ACE Clinical Recommendations for 'Managing hereditary breast and ovarian cancer (HBOC) syndrome: genetic testing and risk-reducing interventions' – Evidence-to-Recommendation Framework

Objective

- To guide appropriate referral and management of downstream interventions for individuals with hereditary breast and ovarian cancer (HBOC) syndrome-related pathogenic/likely pathogenic variants (P/LPVs)

Scope

- Genetic testing referral and downstream interventions with a focus on hereditary breast cancers and hereditary ovarian cancers

Target audience

- These clinical recommendations are relevant to healthcare professionals caring for individuals with HBOC syndrome-related P/LPVs or individuals with personal or family history suggestive of HBOC syndrome

This document outlines the underpinning evidence and rationale for the recommendation statements in the ACE Clinical Recommendations (ACRs) for 'Managing hereditary breast and ovarian cancer (HBOC) syndrome: genetic testing and risk-reducing interventions'.

In the ACRs, the strength of recommendation reflects the confidence that the desirable effects of the recommended practice outweigh undesirable effects across the range of patients for whom the recommendation applies, based on the best available evidence:

- A strong recommendation is usually made when benefits clearly outweigh the risks, based on at least moderate-certainty evidence.
- A weak or conditional recommendation may be needed when there is a closer balance between benefits and harms, evidence is of low certainty, there is significant variability in patients' values and preferences, or important concerns with resourcing and feasibility of the recommended practice.[1]

These recommendations aim to support the management of individuals with HBOC syndrome-related P/LPVs, and are intended to complement, not replace, clinical judgement in delivering patient-centred care. Clinicians are encouraged to consider the patient's goals, preferences and concerns, and actively involve the patient in **shared decision making** to determine the most appropriate management.

When discussing options for genetic testing, surveillance or risk reducing interventions with individuals who carry HBOC syndrome-related P/LPVs, consider the following:

- **Patient goals:** e.g. cancer risk reduction, preservation of quality of life (QoL), minimisation of treatment or follow-up burden
- **Patient preferences:** e.g. preference for conservative management with surveillance versus risk-reducing surgery
- **Patient concerns:** e.g. body image and recovery after surgery, surveillance limitations (e.g. false positive findings, need for additional investigations, overdiagnosis, cumulative radiation exposure, and recall-related anxiety), financial and other psychosocial considerations

Where multiple risk-reducing strategies are being considered, the relative benefits and implications of each should be discussed. Risk-reducing salpingo-oophorectomy (RRSO) has a more established role in reducing ovarian cancer risk and mortality, particularly given the lack of effective intensified ovarian surveillance, whereas decisions regarding risk-reducing mastectomy (RRM) versus intensified breast surveillance are more dependent on the individual's breast cancer risk and values.

Recommendation 1

Refer the following individuals for genetic testing to characterise breast cancer-related gene variants: **a) Individuals with a personal history of breast cancer who have risk factors for hereditary breast cancer (see Annex A A1-A5)** **b) Individuals with a significant family history of breast cancer, and unknown familial genetic status (see B1-B2)** **c) First-degree biological relatives of an individual who carries a pathogenic/likely pathogenic variant (P/LPV) in a breast cancer susceptibility gene; or consider referring second-degree biological relatives if the first-degree relative is unavailable^ (see C1)**	***Strength of recommendation:*** **Strong** **Conditional**
Recommendation remarks: Please refer to Annex A for details of the population groups and indications for genetic testing to characterise breast cancer-related gene variants.	

Recommendation 2

Refer the following individuals for genetic testing to characterise ovarian cancer-related gene variants: **a) Individuals with a personal history of ovarian cancer, which includes those with epithelial ovarian, fallopian tube or peritoneal cancer (see Annex B A1-A3)** **b) Individuals with a significant family history of ovarian cancer, and unknown familial genetic status (see B1-B2)** **c) First-degree biological relatives of an individual who carries P/LPV in an ovarian cancer susceptibility gene; or consider referring second-degree biological relatives if the first-degree relative is unavailable^ (see C1)**	***Strength of recommendation:*** **Strong** **Conditional**
Recommendation remarks: Please refer to Annex B for details of the population groups and indications for genetic testing to characterise ovarian cancer-related gene variants.	

Evidence-to-recommendation considerations

Summary: Genetic testing is strongly recommended for individuals with a personal or significant family history of breast/ovarian cancer or known related pathogenic or likely pathogenic variants (P/LPVs), given its established utility in guiding cancer risk management. Testing is broadly acceptable, with generally transient psychological effects, and genetic counselling and subsidised genetic testing can further address concerns and financial barriers. At-risk first-degree relatives have a higher pre-test probability for PVs than second-degree relatives. When considering extending cascade testing to second-degree relatives, impact on service capacity would need to be weighed against the benefits of increased testing uptake.

Balance of benefits and harms
Genetic testing is recommended when there is a reasonable pre-test probability of identifying a clinically actionable germline P/LPV that may change management for the individual or their relatives. The clinical indicators in the recommendations have been adapted from established guidelines such as National Comprehensive Cancer Network (NCCN) and individualised based on local clinical and resource considerations.[2]

Benefits

Breast Cancer (Annex A)

For individuals with a personal history of breast cancer and features suggestive of hereditary breast cancer risk **[A]**, the following features are associated with higher PV yield:

- breast cancer diagnosed at age ⩽50 years has ~10% detection rate across relevant breast cancer-related genes **[A2i]**,
- triple-negative breast cancer has a 14.6% detection rate across the genes and 11.2-16.8% for *BRCA1* and *BRCA2 (BRCA1/2)* P/LPVs **[A2ii]**,[3]
- male breast cancer carries ~11% detection rate for *BRCA1/2* P/LPVs **[A2v],**[3]
- individuals with multiple primary breast cancers are more likely to harbour a P/LPV than individuals with a single breast cancer (7.1%-13.2% vs 4.2%-9.4%) **[A2iii],**[4, 5]
- lobular breast cancer with a personal or family history of diffuse gastric cancer is included due to association between *CDH1* P/LPVs and lobular breast cancer (64%) **[A2iv]**,[6]
- Ashkenazi Jewish ancestry is associated with a 10% detection rate of *BRCA1/2* P/LPVs [limited local applicability; included for completeness] **[A3]**.[7]

Ovarian Cancer (Annex B)

For individuals with a personal history of epithelial ovarian, fallopian tube or peritoneal cancer **[A]**, epithelial ovarian cancer has a detection rate of 11.3%-14.1% for *BRCA1/2*, 0.9% for *BRIP1*, 1.0% for *RAD51C* or *RAD51D*, 0.4% for *PALB2*, 0.5% for mismatch repair P/LPVs **[A2]**.[8, 9]

Both breast and ovarian cancers (Annex A and B)

- Tumour-detected gene alterations may be somatic or germline. Hence, when a PV with potential germline implications is identified on tumour genetic testing, germline genetic testing clarifies whether the variant is inherited and enables cancer risk management and cascade testing **[A1]**.[2]
- The ≥10% probability of a *BRCA1/2* PV based on prior probability models (e.g. Manchester Score, CanRisk), was adopted as the testing threshold. This is aligned with the threshold used in National Institute for Health and Care Excellence (NICE) and EviQ guidelines,[7, 10] and with overseas economic evaluations indicating that testing is cost-effective at this probability.[11, 12] The lower >5% threshold used by NCCN was not adopted as its cited cost-effectiveness evidence relates primarily to population-based multigene testing in overseas settings and may not be directly transferable to the intended local testing pathway.[2]

Harms

Validation studies of NCCN testing indications for breast cancer-related P/LPVs showed that, when an age threshold of ≤50 years is used, 13.1% of *BRCA1/2* P/LPV carriers and 29.9% of carriers across nine breast cancer susceptibility genes would not have met NCCN testing indications.[13] Expanding testing to all females with breast cancer diagnosed at ≤65 years improves sensitivity from 70% to 90%, but reduces specificity from 53% to 22%.[5] In patients with breast cancer diagnosed at >65 years, more moderate-risk P/LPVs may be detected, for which risk estimates and management implications are less certain, potentially increasing anxiety and over-management.[2] These concerns may be less applicable to ovarian cancer genetic testing as ovarian cancer is substantially less common than breast cancer.[2, 8]

Systematic reviews showed that anxiety typically peaked at result disclosure and declines over time, with no clinically significant impact on depression and QoL.[14, 15]

Certainty of evidence	Values and preferences

The certainty of evidence for individual clinical indicators is low due to the pooling of different indirect evidence from retrospective cohort studies and registry-based analyses. The certainty for the psychological impact of genetic testing is very low, drawn from small observational studies with high loss to follow-up.[14]	Values and preferences for genetic testing vary, with individuals weighing cost, wait time, test accuracy, survival benefit, and detection differently.[16] Cost remains a key determinant across studies; however, participants were willing to pay for testing compared with no testing, and for tests covering multiple cancers compared with a single cancer.[16] Studies also showed value placed on specialist-led testing, private clinic settings, and limiting access to results to health professionals rather than insurers.[16]
Resources and feasibility	**Acceptability and other considerations**
Local clinicians and the literature have reported that risk scoring tools (e.g. Manchester score and CanRisk) are complex and time-consuming **[A5]**.[17] With the implementation of subsidised genetic testing for HBOC syndrome for specified groups of patients, costs to individuals are expected to decrease substantially.	Uptake may not be universal even among eligible individuals because of limited awareness, distrust of results, perceived lack of clinical utility, and concerns about insurance discrimination.[16] These factors suggest that a proportion of eligible individuals may decline testing, and that acceptability is equally influenced by health literacy, trust, and perceived consequences as it is by clinical eligibility. To improve uptake, these barriers should be addressed alongside subsidised access.
Expert Group deliberation of the above factors	
The Expert Group (EG) supported a strong recommendation due to the clinical utility of identifying actionable P/LPVs for individual and familial risk management, despite potential psychological harms and resource implications. The proposed clinical indicators were considered established and feasible for local practice despite low-certainty evidence.	

Recommendation 3

Discuss risk-reducing strategies with individuals at elevated risk of breast cancer, and provide access to genetic counselling prior to any surgical decision:	
a) For females with high-risk P/LPVs, recommend RRM as an option.	***Strength of recommendation:*** **Strong** Conditional
b) For females with moderate-risk P/LPVs and a substantially elevated individual breast cancer risk based on significant family history, reserve recommending RRM as an option.	**Strong** Conditional
c) For males with high- or moderate-risk P/LPVs, do not recommend RRM.	**Strong** Conditional
Recommendation remarks: Risk-reducing strategies for breast cancer include RRM, intensified surveillance, and chemoprevention. Decision should be guided by shared decision-making, considering individualised breast cancer risk (using validated risk models where appropriate), age, family history, comorbidities, and patient values and preferences. Counselling on RRM should include degree of breast cancer risk reduction, reconstruction options, procedural risks, and potential impact on QoL. Chemoprevention and lifestyle modification is beyond the current ACRs' scope and will be discussed in subsequent guidance. Refer to Annex C for details on P/LPVs categorised under high or moderate risk. Individuals with HBOC syndrome-related P/LPVs also have increased risks of other malignancies (e.g. prostate, pancreatic and melanoma). Appropriate specialist assessment and counselling regarding these risks are warranted, but beyond the scope of the HBOC ACRs.	

Evidence-to-recommendation considerations

Summary: RRM substantially reduces breast cancer incidence and mortality in females with high-risk P/LPVs, supporting a strong recommendation despite surgical and psychosocial harms. For females with moderate-risk P/LPVs, RRM should be reserved for those with substantially elevated individual risk. RRM is not recommended for males, given the lower absolute risk and limited evidence of benefit.

Balance of benefits and harms

Benefits: In *BRCA1/2* mutation female carriers, RRM reduced overall mortality (62% reduction; hazard ratio [HR] 0.37, 95% confidence interval [CI] 0.23-0.60) and breast cancer-specific mortality (86% reduction; HR 0.14, 95% CI 0.04-0.49) significantly compared with no surgery.[18] Given the high lifetime risk of breast cancer associated with these variants (60-80% for *BRCA1/2*), the absolute risk reduction achieved with RRM is considerable. RRM may also reduce cancer-related anxiety and the burden of intensified surveillance, with individuals reporting decision satisfaction and decreased worry about developing breast cancer.[10, 19]

Harms: RRM is irreversible and carries perioperative complications such as bleeding, infection, wound complications, seroma formation, and anaesthetic risks.[19] The risk of major early complications requiring reoperation is low (3.7%), though rates are higher with reconstruction.[20] Long-term physical sequelae may include numbness, pain, infection and oedema.[2] Whilst many individuals reported reduced cancer-related distress postoperatively, adverse effects on body image, self-esteem and sexual well-being have been documented.[10, 19]

Benefits/harms balance

The relative benefit of RRM declines with age, as remaining lifetime breast cancer risk decreases.[21] Local data suggested peak breast cancer incidence at around age 55 for *BRCA1/2* P/LPVs, in contrast to European data where peak incidence occurs earlier.[22] Evidence guiding the optimal timing of RRM remains limited, hence decision should consider age, baseline risk, comorbidities and patient values.[18]

For females with high-risk P/LPVs (*BRCA1, BRCA2, TP53, PTEN, PALB2*, *CDH1, STK11*), risk reduction and survival benefits generally outweigh potential harms, although decisions are preference-sensitive. Evidence for non-*BRCA* high-risk genes is extrapolated from *BRCA1/2* carriers with gene-specific differences in absolute risk and tumour phenotype. For instance, for *STK11*-associated Peutz-Jeghers syndrome, although lifetime breast cancer risk is estimated at 32-54%,[2, 23, 24] emerging evidence suggests these tumours may demonstrate slower growth, reduced recurrence and better prognosis than those in *BRCA1/2* carriers.[25] Thus, guidelines, such as the European Hereditary Tumour Group, do not recommend RRM for *STK11* carriers,[26, 27] whereas NCCN and EviQ guidelines allow consideration based on individual risk assessment.[2, 24] RRM may be inappropriate in patients with comorbidities increasing surgical risk, or with poor prognosis.[10] Other risk-reducing strategies include intensified surveillance and chemoprevention. While chemoprevention reduces breast cancer incidence,[28] it has no proven mortality benefit,[28] and is associated with increased risk of thrombosis, endometrial cancer and osteoporosis, limiting suitability for individuals at highest risk.[23]

For females with moderate-risk P/LPVs (*ATM*, *BARD1, CHEK2, NF1, RAD51C, RAD51D*), breast cancer risk is generally lower than in high-risk carriers, and evidence for RRM is largely extrapolated from *BRCA1/2* data with limited direct evidence of benefit.[29, 30] While specific *ATM* variants, notably *ATM* c.7271T>G, confer higher risk, guidelines vary in their RRM recommendations—NCCN and American College of Medical Genetics and Genomics (ACMG) guidelines do not support routine RRM but allow for discussion when individualised risk estimates warrant it,[22, 31] whereas EviQ allows conditional consideration.[29] RRM decisions should therefore be individualised, incorporating family history, hormonal and lifestyle factors, and breast density.[31]

For males, the estimated lifetime male breast cancer risk is very low (approximately 0.2-1.2% for *BRCA1* and 1.8-7.1% for *BRCA2* carriers).[2, 32] Reference guidelines such as NCCN and EviQ all recommended against RRM for males with *BRCA1* or *BRCA2* P/LPVs.[2, 32]

Certainty of evidence	**Values and preferences**
The certainty of evidence for mortality reduction following RRM is low (derived from observational studies, downgraded for serious risk of selection bias but upgraded for large effect size).[18] The certainty of evidence for psychosocial outcomes following RRM is very low (derived from observational studies, downgraded for recall bias).[19]	Despite high value placed on breast cancer risk reduction and availability of non-invasive options,[33] preference for RRM is heterogenous and is shaped by personal and family circumstances — those with first-degree relatives with breast cancer (74% vs 54%) or with children (76% vs 48%) were more likely to opt for surgery.[33] Younger females are often motivated by fear of cancer and transmitting risk to their children, though concerns about partnership and sexual identity may temper this.[34] While over half of *BRCA1/2* carriers in a Korean survey would consider RRM,[35] many initially preferred intensified surveillance but became more accepting of RRM following genetic counselling.[36, 37]
Resources and feasibility	**Acceptability and other considerations**

With subsidised genetic testing, RRM and breast surveillance for high-risk individuals, costs to individuals are expected to decrease substantially. No significant concerns on feasibility were noted, as discussing RRM based on risk level aligns with current clinical practice. Surgical demand is expected to remain manageable, as RRM represents one of several risk management options, with intensified surveillance and chemoprophylaxis remaining as alternatives.	In addition to reducing cancer risk, RRM may alleviate cancer-related anxiety and provide reassurance for some women who perceive their lifetime breast cancer risk to be unacceptably high. The procedure may also reduce the need for intensified surveillance and associated burden of repeated imaging, investigations, and follow-up.[18]
Expert Group deliberation of the above factors	
For females with high-risk P/LPVs, the EG agreed that the substantial reduction in breast cancer risk and mortality generally outweighed the surgical and psychosocial harms of RRM, despite low-certainty evidence. However, given its irreversible nature and heterogeneous preferences, RRM should remain a shared decision. For females with moderate-risk P/LPVs and males, the benefit of RRM did not generally outweigh potential harms.	

Recommendation 4

Offer intensified breast surveillance to females with high- or moderate-risk breast cancer-related P/LPVs who have not undergone RRM, tailoring the surveillance modality based on variant-specific risk, age, breast density and family history.	
a) For females with high-risk P/LPVs: **1. Recommend annual magnetic resonance imaging (MRI) alone for females aged <30 years.**	***Strength of recommendation:*** **Strong** Conditional
2. Consider adding mammography to annual MRI for females aged 30-39 years, based on individualised breast cancer risk assessment	Strong **Conditional**
3. Recommend combined annual MRI and mammography for females aged 40-59 years.	**Strong** Conditional
4. Consider annual mammography alone for older females with lower breast density (e.g. ≥60 years).	Strong **Conditional**
b) For females with moderate-risk P/LPVs, consider MRI or mammography based on age, variant-specific risk level and other imaging considerations.	Strong **Conditional**
c) For males aged ≥50 years with increased breast cancer risk, particularly those with *BRCA2* P/LPVs, consider offering annual mammography.	Strong **Conditional**
Recommendation remarks: Intensified surveillance is an appropriate risk-management option for individuals who have not undergone RRM. This includes individuals with HBOC syndrome-related P/LPVs and a personal history of breast cancer managed with breast-conserving treatment, where intensified surveillance of the treated and contralateral breasts should be continued, with the surveillance strategy tailored to individual breast cancer risk. Table A provides recommended surveillance strategies to guide clinical discussion; adjustment may be appropriate depending on patient-specific factors, availability of imaging modalities, and specialist radiologist advice if needed.	

Table A: Recommended annual breast surveillance modalities for females

Age group for females (years)	High-risk P/LPVs		Moderate-risk P/LPVs	
	BRCA1, BRCA2, PTEN, PALB2, CDH1, STK11	*TP53*[b]	*BARD1, CHEK2, ATM*[c]*, RAD51C/D*	*NF1*[d]
<30[a]	MRI	MRI	Not required	Not required
30-39	MRI, and consider adding MMG	MRI	Consider MRI	Consider MRI
40-49	Combined MRI and MMG	MRI	Consider MMG	Consider MRI
50-59	Combined MRI and MMG	MRI	Consider MMG	Consider MRI
60-74	Low breast density: consider MMG Persistently dense breasts: consider MRI or other imaging	MRI	Consider MMG	Consider MMG
75+	Individualised decisions for continuing surveillance based on residual breast cancer risk, life expectancy, comorbidities and patient preferences			

MMG, mammography; MRI, magnetic resonance imaging; P/LPVs, pathogenic or likely pathogenic variants

[a] Starting age of surveillance varies by PV in the high-risk category:
- *BRCA1, BRCA2*: **25 years old** or **5-10 years before the earliest known age for family breast cancer diagnosis (whichever earlier)**
- *PTEN, PALB2, CDH1, STK11:* **30 years old** or **5-10 years before the earliest known age for family breast cancer diagnosis (whichever earlier)**
- *TP53*: **20 years old**

Note: Breast cancer risk may vary between variants within the same gene, and certain variants may warrant different surveillance strategies from those shown in the table. Surveillance should be guided by variant-specific risk and the individual's overall breast cancer risk. Imaging considerations may also vary by gene within the same risk category due to gene-associated tumour biology. The examples provided below for selected P/LPVs requiring modified surveillance strategy are not exhaustive; refer to the latest clinical guidelines as evidence on variant- and gene-specific risks continue to evolve:

[b] *TP53:* MRI is recommended (instead of MMG) because of the high risk of early-onset breast cancer and concerns regarding radiation sensitivity. Ionising radiation should be minimised where effective non-ionising imaging is available.

[c] *ATM c.7271T>G* carries a substantially higher breast cancer risk than other *ATM* PVs (comparable to other high-risk PVs), hence surveillance should follow the strategy recommended for high-risk PV carriers.[d] *NF1*: MRI is preferred at younger ages because neurofibromas may hinder MMG interpretation and *NF1* carriers have a higher prevalence of early-onset breast cancer. Consider transitioning to MMG when individuals are older, based on individual risk and imaging considerations.

Evidence-to-recommendation considerations

Summary: Intensified surveillance is recommended for high-risk females who have not undergone RRM, with recommendation strength varying by age groups, according to absolute breast cancer risk, sensitivity gains, radiation risk, cost and patients' values and preferences. Recommendations are conditional where incremental benefit is uncertain, evidence is limited or cost is a consideration, for moderate-risk females and males. There is insufficient evidence to support routine male breast surveillance, with individualised consideration for higher-risk contexts such as gynaecomastia and Klinefelter syndrome.

Balance of benefits and harms

Benefits

MRI with contrast demonstrated high sensitivity in high-risk populations, detecting smaller, more likely node-negative tumours than mammography.[29] MRI sensitivity is not meaningfully influenced by age[38] or breast density,[39] though specificity is lower than mammography (MRI: 84.7%, 95% CI 79.0%-89.1% versus mammography: 93.6%, 95% CI 88.8%-96.5%, *p*=0.0101).[38] There is no relevant literature to support the use of MRI without contrast for females at high risk.[40]

Mammography has lower sensitivity in dense breasts, and a higher prevalence of rapidly growing tumours increases difficulty of interpreting mammograms.[2, 10, 41] As breast density and tumour growth rate decline with age, the relative advantages of MRI declines with age.[38] Mammography can also depict MRI-occult ductal carcinoma in situ by identifying microcalcifications.[42] **Combined MRI and mammography** achieves the highest sensitivity across all age groups (98% versus 89% for MRI alone versus 55% for mammography alone), but lowest specificity (79% versus 83% versus 94% respectively).[43]

Ultrasound should not be routinely offered as a primary surveillance modality given limited sensitivity (33-65%) and lack of evidence for standalone use in high- or moderate-risk individuals.[2] It may be considered when MRI or mammography is unavailable, contraindicated, or not tolerated (e.g. claustrophobia), during pregnancy or lactation, or for further characterisation of suspicious findings.[10, 29, 44]

Harms

Mammography involves low-dose ionising radiation, raising concern about cumulative radiation exposure and radiation-induced cancers,[10] and is associated with higher rates of pain (86% versus 12%) and physical discomfort (69% versus 45%) than MRI, while MRI is associated with higher anxiety (37% versus 28%). MRI contrast may cause allergic or infusion reactions and should be avoided in severely renal impaired and pregnant individuals.[45] Gadolinium brain deposition has been observed, with no associated adverse consequences, and its long-term clinical significance remains uncertain.[2, 45-47] Health Sciences Authority (HSA) advised using the lowest effective dose wherever possible and administering repeated doses only after careful benefit-risk assessment.[47]

Balance of benefits and harms:

For females with high-risk P/LPVs:

- <**30 years: Annual MRI alone is recommended** given its substantially higher sensitivity in younger females with dense breast tissue, the prevalence of rapidly growing tumours in this age group, and radiation concerns.[2, 10, 39]
- **30-39 years: Annual MRI alone is recommended and mammography may be added on an individualised basis**.[10] Evidence in females under 40 suggests limited additional benefit from combined imaging, with sensitivity gain for combined imaging not statistically significant compared with MRI alone: 99% (95% CI 97%-100%) versus 85% (95% CI 74%-94%) (*p*=0.091), respectively.[39, 42] Given radiation concerns and limited incremental yield, consider adding mammography for indeterminate MRI findings or specific clinical concerns that warrant additional imaging.
- **40-59 years: Combined annual MRI and mammography is recommended to maximise sensitivity**, with reduced specificity considered an acceptable trade-off given high underlying risk. This is supported by local data showing peak breast cancer incidence in *BRCA1/2* carriers around age 55.[22]
- **≥60 years:** For the purpose of determining surveillance modality in older females, 'non-dense breasts' refers to breasts with Breast Imaging Reporting and Data System (BI-RADS) density categories A (almost entirely fatty) or B (scattered fibroglandular density). **Mammography alone is generally sufficient in non-dense breasts**. Breast density declines post-menopause, which improves mammographic sensitivity and reduces MRI's relative

advantage. However, as **breast density does not change abruptly at any age,[10]** for females **≥60 years with a persistently dense breast pattern, MRI may be offered as an alternative**.

- For genes with limited direct evidence, e.g. *TP53* and *PTEN*, recommendations are extrapolated from *BRCA1/2* data, though gene-specific considerations may warrant deviation from default surveillance approach – e.g. for *TP53*, the loss of *TP53*-mediated DNA repair renders these individuals exceptionally vulnerable to radiation-induced malignancies, informing a stronger preference for MRI over mammography.[10, 41] For *PALB2*, modelling evidence supports MRI from 30 to 35 years, followed by combined imaging from 40 years.[48] For *CDH1* with higher risk of lobular cancers, MRI may be more sensitive than mammography to detect lobular cancers.[30]
- Evidence guiding the optimal age for discontinuing intensified surveillance is limited, as high-risk females ≥75 years were often excluded,[49] and no modelling studies specific to this age group with high-risk P/LPVs were identified. NCCN recommends surveillance for ≥75 years should be individualised, taking into account comorbidities, life expectancy, prior and family history of cancer, patient preference, and willingness to undergo further investigations or treatment, recognising that benefits of continued early detection diminish as remaining lifetime risk of cancer decreases with age.[2]

For females with moderate-risk P/LPVs:

- Direct evidence is limited to small cohort studies, requiring cautious extrapolation from high-risk data.[10] Given lower absolute risk, routine MRI is not recommended and annual mammography is generally sufficient. Annual mammography is not recommended for younger carriers given lower risk of early-onset breast cancer, but it may be warranted from 40 years as risk increases.
- Breast cancer risk may vary between specific variants within the same gene. For example, *ATM* c.7271T>G is associated with substantially higher breast cancer risk than most other *ATM* variants and should follow the high-risk breast surveillance recommendations. Overall, evidence in this space is evolving and indicates that some variants may require different surveillance strategies. For example, the ACMG guideline suggested that C*HEK2* c.470T>C p.(Ser428Phe) and c.1283C>T p.(Ser428Phe) confer lower risk than other *CHECK2* variants.[50]
- Gene-specific characteristics – such as associated tumour biology that affect imaging performance – may warrant deviation from default surveillance approach. For instance, for *NF1*, MRI is preferred over mammography as intramammary and cutaneous neurofibromas can obscure mammographic interpretation, and due to increased risk for early-onset breast cancer in *NF1* carriers.[2, 51]

For males with inherited breast cancer risk:

- Absolute risk of male breast cancer is overall low, with the general male population risk of about 0.12% compared to 11-13% in the general female population. Risk is most clearly increased in *BRCA2* (up to 7-9%) and modest in *BRCA1* P/LPV carriers (up to 1.2%).[32] Risk may be substantially elevated in males with gynaecomastia (odds ratio [OR] 9.78; 95% CI 7.52-12.7) or Klinefelter syndrome (OR 24.7; 95% CI 8.94-68.4).[23]
- Males have presented with advanced stage disease due to lack of screening.[2] One study found that mammography could detect clinically occult, node-negative breast cancers in asymptomatic high-risk males, with sensitivity and specificity comparable to females at population risk.[52] Evidence supporting routine mammography screening in males remains limited.

Certainty of evidence	**Values and preferences**

The overall certainty of evidence for diagnostic accuracy of breast surveillance is high, assessed using Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2).[38, 42] The certainty of evidence of mammography-related radiation-induced cancers is low, based on seven observational studies with serious inconsistencies but an observed dose-response relationship.[10]	There is important variability in values and preferences among *BRCA1/2* carriers who weigh factors including cancer risk reduction, early cancer detection, avoidance of irreversible surgery, body image, physical and sexual well-being, cancer-related worry, screening burden and cost differently.[33, 53] Cultural context, especially in Asian settings, may reduce willingness for surgery, though this may increase with greater knowledge and genetic counselling access.[36] Decisions should therefore be treated as preference-sensitive and supported by shared decision-making.
Resources and feasibility	**Acceptability and other considerations**
MRI costs considerably more than mammography. Both MRI and digital breast tomosynthesis are currently available only in specialist outpatient centres (SOCs), which limit access for eligible individuals who rely on primary care settings for screening. Based on local expert input, intensified surveillance with combined MRI and mammography aligns with international guidelines and current local practice and is not anticipated to raise significant feasibility concerns.	While intensified surveillance is probably acceptable to many, real-world adherence remains variable, with one study finding lower adherence to annual MRI (34%) than annual mammography (48%).[54] Adherence may be affected by time constraints, physical and psychological barriers, and financial barriers for uninsured individuals. Acceptability may be affected by concerns about MRI contrast and claustrophobia, and mammography-related pain and radiation.[55]
Expert Group deliberation of the above factors	
The EG considered that the benefits of intensified surveillance generally outweighed potential harms for females with high- and moderate-risk P/LPVs, but acknowledged that the optimal modality varied with age, breast density and variant-specific risk. Cost, availability and access, particularly to MRI, may affect uptake and adherence. However, the proposed surveillance approach was considered feasible within local practice, with individualisation encouraged where evidence or incremental benefit was less certain.	

Recommendation 5

a) Discuss risk-reducing strategies with females who have ovarian cancer-related P/LPVs, taking into account their individualised ovarian cancer risk, preferences and family planning considerations.	***Strength of recommendation:*** **Strong** **Conditional**
b) For females with high-risk ovarian cancer-related P/LPVs, recommend RRSO with timing guided by variant-specific risk, family history and reproductive planning.	**Strong** **Conditional**
Recommendation remarks: In the absence of effective ovarian cancer surveillance, RRSO plays a key role in ovarian cancer risk reduction. Discussion and counselling regarding RRSO should begin before the suggested age of surgery (Table B) and include discussion of timing in relation to family planning as well as potential harms such as surgical menopause. Chemoprevention, lifestyle modification and aspects of menopausal care are beyond the current ACRs' scope and will be discussed where relevant in subsequent guidance. Please refer to Annex C for details on the P/LPVs categorised under high- or moderate-risk.	

Table B: Suggested age to undergo RRSO

High-risk P/LPVs	Suggested age for RRSO[a]
BRCA1	35-39 years onwards
BRCA2	40-45 years onwards
BRIP1, PALB2[b]*, RAD51C, RAD51D*	From 45 years onwards
P/LPVs, pathogenic or likely pathogenic variants; RRSO, risk-reducing salpingo-oophorectomy [a] Earlier if there is a family history of earlier onset ovarian cancer [b] Given the lower lifetime ovarian cancer risk associated with *PALB2*, consideration of RRSO should be individualised based on family history and reproductive planning.	

Evidence-to-recommendation considerations

Summary: RRSO is strongly recommended for females with high-risk P/LPVs, given its effectiveness in reducing ovarian cancer risk and mortality, and the lack of effective surveillance alternatives. Benefits should be balanced against surgical menopause and impact on QoL. Despite these harms, RRSO appears broadly acceptable, with majority reporting satisfaction and low regret with comprehensive preoperative counselling. Reproductive plans also influence the decision to undergo RRSO and its timing, and should be respected.

Balance of benefits and harms

Ovarian cancer is associated with significant mortality, with 1-, 3- and 5-year survival rates of 73.65%, 61.31% and 59.60%, respectively.[56] Late-stage diagnosis is a major determinant of survival (stage IV vs I, risk ratio [RR] 10.54, 95% CI 9.16-12.13),[57] with early detection hampered by non-specific symptoms[58] and limitation in available screening modalities.[59, 60] Carriers of high-risk P/LPVs such as *BRCA1/2* and *RAD51D* have higher risk of high grade, late-stage ovarian cancer at a younger age than non-carriers.[61]

Benefits:

In *BRCA1/2* carriers, RRSO is effective in reducing ovarian cancer risk (OR 0.29, 95% CI 0.18-0.47), ovarian cancer-specific mortality (OR 0.62, 95% CI 0.51-0.75),[62] all-cause mortality (HR 0.52, 95% CI 0.41-0.64) and breast cancer-specific mortality (RR 0.26, 95% CI 0.18-0.39).[63] Separately, evidence for RRSO reducing breast cancer risk is inconsistent, which may explain why most

guidelines generally do not recommend RRSO specifically for breast cancer risk reduction, with its role remaining primarily for ovarian cancer risk reduction.[2, 10, 23, 63, 64] Evidence for other non-*BRCA1/2* P/LPVs is largely extrapolated from *BRCA1/2* studies.

Harms:
RRSO induces surgical menopause but is not associated with increased cardiovascular diseases, non-breast cancer mortality, contralateral breast cancer, or depression in several *BRCA1/2* studies, though these findings should be interpreted cautiously given short follow-up periods and younger study populations.[65-67] RRSO is associated with impaired sexual function and vaginal dryness.[68] Post-operative complications occurred in 6.09% of a small cohort, mostly minor pain or superficial infection.[56]

Suggested ages for RRSO are based on variant-specific cancer risk and typical age at ovarian cancer diagnosis (Table B).[2, 23, 39, 69-72]

Intensified ovarian surveillance:
A NICE systematic review found no randomised or comparative observational studies on intensified surveillance, with available evidence limited to non-comparative studies on diagnostic performance.[69] Low cancer prevalence introduced considerable uncertainty in estimates, particularly sensitivity, limiting confidence in the effectiveness of surveillance strategies.[69] Evidence for mortality benefits of intensified surveillance with transvaginal ultrasound (TVUS) and cancer antigen 125 (CA-125) remains limited.[73, 74] The Risk of Malignancy Index (RMI) which incorporates TVUS, menopausal status and CA-125 has a pooled sensitivity of 78% (95% CI 71-85%) and specificity of 87% (95% CI 83-91%),[59] but sensitivity drops to 57.9% (95% CI 44.1-70.6%) for predicting stage I ovarian cancer.[60]

Certainty of evidence	**Values and preferences**
The overall certainty of evidence for effectiveness and harms of RRSO for high-risk P/LPVs is moderate, downgraded for indirectness of evidence to non-BRCA P/LPVs. The certainty of evidence for ovarian cancer intensified surveillance is low with small number of observational studies available.	Several factors are associated with higher RRSO uptake, including older age, parenthood, *BRCA1/2* carrier status, mastectomy history, and perceived ovarian cancer risk and advantages of RRSO, whereas objective cancer risk was not significantly associated with RRSO uptake.[75, 76] Similar findings of preference to delay RRSO to 40 years was noted amongst *BRCA1/2* carriers.[77]
Resources and feasibility	**Acceptability and other considerations**
The recommended age for RRSO aligns with international practice.[2, 23, 39, 69-72] The recommendation is presumably feasible considering its similarity to existing practice locally. With the implementation of subsidised genetic testing for HBOC syndrome and the corresponding downstream intervention (including RRSO) for high-risk individuals, costs to individuals are expected to decrease substantially.	RRSO appears broadly acceptable to most high-risk females — 89.71% expressed complete satisfaction with surgery, 5.88% reported persistent stress.[78] QoL, anxiety and depression did not differ significantly in females who received RRSO versus screening only.[79]

Expert Group deliberation of the above factors

The EG strongly recommended RRSO in females with high-risk P/LPVs, as the substantial reductions in ovarian cancer risk and mortality outweighed the harms of surgery and surgical menopause, particularly given the lack of effective ovarian cancer surveillance. The EG agreed that RRSO counselling should begin before the suggested age of RRSO to facilitate shared decision-making, reproductive planning and discussion of menopause.

Annex A: Population groups recommended for genetic testing to characterise breast cancer-related gene variants*

**ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11* or *TP53*

A. Individuals with a personal history of breast cancer, who have risk factors for hereditary breast cancer who meet **any** of the following**:**

A1. A pathogenic variant (PV) identified on tumour genomic testing that would have clinical implications if confirmed to be germline; or

A2. A personal history of breast cancer with specific features:

i. ≤50 years old; or
ii. Triple-negative breast cancer; or
iii. Multiple primary breast cancers (synchronous or metachronous); or
iv. Lobular breast cancer with personal or family history of diffuse gastric cancer; or
v. Male breast cancer; or

A3. Ancestry: Ashkenazi Jewish ancestry; or

A4. A family history of:

i. ≥1 close biological relative (includes first-, second-, and third-degree relatives on the same side of the family) with:
   - Breast cancer at age ≤50 years old; or
   - Male breast cancer; or
   - Ovarian cancer; or
   - Pancreatic cancer; or
   - Prostate cancer with metastasis, or high- or very-high-risk group; or

ii. ≥3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer

A5. An estimated ≥10% probability of a *BRCA1/2* PV based on prior probability models (e.g. Manchester Score, CanRisk), even if criteria A1-A4 are not met

B. Individuals with a significant family history of breast cancer, and unknown familial genetic status. These individuals should meet **both** of the following**:**

B1.

- The individual has a first-degree biological relative with breast cancer who is unavailable for genetic testing; or
- The individual has a second-degree relative with breast cancer (unavailable for genetic testing), if no first-degree relative is available^; and

B2. An estimated ≥10% probability of a *BRCA1/2* PV based on prior probability models (e.g. Manchester Score, CanRisk)

C. Biological relatives of a known pathogenic/likely pathogenic variant (P/LPV) carrier:

C1.

- First-degree biological relatives of an individual who carries a P/LPV in a breast cancer susceptibility gene; or
- Second-degree biological relatives may be considered if the first-degree relative is unavailable^

---

^HBOC syndrome-related P/LPVs are typically inherited in an autosomal-dominant manner. As a result:

- *First-degree relatives (i.e. biological parents, children, siblings) of an individual with a PV have an estimated 50% chance of inheriting the variant and are therefore prioritised for cascade genetic screening*
- *Second-degree relatives to index patients (i.e. biological grandparents, aunts/uncles, nieces/nephews, grandchildren) have an estimated 25% chance of inhering the variant.*

*- If a first-degree relative is **unavailable for genetic testing (e.g. deceased, declined genetic testing or uncontactable)** and his/her genetic result is unknown, a second-degree relative in the direct lineage of the first-degree relative (e.g. the child of the affected first degree relative) may be considered for genetic testing.*

- Where a first-degree relative is known to test negative for the familial PV, testing of second-degree relatives is not required.

- At present, subsidised HBOC genetic testing is available for eligible first-degree relatives only. Eligibility criteria should be checked against the prevailing funding guidance, which may be updated over time.

Annex B: Population groups recommended for genetic testing to characterise ovarian cancer-related gene variants**

** *BRCA1, BRCA2, BRIP1, PALB2, RAD51C and RAD51D. EPCAM, MLH1, MSH2, MSH6 and PMS2, which are associated with an increased risk of ovarian cancers, are excluded from this annex because guidance on the downstream management of carriers will be addressed in upcoming Lynch Syndrome ACRs.*

A. Individuals with a personal history of ovarian cancer, which includes those with epithelial ovarian, fallopian tube or peritoneal cancer, who meet **any** of the following**:**

A1. A pathogenic variant (PV) identified on tumour genomic testing that would have clinical implications if confirmed to be germline; or

A2. A personal history of epithelial ovarian, fallopian tube or peritoneal cancer at any age; or

A3. An estimated ≥10% probability of a *BRCA1/2* PV based on prior probability models (e.g. Manchester Score, CanRisk), even if criteria A1- A2 are not met

B. Individuals with a significant family history of ovarian cancer and unknown familial genetic status. These individuals should meet **both** of the following**:**

B1.

- The individual has a first-degree biological relative with ovarian cancer who is unavailable for genetic testing; or
- The individual has a second-degree relative with ovarian cancer (unavailable for genetic testing), if no first-degree relative is available^; and

B2. An estimated ≥10% probability of a *BRCA1/2* PV based on prior probability models (e.g. Manchester Score, CanRisk)

C. Biological relatives of a known pathogenic/likely pathogenic variant (P/LPV) carrier:

C1.

- First-degree biological relatives of an individual who carries a P/LPV in an ovarian cancer susceptibility gene; or
- Second-degree biological relatives may be considered if the first-degree relative is unavailable^

---

^ *HBOC syndrome-related P/LPVs are typically inherited in an autosomal-dominant manner. As a result:*

- *First-degree relatives (i.e. biological parents, children, siblings) of an individual with a PV have an estimated 50% chance of inheriting the variant and are therefore prioritised for cascade genetic screening*
- *Second-degree relatives to index patients (i.e. biological grandparents, aunts/uncles, nieces/nephews, grandchildren) have an estimated 25% chance of inhering the variant.*

*- If a first-degree relative is **unavailable for genetic testing (e.g. deceased, declined genetic testing or uncontactable)** and his/her genetic result is unknown, a second-degree relative in the direct lineage of the first-degree relative (e.g. the child of the affected first degree relative) may be considered for genetic testing.*

-Where a first-degree relative is known to test negative for the familial PV, testing of second-degree relatives is not required.

- At present, subsidised HBOC genetic testing is available for eligible first-degree relatives only. Eligibility criteria should be checked against the prevailing funding guidance, which may be updated over time.

Annex C: Absolute risk for breast and ovarian cancers

This annex summarises the estimated lifetime absolute risk of breast cancer associated with pathogenic variants (PVs) in HBOC syndrome-related genes. The risk estimates in the tables below are primarily for females, for whom more comprehensive gene-specific estimates are available. For males, the absolute risk of breast cancer is substantially lower than females, estimated at approximately 0.2-1.2% for *BRCA1* and 1.8-7.1% for *BRCA2* carriers and population level risk is 0.12%.[2, 32]

Risk estimates are presented as ranges and have been compiled from international guidelines such as NCCN, European Society for Medical Oncology (ESMO), EviQ and American College of Medical Genetics and Genomics (ACMG). As Asian-specific risk estimates are currently limited for many genes, the figures presented are primarily derived from non-Asian populations and should be interpreted accordingly. These risk estimates are intended to serve as a reference to support clinical decision-making and risk discussions with patients. Cancer risk may vary between specific variants within the same gene, and gene-level risk estimates may not apply equally to all variants. Decisions on risk-reducing interventions should therefore consider variant-specific risks, alongside family history and other individual risk factors.

As evidence and variant classifications continue to evolve, users should refer to up-to-date resources such as ClinVar, ClinGen, NCCN, eviQ, for latest information, including variant-specific cancer risks and updates on variants of uncertain significance (VUS).

Category	PVs	Absolute risk for **breast** cancer for females
High risk	*BRCA1*	60-85%[2, 10, 23, 39] (local 57-61%)[22]
	BRCA2	40-85%[2, 10, 23, 39] (local 43-47%)[22]
	TP53	40-85%[2, 23, 41]
	PTEN	40-80%[2, 23, 80]
	PALB2	32-60%[2, 23, 70, 81]
	CDH1	37-55%[18, 30, 37]
	STK11	32-54%[2, 23, 24]
Moderate risk	*ATM*	Typical ~20-25%[31]; c.7271T>G: higher risk 52%[29]
	BARD1	17-30%[2, 23]
	CHEK2	~20-50%[2, 23, 50, 82]
	NF1	20-40%[2, 51]
	RAD51C	20-21%[10, 23, 71, 83]
	RAD51D	~20%[10, 23, 71, 83]
Population level risk	-	11-13%[2, 23, 39]

Category	PVs	Absolute risk for **ovarian** cancer for females
High risk	*BRCA1*	39-58%[2, 39, 84, 85] (local ~ 42%)[22]
	BRCA2	13-29%[2, 39, 84, 85] (local ~20%)[22]
	BRIP1	5-15%[2, 72, 84]
	RAD51C	10-15%[2, 71, 84]
	RAD51D	10-20%[2, 71, 84]
	PALB2	3-5%[2, 70, 84]
Population level risk	-	1.45% (local)[86]

References

1. Neumann I, Schünemann H, editor. The GRADE Book [Internet]. Version. Milan: GRADE Working Group; 2024. Available from: https://book.gradepro.org. ISBN 979-12-243-3917-5.
2. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (Version 3.2026) 2026. cited April 9, 2026. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=2&id=1545
3. 3413 v.9-Breast cancer – panel testing [Internet]. EviQ. Cancer Institute NSW 2025 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/genetic-testing-using-cancer-gene-panels/3413-breast-cancer-panel-testing#result-interpretation.
4. Maxwell KN, Wenz BM, Kulkarni A, et al. Mutation Rates in Cancer Susceptibility Genes in Patients With Breast Cancer With Multiple Primary Cancers. JCO Precis Oncol. 2020;4.
5. Weitzel JN, Kidd J, Bernhisel R, et al. Multigene assessment of genetic risk for women for two or more breast cancers. Breast Cancer Res Treat. 2021;188(3):759-768.
6. Abdel-Salam H, Mansfield PF, Moskowitz JB, et al. CDH1 incidental findings in patients with personal or family history of breast cancer. Journal of Clinical Oncology. 2023;41(16_suppl):10524-10524.
7. 620 v.16-BRCA1, BRCA2 and PALB2 – genetic testing [Internet]. EviQ. Cancer Institute NSW 2025 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/genetic-testing-for-heritable-pathogenic-variants/620-brca1-brca2-and-palb2-genetic-testing#probability-of-a-heritable-pathogenic-variant.
8. 3783 v.3-Ovarian cancer (epithelial) – panel testing [Internet]. EviQ. Cancer Institute NSW 2024 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/genetic-testing-using-cancer-gene-panels/3783-ovarian-cancer-epithelial-panel-testing#probability-of-a-heritable-pathogenic-variant.
9. Alsop K, Fereday S, Meldrum C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol. 2012;30(21):2654-2663.
10. National Institute for Health and Care Excellence: Guidelines. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer: National Institute for Health and Care Excellence (NICE); 2023.
11. Medical Services Advisory Committee. Clinical utility card for heritable mutations which increase risk in breast and/or ovarian cancer. Australia: Medical Services Advisory Committee; 2015.
12. National Institute for Health and Care Excellence. Cost-effectiveness evidence review: Familial breast cancer: Classification and care of women at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer. 2013.
13. Yadav S, Hu C, Hart SN, et al. Evaluation of Germline Genetic Testing Criteria in a Hospital-Based Series of Women With Breast Cancer. J Clin Oncol. 2020;38(13):1409-1418.
14. Nelson HD, Pappas M, Cantor A, et al. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. Jama. 2019;322(7):666-685.
15. Isselhard A, Lautz Z, Rhiem K, et al. Assessing Psychological Morbidity in Cancer-Unaffected BRCA1/2 Pathogenic Variant Carriers: A Systematic Review. Curr Oncol. 2023;30(4):3590-3608.
16. Morrish N, Snowsill T, Dodman S, et al. Preferences for Genetic Testing to Predict the Risk of Developing Hereditary Cancer: A Systematic Review of Discrete Choice Experiments. Med Decis Making. 2024;44(3):252-268.
17. Lim GH, Borje E, Allen JC, Jr. Evaluating the performance of National Comprehensive Cancer Network (NCCN) breast and ovarian genetic/familial high risk assessment referral criteria for breast cancer women in an Asian surgical breast clinic. Gland Surg. 2017;6(1):35-42.
18. O'Reilly C, McGarry JL, Zaborowski AM, et al. Risk-Reducing Bilateral Mastectomy and Mortality in Carriers of BRCA1 and BRCA2 Variants: A Systematic Review and Meta-Analysis. JAMA Surg. 2026;161(3):260-267.
19. Carbine NE, Lostumbo L, Wallace J, et al. Risk-reducing mastectomy for the prevention of primary breast cancer. Cochrane Database Syst Rev. 2018;4(4):Cd002748.

20. Wiberg R, Hägglund S, Numan Hellquist B, et al. Surgical Outcomes After Risk-Reducing Mastectomy Among BRCA1 and BRCA2 Carriers. JAMA Netw Open. 2026;9(4):e262574.
21. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. Jama. 2017;317(23):2402-2416.
22. Ho WK, Hassan NT, Yoon SY, et al. Age-specific breast and ovarian cancer risks associated with germline BRCA1 or BRCA2 pathogenic variants - an Asian study of 572 families. Lancet Reg Health West Pac. 2024;44:101017.
23. Sessa C, Balmaña J, Bober SL, et al. Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline. Ann Oncol. 2023;34(1):33-47.
24. 395 v.11-STK11 (Peutz-Jeghers) – risk management [Internet]. EviQ. Cancer Institute NSW 2026 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/395-stk11-peutz-jeghers-risk-management.
25. Loehrer E, Wagner A, Bahar M, et al. The clinicopathological features of breast cancer in Peutz-Jeghers syndrome: results from an international survey. Fam Cancer. 2025;24(2):41.
26. Wagner A, Aretz S, Auranen A, et al. The Management of Peutz-Jeghers Syndrome: European Hereditary Tumour Group (EHTG) Guideline. J Clin Med. 2021;10(3).
27. Lee JH, Ryu JM, Park JS, et al. Risk-Reducing Mastectomy in BRCA1/2 and Other High-Risk Gene Carriers: Current Evidence and Practical Guidance. J Breast Cancer. 2026;29(1):1-16.
28. Paluch-Shimon S, Cardoso F, Partridge AH, et al. ESO-ESMO fifth international consensus guidelines for breast cancer in young women (BCY5). Ann Oncol. 2022;33(11):1097-1118.
29. 1610 v.11-ATM (monoallelic pathogenic variants) – risk management [Internet]. EviQ. Cancer Institute NSW 2024 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/1610-atm-monoallelic-pathogenic-variants-risk#evidence-for-risk-management-guidelines.
30. 1090 v.11-CDH1 – risk management [Internet]. EviQ. Cancer Institute NSW 2021 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/1090-cdh1-risk-management.
31. Pal T, Schon KR, Astiazaran-Symonds E, et al. Management of individuals with heterozygous germline pathogenic variants in ATM: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2025;27(1):101243.
32. 656 v.12-BRCA1 or BRCA2 – risk management (male) [Internet]. EviQ, Cancer Institute NSW. 2025 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/656-brca1-or-brca2-risk-management-male.
33. Mansfield CA, Metcalfe KA, Snyder C, et al. Preferences for breast cancer prevention among women with a BRCA1 or BRCA2 mutation. Hered Cancer Clin Pract. 2020;18:20.
34. Glassey R, O'Connor M, Ives A, et al. Influences on decision-making for young women undergoing bilateral prophylactic mastectomy. Patient Educ Couns. 2018;101(2):318-323.
35. Park B, Kim D, Kim J, et al. Attitudes toward Risk-Reducing Mastectomy and Risk-Reducing Salpingo-oophorectomy among Young, Unmarried, Healthy Women in Korea. Cancer Res Treat. 2022;54(2):375-382.
36. Fang SY, Hsieh LL, Hung CF, et al. Attitude towards hereditary cancer risk management among women with cancer in Taiwan. Support Care Cancer. 2022;30(4):3625-3632.
37. Woo J, Gwak G, Park I, et al. Preoperative diagnosis of BRCA1/2 mutation impacts decision-making for risk-reducing mastectomy in breast cancer patients. Sci Rep. 2021;11(1):14747.
38. Phi XA, Houssami N, Obdeijn IM, et al. Magnetic resonance imaging improves breast screening sensitivity in BRCA mutation carriers age ≥ 50 years: evidence from an individual patient data meta-analysis. J Clin Oncol. 2015;33(4):349-356.
39. 3814 v.5-BRCA1 or BRCA2 – risk management (female) [Internet]. EviQ. Cancer Institute NSW. 2025 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/3814-brca1-or-brca2-risk-management-female#.
40. Yeh ED, Brown A, Freer PE, et al. ACR Appropriateness Criteria® Female Breast Cancer Screening: 2025 Update. J Am Coll Radiol. 2025;22(11s):S508-s530.
41. 749 v.12-TP53 (Li-Fraumeni) – risk management (adult) [Internet]. EviQ. Cancer Institute NSW 2024 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-

management/749-tp53-li-fraumeni-risk-management-adult#cancer-tumour-risk-management-guidelines.
42. Li M, Lin Y, Poelhekken K, et al. Diagnostic sensitivity of mammography and magnetic resonance imaging for ductal carcinoma in situ in high-risk breast cancer screening: A systematic-review and meta-analysis. Chin J Cancer Res. 2025;37(6):973-983.
43. Phi XA, Houssami N, Hooning MJ, et al. Accuracy of screening women at familial risk of breast cancer without a known gene mutation: Individual patient data meta-analysis. Eur J Cancer. 2017;85:31-38.
44. Evans A, Trimboli RM, Athanasiou A, et al. Breast ultrasound: recommendations for information to women and referring physicians by the European Society of Breast Imaging. Insights Imaging. 2018;9(4):449-461.
45. Domingo JL, Semelka RC. Gadolinium toxicity: mechanisms, clinical manifestations, and nanoparticle role. Arch Toxicol. 2025;99(10):3897-3916.
46. 742 v.8-Breast cancer (high risk with ovarian cancer family history) – risk management (female) [Internet]. EviQ. Cancer Institute NSW 2026 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/742-breast-cancer-high-risk-with-ovarian-cancer-f.
47. Health Sciences Authority (HSA). Gadolinium-based contrast agents and risk of gadolinium brain deposits 2018. cited 7 Oct 2026. Available from: https://www.hsa.gov.sg/announcements/gadolinium-based-contrast-agents-and-risk-of-gadolinium-brain-deposits/
48. Lowry KP, Geuzinge HA, Stout NK, et al. Breast Cancer Screening Strategies for Women With ATM, CHEK2, and PALB2 Pathogenic Variants: A Comparative Modeling Analysis. JAMA Oncol. 2022;8(4):587-596.
49. Lee CS, Monticciolo DL, Moy L. Screening Guidelines Update for Average-Risk and High-Risk Women. AJR Am J Roentgenol. 2020;214(2):316-323.
50. Hanson H, Astiazaran-Symonds E, Amendola LM, et al. Management of individuals with germline pathogenic/likely pathogenic variants in CHEK2: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2023;25(10):100870.
51. 752 v.13-NF1 (Neurofibromatosis type 1) – risk management [Internet]. EviQ. Cancer Institute NSW 2025 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/752-nf1-neurofibromatosis-type-1-risk-manageme.
52. Gao Y, Goldberg JE, Young TK, et al. Breast Cancer Screening in High-Risk Men: A 12-year Longitudinal Observational Study of Male Breast Imaging Utilization and Outcomes. Radiology. 2019;293(2):282-291.
53. Fitch KC, Yang JC, Ryan ES, et al. Preferences of BRCA mutation carriers for attributes of risk-reducing surgical options for breast and ovarian cancer. Cancer. 2025;131(22):e70148.
54. Knerr S, Guo B, Wernli KJ, et al. Longitudinal adherence to breast cancer surveillance following cancer genetic testing in an integrated health care system. Breast Cancer Res Treat. 2023;201(3):461-470.
55. Geuzinge HA, Heijnsdijk EAM, Obdeijn IM, et al. Experiences, expectations and preferences regarding MRI and mammography as breast cancer screening tools in women at familial risk. Breast. 2021;56:1-6.
56. Holst Lund AK, Naver KV, Petersen KR, et al. Surgical Complications of Salpingo-Oophorectomy in Women Undergoing Risk-Reducing Surgery for Hereditary Breast and Ovarian Cancer-A Retrospective Cohort Study. Journal of minimally invasive gynecology. 2026:S1553-4650(1526)00080-00084.
57. Gaitskell K, Hermon C, Barnes I, et al. Ovarian cancer survival by stage, histotype, and pre-diagnostic lifestyle factors, in the prospective UK Million Women Study. Cancer Epidemiology. 2022;76:102074.
58. Caruso G, Weroha SJ, Cliby W. Ovarian Cancer: A Review. JAMA. 2025;334(14):1278-1291.
59. Geomini P, Kruitwagen R, Bremer GL, et al. The Accuracy of Risk Scores in Predicting Ovarian Malignancy: A Systematic Review. Obstetrics & Gynecology. 2009;113(2 Part 1).

60. Ngu SF, Chai YK, Choi KM, et al. Diagnostic Performance of Risk of Malignancy Algorithm (ROMA), Risk of Malignancy Index (RMI) and Expert Ultrasound Assessment in a Pelvic Mass Classified as Inconclusive by International Ovarian Tumour Analysis (IOTA) Simple Rules. Cancers. 2022;14(3):810.
61. Innella G, Godino L, Erini G, et al. Factors predicting BRCA1/2 pathogenic variants in patients with ovarian cancer: a systematic review with meta-analysis. Journal of Clinical Pathology. 2023;76(8):510.
62. Liu T, Yu J, Gao Y, et al. Prophylactic Interventions for Hereditary Breast and Ovarian Cancer Risks and Mortality in BRCA1/2 Carriers. Cancers. 2023;16(1).
63. Gaba F, Blyuss O, Tan A, et al. Breast Cancer Risk and Breast-Cancer-Specific Mortality following Risk-Reducing Salpingo-Oophorectomy in BRCA Carriers: A Systematic Review and Meta-Analysis. Cancers. 2023;15(5).
64. Wang Y, Song Z, Zhang S, et al. Risk-reducing salpingo-oophorectomy and breast cancer risk in BRCA1 or BRCA2 mutation carriers: A systematic review and meta-analysis. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2022;48(6):1209-1216.
65. Hassan H, Allen I, Rahman T, et al. Long-term health outcomes of bilateral salpingo-oophorectomy in BRCA1 and BRCA2 pathogenic variant carriers with personal history of breast cancer: a retrospective cohort study using linked electronic health records. The Lancet Oncology. 2025;26(6):771-780.
66. Moraes FCAd, Moro LD, Souza MEC, et al. Prevalence of cardiometabolic outcomes in women who underwent salpingo-oophorectomy to prevent hereditary breast and ovarian cancer: a meta-analysis. Familial cancer. 2024;24(1):5.
67. Gootzen TA, van Gelder MMHJ, Hermens RPMG, et al. Development of cardiovascular risk factors in women with a BRCA1/2 pathogenic variant within five years after tubo-ovarian cancer risk reduction in the TUBA study. Maturitas. 2026;207:108886.
68. Kershaw V, Hickey I, Wyld L, et al. The impact of risk reducing bilateral salpingo-oophorectomy on sexual function in BRCA1/2 mutation carriers and women with Lynch syndrome: A systematic review and meta-analysis. European journal of obstetrics, gynecology, and reproductive biology. 2021;265:7-17.
69. National Institute for Health and Care Excellence: Clinical Guidelines. Ovarian cancer: identifying and managing familial and genetic risk: National Institute for Health and Care Excellence (NICE); 2024.
70. 1609 v.10-PALB2 – risk management [Internet]. EviQ. Cancer Institute NSW 2025 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/1609-palb2-risk-management.
71. 4117 v.1-RAD51C or RAD51D – risk management (female) [Internet]. EviQ. Cancer Institute NSW 2026 [cited 10 June 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/4117-rad51c-or-rad51d-risk-management-female.
72. 4118 v.1-BRIP1 – risk management (female) [Internet]. EviQ. Cancer Institute NSW 2026 [cited 26 June 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/4118-brip1-risk-management-female.
73. Menon U, Gentry-Maharaj A, Burnell M, et al. Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet (London, England). 2021;397(10290):2182-2193.
74. Pinsky PF, Yu K, Kramer BS, et al. Extended mortality results for ovarian cancer screening in the PLCO trial with median 15 years follow-up. Gynecologic Oncology. 2016;143(2):270-275.
75. Park S-Y, Kim Y, Kim S. Factors associated with the decision to undergo risk-reducing salpingo-oophorectomy among women at high risk for hereditary breast and ovarian cancer: a systematic review. Korean J Women Health Nurs. 2020;26(4):285-299.
76. Howard AF, Balneaves LG, Bottorff JL. Women's decision making about risk-reducing strategies in the context of hereditary breast and ovarian cancer: a systematic review. Journal of genetic counseling. 2009;18(6):578-597.

77. Fitch KC, Yang J-C, Ryan ES, et al. Preferences of BRCA mutation carriers for attributes of risk-reducing surgical options for breast and ovarian cancer. Cancer. 2025;131(22):e70148.
78. Ha X, Feng Z, Xia J, et al. Psychophysical and social impact of risk-reducing salpingo-oophorectomy in China: a cross-sectional study. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2026;36(4):102135.
79. Mai PL, Huang HQ, Wenzel LB, et al. Prospective follow-up of quality of life for participants undergoing risk-reducing salpingo-oophorectomy or ovarian cancer screening in GOG-0199: An NRG Oncology/GOG study. Gynecologic Oncology. 2020;156(1):131-139.
80. 546 v.13-PTEN (PTEN hamartoma/Cowden) – risk management [Internet]. EviQ. Cancer Institute NSW 2024 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/546-pten-pten-hamartoma-cowden-risk-management.
81. Tischkowitz M, Balmaña J, Foulkes WD, et al. Management of individuals with germline variants in PALB2: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(8):1416-1423.
82. 3701 v.6-CHEK2 – risk management [Internet]. EviQ. Cancer Institute NSW 2024 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/3701-chek2-risk-management-female.
83. Ngeow J, Chiang J, Astiazaran-Symonds E, et al. Management of individuals with heterozygous germline pathogenic variants in RAD51C, RAD51D, and BRIP1: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2025;27(11):101557.
84. Cancer Service Lin Development (CSLD) Workgroup. Cancer Service Lin Development (CSLD) Workgroup for Cancer Genetics of National Cancer Centre Singapore (NCCS) version 2. 2023. 2023.
85. Chen J, Bae E, Zhang L, et al. Penetrance of Breast and Ovarian Cancer in Women Who Carry a BRCA1/2 Mutation and Do Not Use Risk-Reducing Salpingo-Oophorectomy: An Updated Meta-Analysis. JNCI cancer spectrum. 2020;4(4):pkaa029.
86. Singapore Cancer Registry (Health Promotion Board). Singapore Cancer Registry Annual Report 2022 [Internet]. 2024 [cited 2026 Jun 15]. Available from: https://www.nrdo.gov.sg/docs/librariesprovider3/default-document-library/scr-ar-2022_web-report6c6e8522-cf39-416f-9390-5fe903065927.pdf?sfvrsn=3712e8bb_1.