Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening†

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The guidelines will focus on cancer prevention and screening among individuals known to harbour a pathogenic BRCA1/2 mutation. The presence of a BRCA1 or BRCA2 mutation accounts for the majority of hereditary breast and ovarian cancer syndromes.

Genetic susceptibility to breast or ovarian cancer might also be associated with mutations in other genes, some of which are associated with known hereditary cancer syndromes, such as p53, PTEN, CDH1, STK11, MLH1, MSH2, MSH6 and PMS2. The cancer risk association with other genes, such as PALB2, CHEK2, ATM, RAD51C, RAD51D and BRIP1, is still under research or clinical validation. An overview of prevention and screening strategies for these mutations is summarised in Table 1.

For initial risk assessment and the decision when to perform genetic counselling and testing, the reader is referred to the recently updated National Comprehensive Cancer Network (NCCN) guidelines on genetic/familial high-risk assessment [1], and The National Institute for Health and Clinical Excellence (NICE) guidelines [2].

Many of the recommendations in the guidelines are based on expert opinion reflecting the need for international collaborations and databases to optimise recommendations and care for screening, prevention and follow-up in this population.

prevalence and epidemiology

Hereditary cancer syndromes arise from a germline mutation, inherited from either parent, resulting in a significantly elevated risk of cancer development relative to that of the general population that does not harbour a mutation in a cancer susceptibility gene. Specifically, a germline mutation in BRCA1 or BRCA2 results in a significantly elevated lifetime risk of developing breast and ovarian cancer, estimated at up to 7 and 25 times (respectively) that of the average risk population [3–5], depending on the population studied. The presence of a mutation in BRCA2 has also been demonstrated in multiple studies to be associated with an increased risk in prostate cancer, melanoma and pancreatic cancer [6]. The association between BRCA1 and BRCA2 mutations and elevated risk of gastric cancer, colorectal cancer and uterine cancers remains weak and thus screening and prevention of these cancers among BRCA1/2 mutation carriers is generally not indicated. More than 90% of hereditary cases of breast and ovarian cancer are thought to be a result of a mutation in BRCA1/2 [7]. The estimated prevalence of BRCA1 and BRCA2 mutations is dependent on the population and can vary between 1 in 300 and 1 in 800, respectively. More than 2000 different mutations have been identified in BRCA1/2 genes, and in some populations, founder mutations are the most prevalent ones—for example up to 2.5% of the general Ashkenazi Jewish population will harbour a mutation in BRCA1 (185delAG [= c.68_69delAG], 5382InsC [= c.5266dupC]) or BRCA2 (6174delT [= c.5946delT]) [8]. Founder mutations have also been described in Northern, Western and Eastern Europe. The penetrance is variable and not clearly understood, but a recent population screening study suggested that even among those with no family history of cancer the lifetime risk of developing breast or ovarian cancer by the age of 80 was up to 83% (±7%) in the presence of BRCA1, 76% (±13%) in the presence of a BRCA2 mutation and the risk was higher in the more contemporary birth cohorts [9]. Among men harbouring a BRCA1 or BRCA2 mutation, there is an estimated lifetime risk of breast cancer of 1.2% to ≤8%, respectively [10, 11], and a doubling of prostate cancer risk.
initial counselling and follow-up of BRCA mutation carriers

Following a diagnosis of the presence of a BRCA1/2 mutation, follow-up counselling outlining options for screening for early detection, risk-reducing measures and issues pertaining to fertility in women who have not completed their family is fundamental [V, B]. The difference between the goals of screening and those of risk-reducing measures (including surgery, chemoprevention and lifestyle measures) should be clarified and the

<table>
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<th>Table 1. Prevention and screening strategies for specific mutations</th>
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<td><strong>Screening</strong></td>
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| LiFraumeni Syndrome  -  p53 mutation | 1) Clinical breast examination every 6–12 months starting from age 20–25 [V]  
2) Annual breast MRI at age 20–75. If MRI is not available, mammography may be considered [V]  
3) Colonoscopy every 5 years from the age of 25 or as clinically indicated  
4) Annual dermatological and neurological examination  
5) Consider annual whole-body MRI and 6-monthly complete blood count | 1) Avoid ionising radiation, e.g. CT  
2) Consider offering PGD before pregnancies  
3) Consider risk-reducing mastectomy |
| PTEN/Cowden Syndrome | 1) Clinical breast examination every 6–12 months starting from age 20–25 [V]  
2) Annual breast MRI and/or mammogram at age 30–75 [V]  
3) Annual endometrial ultrasound ± biopsies from age 30–35 | 1) Consider risk-reducing mastectomy  
2) Consider risk-reducing hysterectomy  
3) Consider offering PGD before pregnancies |
| ATM mutation | 1) Consider annual breast MRI (no evidence regarding the age of onset) |  |
| Lynch Syndrome  -  MLH1, MSH2,MSH6, EPCAM and PMS2 mutations | 1) Annual colonoscopy from age 20–25  
2) Annual neurological examination for screening of CNS tumours may be considered  
3) Annual endometrial ultrasound ± biopsies from age 30–35 may be considered | 1) Consider risk-reducing hysterectomy and RRSO after completion of childbearing |
| RAD51 mutation |  |
| BRIP1 mutation | 1) Consider RRSO after the age of 45  
2) Consider RRSO after the age of 45 |
| PALB2 mutation | 1) Clinical breast examination every 6–12 months starting from age 20–25 [V]  
2) Annual breast MRI from age 20–29  
3) Annual breast MRI and/or mammogram at age 30–75 [V] | 1) Consider risk-reducing mastectomy |
| CHEK2 mutation | 1) Clinical breast examination every 6–12 months starting from age 20–25 [V]  
2) Annual breast MRI from age 20–29  
3) Annual breast MRI and/or mammogram at age 30–75 [V] |  |
| STK11 mutation (Peutz–Jeghers Syndrome) | 1) Clinical breast examination every 6–12 months starting from age 20–25 [V]  
2) Annual breast MRI from age 20–29  
3) Annual breast MRI and/or mammogram at age 30–75 [V]  
4) Upper endoscopy and colonoscopy every 2–3 years from late teens  
5) Screening for pancreatic cancer with EUS or MRI from the age of 30  
6) Annual testicular examination from childhood  
7) Routine annual gynaecological surveillance  
8) Counselling to reduce lung cancer risk | 1) Consider risk-reducing mastectomy |
| CDH1 mutation | 1) Clinical breast examination every 6–12 months starting from age 20–25 [V]  
2) Annual breast MRI from age 20–29  
3) Annual breast MRI and/or mammogram at age 30–75 [V] | 1) Consider risk-reducing mastectomy |

MRI, magnetic resonance imaging; CT, computed tomography; PGD, pre-implantation genetic diagnosis; CNS, central nervous system; RRSO, risk-reducing salpingo-oophorectomy; EUS, endoscopic ultrasound.
limitations in available evidence for these measures should be clearly stated. Discussion with individuals should address issues of quality of life and the psychosocial impact of risk-reducing interventions [V, B]. Recommendations should emphasise the early onset of disease characteristics among BRCA1/2 mutation carriers and the limitations in techniques for early detection of ovarian cancer. Individuals above the age of 25 years from a family known to harbour a BRCA1/2 mutation who have not yet been tested should be encouraged to undergo testing and, if positive, to consider risk-reducing measures [V, B]. Until mutation status has been assessed and in women declining genetic testing or risk reduction measures, screening recommendations as for known mutation carriers should be followed.

If available, carriers should be encouraged to participate in dedicated high-risk follow-up clinics that specifically focus on follow-up and screening of individuals with a known hereditary cancer syndrome [V, B].

**breast cancer risk reduction**

### lifestyle modifications

Numerous observational studies have suggested that breastfeeding may reduce the risk of breast cancer among BRCA1/2 carriers. Therefore, if possible, breastfeeding should be encouraged [IV, B]. Regular exercise, maintaining healthy body weight and limiting alcohol consumption should also be encouraged, and hormone replacement therapy (HRT) should be avoided [V, B].

### screening

Clinical breast examination every 6–12 months is recommended from the age of 25 or 10 years before the youngest breast cancer diagnosis in the family, whichever is earlier [V, B]. All carriers should be encouraged to be 'breast-aware' and to seek immediate medical attention if they perceive any changes in their breasts or lumps in the axilla [V, B].

Breast magnetic resonance imaging (MRI) is well established as the most sensitive screening tool for the high-risk population [12–15]. Annual screening MRI should be commenced from the age of 25 with the addition of annual mammography from the age of 30 [II, A]. Retrospective data suggest an association between increased breast cancer risk and exposure to diagnostic radiation before the age of 30 [16]. Thus, if MRI screening is not available, annual mammography should be utilised from the age of 30 [III, B].

The decision to implement breast mammography under the age of 40 should take into consideration any increased breast density at younger ages and the availability of annual screening MRI.

In women under 30 years of age, breast ultrasonography can be considered if MRI is unavailable [IV, B]. There are no robust data supporting alternating 6-monthly radiology surveillance with MRI and mammography in the high-risk population; results from a study evaluating this issue are awaited.

Ultrasound may be considered as an adjunct to mammography at all ages and as an alternative when MRI is not available (at all ages).

risk-reducing agents

Limited data are available about the use of selective oestrogen receptor modulators (tamoxifen, raloxifene) and aromatase inhibitors as primary prevention among BRCA1/2 mutations carriers. Use of tamoxifen may be considered; however, the level of evidence is weak [IV, C].

Several observational studies have suggested that among BRCA1/2-associated breast cancer patients, tamoxifen use reduces the risk of contralateral breast cancer [17, 18]. One study suggested a benefit for contralateral risk reduction even among patients with oestrogen receptor negative tumours who received tamoxifen; however, the study numbers were limited, and the majority of patients had received chemotherapy [17]. There is no evidence to suggest that, with respect to hormonal therapy, patients with BRCA1/2-associated breast cancer should be treated any differently to those with non-BRCA-associated breast cancer; as such, adjuvant hormonal therapy should be administered as clinically indicated, irrespective of BRCA status.

### risk-reducing surgery

Bilateral risk-reducing mastectomy (RRM) is the most effective method for reducing breast cancer risk among BRCA1/2 mutation carriers [III, B]. RRM reduces the risk of breast cancer by ~90% depending on the study reported and depending on the type of surgery carried out [19–26]. The studies have been either retrospective or prospective in nature, many with over 10 years of long-term follow-up, and all but one study demonstrated a benefit in risk reduction [27]. However, no randomised controlled studies on this issue have been carried out. No survival benefits have been demonstrated in women who have undergone RRM. A variety of techniques exist: ranging from total mastectomy, through to skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM), which aim to improve cosmetic results. Immediate breast reconstruction should be offered [V, C] [28]. SSM and NSM have similar safety outcomes as total mastectomy, after breast cancer diagnosis [29, 30]. Limited data exist about these techniques as a risk-reducing measure. However, available data on safety are encouraging and cosmetic outcome is improved. Thus, SSM and NSM are accepted alternatives to total mastectomy [III, C]. It can be assumed that following NSM there is a slightly higher residual risk, as the technique leaves behind the breast envelope and nipple areola complex. Benefits, limitations, risks of surgical complications and psychosocial impact should be discussed with the individual patient/carrier. The possibility of an occult breast cancer being diagnosed at the time of surgery is <5%, and thus, routine sentinel lymph node biopsy is not indicated.

Studies assessing psychosocial aspects of RRM have, for the most part, demonstrated a favourable impact among women undergoing the procedure both in short- and long-term follow-up. These studies identified an association between reconstruction complications and communication issues with the treating physician as causes for dissatisfaction and also found that women that chose risk-reducing surgery (RRS) were more likely to perceive their risk of breast cancer more highly than women who did not opt for surgery. These issues should be taken into consideration when counselling women about RRM.
Contralateral risk-reducing mastectomy (CRRM) among patients with a previous breast cancer diagnosis can be considered [III, B]. Several retrospective and prospective studies with long-term follow-up have all demonstrated a significant reduction in contralateral breast cancer events, and two studies demonstrated a significant reduction in the risk of breast cancer-related death [31–33]. It is important to note that, in these studies, the majority of patients were under 50 years of age at the time of surgery and the majority had early (stage I–II) breast cancer at initial diagnosis.

Risk-reducing salpingo-oophorectomy (RRSO) has repeatedly been reported in several retrospective and prospective studies to reduce the risk of breast cancer among BRCA1/2 mutation carriers when carried out in premenopausal women [24, 34, 35]. However, a recent prospective cohort study, controlling for potential biases, suggested that no benefit in breast cancer risk reduction existed following RRSO [36].

ovarian cancer risk reduction

lifestyle modifications/exposures

Use of the oral contraceptive pill (OCP) has consistently been demonstrated to have a significant risk-reducing effect on the development of ovarian cancer by 40%–60% [37]. The use of the OCP may be considered as a risk-reducing measure for ovarian cancer [II, C], particularly among those seeking a form of contraception during their reproductive years. It should however be noted that there are conflicting data whether OCP increases breast cancer risk among BRCA1/2 carriers [37]. The long-term clinical significance of OCP use as a risk reduction measure for ovarian cancer is unclear, given that mutation carriers are encouraged to undergo RRSO by age 40 and that, before age 40, ovarian cancer is relatively uncommon even among mutation carriers.

screening

There are no data proving that screening for ovarian cancer reduces mortality. A recent study in the UK, in the average-risk population, demonstrated promising results with serial Ca125 screening [38]. A sister trial for high-risk women is ongoing (https://www.ucl.ac.uk/instituteforwomenshealth/womens-cancer/gcr/ukfocss) as is the GOG 19–9 trial [39]. Before RRSO, 6-monthly, trans-vaginal ultrasound and measures of serum Ca125 may be considered from the age of 30; however, the limited value of these tools as an effective screening measure should be communicated to individuals [V, C].

risk-reducing surgery

The most effective measure for reducing the risk of ovarian cancer is RRSO [I, A] (specifically RRS should incorporate removal of both the ovaries and the fallopian tubes), which has consistently been shown to reduce the risk by 80%–90% and to reduce mortality [24, 35, 40, 41]. Mutation type, the patient’s preferences and family history should be taken into consideration when deciding on the age for RRSO. Among BRCA1 carriers, the incidence of occult ovarian cancer at the time of RRSO was 1.5% before the age of 40 and 3.8% for 40- to 49-year olds [40]. Among BRCA2 carriers, the risk of ovarian cancer before the age of 50 is only 1%. RRSO should be carried out at age 35–40 [II, B].

There is an increasing body of evidence suggesting that ovarian cancer originates in the fimbria or fallopian tubes [42]. This, combined with epidemiological data demonstrating that tubal ligation and salpingectomy are associated with a lower incidence of ovarian cancer, has resulted in a growing interest in risk-reducing salpingectomy in the high-risk population. Risk-reducing salpingectomy alone cannot yet be recommended, outside the setting of a clinical trial [V, C] [42].

screening recommendations following risk-reducing surgery

Following RRS, the residual annual risk of breast and/or ovarian/peritoneal cancer is often at levels lower than the general population risk. No validated data are available from prospective, long-term follow-up studies to support offering screening schedules after RRS. It is not clear whether any surveillance regimen is necessary, effective or cost-beneficial; thus, there is no currently recommended surveillance schedule after RRS [V, C]. Following NSM in which there is more residual breast tissue, continued screening with annual breast MRI or ultrasound may be considered.

screening recommendations following a diagnosis of breast and ovarian cancer

Screening recommendations are not different for a woman who has a previous diagnosis of cancer.

reproductive considerations in BRCA mutation carriers

A multitude of fertility-related issues face female carriers. BRCA1/2 carriers can be reassured that there is no convincing evidence that mutation carriers have reduced ovarian reserve or fertility [IV, C] [43].

All women harbouring a BRCA1/2 mutation should be encouraged to complete childbearing before planned RRSO [V, C]. For women who wish to undergo RRSO and have not yet completed childbearing, fertility preservation options such as oocyte and embryo cryopreservation should be discussed [V, C].

Women harbouring a BRCA1/2 mutation who have been diagnosed with a malignancy should be counselled about options for fertility preservation before the commencement of oncology treatment [V, B]. For a full discussion of fertility preservation options, the reader is referred to the ESMO guidelines [44].

BRCA1/2 mutation carriers (male and female) planning to conceive should be made aware of the options of prenatal diagnosis (via chorionic villous or amniotic fluid sampling in weeks 11–20 of gestation) and pre-implantation genetic diagnosis (PGD) [V, C]. The risks and benefits of both approaches need to be carefully outlined and the need for in vitro fertilisation (IVF), irrespective of fertility status, if PGD is chosen must be clearly stated. A multitude of factors, including religious, cultural, ethical and socioeconomic factors, can influence an individual’s
### Table 2. Summary of recommendations

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<th>Recommendations</th>
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<td>Discussion with individuals should address issues of quality of life and the psychosocial impact of risk-reducing interventions</td>
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<td>For individuals above the age of 25 years from a family known to harbour a BRCA1/2 mutation, until mutation status has been assessed or in women declining genetic testing or risk-reduction measures, screening recommendations as for known mutation carriers should be followed</td>
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<td><strong>Breast cancer risk reduction</strong></td>
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<td><strong>Lifestyle modifications</strong></td>
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<td>Breastfeeding should be encouraged IV, B</td>
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<tr>
<td>Regular exercise, maintaining healthy body weight and limiting alcohol consumption should be encouraged and HRT should be avoided V, B</td>
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<td>Annual screening MRI should be commenced from the age of 25 with the addition of annual mammography from the age of 30 II, A</td>
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<td>If MRI screening is not available, annual mammography should be utilised from age 30 III, B</td>
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<tr>
<td>Breast ultrasonography can be considered if MRI is unavailable and may also be used as an adjunct to mammography IV, B</td>
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<td><strong>Risk-reducing agents</strong></td>
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<tr>
<td>Tamoxifen as primary prevention may be considered, although the level of evidence is weak IV, C</td>
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<td><strong>Risk-reducing surgery</strong></td>
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<td>Bilateral RRM is the most effective method for reducing breast cancer risk among BRCA1/2 mutation carriers III, B</td>
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<td>Immediate breast reconstruction should be offered V, C</td>
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<td>CRRM among patients with a previous breast cancer diagnosis can be considered III, B</td>
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<td><strong>Ovarian cancer risk reduction</strong></td>
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<td><strong>Lifestyle modifications/exposures</strong></td>
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<tr>
<td>The use of the OCP may be considered as a risk-reducing measure for ovarian cancer II, C</td>
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<td>RRSO should be carried out at age 35–40 II, B</td>
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<td>Risk-reducing salpingectomy alone is not recommended, outside the setting of a clinical trial V, C</td>
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<tr>
<td><strong>Screening recommendations following risk-reducing surgery</strong></td>
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<td>There is no currently recommended routine surveillance schedule following RRS V, C</td>
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<td><strong>Reproductive considerations in BRCA mutation carriers</strong></td>
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<td>Women harbouring a BRCA1/2 mutation who have been diagnosed with a malignancy should be counselled about options for fertility preservation before the commencement of oncology treatment V, B</td>
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<tr>
<td>Appropriate counselling should be available and vaginal moisturisers and lubricants should be prescribed to all women following RRS V, C</td>
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<tr>
<td>Short-term use of HRT to alleviate menopausal symptoms following RRSO is safe among healthy BRCA1/2 mutation carriers III, B</td>
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<tr>
<td>No safety data are available about the use of HRT among BRCA1/2 carriers with a previous diagnosis of breast cancer. The relationship between hormonal influences and the development of different breast cancer subtypes, including triple negative breast cancers, has not been fully elucidated, thus HRT in the setting of a past breast cancer diagnosis should be strongly discouraged—irrespective of endocrine status of the initial tumour V, B</td>
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Continued
choice to utilise prenatal diagnosis or PGD, and any decision should be respected. Of note, these technologies are not available everywhere.

Following RRSO, many women will suffer from menopausal symptoms including vasomotor symptoms, altered libido and vaginal dryness. Many of these will further compound psychological distress as a result of changes in body image and sexuality. Appropriate counselling should be available and vaginal moisturisers and lubricants should be prescribed to all women following RRS [V, C]. With respect to menopausal symptoms, several studies have indicated that short-term use of HRT to alleviate menopausal symptoms following RRSO is safe among healthy BRCA1/2 mutation carriers [III, B] [45]. No safety data are available about the use of HRT among BRCA1/2 carriers with a previous diagnosis of breast cancer. The relationship between hormonal influences and the development of different breast cancer subtypes, including triple-negative breast cancers, has not been fully elucidated; thus, HRT in the setting of a prior breast cancer diagnosis should be strongly discouraged—irrespective of endocrine status of the initial tumour [V, B].

There are limited data about the use of topical vaginal oestrogens and systemic absorption seems to be variable [46]; thus, topical oestrogens to alleviate vaginal dryness may be used with caution [V, C]. Premature menopause adversely impacts bone health. Following RRSO (or following chemotherapy or LHRH analogue-induced amenorrhoea for those with a previous cancer diagnosis), women should be encouraged to have bone health checked regularly; they should also be encouraged to ensure adequate dietary intake of calcium and vitamin D [i.e. adequate intake of calcium through diet and supplements (1000 mg/day) and vitamin D (800–1000 UI/day)] and to perform regular weight-bearing exercise [I, A]. Treatment-related bone loss should be managed in accordance with ESMO Guidelines for Bone Health [47].

**Prevention and screening of other BRCA-associated cancers and approach to male carriers**

BRCA2 carriers may consider annual skin and eye examination as screening for melanoma [V, C]. BRCA2 carriers may consider annual screening for pancreatic cancer with EUS or MRI/MRCP while being informed that data supporting this approach is very limited. There is no consensus when screening should commence—however, age 50 or 10 years before the earliest diagnosed case in the family would be reasonable [V, C]. Carriers should be strongly encouraged to participate in clinical trials evaluating the efficacy of screening techniques for pancreatic cancer [V, C]. Male carriers should be advised to undergo annual clinical breast examination by a physician, starting from the age of 30. No evidence exists to justify or support routine annual breast imaging among male carriers [V, C]. Annual screening for prostate cancer may be considered from the age of 40, particularly for BRCA2 carriers [V, C]. Screening recommendations for BRCA-associated malignancies should be tailored to an individual’s family history of malignancy [V, C].

**Prevention and screening of cancer in the presence of other moderate- to high-risk genetic mutation syndromes**

Advances in sequencing technologies have resulted in the growing availability of multi-gene panel testing for hereditary
cancer syndromes. The clinical validity and utility of these tests are not robustly established. Importantly, accurate and reliable risk estimation and stratification for malignancy risk is highly problematic for most of the genes identified in these panels [49].

The following genes might have moderate- to high-penetration germline mutations for breast or ovarian cancer: p53, PTEN, CDH1, PALB2, CHEK2, ATM, RAD51C, STK11, RAD51D, BRIP1, MLH1, MSH2, MSH6 and PMS2. Prevention and screening strategies for these mutations are summarised in Table 1—due to limited research in individuals harbouring these mutations, the level of evidence for these recommendations is mostly expert opinion, and a full discussion is beyond the scope of these guidelines.

personalised medicine and future directions

Individuals with a BRCA1/2 mutation of unknown significance should seek individual counselling and have screening and prevention tailored after careful consideration of pedigree, family history and, when possible, testing of other affected family members [V]. International collaborative efforts are strongly encouraged to ensure that data pertaining to variants of unknown significance (VUS) are publicly available.

Further understanding of genetic and non-genetic risk modifiers are imperative to personalise risk assessment and tailor recommendations for screening and risk-reducing measures. Genome-wide association studies (GWASs) have identified modifiers of cancer risk among BRCA1/2 carriers. Additionally, studies have been carried out assessing the putative effect of variants in candidate genes to affect the penetrance of BRCA mutant alleles in genes that interact with BRCA1 and BRCA2 proteins. Specifically, ovarian cancer cluster regions and breast cancer cluster regions among BRCA1/2 mutation carriers have been identified and each associated with modified risk of ovarian or breast cancer [50]. These results will need to be validated and their clinical utility assessed before reaching clinical practice. In the future, the growing availability and affordability of whole exome/genome studies may bring further insights into risk modification.

methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development, www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of recommendations is given in Table 2. Levels of evidence and grades of recommendation have been applied using the system presented in Table 3. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer-review process.

conflict of interest

The authors have declared no potential conflicts of interest in relation to this manuscript.

references