Hereditary breast cancer: an integrated review of diagnostic testing and management recommendations in Belgium

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SUMMARY

Hereditary breast cancer is most commonly linked to pathogenic germline variants in *BRCA1* and *BRCA2* (g*BRCAm*), and are associated with significant clinical implications. Carriers face elevated lifetime risks of breast, ovarian, prostate, and pancreatic cancers, making timely identification essential for prevention and treatment. Genetic results guide surveillance strategies, risk-reducing surgeries, and reproductive decisions in younger women. They also guide systemic therapy, with poly(ADP-ribose) polymerase inhibitors (PARPi) now standard in high-risk early and metastatic human epidermal growth factor receptor 2 (HER2)-negative g*BRCA*m breast cancer, as well as other tumour types. In Belgium, the 2023 update of the College of Genetics guidelines expanded testing criteria beyond age and family history to include therapeutic eligibility. Additionally, multigene panel testing has become routine in clinical practice, reflecting a shift toward broader and more inclusive genetic screening. Importantly, germline and tumour testing are increasingly initiated not only by clinical geneticists but also by medical oncologists, facilitating faster access to precision therapies.

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Despite these advances, undertesting remains a challenge. Referral rates by oncologists vary by region, highlighting the need for oncologist-led mainstreaming and strong collaboration with genetics teams. Mainstream genetic testing is effective for patients with cancer, but for predictive testing in unaffected individuals the expertise of clinical geneticists is essential. When a proband with a pathogenic variant is identified, it is critical that at-risk relatives are referred to clinical genetics for targeted predictive testing to enable timely prevention and early detection. In Belgium an initiative is underway to explore the feasibility and impact of population-based testing. Together, these combined efforts aim to ensure that more patients and families benefit from personalised cancer care and precision oncology.
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INTRODUCTION

Hereditary breast cancer represents a subset of breast cancer with important implications for prevention, diagnosis and treatment. The majority of cases are linked to germline pathogenic variants (PVs) in the *BRCA1* and *BRCA2* genes (g*BRCA*m).[1] *BRCA1* and *BRCA2* are key for the detection and repair of double-strand DNA breaks via the homologous recombination repair pathway.[2] Loss of function through PVs leads to homologous recombination deficiency, forcing reliance on error-prone DNA repair mechanisms such as non-homologous end joining. This genomic instability drives carcinogenesis and renders *BRCA*-associated cancers sensitive to DNA-damaging agents. g*BRCA*m significantly raise the lifetime risk of other cancers as well, such as ovarian, prostate and pancreatic cancer (*Table 1*).[1,3-5] The identification of g*BRCA*m is critical to guide patient management as well as cascade testing within families. In addition to *BRCA1* and *BRCA2*, several other genes such as *PALB2*, *CHEK2*, *ATM*, *TP53*, *PTEN*, *CDH1*, *BARD1*, *RAD51C*, and *RAD51D* contribute to breast cancer predisposition, though with variable penetrance and frequency. Furthermore, mismatch repair genes (*MLH1*, *MSH2*, *MSH6*) and certain DNA repair genes (*e.g. BRIP1*) are also included as they are only modestly associated with increased breast cancer risk but are of clearer importance due to their established contribution to elevated ovarian cancer risk.[6-8]

Women carrying a g*BRCA*m face an estimated 70% cumulative risk of developing breast cancer by the age of 80, with breast cancer incidence peaking earlier for *BRCA1* (age 30-40 years) than for *BRCA2* (age 40-50 years).[1] Population-level studies show that PVs in *BRCA1*, *BRCA2*, and *PALB2* combined occur in 3.00% of unselected breast cancer patients, while PVs in *CHEK2* and *ATM* together account for 2.12% of cases.[6] PVs of other susceptibility genes generally exhibit very low frequencies.[6] The prevalence of g*BRCA*m is higher in patients with a family history of breast or ovarian cancer, approaching 25% in some cohorts.[9] The prevalence

TABLE 1. The presence of gBRCAm is associated with an increased lifetime risk of breast, ovarian, prostate and pancreatic cancers.[1,3-5]
**relative risk compared with non-carriers*

	Lifetime risk of developing cancer (%)		
	General population	Harbouring g*BRCA1* mutation	Harbouring g*BRCA2* mutation
Breast (women)	13.0[5]	55-79[1,4]	45-77[1,4]
Breast (men)	<1%[5]	1.2[4]	6.8[4]
Ovarian (women)	1.1[5]	36-53[1]	11-25[1,4]
Pancreatic (men & women)	1.6[5]	2- to 4-fold increase*[3]	5-10[3]
Prostate (men)	12.9[5]	9.5[4]	20[4]

of g*BRCA*m in breast cancer patients varies widely across countries, subgroups, and studies, making the results often difficult to compare.[9]

Breast cancer resulting from g*BRCA*m has distinct clinicopathological characteristics compared to sporadic cases. These include younger age at diagnosis, higher tumour grade, and increased rates of contralateral/ipsilateral disease.[1,10-12] Moreover, g*BRCA*m carriers with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) early-stage disease, generally, have higher tumour recurrence scores compared to non-carriers.[13] g*BRCA1*m carriers are more likely to develop triple-negative breast cancer (TNBC) whereas g*BRCA2*m carriers often develop HR+ disease.[14-16] In young *BRCA* carriers, HR+ status is not a favourable prognostic factor, with *BRCA2*-associated tumours showing particular aggressiveness and warranting optimised treatment strategies.[17] g*BRCA*m testing is well-established in TNBC, but less attention has been given to HR+/HER2- breast cancer. The HR+/HER2- subtype represents 60-70% of breast cancers, compared to 10-15% for TNBC. Although g*BRCA*m prevalence is higher in TNBC (10-20%) than in HR+/HER2- disease (~5%), the total number of carriers is greater in the latter group.[9,18]

The detection of a g*BRCA*m significantly impacts a patient's care plan, including surgical and systemic treatment decisions.[19] Breast cancer resulting from g*BRCA*m may show increased sensitivity to DNA-damaging agents, such as platinum-based chemotherapies, and to targeted agents like poly(ADP-ribose) polymerase inhibitors (PARPi).[19,20] Conversely, in case of HR+/HER2- breast cancer, they may display reduced sensitivity to endocrine therapy ± cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i), although this remains an area of active investigation.[21,22] Given the therapeutic implications, timely identification of the g*BRCA*m status is crucial for guiding treatment decisions in both early and advanced breast cancer. A growing body of evidence supports the incorporation of genetic testing into the diagnostic workup to ensure that eligible patients can benefit from targeted therapies such as PARPi. Additionally, prediagnostic awareness of g*BRCA*m status is associated with earlier-stage breast cancer diagnosis and lower treatment burden.[15] In this review, we examine current genetic testing strategies and guidelines, challenges to testing, and management of patients with g*BRCA*m breast cancer, with a focus on the early disease setting. We aim to support clinical practice from a Belgian perspective.

DIAGNOSTIC TESTING FOR HEREDITARY BREAST CANCER: WHAT DO THE GUIDELINES SAY?

There are numerous (inter)national guidelines for g*BRCA*m testing in breast cancer, often with inconsistent recommendations, leading to variability in practice.[23,24] Major professional organisations have progressively broadened their recommendations, since *BRCA1/2* are recognised as important biomarkers for targeted therapies, reflecting a better understanding of the therapeutic value of timely detection.

Earlier studies demonstrated that a significant proportion of breast cancer patients with PVs in *BRCA* genes were not eligible for g*BRCA* testing according to older testing criteria.[25,26] At that time, the cost of sequencing large genes like *BRCA1/2* was much higher. Clinical criteria for genetic testing were originally based on personal and family history to ensure high clinical utility, typically warranting a 10% mutation detection rate. However, broader criteria are now being applied with a lower detection threshold, due to therapeutic implications. In the US, PVs in *BRCA* genes have been identified in up to 11% of breast cancer patients without a family history of breast or ovarian cancer.[25-27] Furthermore, 20% of patients with PVs in *BRCA* did not meet prior National Comprehensive Cancer Network (NCCN) testing criteria.[25] These findings prompted guideline revisions and fuelled calls for a less restrictive approach. The NCCN currently recommends testing for all patients diagnosed with breast cancer at age ≤50 years, and considers testing in conjunction with genetic counselling for patients under 60 years old with a personal history of breast cancer but not meeting the testing criteria.[28] The American Society of Clinical Oncology – Society of Surgical Oncology (ASCO-SSO) has gone further, advocating testing of all patients up to the age of 65 years.[29] Other experts suggest that all women up to 60 years of age diagnosed with breast cancer should undergo testing, and risk-based testing should be offered to those older than 60 years.[30] Finally, the American Society of Breast Surgeons advocates for testing all breast cancer patients, regardless of age.[31] Several studies have demonstrated that such expanded approaches are cost-effective; and cost-effectiveness is even further improved if complemented with cascade testing in family members of mutation carriers.[32-36]

The main differences between US and Belgian guidelines relate to age limits, with US guidelines adopting a relatively broad testing approach (*Tables 2, 3*).[28,29,37] As mentioned earlier, NCCN recommends testing for all patients diagnosed

TABLE 2. Criteria recommended by the NCCN, ASCO-SSO, ESMO and the Belgian College of Genetics to assess eligibility for g*BRCA*m testing in patients with a personal history of breast cancer.[28,29,37-39]

NCCN Guidelines v1.2026 – testing criteria for high-penetrance breast cancer susceptibility genes
• Any patient with breast cancer diagnosed ≤50 years of age
• At any age: ◦ Early disease setting: to aid in adjuvant treatment decisions with olaparib for high-risk, HER2-negative breast cancer ◦ Metastatic disease setting: to aid in systemic treatment decisions using PARPi for breast cancer ◦ TNBC ◦ Multiple primary breast cancers (synchronous or metachronous) or lobular breast cancer with personal or family history of diffuse gastric cancer ◦ Male breast cancer ◦ Ashkenazi Jewish ancestry ◦ Family history: - ≥1 close blood relative with any of: breast cancer ≤50 years of age, male breast cancer, ovarian cancer, pancreatic cancer, prostate cancer (metastatic, or high/very high-risk group) - ≥3 diagnoses of breast cancer and/or prostate cancer (any grade) on the same side of the family, including the patient with breast cancer
ASCO-SSO 2024 guideline recommendations – criteria for g*BRCA*m testing
• Newly diagnosed breast cancer ◦ Patients diagnosed with breast cancer ≤65 years of age ◦ Patients >65 years of age diagnosed with breast cancer if: - They are candidates for PARPi therapy for early-stage or metastatic disease - They have TNBC - Their personal or family history suggests the possibility of a PV - They were assigned male sex at birth - They are of Ashkenazi Jewish ancestry or are members of a population with an increased prevalence of founder mutations
• Recurrent breast cancer ◦ Candidates for PARPi therapy regardless of family history ◦ Patients with a second primary cancer either in the contralateral or ipsilateral breast
• Other ◦ All patients with prior history of breast cancer and without active disease, testing should be offered to all patients diagnosed <65 years and selectively in patients diagnosed over age 65, if it will inform personal or family risk ◦ Testing for high-penetrance cancer susceptibility genes beyond *BRCA1/2* should be offered to those with supportive family histories; testing for moderate-penetrance genes may be offered if necessary to inform personal and family cancer risk.
ESMO 2024 (early breast cancer) & 2021 (metastatic breast cancer) guideline recommendations
• Patients with early breast cancer: germline testing and subsequent genetic counselling for PVs in BRCA1/2 should be offered to patients who meet the respective national criteria and to those who are candidates for adjuvant olaparib therapy
• Patients with metastatic disease: gBRCAm testing at first diagnosis of HER2-negative metastatic breast cancer

at age ≤50, and ASCO-SSO extends this threshold to ≤65 years at diagnosis.[28,29] Both organisations also include older patients (of any age) based on tumour subtype (TNBC), ancestry, family history, or therapeutic implications.[28,29] The Belgian College of Genetics adopts an age threshold of ≤50 years, and includes additional family-based criteria and specific age limits for bilateral breast cancer (<60 years) or TNBC (<60 years).[37] The approach of the European Society of Medical Oncology (ESMO) is less prescriptive on age and instead ties recommendations to national testing criteria and treatment indications.[38,39] All four guidelines recognise the importance of g*BRCA*m testing to guide PARPi therapy in both early-stage and metastatic HER2-negative breast cancer.[28,29,37-39] Male breast cancer patients and individuals

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Belgian college of genetics 2024 recommendations
• Women with breast cancer and one of the following: ◦ Personal history: - Diagnosed ≤50 years of age - Bilateral breast cancer if the first cancer was diagnosed <60 years of age - TNBC diagnosed <60 years of age - HER2-negative breast cancer eligibile for PARPi: in high-risk (neo)adjuvant or metastatic setting - Ovarian or pancreatic cancer at any age ◦ Family history: - Diagnosed <60 years of age and one relative with bilateral breast cancer, or breast cancer <60 years, or prostate cancer diagnosed <60 years - A first or second degree relative with male breast cancer, ovarian cancer, pancreatic adenocarcinoma, or metastatic prostate cancer - ≥3 individuals with breast cancer and/or prostate cancer, one is a first degree relative of the other two (excluding male transmitters if father is not affected) and one diagnosed at an early age (<60 years) ◦ Other: - Individual of ethnicity associated with a higher frequency of specific mutations (*e.g.*, Ashkenazi Jewish): eligible for founder mutation testing - Other family situations with a priori chance of mutation >10% according to BRCAPRO or Evans criteria or Manchester score
• Women with high-grade epithelial ovarian cancer at any age (excluding mucinous ovarian cancer)
• Male with breast cancer

of Ashkenazi Jewish ancestry are consistently included across NCCN, ASCO-SSO, and Belgian recommendations.[28,29,37] Both the NCCN and Belgian recommendations contain detailed family history thresholds, while ASCO-SSO uses a more flexible 'suggestive of PV' criterion.[28,29,37] Although family history of certain cancers other than breast cancer can also be a criterion for testing, this may be unknown to some patients and should not preclude eligibility for g*BRCA*m testing if other criteria are met. A German survey showed that in patients with unknown family history, testing was more often performed in TNBC compared to HR+/HER2- breast cancer, though numerically more g*BRCA*m carriers have HR+/HER2- breast cancer.[40]

The Belgian guidelines aim for balance, avoiding over-complexity while ensuring relevance based on emerging data. In addition, the guidelines aim to balance cost-effectiveness and accessibility within a fixed healthcare budget. The Belgian guideline process is dynamic. The criteria are reviewed two to three times per year, with revisions driven by new clinical evidence, new therapeutic indications, availability of novel treatments, prevalence data in specific subgroups, and age-related incidence trends. The latest Belgian guideline updates illustrate this adaptive approach: the 2023 update underscored that germline status has direct therapeutic implications, particularly in HER2-negative breast cancer, and the 2024 update broadened the age criteria.[37]

Preliminary findings from a recent Belgian survey conducted across eight genetic centres offer valuable insights into current testing practices [unpublished data]. Since 2022, there has been an estimated annual 10% increase in the number of women with breast or ovarian cancer undergoing germline genetic testing, reflecting growing awareness and improved implementation of guideline recommendations. Mutation detection ratios remained quite stable (varying between 9-12% over the years), but the proportion of (likely) PVs in the high penetrant genes (*BRCA1/2*, *PALB2*) slightly dropped, while those for genes with moderate penetrance (like *ATM* and *CHEK2*), increased. A similar upward trend in number of individuals undergoing targeted testing for familial mutations is observed, with the exception of 2020-2021, when testing volumes temporarily declined, possibly linked to the impact of the COVID-19 pandemic. Typically, predictive testing is performed following counselling by a clinical geneticist. However, the survey revealed considerable variability in referral pathways between Belgian centres. In some centres, medical oncologists refer over 50% of breast cancer patients undergoing germline testing, while in others,

TABLE 3. Comparison of eligibility criteria for gBRCAm testing in patients with a personal history of breast cancer according to the NCCN, ASCO-SSO, ESMO, and Belgian College of Genetics guidelines.[28,29,37-39]

Criteria	NCCN v1.2026	ASCO-SSO 2024	ESMO 2024 & 2021	Belgian College of Genetics 2024
Age at diagnosis	≤50 years	≤65 years	National criteria	≤50 years
TNBC	Any age	Any age	National criteria	<60 years
Therapy-driven testing	Adjuvant olaparib (early high-risk HER2-), PARPi metastatic setting	PARPi candidates (early/metastatic)	Early setting: adjuvant olaparib candidates; metastatic setting: all HER2- at first diagnosis	HER2- high-risk (neo) adjuvant or metastatic setting
Multiple primaries	Multiple primary (synchronous/ metachronous)	Second ipsilateral/ contralateral primary	National criteria	Bilateral breast cancer if first <60 years
Lobular cancer	Included	Not specified	National criteria	Not specified
Other cancers	Ovarian, pancreatic, prostate (metastatic/high risk) in relatives	Not specified	National criteria	Ovarian, pancreatic in patient or relatives; metastatic prostate in relatives
Male breast cancer	Included	Included	National criteria	Included
Ancestry	Ashkenazi Jewish	Ashkenazi Jewish or other founder mutation populations	National criteria	Ashkenazi Jewish or other founder mutation populations
Family history	≥1 relative with BC ≤50, male BC, ovarian, pancreatic, or high-risk prostate cancer; ≥3 BC/prostate cancers (any grade) same side of family	Suggestive of PV	National criteria	Detailed thresholds: relative age, cancer type, relationship degree; ≥3 BC/prostate cancers, one early onset; specific combinations
Gene panels	*BRCA1, BRCA2, PALB2, ATM, CHEK2, TP53, CDH1, PTEN, STK11, MMR* genes, *etc.* (broad panels)	*BRCA1*, *BRCA2*, and other relevant genes	*BRCA1*, *BRCA2*, others as per clinical context	*BRCA1, BRCA2, PALB2, BARD1, BRIP1, RAD51C, RAD51D, ATM, CHEK2, TP53, MLH1, MSH2, MSH6*

referrals are predominantly initiated by clinical geneticists. This variability underscores the need for national harmonisation of testing pathways to ensure equitable access to genetic services across Belgium. Ensuring consistent referral practices will be key to maximising the impact of genetic testing on patient care and family risk management.

The increasing use of next-generation sequencing (NGS) in oncology has facilitated the identification of PVs in *BRCA1/2* and other hereditary breast cancer genes through tumour testing.[41] These alterations may be either of somatic or germline origin. Current guidelines recommend that any (likely) pathogenic *BRCA1/2* variant detected in tumour tissue should trigger reflex germline testing, as this can guide both treatment decisions and genetic counselling for relatives at risk.[42] In daily clinical practice, patients with a tumour *BRCA* PV —or other hereditary breast cancer gene PV— are typically referred to a laboratory accredited for germline analysis for confirmatory germline testing if the variant allele frequency (VAF) exceeds 30% for single nucleotide variants (SNVs) or 20% for small insertions/deletions.[41] While tumour testing can uncover germline mutations that were previously unrecognised, it is unfortunate that some carriers are only identified at an advanced disease stage, when preventive measures for the patient are no longer feasible. Nonetheless, such findings remain highly valuable for the patient who

can benefit from PARPi and for family members, who can then benefit from targeted genetic counselling and appropriate cancer prevention strategies. This highlights the importance of close collaboration between oncology, clinical genetics, molecular tumour laboratories and germline genetics laboratories, to ensure consistent variant classification and timely referral for genetic evaluation when actionable variants are detected.

SURVEILLANCE AND RISK-REDUCING SURGERY FOR UNAFFECTED g*BRCA*m CARRIERS

Individuals with germline PVs in hereditary breast cancer genes require comprehensive surveillance, prevention and tailored treatment strategies. g*BRCA*m carriers face an increased lifetime risk of developing not only breast cancer, including contralateral breast cancer, but also ovarian, prostate, and pancreatic cancer (*Table 1*).[1,3-5]

BREAST SURVEILLANCE

The goal of intensified surveillance is early detection at a curable stage. Several clinical practice guidelines developed recommendations for hereditary breast cancer screening.[43] Most are consistent and focus on annual mammography and magnetic resonance imaging (MRI). According to the ESMO guidelines, women with high-risk PVs (*BRCA1*, *BRCA2*, *PALB2*) should be offered intensified screening, including breast MRI if they do not opt for risk-reducing mastectomy (RRM).[44] Intensified screening should start at the age of 30 years, or five years younger than the youngest family member with breast cancer.[44] The duration of intensified screening should be individualised and based on factors such as breast density, comorbidities, and the patient's priorities.[44] Annual intervals are recommended, except for *BRCA1*, where six-monthly screening should be considered.[44] There is no evidence to support continued routine breast imaging following RRM.[44] The Belgian College of Genetics recommendations are shown in *Table 4*, and do not differentiate between high-risk PVs (*BRCA1*, *BRCA2*, *PALB2*) regarding screening intervals.[45] Among the Belgian genetic centres, it is decided to consider a one-time breast MRI to evaluate residual tissue after bilateral risk-reducing mastectomy (BRRM) and a breast ultrasound yearly following BRRM depending on the amount of residual glandular tissue.

RISK-REDUCING BREAST SURGERY

Women carrying PVs associated with hereditary cancer syndromes may benefit from risk-reducing surgeries. BRRM remains the most effective strategy to reduce breast cancer risk in unaffected *BRCA1/2* carriers and should be discussed in the context of individually tailored decision making.[44,46,47] However, the impact of BRRM on survival remains uncertain.[48,49] Nonetheless, BRRM can have an impact on quality of life when treatments such as chemotherapy and endocrine therapy can be avoided. BRRM should also be discussed in carriers of other high-risk genes alongside family history, *i.e.*, *TP53*, *PTEN*, *STK11*, *CDH1* and *PALB2*.[44]

OVARIAN CANCER RISK REDUCTION

The ESMO guidelines recommend risk-reducing bilateral salpingo-oophorectomy (RRBSO) in women who have completed childbearing, at age 35-40 for *BRCA1* PV carriers and at age 40-45 for women with *BRCA2* PVs.[44] The Belgian College of Genetics recommends to strongly consider RRBSO below the age of 40 in *BRCA1* PV carriers, and below the age of 50 in *BRCA2* PV carriers (*Table 4*).[45] The timing of surgery should take into consideration family history. As early menopause, induced by RRBSO, is associated with comorbidities and impacts quality of life, alternative approaches are being investigated. The TUBA WISP II trial (NCT04294927), currently recruiting patients in Belgium, is investigating tubectomy with delayed oophorectomy as a strategy to reduce ovarian cancer risk while mitigating premature menopause.

MANAGEMENT OF PATIENTS WITH g*BRCA*m BREAST CANCER

BREAST SURVEILLANCE

According to the ESMO guidelines, women in follow-up after breast-conserving treatment (BCT) or unilateral mastectomy for non-metastatic hereditary breast cancer should continue with intensified imaging screening.[44]

CONTRALATERAL RISK-REDUCING MASTECTOMY

For high-risk PV carriers already diagnosed with unilateral breast cancer, contralateral risk-reducing mastectomy (CRRM) reduces the incidence of contralateral breast cancer but there is insufficient evidence that CRRM clearly improves survival.[46,49] Some studies, such as a recent cohort study in young *BRCA* carriers with a prior history of breast cancer (diagnosis <40 years of age) found that both RRM and RRSO were associated with a significant improvement in overall survival (OS).[52]

Young women with breast cancer have a significant risk of contralateral and ipsilateral breast cancer, warranting discussion of prophylactic mastectomy and CRRM.[53] A pro-

TABLE 4. Belgian College of Genetics surveillance and prevention strategies in patients harbouring germline BRCA1, BRCA2, or PALB2 mutations. For strategies in other genes associated with hereditary breast cancer, refer to the full guidelines.[45]
**Or 5 year younger than youngest diagnosis in the family if diagnosis <30 years*
BRRM= bilateral risk-reducing mastectomy; DRE= digital rectal examination; MRI= magnetic resonance imaging; PSA= prostate-specific antigen; q6m= every six months; RRBSO= risk-reducing bilateral salpingo-oophorectomy; RRM= risk-reducing mastectomy; US= ultrasound.

Germline mutation	**Breast cancer**	
	Screening	**Risk-reducing surgery**
BRCA1 or *BRCA2* or *PALB2*	Clinical examination q6m from 25* years AND • 25*-35 years: annual breast MRI • Consider baseline mammogram once at 30 years (microcalcifications) • 35-65 years: annual breast MRI + annual mammogram (± US if indicated) alternating q6m • 65-75 years: annual mammography • >75 years: consider mammogram every 2 years	BRRM (no standard follow-up with imaging after RRM, nipple preservation is considered safe)
Germline mutation	**Ovarian cancer**	
	Screening	**Risk-reducing surgery**
BRCA1	Not recommended (tailored programme if patient refused RRBSO ≥40 years)	Strongly consider RRBSO <40 years
BRCA2	Not recommended (tailored programme if patient refused RRBSO ≥50 years)	Strongly consider RRBSO <50 years
PALB2	Not recommended (tailored programme if patient refused RRBSO ≥50 years)	Strongly consider RRBSO at age of menopause (or earlier depending on family history)
Germline mutation	**Prostate cancer**	
	Screening	
BRCA1	Annual PSA and DRE from age 50 years (or 10 years earlier than youngest diagnosis, whichever comes first)	
BRCA2	Annual PSA and DRE from age 40 years (or 10 years earlier than youngest diagnosis, whichever comes first)	
Germline mutation	**Pancreatic cancer**	
	Smoke cessation	**Screening (preferentially in clinical trial)**
BRCA1 or *PALB2*	Recommended	If ≥1 first-degree relative with pancreatic cancer: consider discussing pros and cons of screening according to CAPS guidelines (Goggins et al, Gut 2020)
BRCA2	Recommended	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)

spective cohort study showed that the 20-year cumulative risk of contralateral breast cancer was 40% for *BRCA1* and 26% for *BRCA2* carriers.1 Another study showed that among premenopausal women, the 10-year cumulative incidence of contralateral breast cancer was estimated to be 33% for *BRCA1* and 27% for *BRCA2* carriers.[54] The risk assessment of contralateral breast cancer and the benefit of CRRM in *BRCA1* and *BRCA2* carriers should consider age at diagnosis, family history of breast cancer, the overall prognosis from the first breast cancer or other cancers, the ability of the patient to undergo proper breast surveillance, comorbidities, and life expectancy.[53] The ESMO guidelines do not specifically mention recommendations regarding CRRM in affected individuals.[44]

TARGETED THERAPY WITH PARPi

PARPi competitively block PARP enzyme activity, preventing repair of single-strand DNA breaks. In homologous recombination repair-deficient cells (*e.g.*, with *BRCA1/2* mutations), this results in accumulation of double-strand breaks, reliance on error-prone repair pathways, and ultimately cancer-specific cell death through synthetic lethality.[55-58]

In the metastatic setting, ESMO recommends considering a PARPi such as olaparib or talazoparib for g*BRCA*m HER2-negative breast cancer, as second-line therapy for HR+ patients and as first-line therapy for patients with PD-L1-negative TNBC.[39,59] Pivotal trials like OlympiAD (olaparib) and EMBRACA (talazoparib) have demonstrated improved progression-free survival (PFS) and quality of life compared to standard chemotherapy in this patient population.[60,61]

In the adjuvant setting for early breast cancer, the OlympiA trial showed that for high-risk, HER2-negative early breast cancer (TNBC and HR+) with a confirmed g*BRCA*m, one year of olaparib treatment significantly improved invasive disease-free survival (DFS) and OS compared to placebo.[62-64] In patients with g*BRCA*m early TNBC, the ESMO guidelines recommend adjuvant olaparib in case of residual disease following neoadjuvant chemotherapy ± pembrolizumab.[38] The combination of adjuvant pembrolizumab and olaparib may be considered on an individual basis, if the patient received pembrolizumab in the neoadjuvant setting.[38] In patients with high-risk HR+/HER2- early breast cancer, olaparib, abemaciclib, and ribociclib are potential treatment options, and both olaparib and abemaciclib demonstrated an OS benefit.[38,64,65] However, the efficacy of olaparib has been specifically demonstrated in patients with HR+/HER2- early breast cancer who have g*BRCA*m.[64] In monarchE, only 3.5% of patients had a g*BRCA*m and results are inconclusive on the outcomes of abemaciclib in the HR+/HER2- early breast cancer g*BRCA*m population.[66] Given that abemaciclib can be initiated up to 16 months after surgery, sequential use with olaparib first is feasible and recommended by the ESMO guidelines.[38,67] These guidelines further advise to not combine the two agents due to overlapping toxicities.[38] In the metastatic setting, several real-world studies suggest inferior outcomes with endocrine therapy plus CDK4/6i in g*BRCA*m carriers compared to non-carriers.[68,69] This was confirmed in a recent meta-analysis reporting shorter PFS (HR=1.68) and OS (HR=1.73) with CDK4/6i in g*BRCA*m *versus* non-g*BRCA*m carriers.[70] Based on this knowledge, a recent publication recommends prioritising olaparib over CDK4/6i in g*BRCA*m patients in the adjuvant setting due to the potential for CDK4/6i resistance.[71] An individual patient data meta-analysis further indicated a poorer prognosis in *BRCA*2m carriers but not *BRCA*1m carriers.[22] HR+/HER2- *BRCA*m breast cancers are enriched with endocrine-resistant, high-risk luminal B tumours, which might partly explain their reduced benefit from endocrine therapy ± CDK4/6i.[22] In *BRCA*2m disease, frequent co-loss of *RB1* likely contributes further to CDK4/6i resistance, as supported by genomic studies and clinical outcome data.[22]

In the neoadjuvant setting, use of a single-agent PARPi (talazoparib, niraparib) has shown promising tumour responses and pathological complete response (pCR) rates in phase I/II studies including *BRCA*m breast cancer patients.[72-74] However, combining a PARPi with neoadjuvant chemotherapy has faced clinical challenges due to (haematological) toxicities. Studies like the phase II GeparOLA trial (olaparib with paclitaxel) showed improved tolerability and numerically higher pCR rates compared to carboplatin-paclitaxel.[75] However, long-term survival benefit tended to be inferior with olaparib, particularly in patients without germline or somatic *BRCA*m.[75] In the subset of patients with germline or somatic *BRCA*m, invasive DFS rates were comparable between both treatment arms.[75] The phase II/III PARTNER trial observed improvements in event-free survival (EFS) and OS in g*BRCA*m patients with TNBC who received a neoadjuvant gap schedule of olaparib with paclitaxel and carboplatin, despite no overall improvements in pCR rates, EFS, or OS for non-g*BRCA*m TNBC.[76,77] These results need confirmation in larger trials.

Future progress is anticipated with new PARPi combinations and the emergence of next-generation PARP1 selective inhibitors.[78] Ongoing clinical trials, such as OlympiaN, are

exploring risk-based approaches to neoadjuvant treatment, combining olaparib with durvalumab for higher-risk patients, and other trials are evaluating olaparib with pembrolizumab (NCT05203445, NCT05485766) for HER2-negative breast cancer. Saruparib, a potent and highly selective PARP1 inhibitor, is being evaluated in the ongoing EvoPAR-BR01 phase III trial, in combination with camizestrant against standard therapies for HR+/HER2- advanced breast cancer patients with *BRCA1/2* or *PALB2* mutations. HRS-1167, another next-generation selective PARP1 trapping inhibitor, has similarly demonstrated encouraging clinical activity in phase I trials. More and more trials are ongoing to evaluate the use of PARPi in patients carrying *PALB2* mutations. The phase II TBCRC-048 study showed that olaparib is an effective treatment option for patients with metastatic breast cancer and germline *PALB2* or somatic *BRCA1/2* mutations.[79] The Precision 2 trial (EudraCT number 2018-002966-37) is evaluating the efficacy of olaparib in advanced breast cancer patients carrying a germline or somatic mutation in homologous recombination repair genes, other than *BRCA1/2*. Part 2 of this trial includes patients with *PALB2* mutations, and results are awaited.

PLATINUM-BASED CHEMOTHERAPY

The clinical value of adding platinum therapy to neoadjuvant chemotherapy for g*BRCA*m tumours remains inconclusive. The phase III TNT trial found that carboplatin was superior to docetaxel in g*BRCA*m breast cancer in terms of objective response rate (68% *versus* 33%).[80] However, only 43 patients included in the study had g*BRCA*m (25% HR+ disease, 75% TNBC).[80] The phase II INFORM trial specifically included patients with HR+/HER2- g*BRCA*m breast cancer and found that neoadjuvant cisplatin did not improve pCR rates compared to doxorubicin-cyclophosphamide.[81]

FERTILITY PRESERVATION

Given that g*BRCA*m carriers are often younger at the time of breast cancer diagnosis, they face distinctive reproductive challenges, including potential reduced ovarian reserve from both the mutation itself and cancer treatments, as well as the impact of risk-reducing surgeries. Despite these challenges, all young women diagnosed with cancer during their reproductive years should be offered the opportunity to access fertility preservation strategies before initiating systemic anticancer therapies.[82,83] A significant proportion of pregnancies after breast cancer in *BRCA* carriers are achieved using assisted reproductive technology, including embryo transfer after oocyte/embryo cryopreservation, oocyte donation, or ovarian stimulation.[84]

FUTURE OUTLOOK AND PERSPECTIVE ON TESTING AND MANAGEMENT

The success of hereditary breast cancer testing depends not only on scientific advances but also on practical implementation in daily practice. Tests must be affordable, accessible, and delivered with short turnaround times to ensure timely treatment decisions. Traditionally, genetic testing required referral to specialised genetic departments for pre-test genetic counselling, consent, sample collection, and result discussion. However, in practice, referral rates remain suboptimal, leading to underdiagnosis despite guideline recommendations.[85] A recent US study among commercially insured women showed that nearly one-third of women who had breast cancer at age 50 or younger had no g*BRCA*m testing within one year of diagnosis, although they were eligible for genetic counselling according to 2024 guidelines.[86] Therefore, healthcare providers have an important role in offering genetic services to women and their families, ensuring that eligible women receive recommended care.[86]

MAINSTREAM GENETIC TESTING

Strategies are needed to ease the burden on already overstretched genetic counselling services, such as oncologist-led mainstreaming. In mainstream genetic testing pathways, medical oncology teams handle pre-test genetic counselling, obtain consent, schedule the genetic test, and use the results to guide treatment decisions. Mainstream models have already proven highly effective in ovarian cancer, significantly increasing the proportion of those offered genetic testing.[87-89] Similar approaches in breast cancer have shown higher detection rates of PVs and reduced burden on genetic services.[90,91] Other studies indicated that oncologist-led mainstreaming leads to higher testing uptake and faster test turnaround times.[92,93] Patients generally welcome oncologist-led testing, reporting high satisfaction when results are delivered by their cancer team.[90,94,95] In Belgium, since g*BRCA1/2* have become therapeutic targets, there has been an increasing proportion of referrals for germline testing initiated by the treating (gynaeco-)oncologists [unpublished data]. This trend reflects the growing importance of mainstreaming genetic testing into routine oncology care for patients diagnosed with cancer. However, referral patterns still vary between centres, indicating that the implementation of mainstreaming is not yet uniform. Continued efforts are needed to harmonise referral pathways and ensure that all eligible patients are identified and referred for genetic evaluation in a timely manner.

However, mainstream genetic testing introduces new challenges. Oncologists may have knowledge gaps regarding

the prevalence of germline PVs, as well as the appropriate screening, testing, and interpretation of results.[96] Therefore it is of utmost importance to provide training and education for oncologists who are involved in mainstream testing. A variety of educational initiatives have been developed to support this, including webinars and courses organised by the European Reference Networks Genetic Tumour Risk Syndromes (ERN GENTURIS) and ESMO, as well as other resources designed to enhance genetic literacy among healthcare professionals.[91,97] Importantly, while mainstream genetic testing is effective for patients diagnosed with cancer, predictive testing in unaffected individuals should remain the responsibility of clinical geneticists. This ensures that comprehensive counselling can address the benefits, limitations, and psychosocial implications of testing, including preconceptional advice where relevant. In Belgium, genetic counselling is completely reimbursed.

POPULATION-BASED SCREENING

Looking further ahead, population-based screening may transform hereditary cancer prevention. In Belgium, an ongoing project funded by *'Kom op tegen Kanker'* will evaluate the feasibility and cost-effectiveness of offering g*BRCA*m testing to the general population through general practitioners. Earlier modelling studies suggest that the cost-effectiveness of population-based genomic screening for hereditary breast cancer and ovarian cancer in unselected women may depend on the age of the individuals screened.[98] On the other hand, there may be false reassurance from negative test results, psychological distress from results like variants of unknown significance (VUS) or positive findings, health disparities in access to testing and care, limited test utility from incomplete testing or lack of genetic counselling, and misinformation spread regarding cancer risks and necessary management. The need for repeat testing needs also to be taken into account in this study. This Belgian initiative will provide critical local evidence to inform future policy.

BROADER PANEL TESTING

Testing strategies are also evolving beyond *BRCA1/2*. All Belgian genetic centres have agreed in 2019 to use broad multigene panels including *BRCA1*, *BRCA2*, *PALB2*, *BARD1*, *BRIP1*, *RAD51C*, *RAD51D*, *ATM*, *CHEK2*, *TP53*, *MLH1*, *MSH2*, *MSH6*.[37] In 2025, *PTEN*, *STK11* and *CDH1* were added, as all Belgian centres had already been using these broader panels in clinical practice. The formal inclusion of additional genes in 2025 reflects an alignment with evolving clinical needs and accumulated experience. This approach increases the likelihood of detecting clinically actionable variants across multiple pathways relevant to cancer risk and treatment response. When a germline PV is identified, targeted testing for that specific familial mutation remains the standard for relatives.

The broad Belgian panel differs from the ESMO recommendations, which suggest limiting mainstream testing to *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, *RAD51D* and *TP53*.[99] *CHEK2* and *ATM* were judged to offer insufficient evidence for improving cancer-related mortality, and inclusion of syndromic genes such as *STK11*, *PTEN*, *NF1* and *CDH1* is not recommended for routine inclusion due to their complex management implications.[99]

The Belgian national consensus ensures uniformity in testing strategies, reducing disparities in access and interpretation of results across regions. Identifying variants in genes like *CHEK2* or *ATM* can inform surveillance strategies, risk-reducing measures, and cascade testing in families. Including syndromic genes allows for earlier identification of individuals at risk for complex hereditary cancer syndromes, enabling timely referral to specialised care and multidisciplinary management. Belgium is a small country and has a well-organised healthcare infrastructure, allowing streamlined access to genetic services. This facilitates the implementation of broader testing strategies and ensures that patients across the country can benefit from comprehensive genetic evaluation without significant logistical barriers.

CONCLUSIONS

Hereditary breast cancer represents a distinct clinical entity, with implications that extend well beyond the individual patient to families and healthcare systems. Germline PVs in *BRCA1/2* and other genes shape cancer risk, surveillance strategies, preventive interventions, and systemic treatment choices. Their detection is therefore essential for truly personalised oncology care.

In Belgium, the College of Genetics testing guidelines have broadened testing criteria and explicitly integrated therapeutic indications, ensuring that patients eligible for PARPi are systematically identified, and broadened age criteria.[37] At the same time, Belgian genetic centres now employ broad multigene panels, reflecting the evolving spectrum of clinically relevant hereditary cancer genes.[37]

Despite this progress, undertesting remains a challenge. It is difficult to estimate how many patients with PVs remain untested, and thus miss the opportunity for targeted

KEY MESSAGES FOR CLINICAL PRACTICE

1. **Breast cancer resulting from gBRCAm has distinct clinicopathological characteristics compared to sporadic cases and requires tailored treatment strategies.**
2. **All eligible breast cancer patients should undergo germline testing according to the Belgian College of Genetics guidelines, not only for risk assessment, but also for appropriate treatment selection in patients with HER2-negative (HR+ or HR-) breast cancer in the metastatic and high-risk (neo)adjuvant setting. Testing should be integrated early into the diagnostic pathway as timely results influence surgery, systemic therapy, and fertility planning.**
3. **Oncologist-led mainstream genetic testing can improve uptake and reduce delays, but must be supported by training and close collaboration with clinical genetics teams and diagnostic laboratories involved in tumour and germline testing.**
4. **Predictive testing of unaffected individuals should remain the remit of clinical geneticists, ensuring accurate genetic counselling and cascade testing in the family.**
5. **Broad gene panel testing is now standard across Belgian centres, enabling detection of both BRCA and non-BRCA variants with therapeutic or preventive implications.**

treatment and family risk reduction. Over the last years, substantial progress has been made in mainstreaming genetic testing within oncology practice, alongside education for oncologists and ongoing collaborations between oncologists and geneticists, however, there may still be large regional differences.

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