# Oncogenetic testing and follow-up for women with hereditary breast cancer

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## *1. General Approach*

For women with a family history suggesting a hereditary risk of breast cancer, referral to a centre of human genetics specialised in cancer genetics for counselling and testing should be considered, **whether the woman is affected by breast cancer or not.**
If **not affected**, it is advisable that the referring physician asks the unaffected patient to refer an affected family member if possible.
If possible, the genetic testing of a family should usually **start with the testing of an affected individual** (mutation searching/screening) to try to identify a mutation in the appropriate gene (such as BRCA1, BRCA2 or TP53).
For **affected women**, the timing of counselling and testing should be compatible with the treatment that has to be installed.

**If a mutation is identified**, further testing of family members should follow a stepwise approach, based on the degree of relationship. Exceptions to the stepwise approach for testing of family members can be made if the relatives died or cannot be reached for various reasons, taking into account elements of the family history described below.

## *2. Family History*

Following elements in the patient history should be taken into account when making a judgment if the woman is at high risk, but there remains room for clinical judgement:
**Individuals with an informative family are considered at high risk for hereditary breast cancer because in the family there are:**

- two first-degree or second-degree relatives from the same side of the family diagnosed with breast cancer at younger age than the average age of 50 years of the relatives concerned (at least one must be a first-degree relative),

OR

- three first-degree or second-degree relatives from the same side of the family diagnosed with breast cancer at younger age than the average age of 60 years of the relatives concerned (at least one must be a first-degree relative),

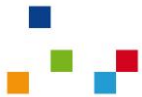
OR

- four relatives from the same side of the family diagnosed with breast cancer at any age (at least one must be a first-degree relative).

**However, not all families will prove informative. In these cases the threshold for testing is to be considered on a case by case basis after the initial assessment at a centre of human genetics specialised in cancer genetics.**

**Clinicians should seek further advice from a centre of human genetics specialised in cancer genetics for individuals in families containing any of the following, in addition to breast cancer:**

- ethnic groups with founder mutations,
- bilateral breast cancer,
- male breast cancer,
- ovarian cancer,



- sarcoma in a relative younger than 45 years of age,
- glioma or childhood adrenal cortical carcinomas,
- complicated patterns of multiple cancers at a young age,
- triple negative breast cancer under the age of 60 years.

**Clinicians should also consider to refer their patients to a cancer genetics clinic in case of:**

- breast cancer at very young age (< 35 years),
- epithelial ovarian cancer,
- pancreatic cancer and two first-degree relatives with pancreatic or ovarian or breast cancer.

### *3. Additional recommendations*

- Women with a high breast cancer risk based on the above mentioned criteria should be offered individual risk assessment in order to give individual advice on screening strategy, genetic tests and prophylactic measures. Individual risk assessment should be done by professionals with sufficient skills and experience, and should include extensive counselling and sufficient attention to patient preferences and support.

- Use of prediction models can be considered.

- When using a formal carrier prediction model, a cut-off point for the BRCA1/BRCA2 mutation carrier probability of 5 to 10% can be used. If a prediction model is used than 5% is the lower limit for testing and otherwise the BeSHG criteria should be used (see 'Guidelines for hereditary breast and/or ovarian cancer syndrome diagnostic testing criteria' of the College for Medical Geneticists available at http://www.beshg.be).

- If there are problems with using or interpreting carrier probability calculation methods, refer to the testing criteria 'Guidelines for hereditary breast and/or ovarian cancer syndrome diagnostic testing criteria' of the College for Medical Geneticists to support your decision (available at http://www.beshg.be).

- No recommendations can be formulated concerning testing for low- and moderate-penetrance genes in routine clinical practice, as there is still debate on the clinical implications of those tests. Future data, however, may yield more insights into the clinical utility of testing for additional breast cancer predisposing genes. In this context, PALB2 was recently identified to have a penetrance that could be up to as high as BRCA2 in recent birth cohorts.[1]

### *4. Follow-up of women at high risk*

- For women at proven high risk for breast cancer, yearly MRI is recommended from the age of 25 years onwards.
- Screening mammography should be used with prudence between 30 and 40 years and not before age 30.
- For women with a proven BRCA1 or BRCA2 mutation (or a similarly high risk, based on other information) and who opt for screening rather than for prophylactic bilateral mastectomy, yearly MRI and yearly mammography with an interval of six months between both examinations can be used from the age of 40 years onwards.
- Ultrasound is useful to reduce the number of false positives when MRI is difficult to interpret.

*References*

1. Nelen MR, Kremer H, Konings IB, Schoute F, van Essen AJ, Koch R, et al. Novel PTEN mutations in patients with Cowden disease: absence of clear genotype-phenotype correlations. Eur J Hum Genet. 1999;7(3):267-73.

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