*The results of molecular genetic diagnostics can be, as a rule, evaluated unambiguously.
Single exon deletions / duplications identified by MLPA must be verified either by sequencing that exon or by a second independent method (e.g. long range PCR, transcript analysis).
Mosaics may pose diagnostic problems.*

2.8 Estimated Frequency of the Disease in Germany

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

*Prevalence at birth: 0%
Prevalence in general population: 2.3 - 3.2 per 100.000.
Incidence: About 1:10.000.*

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

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 diagnosis is almost never requested. FAP being a relatively late-manifest, treatable disease, prenatal diagnosis 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% with constitutional germ-line mutations.

Can be distinctly less in mosaic cases, depending on degree of mosaic and analysed tissue. In these cases, screening methods (PTT, DHPLC) often appear to be more sensitive than direct sequencing.

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.

Classic FAP: About 80%

AFAP: About 20 - 30%

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).

Penetrance in proven mutation carriers is almost 100%: Due to the high clinical variability, clinically mildly affected persons may not be diagnosed or will be deceased for other reasons during presymptomatic (sub-clinical) 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%

Index case in that family had not been tested:

FAP: about 80% (rate of mutation detection).

AFAP: about 20-30% (rate of mutation detection).

This is not a meaningful approach and should be avoided because persons at risk with normal mutation screening results still cannot be released from preventive programs.

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 FAP and MUTYH associated polyposis (MAP) 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 to participate in specific preventive check-ups, eventually colectomy.

In some cases family planning, choice of profession.

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 as for proven mutation carriers:

Close-meshed early diagnosis programs, colectomy when polyps have been detected. Yet, these measures are taken in vain in half of the persons at risk (non-carriers).

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.

By exclusion of a carrier status in predictive diagnostics, superfluous preventive investigations can be avoided and psychological relief is obtained.

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 a proven 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, the patients' usual assumption of 'own fault' as cause of their disease (exogenous poisons, 'wrong conduct') can be lapsed with relief.

The main benefits of genetic diagnostics in FAP are the differentiation from MAP, a precise recurrence risk for close relatives, and relief of non-carriers during predictive diagnostics. The molecular genetic result often enables a more precise human genetic counselling.