Belgian Society for Human Genetics

Belgian guidelines for Managing Hereditary Breast and Ovarian Cancer: 09/2020 Update

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BRCA1

Table 1: BRCA 1 risk figures

Tumor	Risk	Comment
Breast cancer	60 – 80 % at 80 y	
Contralateral breast cancer	Around 40% after 20 y	Risk table[1] can be used during counseling for a more accurate risk estimate
Male breast cancer	1%	
Ovarian cancer	Around 40% at 80 y	
Prostate cancer	Moderate increase	
Pancreatic cancer	Small but increased risk	Not in patient folder
Endometrial cancer	< 5%	Should not be reported in patient folder
Colorectal cancer	Slight increase (only < 50 y)	Should not be reported in patient folder

Table 2: Recommendations for BRCA1 carriers

Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25* y AND • 25* – 35 y: Annual breast MRI • One mammogram at age of 30: if microcalcifications are present also do yearly mammogram (+/- US when indicted by radiologist) from age 30, else from age of 35 • 35 – 65 y: annual breast MRI and annual mammogram (+/- US when indicted by radiologist) alternating every 6 months • 65 – 75 y: Annual mammography (if quality is sufficient) • >75y: Consider mammogram every 2 y *Or 5 y younger than youngest diagnosis in the family if diagnosis <30y
	Risk reducing surgery	Bilateral mastectomy (comments: no standard follow-up with imaging after risk reducing mastectomy, nipple preservations is considered safe)
Ovarian cancer	Screening **(not in folder)**	Not recommended (comment: tailored program could be offered if patient refused risk reducing BSO ≥ 40 y)
	Risk reducing surgery	Strongly consider BSO < 40 y
Prostate cancer	Screening	Annual PSA and digital prostate exam from age 50 y (or 10y earlier than youngest diagnosis, whichever comes first)
Pancreatic cancer (not in folder)	Smoke cessation	Recommended
	Screening (preferentially in clinical trial)	**If ≥1 first degree relative with pancreatic cancer**: consider discussing pros and cons of screening according to CAPS guidelines (Goggins et al, Gut 2020)

Male breast cancer: **Routine screening not recommended**

Offer PGD/PND? **YES** **(in folder: fertility intervention possible, discussed with patient)**

Bi-allelic *BRCA1* mutations is a very rare cause of Fanconi Anemia (only a few case reports: all at the 3' of the alternate splice donor in exon 11), because *BRCA1* is essential for embryonic survival.[2]

[1] Kuchenbaecker et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA*. 2017 Jun 20;317(23):2402-2416. doi: 10.1001/jama.2017.7112. (**Table 2, 3 and 4**)

[2] Seo at al. Mechanism for survival of homozygous nonsense mutations in the tumor suppressor gene BRCA1. PNAS May 15, 2018. 115 (20) 5241-5246.

BRCA2

Table 3: BRCA2 risk figures

Tumor	Risk	Comment
Breast cancer	60 – 80 % at 80 y	
Contralateral breast cancer	Around 25% after 20 y	Risk table[1] can be used during counseling for a more accurate risk estimate
Male breast cancer	7%	
Ovarian cancer	Around 20% at 80 y	
Prostate cancer	15% before 65 y	
Pancreatic cancer	Small but increased risk	Not in patient folder

Table 4: Recommendations for BRCA2 carriers

Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25* y AND • 25* – 35 y: Annual breast MRI • One mammogram at age of 30: if microcalcifications are present also do yearly mammogram (+/- US when indicted by radiologist) from age 30, else from age of 35 • 35 – 65 y: annual breast MRI and annual mammogram (+/- US when indicted by radiologist) alternating every 6 months • 65 – 75 y: Annual mammography (if quality is sufficient) • >75y: Consider mammogram every 2 y *Or 5 y younger than youngest diagnosis in the family if diagnosis <30y
	Risk reducing surgery	Bilateral mastectomy (comments: no standard follow-up with imaging after risk reducing mastectomy, nipple preservations is considered safe)
Ovarian cancer	Screening **(not in folder)**	Not recommended (comment: tailored program could be offered if patient refused risk reducing BSO ≥ 50 y)
	Risk reducing surgery	Strongly consider BSO < 50 y
Prostate cancer	Screening	Annual PSA and digital prostate exam from age 40 y (or 10y earlier than youngest diagnosis, whichever comes first)
Pancreatic cancer (not in folder)	Smoke cessation	Recommended
	Screening (preferentially in clinical trial)	**If ≥1 first degree relative or ≥ 2 relatives of any degree with pancreatic cancer:** consider discussing pros and cons of screening according to CAPS guidelines (Goggins et al, Gut 2020)

Male breast cancer: Consider annual clinical exam by physician from age 40 y

Offer PGD/PND? YES

Consider counselling small, but possible risk of **Fanconi Anemia if positive family history in partner**. Partner screening not recommended.

[1] Kuchenbaecker et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA*. 2017 Jun 20;317(23):2402-2416. doi: 10.1001/jama.2017.7112. (**Table 2, 3 and 4**)

PALB2

Table 5: PALB2 risk figures

Tumor	Risk	Comment
Breast cancer	30 – 60 %	Depending on family history
Contralateral breast cancer	Increased	Risk table[1] can be used during counseling for a more accurate risk estimate
Male breast cancer	1%	
Ovarian cancer	5 – 15 %	Depending on family history
Pancreatic cancer	Small but increased risk	Not in patient folder

Table 6: Recommendations for PALB2 carriers

Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25* y AND • 25* – 35 y: Annual breast MRI • One mammogram at age of 30: if microcalcifications are present also do yearly mammogram (+/- US when indicted by radiologist) from age 30, else from age of 35 • 35 – 65 y: annual breast MRI and annual mammogram (+/- US when indicted by radiologist) alternating every 6 months • 65 – 75 y: Annual mammography (if quality is sufficient) • >75y: Consider mammogram every 2 y *Or 5 y younger than youngest diagnosis in the family if diagnosis <30y
	Risk reducing surgery	Bilateral mastectomy (comments: no standard follow-up with imaging after risk reducing mastectomy, nipple preservations is considered safe)
Ovarian cancer	Screening **(not in folder)**	Not recommended (comment: tailored program could be offered if patient refused risk reducing BSO ≥ 50 y)
	Risk reducing surgery	Strongly consider BSO at age of menopause (or earlier depending on family history
Pancreatic cancer (not in folder)	Smoke cessation	Recommended
	Screening (preferentially in clinical trial)	**If ≥1 first degree relative with pancreatic cancer:** consider discussing pros and cons of screening according to CAPS guidelines (Goggins et al, Gut 2020)

Male breast cancer: **Routine screening not recommended**

Offer PGD/PND? **YES**

Consider counselling small, but possible risk of **Fanconi Anemia if positive family history in partner**. Partner screening not recommended.

[1] Kuchenbaecker et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA*. 2017 Jun 20;317(23):2402-2416. doi: 10.1001/jama.2017.7112. (**Table 2, 3 and 4**)

CHEK2

Table 7: CHEK2 risk figures

Tumor	Risk	Comment
Breast cancer	20 – 45 %	Depending on family history. **Non-carriers** still have a mild increased risk (20% lifetime risk)
Contralateral breast cancer	25% after 20 y	
Male breast cancer	0,5 – 1%	
Prostate cancer	Moderate increase	
Colorectal cancer	8 – 10%	

Table 8: Recommendations for CHEK2 carriers

Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25 y AND 35 – 65 y: Breast MRI every 2y and mammography (+/- echo) every 2y, alternating annually (or start 5 y before youngest diagnosis in family if diagnosis <40y) 65 – 75 y: Annual mammography (+/- ultrasound when indicted by radiologist) >75y: Consider mammogram every 2 y (if patient is in good health)
	Risk reducing surgery	If strong family history or if diagnosed with breast cancer: consider risk reducing bilateral mastectomy
Prostate cancer	Screening	Annual PSA and digital prostate exam from age 50 y (or 10y earlier than youngest diagnosis)
Colorectal cancer	Screening	Colonoscopy every 5 y from age 40 y (or start 10 y before youngest diagnosis of colorectal cancer in family)

Comment: when a coincidental *CHEK2* mutation is found in absence of a family history of breast cancer (and an informative pedigree) it is reasonable to downgrade screening to annual mammogram starting at 40y, as breast cancer risk is estimated to be 20% for *CHEK2* women without family history (first and second degree)

Homozygous CHEK2 carriers: Breast cancer screening as for BRCA carriers or bilateral mastectomy

Male breast cancer: Routine screening not recommended

Offer PGD/PND? **No,** but PGD for CHEK2 could be considered in exceptional situations (for example: when patient will undergo IVF for infertility)

Female non-carriers in *CHEK2* breast cancer families

Table 9: Recommendations for non-carries in CHEK2 positive breast cancer families

Tumor	Intervention	Recommendation
Breast cancer	Screening	40 – 50 y: Annual mammogram 50 – 75 y: screening within population screening program

ATM

Table 10: ATM risk figures

Tumor	Risk	Comment
Breast cancer	Around 30%	(Probably depending on family history) **Non-carriers** will probably still have a mild increased risk
Contralateral breast cancer	Unclear	
Male breast cancer	0,5 – 1%	
Prostate cancer	Moderate increase	
Pancreatic cancer	Small, but increased	Not in patient folder

Table 11: Recommendations for ATM carriers

Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25 y AND 35 – 40y: Annual breast MRI starting (or start 5 y before youngest diagnosis in family if diagnosis <40y) 40 -65y: Breast MRI every 2y and mammogram (+- echo) every 2y, alternating annually 65 – 75y: Annual mammogram (+- echo) >75y: Consider mammogram every 2 y (if patient is in good health)
	Risk reducing surgery	Bilateral mastectomy can be considered based on patient preference
Prostate cancer	Screening	Annual PSA and digital prostate exam from age 50 y (or 10y earlier than youngest diagnosis)
Pancreatic cancer (not in folder)	Smoke cessation	Recommended
	Screening (preferentially in clinical trial)	**If ≥1 first degree relative with pancreatic cancer**: consider discussing pros and cons of screening according to CAPS guidelines (Goggins et al, Gut 2020)

- *ATM* c.7271T>G (V2424G) is a high risk variant: BRCA breast screening according to literature[1]

- It might be prudent to avoid diagnostic radiation if possible
- Counsel possible risk for **Ataxia-Telangiectasia** syndrome → **Carrier screening** for partner is possible if childbearing age/desire to have children (without MLPA)

Male breast cancer: Routine screening not recommended

Offer PGD/PND? NO (unless both parents are carrier to prevent AT-syndrome)

[1]van Os et al. Health risks for ataxia-telangiectasia mutated heterozygotes: a systematic review, meta-analysis and evidence-based guideline. Clin Genet. 2016 Aug;90(2):105-17.)

Female non-carriers in *ATM* breast cancer families

Tumor	Intervention	Recommendation
Breast cancer	Screening	40 – 50 y: Annual mammogram 50 – 75 y: Screening within population screening program

BRIP1, RAD51C and RAD51D

Table 12: Risk figures for BRIP1, RAD51C and RAD51D

Tumor	Risk	Comment
Ovarian cancer	5 – 10%	
Breast cancer (only for RAD51C and RAD51D)	20 – 45%	Depending on family history. **Non-carriers may still have an increased risk if there is a high breast cancer burden?** Only for RAD51C and RAD51D (breast cancer risk NOT sufficiently proven for BRIP1)

Table 13: Recommendations for BRIP1, RAD51C and RAD51D carriers

Tumor	Intervention	Recommendation
Breast cancer (only for RAD51C and RAD51D, **NOT for BRIP1**)	Screening	Clinical examination every 6 months from 25 y AND • **If <u>positive</u> family history (1st or 2nd degree) of breast cancer**: 35 – 65 y: Breast MRI and mammography alternating annually (or start 5 y before youngest diagnosis in family if diagnosis <40y) 65 – 75 y: Annual mammography (+/- ultrasound when indicted by radiologist) >75y: Consider mammogram every 2 y (if patient is in good health)
	Risk reducing surgery	If strong family history or if diagnosed: consider risk reducing bilateral mastectomy
Ovarian cancer	Screening **(not in folder)**	Not recommended (comment: tailored program could be offered if patient refused risk reducing BSO ≥ 50 y)
	Risk reducing surgery	Consider BSO < 50 y

Comment: when a coincidental RAD51C/RAD51D mutation is found in absence of a family history of breast cancer (and an informative pedigree) it is reasonable to downgrade screening to annual mammogram starting at 40y, as breast cancer risk is estimated to be 20% for RAD51C/RAD51D women without family history (first and second degree)

Offer PGD/PND? NO (unless both parents are a *BRIP1* or *RAD51C* carrier)

***BRIP1* and *RAD51C*:** Consider counselling small, but possible risk of **Fanconi Anemia if positive family history in partner**. Partner screening not recommended. (Not in folder)

MLH1, MSH2 and MSH6

Table 14: ***Risk figures for MLH1, MSH2 and MSH6***

Tumor	Risk	Comment
Colorectal cancer	20 – 60%	
Ovarian cancer	5 – 15%	Depending on mutated gene
Endometrial cancer	15 – 70%	Depending on mutated gene
Pancreatic cancer	Small, but increased	Not in patient folder
Prostate cancer	Moderate to high	MSH2 is high risk

Note: not all cancers are described

For more details and surveillance recommendations according to Lynch guidelines (cfr Lynch workgroup)

Offer PGD/PND? YES

Comment: Other risk figures and screening recommendations were not discussed.

TP53 mutations in NGS panels

- **Variant classification**: Classification of TP53 missense variants, in agreement with the ACMG/AMP guidelines, is based on several items including **phenotypical data** (identified in patients fulfilling the Chompret criteria); **frequency** of the variant in the **general population**, as reported the Genome Aggregation Database (gnomAD; **https://gnomad.broadinstitute.org/**), **bioinformatics predictions** of the variant impact on protein or RNA splicing using different algorithms, and **functional analyses** of the variants performed using different in vitro assays performed either in yeast or cultured cells (Kato et al., 2003; Zerdoumi et al., Hum Mol Genet. 2017; Giacomelli et al., 2018; Kotler et al., Mol Cell Oncol. 2018; **http://p53.iarc.fr/**). *Optimized and stringent ACMG/AMP criteria for a specific classification of germline TP53 variants, integrating the above considerations, are being developed by a TP53 variant curation expert panel, under the umbrella of ClinGen*. This will allow a progressive allocation or re-classification of TP53 variants into the different ACMG/AMP classes. Since the distinction between class 5 (pathogenic) and class 4 (likely pathogenic) variants is particularly subtle for TP53 variants, these variants are designated in the current ERN guideline as “disease-causing” variants.

- **Mosaicism:** advice ERN GENTURIS TP53 guidelines: "Therefore, when a TP53 variant is detected in a small fraction of NGS reads from blood, it is critical to respect the following rules, before concluding to the presence of a mosaic TP53 alteration:
  (i) **consider the clinical presentation** (suggestive or not of the presence of a disease-causing TP53 variant) and medical history (treatments, metastases...)
  (ii) **confirm the presence of the variant in the tissue from which the tumour originated**. → **consider asking pathologist to evaluate for infiltrating lymphocytes.**
  (iii) Further confirmation in an **unaffected tissue with no lymphocyte content**, such as a hair follicle, skin biopsy or nail clippings, should also be considered **if circulating tumour DNA is suspected from metastatic disease**.

- **Surveillance: see international guidelines (GENTURIS, adapted Toronto guidelines, …)**

Recommendations for non-affected family members in case of a family history of breast cancer without detectable predisposing mutations:

The absolute cumulative risk for non-affected relatives can be estimated through several prediction tools: KCE table, IBIS (http://www.ems-trials.org/riskevaluator/) or BOADICEA tool (https://canrisk.org/).

These estimates can be used to guide screening according to the KCE 172A guidelines (https://kce.fgov.be/sites/default/files/atoms/files/KCE_172A_borstkankerscreening.pdf)

The abovementioned guidelines were prepared by an ad hoc Working Group Oncogenetics of the College of Genetics and Rare diseases and BeSHG (25/09/2020), and reviewed and approved by the College of Genetics and Rare Diseases (02/10/20)