COLLEGE GENETICS

Belgian Society for Human Genetics

Belgian guidelines for Managing Hereditary Breast and Ovarian Cancer: 05/2023 Update

Working Group Oncogenetics : Robin de Putter, Cindy Badoer, Martin Blanche, Carlijn Brekelmans, Hilde Brems, Kathleen Claes, Karin Dahan, Anne De Leener, Ellen Denayer, Elisa Docampo, Elodie Fastre, Damien Feret, Frederik Hes, Pascale Hilbert, Eric Legius, Marie Martin, Nathalie Mouthuy, Karin Segers, Sara Seneca, Katrien Storm, Daphné t'Kint de Roodenbeke, Griet Van Buggenhout, Isabelle Vandernoot, Sara Van Lent and Jenneke van den Ende

BRCA1

Table 1: BRCA 1 risk figures

Tumor	Risk	Comment
Breast cancer	60 – 80 % at 80 y	Higher risk for triple negative breast cancer
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 • Consider baseline mammogram once at 30y to detect potential microcalcifications • 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**

PGD/PND for BRCA1? **PGT is offered in every center; PND is not offered by every genetic center**

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.

!! This is a general guideline: **exceptions or adaptations** may be necessary in specific cases based on clinical and/or genetic arguments (e.g. very strong family history, hypomorphic variants with lower penetrance, etc.)

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 • Consider baseline mammogram once at 30y to detect potential microcalcifications • 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

PGD/PND for BRCA2? **PGT is offered in every center; PND is not offered by every genetic center**

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**)

!! This is a general guideline: **exceptions or adaptations** may be necessary in specific cases based on clinical and/or genetic arguments (e.g. very strong family history, hypomorphic variants with lower penetrance, etc.)

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 • Consider baseline mammogram once at 30y to detect potential microcalcifications • 35 – 65 y: annual breast MRI and annual mammogram (+/- US when indicated 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**

PGD/PND for PALB2? **PGT is offered in every center; PND is not offered by every genetic center**

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**)

!! This is a general guideline: **exceptions or adaptations** may be necessary in specific cases based on clinical and/or genetic arguments (e.g. very strong family history, hypomorphic variants with lower penetrance, etc.)

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 (up to 20% lifetime risk)
Contralateral breast cancer	25% after 20 y	
Male breast cancer	0,5 – 1%	
Prostate cancer	Moderate increase	

Table 8: Recommendations for CHEK2 carriers

Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25 y AND 35 – 65 y: At least yearly breast MRI with 1-incidence mammogram +/- US if indicated by radiologist (or start 5 y before youngest diagnosis in family if diagnosis <40y) 65 – 75 y: Annual mammography (+/- ultrasound) >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 10 y earlier than youngest diagnosis)

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**

Female non-carriers with a 1st degree relative with breast cancer

Table 9: Recommendations for non-carrier with a first degree relatives (sister, daughter/mother) with breast cancer in CHEK2 families

Tumor	Intervention	Recommendation
Breast cancer	Screening	40 – 50 y: Annual mammogram 50 – 75 y: Mammogram every 2 years

!! This is a general guideline: **exceptions or adaptations** may be necessary in specific cases based on clinical and/or genetic arguments (e.g. very strong family history, hypomorphic variants with lower penetrance, etc.)

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 – 65y: At least yearly breast MRI with 1-incidence mammogram +/- US if indicated by radiologist (or start 5 y before youngest diagnosis in family if diagnosis <40y) 65 – 75y: Annual mammogram (+/- ultrasound) >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 with a 1st degree relative with breast cancer

Table 12: Recommendations for non-carrier with a first degree relatives (sister, daughter/mother) with breast cancer in ATM families

Tumor	Intervention	Recommendation
Breast cancer	Screening	40 – 50 y: Annual mammogram 50 – 75 y: Mammogram every 2 years

!! This is a general guideline: **exceptions or adaptations** may be necessary in specific cases based on clinical and/or genetic arguments (e.g. very strong family history, hypomorphic variants with lower penetrance, etc.)

RAD51C and RAD51D

Table 123: Risk figures for RAD51C and RAD51D

Tumor	Risk	Comment
Ovarian cancer	5 – 10%	
Breast cancer	20 – 45%	Risk depends on family history. (Non-carriers may still have an increased familial risk if there is a high breast cancer burden) Higher risk for triple negative breast cancer
Contralateral breast cancer	Unclear	

Table 134: Recommendations for RAD51C and RAD51D carriers

Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25 y AND • 35 – 65 y: At least yearly breast MRI with 1-incidence mammogram +/- US if indicated by radiologist (or start 5 y before youngest diagnosis in family if diagnosis <40y) • 65 – 75 y: Annual mammography (+/- US 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

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

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

Female <u>non-carriers</u> with a 1st degree relative with breast cancer

Table 15: Recommendations for <u>non-carrier</u> with a first degree relatives (sister, daughter/mother) with breast cancer in RAD51/D families

Tumor	Intervention	Recommendation
Breast cancer	Screening	40 – 50 y: Annual mammogram 50 – 75 y: Mammogram every 2 years

!! This is a general guideline: **exceptions or adaptations** may be necessary in specific cases based on clinical and/or genetic arguments (e.g. very strong family history, hypomorphic variants with lower penetrance, etc.)

BARD1

Table 146: Risk figures for BARD1

Tumor	Risk	Comment
Breast cancer	20 – 45%	Risk depends on family history. (Non-carriers may still have an increased familial risk if there is a high breast cancer burden) Higher risk for triple negative breast cancer
Contralateral breast cancer	Unclear	

Table 157: Recommendations for BARD1 carriers

Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25 y AND • 35 – 65 y: At least yearly breast MRI with 1-incidence mammogram +/- US if indicated by radiologist (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

Comment: when a coincidental *BARD1* 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 lower for *BARD1* women without family history

Offer PGD/PND? NO

Female non-carriers with a 1st degree relative with breast cancer

Table 18: Recommendations for non-carrier with a first degree relatives (sister, daughter/mother) with breast cancer in BARD1 families

Tumor	Intervention	Recommendation
Breast cancer	Screening	40 – 50 y: Annual mammogram 50 – 75 y: Mammogram every 2 years

!! This is a general guideline: **exceptions or adaptations** may be necessary in specific cases based on clinical and/or genetic arguments (e.g. very strong family history, hypomorphic variants with lower penetrance, etc.)

BRIP1

Table 16: Risk figures for BRIP1

Tumor	Risk	Comment
Ovarian cancer	5 – 10%	

Table 20: Recommendations for BRIP1

Tumor	Intervention	Recommendation
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

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

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

!! This is a general guideline: **exceptions or adaptations** may be necessary in specific cases based on clinical and/or genetic arguments (e.g. very strong family history, hypomorphic variants with lower penetrance, etc.)

MLH1, MSH2 and MSH6

Table 21: ***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: www.Belgianfapa.be)

Offer PGD/PND? YES

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

!! This is a general guideline: **exceptions or adaptations** may be necessary in specific cases based on clinical and/or genetic arguments (e.g. very strong family history, hypomorphic variants with lower penetrance, etc.)

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)

Rare cancer predisposition syndromes

See ERN GENTURIS: www.genturis.eu → guidelines and pathways → Clinical practice guidelines

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, …)**

!! This is a general guideline: **exceptions or adaptations** may be necessary in specific cases based on clinical and/or genetic arguments (e.g. very strong family history, hypomorphic variants with lower penetrance, etc.)

The above mentioned guidelines were prepared by an ad hoc Working Group Oncogenetics of the College of Genetics and Rare diseases and BeSHG (26/05/2023), and reviewed and approved by the College of Genetics and Rare Diseases on 08/09/2023.

!! This is a general guideline: **exceptions or adaptations** may be necessary in specific cases based on clinical and/or genetic arguments (e.g. very strong family history, hypomorphic variants with lower penetrance, etc.)