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SPECIAL ARTICLE

Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline☆

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INCIDENCE AND EPIDEMIOLOGY

Hereditary breast and ovarian cancer syndrome (HBOC) is clinically defined by family history criteria, and molecularly defined by identification of germline pathogenic variants (PVs) in clinically validated HBOC genes.[1] These genes are broadly classified as high-risk genes, increasing breast and/or tubo-ovarian cancer risk by at least fourfold, and moderate-risk genes, increasing risk by two- to fourfold (Table 1). There is a large overlap between clinical and molecular HBOC, i.e. individuals with both family history and a PV. The genetic basis of about half of clinical HBOC, however, is currently unknown or unexplained by single-gene variants,[2] and conversely, approximately half of individuals who harbour PVs in HBOC genes do not have a suggestive family history.[3]

Studies of the prevalence of clinical and molecular HBOC are largely based on high-risk genes in individuals of Caucasian/European ancestry, whereas population-level data in unaffected persons are limited. Clinically, HBOC has been estimated to underlie ∼10% of breast cancers. Molecularly, ∼6% of breast cancer patients harbour PVs in HBOC genes: about half (∼3%) in *BRCA1*, *BRCA2* and other high-risk genes (e.g. *PALB2*), and half (∼3%) in moderate-risk genes (e.g. *ATM*, *CHEK2*).[4,5] The remaining 4% are yet unidentified factors that may be genetic, environmental or a combination of both. In patients with high-grade ovarian cancer, germline PVs are identified in ∼15% of cases.[6]

Based on objectively determined genealogy and cancer incidence data, ∼12% of unaffected individuals have family history fulfilling the National Comprehensive Cancer Network (NCCN) testing criteria,[7] a rough surrogate for clinical HBOC. The prevalence of molecular HBOC in unaffected individuals varies based on family history and ethnicity. Family history is incorporated into tools to predict the probability of harbouring a hereditary PV[8,9]—some populations harbour founder PVs with high carrier frequencies, e.g. 2.5% (1:40) for the three *BRCA1* and *BRCA2* founder PVs in Ashkenazi Jews,[10] and 0.7%-0.8%

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Table 1. Lifetime cancer risks in HBOC-associated PVs

	Breast cancer[a]	Tubo-ovarian cancers[b]	Pancreatic cancer[c]	Colon cancer[d]	Other cancers
ATM	Yes 25%-30%	Yes ≤5%	Yes <5%	No	Prostate 30%
BARD1	Yes ∼20%	No	No	No	No
BRCA1	Yes >60%	Yes 40%-60%	Yes <5%	No	
BRCA2	Yes >60%	Yes 15%-30%	Yes <5%	No	Prostate 33%
BRIP1	No	Yes 5%-10%	No	No	No
CDH1	Yes (LBC) 40%	No	No	No	Diffuse gastric cancer 35%-45%
CHEK2	Yes 25%-30%	No	No	Yes 15%	
PALB2	Yes 40%-60%	Yes 3%-5%	Yes 2%-3%	No	No
PTEN	Yes 40%	No	No	Yes 10%	Thyroid 20%; endometrial 20%
RAD51C	Yes 20%	Yes 10%	No	No	No
RAD51D	Yes 10%	Yes 10%	No	No	No
STK11	Yes 40%	No	Yes 10%-30%	Yes 30%	Gastric 30%; Sertoli-Leydig 10%-20%
TP53	Yes 40%	No	Possibly	Possibly	Sarcoma, brain, leukaemia, adrenocortical carcinoma

HBOC, hereditary breast and ovarian cancer syndrome; LBC, lobular breast cancer; PV, pathogenic variant.
Lifetime risk in general 'average-risk' population:
[a]breast cancer 11%.
[b]ovarian cancer 1.3%.
[c]pancreatic cancer 1.6%.
[d]colon cancer 4%.

(1:125-140) for the *BRCA2* founder PV in Iceland.[11] Studies carried out in non-founder populations, largely of individuals with Caucasian/European ancestry, suggest that the carrier frequency for high-risk genes (i.e. *BRCA1*, *BRCA2*, *PALB2*) is approximately 1:150,[12-14] which is consistent with early epidemiological estimates and is discussed further in Section 1 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.004.

Recommendations

- Individuals with significant family history should be offered genetic testing using multigene panels of clinically validated HBOC genes [A].
- Clinicians should be aware that family history-based testing misses about half of HBOC syndrome gene carriers, and strategies to identify these high-risk individuals are being developed [A].

POST-TEST COUNSELLING AND FOLLOW-UP OF INDIVIDUALS WITH HBOC

Genetic counselling

Once HBOC syndrome is identified, genetic counselling should address the medical and potential psychological implications for both individuals and their families. Medical implications include impact on treatment of any current cancer and interventions for prevention or early detection of future cancers. Discussion of risks should include the risks for specific types of cancers compared with the population risks.[15] As much as possible, risk assessment should be comprehensive and tailored, incorporating not only the specific gene and variant identified, but also other individual risk factors, both non-genetic (e.g. age, reproductive history) and genetic.[16] Available, validated online tools that can aid in this evaluation include CanRisk (https://www.canrisk.org/). Risk reduction and screening recommendations should be evidence-based, where available, and include discussion of personal circumstances and preferences (e.g. family history, family planning and reproductive options).[17] Counselling must include clear explanations of familial implications, indicating which relatives, both female and male, need to be informed and offered counselling and testing in addition to counselling on reproductive implications and options [e.g. pregestational testing (PGT)]. Currently, testing is recommended only in adult relatives (except for *TP53*), although this is an evolving topic.[17,18] The age of testing of adults can be based on legal adulthood (18 years in most countries) or on the age of potential medical actionability of the PV, which is from approximately age 25. Timing of testing should be tailored to family history, patient preference and if PGT is being considered. Strategies that improve familial testing, including allowing direct communication by the medical team, should be sought.

Follow-up

Follow-up is a lifelong endeavour for individuals with HBOC, who manage complex schedules of serial imaging, risk-reducing surgeries (RRSs), risk-reducing medications (RRMeds) and ensuing quality-of-life (QoL) issues. This is best undertaken in specialised, multidisciplinary high-risk clinics including imaging services, gynaecologists, breast and plastic surgeons, genetic counsellors, psychologists and linked oncologists. Such clinics have several advantages: (i) clinical expertise in the high-risk setting, including access to clinical trials; (ii) continuity of care, including updating risk assessment and recommendations based on new evidence; (iii) consistency of care—ensuring that patients do not receive conflicting recommendations; and (iv) a bio-psychosocial approach that provides emotional as well as medical support.

Recommendations

- Post-test genetic counselling should include discussion of medical and psychological implications for both the individual and the family [A].
- Risk management should be individualised and, when available, validated tools should be used to aid decision making [B].
- Risk management should be carried out in specialised high-risk clinics that are multidisciplinary and include psychologists where possible [A].
- Enhancing awareness and availability of testing in at-risk relatives should be a priority [A].

BREAST CANCER RISK MANAGEMENT

Imaging screening for women with high-risk PVs (BRCA1, BRCA2, PALB2)

Recommendations for breast cancer screening and risk reduction in carriers of *BRCA1* and *BRCA2* PVs are shown in Figures 1 and 2.

In the presence of a PV in *BRCA1, BRCA2* or *PALB2*, screening should commence 5 years before the youngest affected family member, or latest at age 30. Clinical breast examination is of no value as a screening tool.[19] Young age is associated with a higher breast density, which interferes with mammographic detection of breast cancer.[20] Magnetic resonance imaging (MRI) has consistently demonstrated improved early diagnosis of cancer compared with digital mammography and/or ultrasound in women with or without causative PVs.[21,22] Breast cancer among women with *BRCA1* PVs exhibits fast growth rates more often than sporadic breast cancer. This shortens the 'lead time', i.e. the time available to detect the cancer while it is still in a subclinical phase, and explains the need for closer screening intervals, particularly for *BRCA1* carriers. In fact, for carriers of a *BRCA1* PV, 6-monthly screening is recommended.[23] For *BRCA1* carriers, there appears to be little benefit of additional mammographic screening, irrespective of age; however, in *BRCA2* carriers, there may be some added benefit, with no data on *PALB2*.[24-27] Whereas 6-monthly MRI would be the optimal strategy for *BRCA1* PV carriers,[23] in most countries, 6-monthly screening MRI is not available; thus, annual MRI may be supplemented (in between the annual MRIs) by ultrasound or mammography depending on age, availability and local guidelines.

There are no data on a cessation date of MRI for screening. Current guidelines recommend continuing MRI for as long as the woman is in good health.[28] Of note, it is not only breast density that drives the lower sensitivity of other breast imaging modalities in PV carriers. Accordingly, it is not recommended to 'switch' to mammography screening once density decreases with increasing age.

Retrospective studies demonstrate that 'intensified screening' results in earlier breast cancer diagnosis and improved outcomes.[29] 'Intensified screening' is defined as screening beyond the level recommended for individuals at average risk. It includes (i) the recommended age of screening onset, (ii) the recommended screening intervals and (iii) the methods involved for screening, as outlined in the summary recommendations below. 'Intensified screening' is also cost-effective.[30] Risk-reducing mastectomy (RRM) results in a remaining breast cancer risk lower than that of average risk women with natural breasts. Routine intensified screening is not indicated following RRM; however, a baseline MRI in the first year after RRM to evaluate the amount of residual breast tissue is reasonable and further decisions on whether any imaging screening is mandated should be made on a case-by-case basis. Although there is no available evidence on adopting this approach, it is suggested in order to compensate for the variable surgical styles with which skin-sparing and nipple-sparing RRM is carried out. Of note, there are no validated tools for measuring and quantifying residual breast tissue or for defining the amount of residual tissue that justifies or requires continued surveillance—this is an important area for research.

In women with ovarian cancer (including early and advanced stages at diagnosis) in a prolonged remission, intensified breast screening should be considered. Based on data from maintenance poly (ADP-ribose) polymerase (PARP) inhibitor trials in this population, it is reasonable to consider a 'prolonged remission' as being free from recurrence for at least 3 years from diagnosis.

Institutions that offer screening of HBOC families must establish the same rigorous quality assurance for MRI as done for mammography screening; clinical experience with magnetic resonance (MR)-guided vacuum-assisted biopsy must be available. There are ongoing initiatives in Europe and the United States to collect evidence on the long-term safety of repeated gadolinium exposure; however, to date there are no data to suggest adverse outcomes in the absence of renal insufficiency.

Recommendations

- Women with HBOC should be offered intensified screening if they do not opt for RRM [A].
- Breast MRI should be considered the essential component of intensified screening programmes [A].

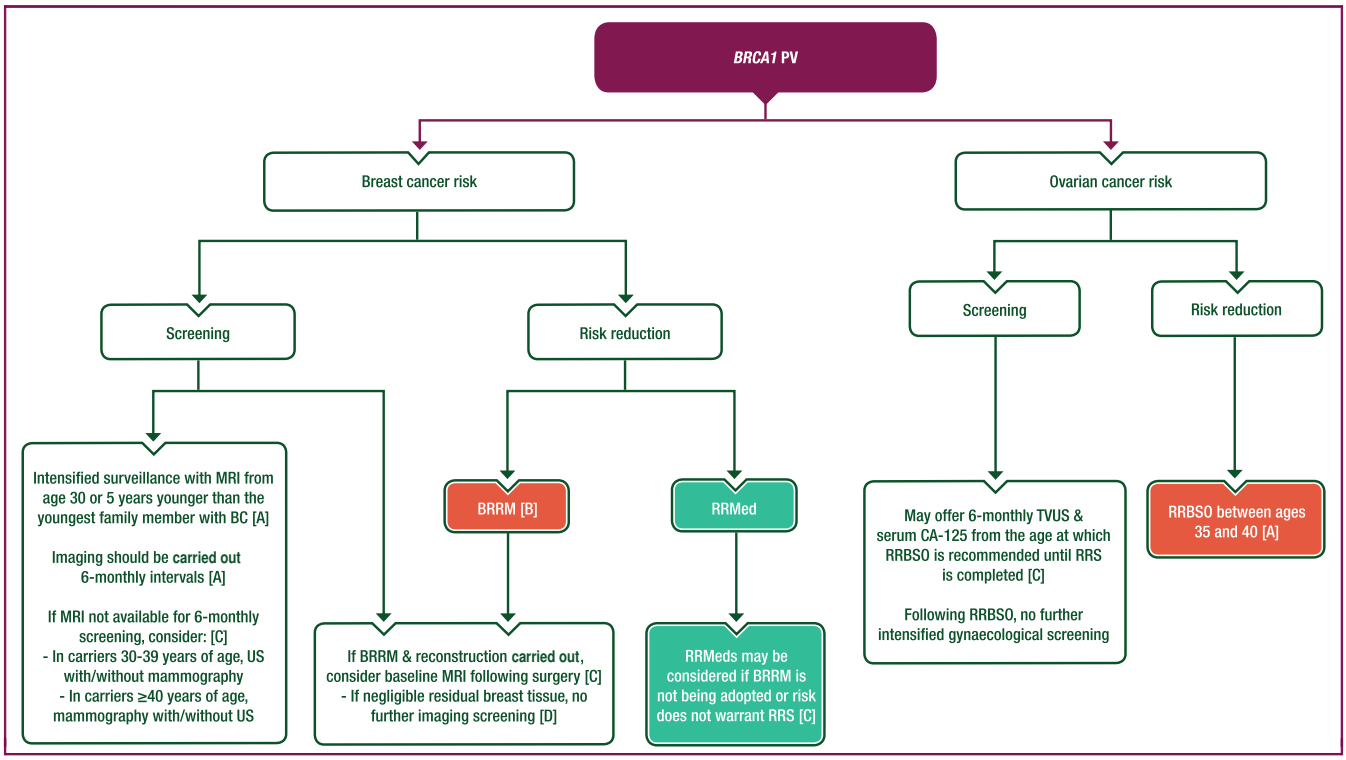

Figure 1. Breast and ovarian cancer screening and risk reduction: *BRCA1*.
Grade of recommendation is shown in square brackets. Purple: general categories or stratification; red: surgery; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
BC, breast cancer; BRRM, bilateral risk-reducing mastectomy; CA-125, cancer antigen 125; MRI, magnetic resonance imaging; PV, pathogenic variant; RRBSO, risk-reducing bilateral salpingo-oophorectomy; RRMed, risk-reducing medication; RRS, risk-reducing surgery; TVUS, transvaginal ultrasound; US, ultrasound.

- In the presence of a *BRCA1*, *BRCA2* or *PALB2* PVs, intensified screening should start at age 30, or 5 years younger than the youngest family member with breast cancer [A].
- There is currently no evidence on the appropriate end date of intensified screening; it is suggested to base the decision on individual factors such as breast density, comorbidities and the patient's priorities [C].
- Annual screening intervals are recommended, except for *BRCA1* where 6-monthly screening should be considered [A].
- If 6-monthly screening is considered, this may be best achieved by annual MRI and, depending on availability, resources and local guidelines, the following imaging may be considered in between annual MRI studies:
  - o in carriers 30-39 years of age, ultrasound with or without mammography [C].
  - o in carriers ≥40 years of age, mammography with or without ultrasound [C].
- There is no evidence to support continued routine breast imaging after RRM [D]. A baseline MRI in the first year after RRM to evaluate the amount of residual breast tissue is reasonable, however, and further decisions on imaging screening should be made accordingly on a case-by-case basis [C].
- Women in follow-up after breast-conserving treatment or unilateral mastectomy for non-metastatic hereditary breast cancer should continue with intensified screening [A].
- In women with ovarian cancer (including early and advanced stages at diagnosis) with no evidence of recurrence in a prolonged remission, intensified breast screening should be considered [C].
- There should be rigorous quality assurance of intensified screening programmes, including benchmarking of programme sensitivity, false-positive rate and recall rates and availability of MR-guided biopsy [A].

Lifestyle factors and breast cancer risk

All studies of lifestyle factors and hereditary breast cancer risk are observational, with potential for bias and residual confounding. Many risk factors confer consistent relative risks (RRs) across the risk spectrum, resulting in greater absolute increases for those with higher underlying genetic risk. Studies of *BRCA1/2* PV carriers are limited by relatively small sample sizes and selection bias, but findings are mostly consistent with those for the general population.

Physical inactivity and being overweight postmenopausally are associated with increased breast cancer risk in those at increased familial risk.[31,32] Breastfeeding is associated with reduced breast cancer risk for *BRCA1* PV carriers, but less so for *BRCA2*,[33,34] which is consistent with studies in the general population demonstrating a stronger inverse association for estrogen receptor-negative disease. Conversely, the inverse associations with breast cancer risk seen in the general population for earlier age at first birth and higher parity are less clear for *BRCA1/2* PV carriers.[33,34] Current use of hormonal contraceptives and combined hormone replacement therapy (HRT) is associated with increased breast cancer risk in the general population;[35,36] but whether this holds true for

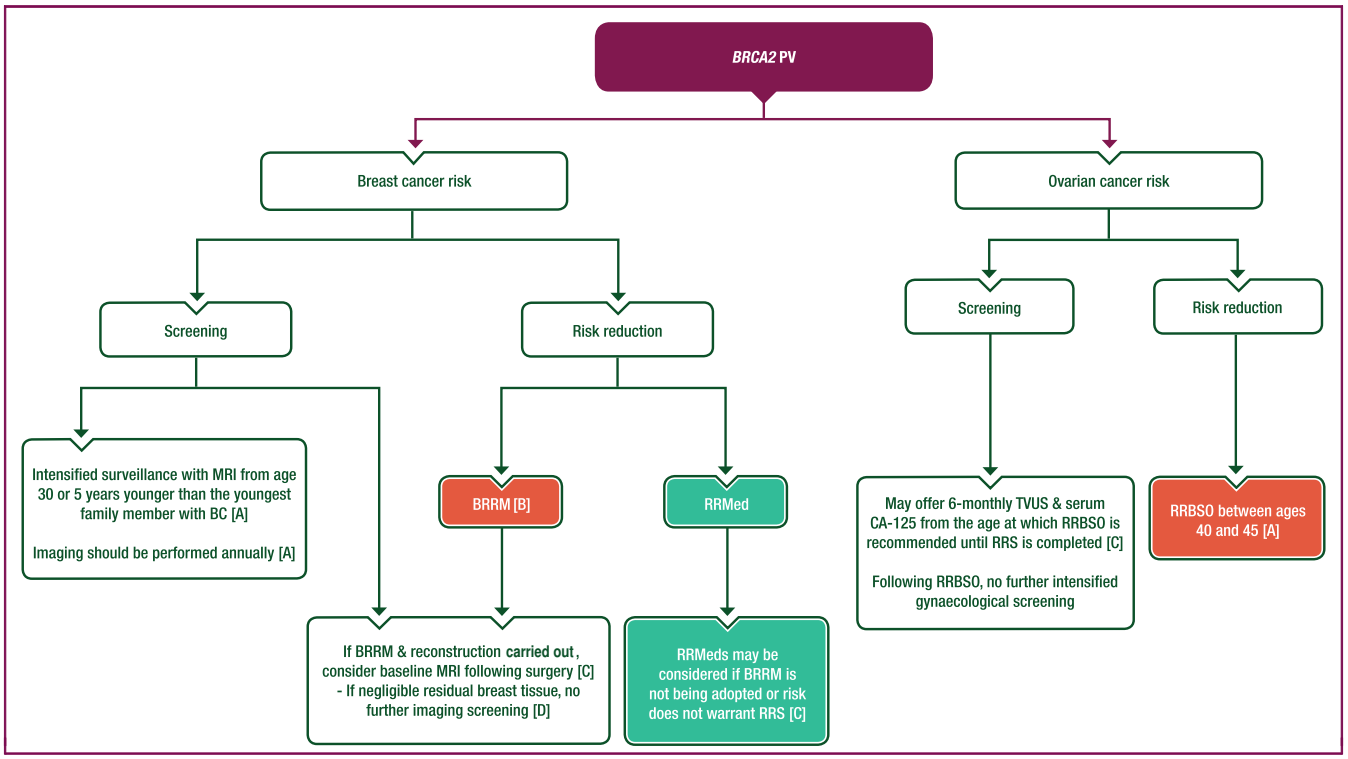

Figure 2. Breast and ovarian cancer screening and risk reduction: *BRCA2*.
Grade of recommendation is shown in square brackets. Purple: general categories or stratification; red: surgery; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
BC, breast cancer; BRRM, bilateral risk-reducing mastectomy; CA-125, cancer antigen 125; MRI, magnetic resonance imaging; PV, pathogenic variant; RRBSO, risk-reducing bilateral salpingo-oophorectomy; RRMed, risk-reducing medication; RRS, risk-reducing surgery; TVUS, transvaginal ultrasound; US, ultrasound.

BRCA1/2 PV carriers is less clear.[34,37,38] Although alcohol is associated with increased risk for breast cancer in the general population,[39] studies have not demonstrated a clear association for *BRCA1/2* PV carriers.[34,40]

Recommendations

- Physical exercise most days at moderate or strenuous intensity should be encouraged if appropriate (more is better); avoid being overweight or obese and encourage breastfeeding [B].
- Minimise alcohol intake [C].
- Decisions about hormonal contraception should weigh the possible increase in breast cancer risk against contraceptive efficacy, convenience and reduction in risk of ovarian cancer [C].

Risk-reducing medication

RRMed is an option for women who postpone, or do not undergo, elective bilateral RRM (BRRM). In randomised placebo-controlled trials for women with an elevated lifetime risk (LTR) of breast cancer (genetic status was only available in a very small subset of these women), the selective estrogen receptor modulators, tamoxifen and raloxifene, and the aromatase inhibitors, anastrozole and exemestane, reduced breast cancer incidence by ~30%-60%, especially estrogen receptor-positive disease. The absolute risk of serious side-effects was low, particularly for premenopausal women.[41] Five years of daily tamoxifen (20 mg) or anastrozole (1 mg) reduces risk for at least 20 and 10 years, respectively. Lower dose, shorter-duration tamoxifen is an option if the 20 mg dose is not tolerated. Tamoxifen is the only option for premenopausal women. Side-effect profiles should be considered when choosing between agents for postmenopausal women, including risks of thrombosis, endometrial cancer and osteoporosis.

Data pertaining specifically to women with PVs in germline predisposition genes are extremely limited. The underpowered LIBER trial showed no reduction in first breast cancers in carriers of *BRCA1/2* PVs randomised to letrozole versus placebo.[42] A subgroup analysis of the effect of tamoxifen for individuals with *BRCA1* and *BRCA2* in the NSABP-P1 trial was too small and thus uninterpretable.[43] Observational studies of tamoxifen and aromatase inhibitors for risk reduction of contralateral breast cancer have suggested benefits for carriers of both *BRCA1* and *BRCA2* PVs.[44] There are no data pertaining to PVs in other breast cancer predisposition genes.

Recommendation

- RRMeds can be considered for primary risk reduction of breast cancer and risk reduction of contralateral disease in women who decline BRRM, or who have a risk level that does not warrant surgery [C].

Risk-reducing surgery

BRRM is the most effective method for reducing breast cancer risk among *BRCA1/2* PV carriers.[45] High-risk carriers

who may wish to consider RRM are those with PVs in other high-risk genes: *TP53*, *PTEN*, *STK11*, *CDH1* and *PALB2*. For these rare and less known PVs, RRM should be discussed after careful consideration of individualised risk assessment.[46] In all affected high-risk PV carriers, contralateral RRM (CRRM) lessens the incidence of contralateral breast cancer without proven impact on overall survival.[45,47]

BRRM reduces the risk of breast cancer by ~90% depending on the study and type of surgery carried out.[45] No randomised controlled studies of this procedure have been carried out. One study reported a benefit in disease-specific survival in *BRCA1* carriers despite limitations in the control group.[48]

The benefits of RRM are likely greatest if carried out from the age of 30 (until the age of 30, the cumulative risk of breast cancer for *BRCA1* and *BRCA2* carriers is only 4%);[49] however, beyond age 55, the evidence for benefit is weak.[50] Ultimately, the decision regarding if and when to perform RRM is determined by patient preference and may be influenced by family history.

BRRM is an extensive procedure that needs to be carefully discussed taking into consideration benefits, complications and psychosocial impact.[51] A variety of techniques exist: ranging from total mastectomy (TM) to skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM), which aim to improve cosmetic results. Limited data suggest NSM provides similar risk reduction and possibly superior cosmetic outcomes than TM or SSM; however, follow-up is limited.[52] Immediate breast reconstruction should be offered.

Recommendations

- BRRM is the most effective method for reducing breast cancer risk for *BRCA1/2* carriers and should be discussed in the context of individually tailored decision making [B].
- BRRM should be discussed in carriers of other high-risk genes alongside family history—*TP53*, *PTEN*, *STK11*, *CDH1* and *PALB2* [C].
- NSM is a reasonable alternative to TM [C].
- Immediate reconstruction is safe and should be offered [C].
- In women with stage I-III high-risk PV-associated breast cancer (not including *TP53*), breast conservation with therapeutic radiation is a safe alternative to RRM. RRM should be considered within the context of disease prognosis, risks and benefits and patient preference [C].
- In women with ovarian cancer (including early and advanced stages at diagnosis) in a prolonged remission, RRM may be considered on a case-by case basis [C].

OVARIAN CANCER RISK MANAGEMENT

Imaging and screening

Recommendations for ovarian cancer screening and risk reduction in carriers of *BRCA1* and *BRCA2* PVs are shown in Figures 1 and 2.

All studies of ovarian and fallopian tube cancer screening in HBOC carriers are observational. Potential benefits of screening based on transvaginal ultrasound and a cancer antigen 125 (CA-125) test include disease downstaging and higher rates of complete resection with lower surgical complexity.[53,54] However, it remains unknown whether screening improves survival in high-risk women (see Section 2 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.004). False positive results may lead to unnecessary surgery, which is of particular concern in women below the age at which risk-reducing bilateral salpingo-oophorectomy (RRBSO) is recommended or those who have not completed childbearing.[53,54] An experienced sonographer (level 3 practitioner) can distinguish between benign and malignant ovarian tumours to avoid unnecessary surgeries.[55] Identifying specific histological subtypes, such as high-grade serous cancer, which is the most frequently represented cancer among *BRCA1/2* PV carriers, is desirable.[56]

There are no data to support ongoing gynaecological screening after RRBSO.

Recommendations

- Although of uncertain benefit, ovarian screening with transvaginal ultrasound every 6 months and serum CA-125 determination may be considered starting at the age at which RRBSO is offered (and until RRBSO is carried out). Clear benefits of RRBSO alongside the limitations and harms of screening should be communicated to patients [C].
- Screening, if carried out, should be provided in tertiary care/high-volume centres under structured screening protocols by an experienced sonographer [C].
- There is no evidence to support routine screening after RRBSO [D].

Lifestyle factors and risk-reducing medication

Use of the oral contraceptive pill (OCP) is associated with 40%-60% lower risk for ovarian cancer.[34] As noted earlier, however, there are conflicting data on whether OCP increases breast cancer risk amongst *BRCA1/2* carriers.[34,37] The long-term clinical significance of OCP use as a risk-reduction measure for ovarian cancer is unclear, given that PV carriers are encouraged to undergo RRBSO before the age at which ovarian cancer risk becomes relevant.

Risk-reducing surgery

Considering the absence of reliable screening for early detection and the poor prognosis associated with advanced ovarian cancer, the most effective approach to prevent ovarian and fallopian tube cancers is RRBSO.[57] Pathological evaluation of the surgical specimen should include a Sectioning and Extensively Examining the FIMbriated End (SEE-FIM) protocol.

RRBSO should include bilateral removal of both ovaries and fallopian tubes and should be reserved for patients at high risk of epithelial ovarian and fallopian tube cancer; it is

commonly recommended for patients with PVs in *BRCA1/2*, *BRIP1*, *RAD51C*, *RAD51D* or the Lynch syndrome genes *MLH1*, *MSH2* and *MSH6*. RRBSO may be considered for postmenopausal women with a *PALB2* PV.

In women with a PV in *BRCA1/2*, RRBSO has been shown to be effective in reducing the risk of gynaecological tumours (including ovarian, fallopian tube or primary peritoneal cancers) by 80%-90%, and to decrease the all-cause mortality by 77%.[58]

There is debate about whether RRBSO also significantly reduces the risk of breast cancer, particularly for premenopausal *BRCA1* carriers. Based on current evidence, this surgical procedure is not recommended specifically to decrease the risk of breast cancer.[58,59]

The PV type, patient's preferences and family history should be taken into consideration when deciding the timing of RRBSO. It should be delayed until an age when ovarian cancer risk is increased above that of the general population. Performing RRBSO before the necessary age can have a negative impact on a woman's health including all the consequences of premature menopause (increased risk of osteoporosis, cognitive dysfunction, cardiovascular disease and early mortality)—thus appropriate timing is critical.

The average age of ovarian cancer diagnosis varies with type of PV, and in patients with *BRCA2* PVs is an average of 8-10 years later than in women who are carriers of *BRCA1* PVs. For this reason, RRBSO is recommended once the desire for pregnancy is completed in women aged between 35 and 40 years with *BRCA1* PVs, and in women aged between 40 and 45 years with *BRCA2* PVs.[60] Of note, for women with a *BRCA2* PV, in the absence of family history of early-onset ovarian cancer, it is reasonable to perform RRBSO at 45 years of age.

The most appropriate approach to RRS is through minimally invasive, laparoscopic surgery to reduce morbidity and hospitalisation time and provide a better aesthetic outcome.

The use of salpingectomy with delayed oophorectomy is under investigation as a strategy in *BRCA1* and *BRCA2* PV carriers in several prospective observational trials such as WISP, PROTECTOR, SOROCk and TUBA.[61-64] Given the strong evidence that RRBSO leads to a reduction in mortality, the prospective studies detailed above are necessary before wide implementation of salpingectomy with interval oophorectomy, particularly for *BRCA1* carriers with an earlier onset and higher risk of ovarian cancer.

There are conflicting data on the risk of developing endometrial cancer in patients with *BRCA* PVs. Some studies suggest a connection between *BRCA* PVs and development of serous uterine cancer (primarily in *BRCA1*) with a two- to threefold increased risk and yet a more recent study does not demonstrate any elevated risk.[65] In any case, any absolute risk remains low, and it is not clear if the potential magnitude of benefit associated with hysterectomy is sufficient to justify the risks associated with the procedure.[66-68]

Hysterectomy should not be routinely recommended at the time of RRBSO to reduce cancer risk unless other indications for this procedure exist, such as a PV in the *MLH1*, *MSH2* or *MSH6* genes, other risk factors for endometrial cancer or benign uterine pathology. Current data support a lower risk of endometrial and ovarian cancer in *PMS2* mutation carriers, with insufficient evidence to recommend prophylactic surgery.[69,70] For further information on the management of Lynch syndrome, please refer to https://www.esmo.org/guidelines/guidelines-by-topic/gastrointestinal-cancers/hereditary-gastrointestinal-cancers.

Some carriers may choose to undergo hysterectomy with RRBSO to use estrogen-only HRT, which is associated with a decreased risk of breast cancer, without increasing their risk of endometrial cancer.[71]

Recommendations

- The most effective strategy for ovarian cancer risk reduction in *BRCA1/2* PV carriers is RRBSO [A].
- RRBSO should be carried out in women who have completed childbearing, at age 35-40 for *BRCA1* PV carriers and at age 40-45 for women with *BRCA2* PVs. Timing of surgery should take into consideration family history [B].
- RRBSO should be considered in women who have completed childbearing who are carriers of PVs in *BRIP1*, *RAD51C* or *RAD51D* at age 45-50. RRBSO may be considered for postmenopausal women with a *PALB2* PV [C]. For gynaecological RRS in Lynch syndrome, please refer to https://www.esmo.org/guidelines/guidelines-by-topic/gastrointestinal-cancers/hereditary-gastrointestinal-cancers.
- Risk-reducing salpingectomy (bilateral salpingectomy alone or bilateral salpingectomy followed by delayed oophorectomy) are not recommended outside the setting of a clinical trial [C].

RISK REDUCTION AND SCREENING OF OTHER *BRCA*-ASSOCIATED CANCERS AND APPROACH TO MALE CARRIERS

Male carriers—breast cancer

Cancer risks specific to men include male breast and prostate cancer. The LTR of male breast cancer in the general European population is ~0.1% and prostate cancer 10%-12.5%. There is evidence for an increased risk of male breast cancer for nearly all HBOC genes.[72-75] The most compelling is for men with *BRCA2* PVs, with an LTR of up to 8%.[73] For other genes, LTR is <1%. Risks can be substantially increased by the presence of gynaecomastia (RR 9.8) or Klinefelter syndrome (RR 24.7).[76] There is little evidence of efficacy of routine mammography screening in males.

Male carriers—prostate cancer

The HBOC genes have been widely linked with an increased risk of prostate cancer. The evidence for a significantly increased risk is more robust for *BRCA2*,[77,78] whereas several studies do not demonstrate an elevated risk for *BRCA1*.[65] There is a moderately increased risk for *ATM*[79,80] but inconsistent evidence to confirm an

increased risk with *PALB2*[75] or *CHEK2*.[81] The evidence for prostate cancer screening is largely based on the IMPACT screening study. *BRCA2* carriers had a higher incidence than *BRCA2* non-carriers and were diagnosed significantly younger and with more aggressive disease.[82] Using a prostate-specific antigen (PSA) threshold of 3.0 ng/ml, tumours were detected at a more treatable early stage and prostate cancer screening was recommended for *BRCA2* carriers.

Recommendations

- Annual mammography or ultrasound screening should be considered in male *BRCA2* carriers with additional high-risk features such as gynaecomastia or Klinefelter syndrome from age 50 or 10 years before the earliest male breast cancer in the family [C].
- Male *BRCA2* carriers should be encouraged to be aware of physical changes in the breast and seek medical attention accordingly [C].
- Annual blood PSA screening should be offered to male *BRCA2* carriers from age 40 years [B] and may also be considered for male *ATM* carriers from age 40 years [C].

Pancreatic cancer screening

Several guidelines make recommendations on pancreatic cancer screening[83-86] based on evidence from studies that included individuals with PVs in genes associated with pancreatic cancer and/or those who have strong familial pancreatic cancer risk (at least two first-degree relatives on the same side of the family). Most evidence, however, has been garnered in genetic conditions with higher pancreatic cancer risks than in *BRCA1*, *BRCA2*, *ATM* or *PALB2*,[86-89] such as *STK11* and *CDKN2A* (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.10.004). Some suggest offering screening from age 50 in HBOC carriers with a close relative, defined as a first- or second-degree relative with pancreatic cancer. Although current studies suggest that surveillance can achieve 'downstaging' at diagnosis, advanced interval cancers are common, and there is no evidence for improved survival. Notably, in one recently published screening study for patients considered at high risk for developing pancreatic cancer, the majority of screening-detected pancreatic cancers were stage I with favourable long-term outcomes.[90]

Recommendations

- Screening with annual contrast-enhanced MRI and/or endoscopic ultrasound from age 35 (or 5-10 years younger than the affected relative) may be considered in *STK11* carriers [C].
- Screening (as above) from age 50 (or 5-10 years younger than the affected relative) may be considered in *BRCA1*, *BRCA2*, *ATM*, *TP53* or *PALB2* carriers with at least one first- or second-degree relative with exocrine pancreatic cancer [C].
- Screening should be carried out in a centre with high-volume experience [C].
- All screening should ideally be carried out as part of a clinical trial [A].

COUNSELLING, RISK REDUCTION AND SCREENING IN THE PRESENCE OF OTHER MODERATE-HIGH RISK GENETIC PV HBOCS

Genetic testing for HBOC susceptibility often incorporates screening for PVs in genes beyond *BRCA1* and *BRCA2*. Many of these genes are involved in the homologous DNA repair pathway; however, associated cancer risks (in terms of types of cancer and their LTRs) vary widely gene by gene (Table 1) as do the approaches to screening and risk reduction. During counselling, it is important to differentiate 'other genes' from *BRCA1* and *BRCA2*.

PVs in *PALB2*, *CDH1*, *PTEN*, *STK11* and *TP53* are associated with a high LTR for breast cancer. The latter four are associated with specific syndromes [Hereditary Diffuse Gastric Cancer (*CDH1*), Cowden (*PTEN*), Peutz—Jeghers (*STK11)* and Li—Fraumeni syndromes (*TP53*)] with associated guidelines.[15,18,91-93] Annual MRI screening is recommended from age 20 for *TP53* and from age 30 for *PALB2*, *CDH1*, *PTEN* and *STK11*, tailored to family history. BRRM may be discussed on a case-by-case basis.

PVs in *PALB2* are associated with breast cancer risk of 40%-60%;[75] (approach to screening and RRS described above).[15,85,94] PVs in *ATM* and truncating PVs in *CHEK2* are associated with an LTR of breast cancer of ~25%, although these risks are modified by family history, mammographic breast density and single nucleotide polymorphisms (SNPs) in the context of a polygenic risk score (PRS).[95] Although the United States NCCN guidelines recommend enhanced screening solely on the basis of an *ATM* or truncating *CHEK2* PV,[15] the authors advise that screening recommendations consider integration of these risk factors and the addition of MRI to mammographic screening from age 40. The data regarding *BARD1*, *RAD51C* and *RAD51D* are complicated as they are associated with an increased risk of triple-negative breast cancer without substantially increasing overall risk of breast cancer (RR ~2).[4,5] Screening recommendations need to consider known risk factors including family history and mammographic density.

The LTR of associated ovarian cancer varies widely (Table 1). PVs in *BRIP1*, *RAD51C* and *RAD51D* are associated with risks of ≥10%; thus, RRBSO is recommended by age 45-50.[15] The risk of ovarian cancer in *PALB2* is 3%-5% and that of *ATM* is likely ≤5%. Premenopausal RRBSO is not routinely recommended at this level of risk. In postmenopausal women with *PALB2* PV, RRBSO can be considered. *CHEK2* PVs are not associated with ovarian cancer risk.[96] Recommendations for RRBSO have been discussed previously in this manuscript. Conflicting data exist about the elevated risk of colon cancer associated with *CHEK2* PVs.[96] Risks associated with prostate cancer and pancreatic cancer are discussed earlier.

NBN, *MRE11* and *RAD50* were not validated as breast cancer genes in two recent large international studies.[4,5]

Recommendations

- Women with PVs in *ATM*, *BARD1*, *CHEK2* (truncating), *RAD51C* or *RAD51D* should have comprehensive assessment of breast cancer risk to determine eligibility for breast MRI [C].
- In the presence of *CDH1*, *PTEN* or *STK11* PVs, intensified breast screening should start at age 30, or 5 years younger than the youngest family member with breast cancer and from age 20 for *TP53* [A].
- RRBSO should be considered in women who have completed childbearing who are carriers of PVs in *BRIP1*, *RAD51C* and *RAD51D* at age 45-50. RRBSO may be considered for postmenopausal women with a *PALB2* PV [C]. For gynaecological RRS in Lynch syndrome, please refer to https://www.esmo.org/guidelines/guidelines-by-topic/gastrointestinal-cancers/hereditary-gastrointestinal-cancers.
- Validated risk assessment tools such as CanRisk (https://www.canrisk.org/) may be used to aid individual risk management [C].

REPRODUCTIVE AND ENDOCRINOLOGICAL ISSUES IN INDIVIDUALS WITH HBOC

Several unique reproductive and endocrinological considerations exist for women with HBOC.

Contraception

The most used forms of contraception remain hormonally based—OCP, injectables/implants and the progesterone-intrauterine device (IUD). Reservations about use of the OCP have been addressed earlier. Although not contraindicated, unaffected carriers should be offered alternative non-hormonal forms of contraception when feasible and minimise prolonged periods of exposure to exogenous hormones. Of note, in women interested in tamoxifen chemoprevention, concurrent use of the OCP is contraindicated due to elevated risk of venous thromboembolism (VTE).

Fertility

A growing body of preclinical evidence has suggested that *BRCA* function and *ATM*-mediated DNA double-strand break repair are implicated in ovarian aging.[97] Nevertheless, clinical evidence remains controversial.[97] Therefore, although a potential negative impact on female ovarian reserve and reproductive potential cannot be excluded, no definitive counselling can be made in this regard. In male carriers, gonadal function is apparently normal, but data are limited.[97]

Completion of childbearing before the recommended age for RRBSO should be encouraged. If this is not feasible, oocyte and embryo cryopreservation can be offered at a young age, similar to cancer patient candidates for fertility preservation strategies before chemotherapy.[98] Albeit limited, the available safety data in this setting are reassuring, without apparent increased breast or ovarian cancer risk following ovarian stimulation for oocyte collection.[97]

Carriers with highly penetrant cancer susceptibility syndromes should be informed about the possibility to access prenatal diagnosis or preimplantation genetic testing (PGT) that may be used if they would like to avoid passing on the hereditary PV to future offspring.[99] Carriers should be counselled about any relevant risk of associated autosomal recessive syndromes such as Fanconi Anaemia (may be relevant for *BRCA1/2*, *PALB2*, *BRIP1* and *ATM* PV carriers) and testing of partners. Pros and cons of these strategies, including potential pregnancy termination in the case of prenatal diagnosis and the need for *in vitro* fertilisation (IVF) strategies with PGT, should be clearly discussed. Religious, cultural, ethical and socioeconomic issues, as well as country/centre availability, are important factors affecting the individual's choice to access these technologies.[98] Thorough and balanced counselling, putting couples' autonomy in the centre of the decision-making process, is key.

Management of menopausal symptoms

Healthy carriers undergoing RRBSO at a young age should be informed of short- and long-term health consequences of premature menopause.

Data on the use of HRT in unaffected carriers are limited and mostly retrospective. Results from ongoing prospective studies are awaited. While some data suggest that HRT is safe, a recent study has suggested that this may be true for women up to age 45; however, beyond that, there may be an increased risk of breast cancer.[100,101] Thus, short-term HRT may be offered after RRBSO. Longer-term use of HRT for unaffected carriers >45 years who have also previously undergone BRRM may be considered on a case-by-case basis. Limitations and risks of HRT should be clearly communicated, and while mitigating menopausal symptoms and risk of osteoporosis, any benefits in cardiovascular and cognitive health are controversial.

In contrast to systemic HRT, local vaginal therapies, including low-dose intravaginal estrogens, may be considered to manage genitourinary symptoms of menopause, including vulvovaginal dryness and dyspareunia as well as urinary symptoms of urgency, dysuria or recurrent urinary tract infection (UTI).

Bone health

Regular assessment of clinical risk factors for accelerated bone loss and measurement of bone mineral density is recommended for women who underwent RRBSO while premenopausal.[102] Resistance and weight-bearing exercise, smoking cessation and reduced alcohol intake are highly encouraged, together with vitamin D and calcium supplements and antiresorptive therapy whenever indicated.[102]

Recommendations

- Healthy female carriers should be encouraged to complete childbearing before the recommended age for RRBSO [A]; if this is not feasible, oocyte and embryo cryopreservation can be offered at a young age [B].

- Patients with HBOC should be informed about the options of prenatal diagnosis or PGT [A].
- In unaffected *BRCA1/2* carriers, discussing limitations and risks, HRT after RRBSO may be considered to alleviate menopausal symptoms [C].
- Bone assessment should be considered, tailored to individual risk factors. Preventive/therapeutic measures should be considered as indicated [B].
- Low-dose intravaginal estrogens may be considered to manage genitourinary symptoms of menopause [C].

UNIQUE PSYCHOLOGICAL ISSUES FOR INDIVIDUALS WITH HBOC

Results of observational studies of the psychological impact of HBOC are highly variable.[103] Although it is often assumed that carriers have increased psychological distress (e.g. anxiety, depression), at least half of studies to date report no differences in distress between carriers and non-carriers.[104,105] Moreover, increased levels of psychological distress observed in the immediate weeks following genetic testing disclosure have been shown to return to baseline levels 6-12 months later, with no significant clinically relevant symptoms in the long-term.[106,107] There are, however, individual women who do experience elevated and sustained levels of psychological distress in this setting. Individual risk factors include high levels of anxiety and depression before genetic testing,[106] presence of a cancer diagnosis,[108] being unpartnered and family cancer history.[109] Evidence regarding the effectiveness of psychosocial interventions is emerging but limited,[110] with most interventions focusing on delivering information and emotional support.

Observational studies consistently reveal a negative impact on sexual function, including vaginal dryness and loss of sexual satisfaction following RRBSO. Moreover, studies show that sexual dysfunction is long-lasting and that decrement in function is independent of menopausal status before RRBSO or use of HRT.[111] The impact of HBOC on body image has primarily been assessed in the context of BRRM. In contrast to sexual function, impact of BRRM on body image is more complex.[112] Although quantitative studies demonstrate that most women are satisfied with their decision to undergo RRM,[113] qualitative studies reveal various negative effects, including distress about loss of sensation and discomfort with reconstructed breasts as well as decreased perceived attractiveness and femininity.[114] Salient risk factors for decreased body image include poor reconstruction outcomes, surgical complications and lack of information before surgery.[114]

Recommendations

- The need for further informational and emotional support should be assessed before genetic test disclosure, and individuals should be offered referrals for either psychological counselling and/or further support [B].
- Sexual health concerns should be assessed, and individuals should be offered support and resources, as needed, to address sexual dysfunction. Individuals should be asked about sexual health concerns regardless of age, partner status or sexual orientation [A].

PERSONALISED MEDICINE AND FUTURE DIRECTIONS

The use of germline genetic testing has led to vast improvements in screening, risk reduction and therapies for those with inherited cancer susceptibility. Despite this, there is a need for more individualised risk assessment to inform timing and type of risk-reduction strategies, such as RRM and RRBSO. In *BRCA1* and *BRCA2* PV carriers, for example, *BRCA* genotype, family history and genetic modifiers all impact individual risk. SNPs have been well validated to alter cancer risk both in the general population and in those with inherited cancer susceptibility.[115] A PRS captures the risk associated with SNPs and can be used in models such as CanRisk.[95] PRSs may be particularly important in individuals with inherited PVs in *ATM* or *CHEK2* as some of these individuals will have close to average risk of breast cancer and others quite an elevated risk. Modification by PRS is likely to become increasingly important as individuals without a strong family history of cancer undergo genetic testing. Research is ongoing to understand how to most effectively use PRSs clinically.

Early data from the OlympiA adjuvant study of olaparib suggests a potential role for PARP inhibitors for risk reduction.[116] Studies are needed, however, to examine the risk, benefit and schedule in healthy individuals. Denosumab and acetyl salicylic acid (aspirin) are part of ongoing risk-reduction studies to advance this area in *BRCA1/2* carriers.[117]

An early detection strategy using liquid biopsies targeting tumour-derived mutational, epigenetic or transcriptomic features is another emerging area with relevance to individuals with genetic susceptibility. Techniques which would allow early detection of cancers such as ovarian cancer and pancreatic cancer may fundamentally alter our approach. For example, if stage I ovarian cancer could be reliably detected, routine use and/or timing of RRBSO could be reconsidered. Avoiding surgery-induced menopause in women in their 30s could have a major impact on QoL and long-term outcomes on bone and cardiac health. Early data are provocative; however, these tests may not have the needed performance characteristics in early-stage breast, ovarian and pancreatic cancer, and false positives are common.[118] Thus, they are not recommended for clinical use at this time.

Recommendation

- Use of PRSs, interval salpingectomy, novel risk-reduction strategies and liquid biopsy assays for early detection should continue to be carried out and assessed in the context of clinical trials [A].

METHODOLOGY

This Clinical Practice Guideline was developed in accordance with the European Society for Medical Oncology (ESMO) standard operating procedures for Clinical Practice

Guidelines development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. Grades of recommendation have been applied using the system shown in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.10.004.[119,120] Statements without grading were considered justified standard clinical practice by the authors. Level of evidence has not been provided as no randomised controlled studies are available in this field, with most data being observational/retrospective. For future updates to this CPG, including eUpdates and Living Guidelines, please see the ESMO Guidelines website: https://www.esmo.org/guidelines/guidelines-by-topic/hereditary-syndromes.

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CS has reported non-remunerated activities as Coordinator Gynecological Programme for the European School of Oncology.

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SLB has reported fees as an author for UpToDate. She has also reported non-remunerated activities as the chair of the Scientific Network on Female Sexual Health and Cancer (academic organisation).

MJC has reported fees as an invited speaker for Roche (industry-sponsored symposium in National Conference). She has also reported non-remunerated activities as a member of the Board of Directors of EUSOMA, faculty member of ESO, project lead/lead investigator for the Breast Research Group of INESC TEC and President of MAMA Help (non-profit association for breast cancer patients in Portugal). She serves as a Specialty Editor for *The Breast*.

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SP-S has reported fees paid to her institute for advisory board membership for AstraZeneca, Eli Lilly, Exact Sciences, Medison, Pfizer and Roche; fees paid to her institute as an invited speaker for AstraZeneca, Eli Lilly, Exact Sciences, Medison, Novartis, Pfizer and Roche; fees paid to her institute for consultancy for Medison; personal and institutional research grant for an request for proposal for independent research put out by Shared Progress in Cancer Care and Pfizer.

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