

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

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Indication criteria for disease: Familial breast/ovary cancer [BRCA1/BRCA2]

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):

Familial breast/ovary cancer; Hereditary breast-ovarian cancer syndrome

2.2 OMIM# of the Disease: 114480

2.3 Name of the Analysed Genes or DNA/Chromosome Segments:
BRCA1/BRCA2

According to present knowledge, a mutation analysis in the moderately penetrant genes CHEK2, PALB2, ATM or BRIP1 is commercially not feasible and can be offered within studies only. The same applies to genes with low-risk variants like FGFR2 or TNRC9.

2.4 OMIM# of the Gene(s): 113705 / 600185

2.5 Mutational Spectrum:

Point mutations, deletions and insertions of a few nucleotides, larger deletions

2.6 Analytical Methods:

DHPLC, DNA sequencing, MLPA, high resolution melting (Light Cycler)

2.7 Analytical Validation

almost 100%

2.8 Estimated Frequency of the Disease in Germany

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

Monogenic inheritance of breast cancer in association with a BRCA1/2 mutation is estimated to occur in ca. 2.5% of the cases.

Most probably, 1 in about 250 women carries a mutation in the BRCA1 or BRCA2 gene.

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

Comment: 2.10A only applies in cases where a hereditary breast/ovary cancer is possible. Here, higher risks of new disease exist and specific histopathological anomalies may occur, e.g. in triple-negative tumors with BRCA1 mutations.

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)

approx. 90%

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.

BRCA mutations are found in 50% of cases with clear-cut autosomal-dominant inheritance and at least four affected first-degree relatives or two first-degree relatives with both breast and ovary cancer. For different constellations the prevalence of mutations varies between 10 and 40%. These numbers, however, must be determined separately for each population.

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).

BRCA1 mutation in a woman: 60-80% for breast and 40-55% for ovary cancer.

BRCA2 mutation in a woman: 45-80% for breast and 10-20% for ovary cancer.

BRCA2 mutation in a male: 6-7% for breast cancer.

Mutation carriers have an increased risk for associated tumors, like intestinal, prostate, pancreas and skin cancer, and leukemias.

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:

In familial cases, the constellation has to be taken into account. The remaining genetic risk and the life-time risk of breast cancer must be calculated with an appropriate software, e.g. Cyrillic 2.1.

Index case in that family had not been tested:

A predictive genetic test, as a rule, should only be performed when also an index patient is available for analysis.



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) *When a mutation has been found, an intensive diagnostic screening program for possible secondary tumors (breast or ovary) or tumors in other organs is recommended. After they have completed their family planning, a prophylactic oophorectomy is offered to female carriers of a BRCA1 mutation and recommended to female carriers of a BRCA2 mutation.*

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)

Intensive diagnostic screening program, perhaps prophylactic mastectomy or oophorectomy.

If the test result is negative (please describe)

Usual medical check-up.

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)?

Intensive diagnostic screening program.

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, if a pathogenic mutation has been found.

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

Yes.

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?

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)

Not applicable.