



SEOM clinical guidelines in hereditary breast and ovarian cancer (2019)

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Abstract

Mutations in *BRCA1* and *BRCA2* high penetrance genes account for most hereditary breast and ovarian cancer, although other new high-moderate penetrance genes included in multigene panels have increased the genetic diagnosis of hereditary breast and ovarian cancer families by 50%. Multigene cancer panels provide new challenges related to increased frequency of variants of uncertain significance, new gene-specific cancer risk assessments, and clinical recommendations for carriers of mutations of new genes. Although clinical criteria for genetic testing continue to be largely based on personal and family history with around a 10% detection rate, broader criteria are being applied with a lower threshold for detecting mutations when there are therapeutic implications for patients with breast or ovarian cancer. In this regard, new models of genetic counselling and testing are being implemented following the registration of PARP inhibitors for individuals who display BRCA mutations. Massive sequencing techniques in tumor tissue is also driving a paradigm shift in genetic testing and potential identification of germline mutations. In this paper, we review the current clinical criteria for genetic testing, as well as surveillance recommendations in healthy carriers, risk reduction surgical options, and new treatment strategies in breast cancer gene-mutated carriers.

Keywords Hereditary breast · Ovarian cancer · SEOM guidelines

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Hereditary breast and ovarian cancer syndrome (HBOC): Introduction

Hereditary breast and ovarian cancer (HBOC) is a syndrome that involves increased predisposition primarily to breast cancer (BC), and/or to ovarian cancer (OC).

Most breast and ovarian cancers are sporadic, while hereditary predisposition accounts for 10–15% of the cases, principally with respect to germline mutations in high penetrance *BRCA1/2* genes. Cumulative BC risk for *BRCA1* and *BRCA2* mutation carriers at 70 years of age is about 57%, respectively, while cumulative OC risk is approximately 40% for *BRCA1* and 18% for *BRCA2* mutation carriers [1].

BRCA1/2 genes were discovered in the 1990s and are involved in homologous recombination repair pathway. HBOC families associated with *BRCA1* or *BRCA2* germline mutations present an autosomal dominant hereditary pattern, with early age of cancer onset, bilaterality, and male breast cancer.

Initial studies by the Breast Cancer Linkage Consortium have also pointed toward an association between *BRCA1* and *BRCA2* mutations and prostate and pancreatic adenocarcinomas, among others. Subsequent research has further confirmed these associations [2].

The past 5 years has witnessed substantial advances in the field of cancer genetics. The development of next-generation sequencing (NGS) has enhanced the ability to test for many genes concurrently and significantly lowered the cost of genetic testing. We have gained greater insights into hereditary cancer, with the identification of additional genes found to confer significant risk for either breast or

ovarian cancer, such as *TP53*, *PALB2*, *PTEN*, *CHEK2*, *ATM*, *NF1*, *NBN*, *CDH1*, *STK11*, *RAD50*, *RAD51C*, *RAD51D*, or *BRIP1*, among others [3].

All this progress has not come about without generating new challenges as well, such as the large number of variants of uncertain significance (VUS) detected and the lack of information on the degree and spectrum of risks associated with these new genes.

Moreover, the introduction of PARP inhibitors in cancer therapy can lead to a major change in the framework for genetic testing in oncology patients.

Clinical criteria for germline testing in HBOC risk assessment

We strongly recommend genetic risk evaluation and genetic counselling (before and after germline testing) for patients who are at high risk of harboring a pathogenic mutation in one of the breast/ovarian cancer predisposition genes. Genetic counselling is a process that guarantees a discussion about the benefits and limitations of genetic testing, including information about cancer risk, recommendations for early detection and prophylactic interventions, as well as advice regarding reproductive options, and support for psychological well-being.

At least nine different European guidelines containing recommendations for *BRCA1/2* testing have been published in the last 4 years [4]. These criteria are associated with a probability of $\geq 10\%$ mutation detection. Clinical criteria for genetic testing differ from one set of guidelines to the next, but all of them are based on clinical risk factors such as age, hormone receptor status, ancestry with founder mutations,

Table 1 Selection criteria for germline testing

Regardless of family history:

Women with synchronous or metachronous breast and ovarian cancer

Breast cancer ≤ 40 years

Bilateral breast cancer (the first diagnosed ≤ 50 years)

Triple-negative breast cancer ≤ 60 years

High-grade epithelial non-mucinous ovarian cancer (or fallopian tube or primary peritoneal cancer)

Ancestry with founder mutations

BRCA somatic mutation detected in any tumor type with a allele frequency $> 30\%$ (if it is known)

Metastatic HER2-negative breast cancer patients eligible to consider PARP inhibitor therapy

2 or more first degree relatives with any combination of the following high-risk features:

Bilateral breast cancer + another breast cancer < 60 years

Breast cancer < 50 years and prostate or pancreatic cancer < 60 years

Male breast cancer

Breast and ovarian cancer

Two cases of breast cancer diagnosed before age 50 years

3 or more direct relatives with breast cancer (at least one premenopausal) and/or ovarian cancer and/or, pancreatic cancer or high Gleason (≥ 7) prostate cancer

and personal and family history of cancer (Table 1). The application of these criteria to select patients has two major limitations:

- (a) Most of these guidelines are based predominantly on the probability of carrying pathogenic mutations in *BRCA1* or *BRCA2*. Thus, the sensitivity of these criteria to identify pathogenic mutations in different high or moderate-risk genes is limited.
- (b) Recent research supports BRCA testing in a broader range of individuals, if not in every breast cancer patient. This recommendation is based on the findings of studies that conclude that the traditional approach may miss up to 50% of mutation carriers [5, 6].

New criteria for germline testing, regardless of family history, are arising thanks to improvements in massive tumor sequencing techniques, as well as in predicting response to new therapeutic agents. Following detection of a somatic mutation in a cancer predisposition gene with high allele frequency, it is advisable to rule out a germline mutation considering possible implications in genetic counselling. Use of PARP inhibitors for germline *BRCA1/2* mutated HER2-negative metastatic breast cancer patients obviously implies previous germline testing.

Genetic testing methodologies in HBOC

HBOC linked to pathogenic variants in high and moderate penetrance cancer genes constitutes 5 and 15% of the burden of breast and ovarian cancer, respectively. *BRCA1* and *BRCA2* are the most common mutated susceptibility genes in both tumors, followed by *PALB2* (in BC) and genes with pathogenic variants that confer moderate penetrance cancer risk, such as *ATM/CHEK2* (in BC) and *BRIP1*, *RAD51C*, *RAD51D*, *MLH1*, *MSH2*, and *MSH6* (in OvC) [7]. Clinical validity for *BRCA1/2* and *PALB2* (BC/OvC), and *BRIP1*, *RAD51C*, *RAD51D*, *MLH1*, *MSH2*, *MSH6* (OvC) has been established with subsequent surveillance and preventive clinical options. Therefore, HBOC germline panels including these genes are recommended (Evidence II, Recommendation A) (II, A) [8].

Reported mutations consist chiefly of small deletions/insertions, nonsense mutations, and splice variants resulting in truncated proteins. In addition, large rearrangement alterations may also be found in < 10%. Therefore, genetic testing for these genes should include sequence analysis and deletion/duplication analysis (IIA) [9].

Tumor genomic profiling is becoming an integral part of care in the setting of metastatic cancer. A somatic mutation of *BRCA1/2* is a biomarker for PARPi treatment in ovarian

cancer patients and testing is recommended for treatment decision-making (IIIA).

Clinical guidelines are being developed to provide recommendations to prompt germline testing after a pathogenic variant has been identified in tumor sequencing [10, 11]. Despite the challenges and limitations of assessing variant allele frequency (VAF) in the tumor, a VAF > 30% is within the range to raise suspicions of a germline origin. Based on this and the algorithms used in earlier guidelines, triggering of germline analysis for *BRCA1*, *BRCA2*, *PALB2*, *BRIP1*, *RAD51C*, and *RAD51D* is recommended following identification of a pathogenic variant with > 30% VAF in any of these genes in any tumor at any age. (IIA). The *ATM* and *CHEK2* genes remain controversial, as they might be present in some germline panels although there is no broad agreement regarding their clinical validity and subsequent surveillance recommendations. Multidisciplinary genetic tumor boards should be charged with managing interpretation of variants and referral for germline testing (IIIB).

Cancer screening in carriers of mutated HBOC-involved genes

The current standard of care for patients with moderate-risk germline mutations is based on expert recommendations. We should not extrapolate the same guidelines for the high-risk genes.

There is currently no international consensus regarding the optimal risk threshold for recommending MRI surveillance. Some experts recommend initiating mammographic surveillance at the age when the estimated 5-year risk approaches 1%, and add breast MRI at the age when the risk reaches 2.5% [12]. However, the most practical approach is to begin with mammography and MRI at the same age (Table 2).

Studies on the association of *BRCA1/2* mutations with colorectal cancer have yielded controversial results. A recent meta-analysis concluded that colorectal cancer risk is increased in *BRCA1* (OR 1.49), but not in *BRCA2* [13].

Because *BRCA1/2* mutation carriers have an increased risk of prostate cancer before 65 years of age, and *BRCA2* carriers are diagnosed earlier and are associated with a worse prognosis, it is reasonable to consider prostate cancer screening at the age of 40 and to consider screening annually.

Mutations in *BRCA2*, *PALB2*, and *ATM* have been associated with increased familial risk of pancreatic cancer (PC), but the associated absolute risks are not robust. *ATM*, *BRCA2*, and *PALB2* mutation carriers with a first- or second-degree relative with PC are candidates for clinical trials of PC screening strategies. Issues such as age when screening should be initiated, which is the best imaging technique,

Table 2 Cancer screening in mutation carriers

Gen	Breast cancer screening	Ovarian cancer screening	Other cancer screening
BRCA1/BRCA2	<p>Women</p> <p>Annual breast MRI with contrast from the age of 30–70 years (II,A)^{a,b}</p> <p>Annual mammography from the age of 30 to 75 years (II,A)^{c,d}</p> <p>Men</p> <p>No evidence of clinical benefit of breast screening (III,C). Consider mammography in the case of gynecomastia</p>	<p>6-monthly, transvaginal ultrasound and Ca.125 may be considered from the age of 30 until the age of RRSO or for those who have not elected RRSO (III,C)</p>	<p>Annual screening with PSA for prostate cancer from the age of 40 years, Recommended in BRCA2, and offer in BRCA1 (II,B)</p> <p>Consider pancreatic cancer surveillance with EUS and MRI in carriers with a first-degree-relative with pancreatic cancer from the age of 50 or 10 years before the youngest diagnosis in the family (II,C)</p> <p>Consider skin and eye examination for melanoma screening according personal/familial risk factors (III,C)</p> <p>Discuss pancreatic cancer surveillance with EUS and MRI in carriers with a first-degree-relative with pancreatic cancer from the age of 50 or 10 years before the youngest diagnosis in the family (II,C)</p> <p>Consider offer pancreatic cancer surveillance with EUS and MRI in carriers with a first-degree-relative with pancreatic cancer from the age of 50 or 10 years before the youngest diagnosis in the family (II,C)</p>
PALB2	<p>Annual breast MRI with contrast from the age of 25 years (III,A)^e</p> <p>Annual mammography from the age of 35 years (III,A)^e</p>	<p>Moderate evidence of increased OC risk. Insufficient evidence for recommend RRSO or screening (III,C)</p>	<p>Discuss pancreatic cancer surveillance with EUS and MRI in carriers with a first-degree-relative with pancreatic cancer from the age of 50 or 10 years before the youngest diagnosis in the family (II,C)</p>
ATM	<p>Consider annual breast MRI with contrast from the age of 40 years according personal/familial risk factors (III,A)^e</p> <p>Annual mammography from the age of 40 years (III,A)^e</p>	<p>Potential increase in OC risk. Insufficient evidence for recommend RRSO or screening (III,C)</p>	<p>Consider offer pancreatic cancer surveillance with EUS and MRI in carriers with a first-degree-relative with pancreatic cancer from the age of 50 or 10 years before the youngest diagnosis in the family (II,C)</p>
CHEK2	<p>Consider annual breast MRI with contrast from the age of 40 years (III,A)^e</p> <p>Annual mammography from the age of 40 years (III,A)^e</p>	<p>No evidence of increased risk</p>	<p>Consider colonoscopy from the age of 40 years, and repeat every 5 years (II,B)</p>
RAD51C	<p>Unknown o insufficient evidence for BC risk Recommend BC screening based only on family history</p>	<p>No evidence of clinical benefit. Consider offer annual transvaginal ultrasound and Ca.125 from the age of 40 until the age of RRSO or for those who have not elected RRSO (III,C)</p>	
RAD51D	<p>Unknown o insufficient evidence for BC risk Recommend BC screening based only on family history</p>	<p>No evidence of clinical benefit. Consider offer annual transvaginal ultrasound and Ca.125 from the age of 40 until the age of RRSO or for those who have not elected RRSO (III,C)</p>	
BRIP1	<p>No increased BC risk</p> <p>Recommend BC screening based only on family history</p>	<p>No evidence of clinical benefit. Consider offer annual transvaginal ultrasound and Ca.125 from the age of 40 until the age of RRSO or for those who have not elected RRSO (III,C)</p>	

(**II, A**): (Evidence Level II, Recommendation Grade A)

BC breast cancer, OV ovarian cancer, RRSO bilateral risk reduction salpingo-oophorectomy, EUS endoscopic ultrasound, MRI magnetic resonance imaging

^aOr early if family history of breast cancer before 30 years

^bWhen MRI is unavailable, we recommend screening with mammography and breast ultrasound (II,B)

^cDiscuss delaying until 40 years for BRCA1 if annual MRI screening

^dEven beyond, according to comorbidity

^eIndividualised if family history

interval, or optimum duration of follow-up have yet to be determined. The benefits and limitations of PC screening should be discussed with the carriers. PC screening in high-risk individuals is associated with a higher detection and higher resectability rates and longer survival, but more multicenter and prospective studies are needed to evaluate the benefits of PC screening [14].

Unlike *BRCA1/2* mutations, in the presence of a very strong BC family history, moderate-risk mutations in *CHEK2* or *ATM* account for only a portion of the familial risk. A woman from these families with a negative predictive result of moderate-risk mutation probably remains at some degree of elevated cancer risk and will likely require increased breast cancer surveillance.

Risk-reducing surgery and chemoprevention

Prophylactic mastectomy

Prospective studies suggest that bilateral risk reduction mastectomy (BRRM) decreases the occurrence of breast cancer in women with a moderate-high risk by 90% without a decrease in all-cause mortality [15]. One cohort study suggests that a survival benefit of BRRM may be limited to *BRCA1*, but does not extend to *BRCA2* carriers [16]. In female *BRCA* mutation carriers without a prior history of cancer, BRRM entails a considerable decrease in BC risk (IIB). Prophylactic contralateral mastectomy in patients with BC and *BRCA1/2* mutation significantly decreases the incidence of contralateral BC (IIB). BRRM options include skin-sparing mastectomy or a nipple–areola sparing mastectomy (NASM). There are no studies comparing these surgeries; nevertheless, NASM is deemed safe and effective in reducing BC risk (II, C).

Cumulative life breast cancer risk for *PTEN* (Cowden's syndrome), *CDH1*, *PALB2*, *CHEK2*, *ATM*, and Li–Fraumeni mutation carriers are 85.2%, 39–52%, 35%, 28–37%, 33%, and 5%, respectively. There are no specific data regarding the benefit of BRRM in these populations, although it seems reasonable to discuss this procedure on an individual basis, based on family history, comorbidities, and life expectancy (IIIC) [17].

Bilateral risk reduction salpingo-oophorectomy (RRSO)

A meta-analysis of 10 studies demonstrated a risk reduction of OC, fallopian tube cancer, and primary peritoneal cancer of ~80% in women with *BRCA 1/2* mutation after salpingo-oophorectomy (RRSO). A 1–4.3% residual risk of primary peritoneal carcinoma has been reported. RRSO confers a 77% reduction in all-cause mortality [18]. RRSO is recommended

for women who carry a *BRCA1* mutation and do not wish to have more children (IA), aged 35–40 years; whereas the same recommendation is made for *BRCA2* mutation carriers with ages of 40–45. This age difference is established because *BRCA1* mutated carriers tend to develop OC at younger ages. Individual circumstances and familial patterns of occurrence must be taken into consideration (IIA). Several studies have demonstrated a 50% reduction in BC risk when an RRSO is performed in premenopausal women. However, it is possible that this benefit may have been overestimated. RRSO for breast cancer reduction should be recommended only to women under the age of 50 (IIC). Short-term and low-dose hormone therapy in oophorectomized *BRCA* mutation carriers without a personal history of breast cancer might be considered (IIB).

RRSO in carriers of moderately penetrant pathogenic genes should be contemplated on a case-by-case basis. For *BRIP1* carriers, RRSO is recommended from 45 to 50 years of age. The same recommendations have been proposed for *RAD51C/D* carriers, unless family history suggests an earlier risk of developing ovarian cancer. Cumulative life endometrial and ovarian cancer risk for Lynch syndrome carriers is 60% and 24%, respectively. Therefore, RRSO is also an option to be considered (IIIC).

Pharmacological prevention (chemoprevention)

Preventive treatments are an option for female *BRCA*-mutated carriers who do not want to undergo BRRM, at least initially. In the subgroup of women with *BRCA2* mutations assigned to tamoxifen in the NSABP-P1 study, there was a 62% breast cancer risk reduction compared to placebo, but not in *BRCA1* mutated carriers, although definitive conclusions cannot be drawn due to the small sample size [19]. Thus, tamoxifen in primary prevention could be considered (IIIC). In secondary prevention, several non-randomized observational studies found a reduction in the risk of contralateral breast cancer by 45–60% in *BRCA1/2* mutation carriers with a previous diagnosis of breast cancer and adjuvant treatment with tamoxifen (IIA) [20]. Use of AI for risk Query prevention in *BRCA*-mutated carriers is investigated in the ongoing randomized phase 3 clinical trial LIBER.

Oral contraceptives in *BRCA1/2* mutation carriers can reduce the risk of OC by 50%, with the benefit being greater with longer duration of treatment. Their use is not contraindicated, although there is a possibility of an increased risk of BC.

Treatment strategies in cancer patients with *BRCA* mutations

Surgery

BRCA genetic testing in patients with early stage BC can affect their locoregional treatment because mutation carriers have a higher risk of contralateral BC than non-carrier BC patients. Therefore, patients with a history of unilateral breast cancer may benefit from bilateral mastectomy [21] (IIIA).

Platinum-based chemotherapy

Triple-negative BC platinum-based neoadjuvant chemotherapy significantly increased pathological complete response (pCR); nevertheless, in the 96 *BRCA*-mutated patients included in two randomized controlled trials, the addition of carboplatin was not associated with significantly increased pCR rates [22]. The effect of these compounds on long-term outcomes is unknown (IB). In the metastatic setting, carboplatin has shown a statistically clinical benefit compared to docetaxel among *BRCA* mutation carriers [23]. Platinum salts might be considered in the neoadjuvant setting (IC), and in the metastatic setting among *BRCA*-mutated patients with BC (IA).

Retrospective studies have shown improved prognosis, higher response rates to platinum-containing regimens, and longer treatment-free intervals between relapses in patients with *BRCA1*- and *BRCA2*- (*BRCA1/2*)-mutated ovarian cancer (OC) compared to wild-type *BRCA1/2*.

PARP inhibitors

Poly ADP-ribose polymerase (PARP) inhibitors are a class of targeted agents capable of inducing synthetic lethality in mutated *BRCA1/2* tumor cells and have been proven to improve progression-free survival (PFS) in phase III clinical trials in several types of *BRCA*-related cancer such as ovary, breast, pancreas, and prostate.

In high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, olaparib is indicated as monotherapy in the maintenance treatment of FIGO stages III and IV *BRCA*-mutated (germline and/or somatic) cancer patients who are in response (complete or partial) following completion of first-line platinum-based chemotherapy [24]. Rucaparib is also indicated in the same type of person who has been treated with two or more previous lines of platinum-based chemotherapy and who are unable to tolerate further platinum-based chemotherapy. Large phase III trials have recently reported that niraparib and veliparib as maintenance

treatment after platinum-based chemotherapy in OC have been demonstrated to significantly improve PFS. Patients positive for homologous recombination deficiency (HRD) and mainly, *BRCA*-mutated carriers, obtained the greatest benefit.

Olaparib and talazoparib are indicated as monotherapy for the treatment of *BRCA*-mutated carriers who have HER2-negative, locally advanced or metastatic breast cancer after progression to endocrine therapy and/or chemotherapy.

Currently, olaparib has also shown a clinically meaningful benefit in radiological PFS in men with *BRCA1*, *BRCA2*, or *ATM* mutations in metastatic castration-resistant prostate cancer, and in PFS as maintenance therapy in pancreatic cancer following platinum-based chemotherapy regimen. Nonetheless, indications for each agent will continue to evolve in keeping with upcoming and ongoing clinical trials.

Management of women with familial risk and no germline mutation

For those women with a positive family history of BC and no mutation in a high/moderate penetrance gene, BC risk can be estimated by predictive models, such as BOADICEA or Tyrer-Cuzzyck. In women with a cumulative lifetime BC risk of 25–30%, both annual mammography and breast MRI should be offered (IIB) beginning at the age when their 10-year BC risk reaches 5% (IIIC) [25, 26].

Bilateral mastectomy should be put forth as a risk-reducing option in women at high risk based on predictive models and managed by a multidisciplinary team (IIIC). Neither gynecological screening nor risk-reducing surgery is recommended unless there is a positive family history of OC, in which case medical management should be individualized by a multidisciplinary team.

Tamoxifen, anastrozole, exemestane, and raloxifene might be offered for BC chemoprevention for a maximum of 5 years to women at high and moderate-risk for BC (I, A) [27].

Family history should be updated to refine risk assessment, surveillance protocol, and consideration of additional testing to rule out the possibility of phenocopy.

Other hereditary breast and/or ovarian cancer syndromes

Multi-gene testing is necessary when more than one gene could account for a personal and/or family cancer history. For example, although ovarian cancer is mainly associated with *BRCA1/2* and other homologous recombination repair pathway genes, it can also be associated with variants in mismatch repair genes (*MLH1*, *MSH2*, *PMS2*, *MSH6*, or

EPCAM). Genes linked to hereditary breast cancer also include *TP53*, *PTEN*, *STK11*, and *CDH1*, among others.

It should be noted that germline mutations in these latter genes are often associated with a syndromic phenotype that determines diagnosis and guides genetic testing.

Carriers of a mismatch repair gene mutation (*MLH1*, *MSH2*, *EPCAM*, *PMS2*, or *MSH6*) are at increased risk for endometrial and ovarian cancers (up to 60% and 24%, respectively); however, association with increased risk for breast cancer is controversial.

Li–Fraumeni syndrome is the consequence of germline *TP53* pathogenic variants involved only in about 1% of hereditary breast cancer cases. Carriers show a cumulative lifetime cancer incidence of nearly 100% and a cumulative incidence rate for breast cancer by 70 years of age of at least 50% [28].

The myriad of disorders resulting from germline mutations in *PTEN* are referred to as the *PTEN* hamartoma tumor syndrome (PHTS). The lifetime risk for breast cancer for women diagnosed with Cowden syndrome has been estimated at 25% to 50%, with an average age of 38–50 years at diagnosis [29].

Germline *STK11* pathogenic variants cause the Peutz–Jeghers syndrome (PJS), an autosomal dominant disorder characterized by gastrointestinal polyps, mucocutaneous pigmentation, and elevated risk for gastrointestinal cancers, as well as breast or non-epithelial ovarian cancers. Breast cancer risk in women with PJS is 45% at 70 years of age [30].

Mutations in germline *CDH1* are associated with hereditary diffuse gastric cancer and lobular breast cancer, reporting a cumulative lifetime risk for breast cancer of up to 50% [31].

Compliance with ethical standards

Conflict of interest SGS reports honoraria for speaking from Amgen, Eisai, Novartis, Roche, Pfizer, and Astra–Zeneca; Advisory role for Amgen, Novartis, Roche, Celgene, Astra–Zeneca, and Pfizer, and travel expenses from Pfizer, MSD, and Roche outside the submitted work. TRC reports travel expenses from Pfizer and Astellas. EA reports honoraria for speaking from Roche, Novartis, Pfizer, Astra–Zeneca, Eisai, and MSD; Advisory role for MSD and Pfizer, and travel expenses from MSD, Roche, and Pfizer. JEAM reports honoraria for speaking from MSD, Roche, Pfizer; Advisory role for Roche, Pfizer, BMS, Tesaro, and travel expenses from MSD, Roche, and BMS. RA has nothing to disclose. JB reports advisory role for Astra–Zeneca and Pfizer, honoraria for speaking from Bristol–Myers Squibb, Cor2ED, and Medscape, and grants for research from Astra–Zeneca, Pharmamar, Pfizer, and Tesaro. BG has nothing to disclose. AH reports honoraria for speaking from Roche, Tesaro, MSD, Clovis, and Astra–Zeneca and travel expenses from Roche outside the submitted work. GLL has nothing to disclose. AGdA reports Advisory Board, consultancy, and speaker honoraria/travel support from Pierre Fabre, Roche, Bristol–Myers Squibb, MSD, Pfizer, Novartis, Bayer, Janssen, Sanofi,

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Ethical approval The current study has been conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent As Clinical guideline, patient informed consent does not apply.

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