Prevalence of BRCA1 and BRCA2 Mutations in Patients with Primary Ovarian Cancer – Does the German Checklist for Detecting the Risk of Hereditary Breast and Ovarian Cancer Adequately Depict the Need for Consultation?

Prävalenz von BRCA1- und BRCA2-Mutationen bei Patientinnen mit primärem Ovarialkarzinom – bildet die deutsche Checkliste zur Erfassung des Risikos für erblichen Brust- und Eierstockkrebs den Beratungsbedarf ausreichend ab?

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Key words
ovarian cancer, BRCA mutation, hereditary breast and ovarian cancer, heritability checklist

Schlüsselwörter
Ovarialkarzinom, BRCA-Mutation, hereditäres Mamma- und Ovarialkarzinom, Erblichkeits-Checkliste

ABSTRACT

Background BRCA1/2 mutations are the leading cause of hereditary epithelial ovarian cancer (EOC). The German Consortium for Hereditary Breast and Ovarian Cancer has defined inclusion criteria, which are retrievable as a checklist and facilitate genetic counselling/testing for affected persons with a mutation probability of ≥10%. Our objective was to evaluate the prevalence of the BRCA1/2 mutation(s) based on the checklist score (CLS).

Methods A retrospective data analysis was performed on EOC patients with a primary diagnosis treated between 1/2011–5/2019 at the Central Essen Clinics, where a BRCA1/2 genetic analysis result and a CLS was available. Out of 545 cases with a BRCA1/2 result (cohort A), 453 cases additionally had an extended gene panel result (cohort B).

Results A BRCA1/2 mutation was identified in 23.3% (127/545) in cohort A, pathogenic mutations in non-BRCA1/2 genes were revealed in a further 6.2% in cohort B. In cohort A, 23.3% (127/545) of patients had a BRCA1 (n = 92) or BRCA2 (n = 35) mutation. Singular EOC (CLS 2) was present in 40.9%. The prevalence for a BRCA1/2 mutation in cohort A was 10.8%, 17.2%, 25.0%, 35.1%, 51.4% and 66.7% for patients with CLS 2, 3, 4, 5 and ≥7 respectively. The mutation prevalence

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Deutsche Version unter:
https://doi.org/10.1055/a-1222-0042
in cohort B was 15.9%, 16.4%, 28.2%, 40.4%, 44.8% and 62.5% for patients with CLS 2, 3, 4, 5, 6 and ≥7 respectively.

**Conclusions** The BRCA1/2 mutation prevalence in EOC patients positively correlates with a rising checklist score. Already with singular EOC, the prevalence of a BRCA1/2 mutation exceeds the required 10% threshold. Our data support the recommendation of the S3 guidelines Ovarian Cancer of offering genetic testing to all patients with EOC. Optimisation of the checklist with clear identification of the testing indication in this population should therefore be aimed for.

**ZUSAMMENFASSUNG**


Von 545 Fällen mit BRCA1/2-Ergebnis (Kohorte A) lag in 453 Fällen zusätzlich ein erweitertes Gen-Panel-Ergebnis (Kohorte B) vor.

**Ergebnisse** In 23,3% (127/545) wurde in Kohorte A eine BRCA1/2-Mutation festgestellt, in Kohorte B zeigten sich bei weiteren 6,2% pathogene Mutationen in Nicht-BRCA1/2-Genen. In Kohorte A hatten 23,3% (127/545) der Patienten eine BRCA1- (n = 92) oder BRCA2- (n = 35) Mutation. Ein singuläres EOC (CLS 2) lag in 40,9% vor. Die Prävalenz für eine BRCA1/2-Mutation in Kohorte B betrug 10,8%, 17,2%, 25,0%, 35,1%, 51,4% und 66,7% für Patienten mit CLS 2, 3, 4, 5, 6 bzw. ≥7.

Die Mutationsprävalenz in Kohorte B betrug 15,9%, 16,4%, 28,2%, 40,4%, 44,8% und 62,5% für Patienten mit CLS 2, 3, 4, 5, 6 bzw. ≥7.

**Schlussfolgerungen** Die BRCA1/2-Mutationsprävalenz bei EOC-Patienten korreliert positiv mit steigendem Checklisten-Score. Bereits beim singulärem EOC überschreitet die Prävalenz einer BRCA1/2-Mutation die geforderte 10%-Schwelle. Unsere Daten unterstützen die Empfehlung der S3-Leitlinie Ovarialkarzinom, allen Patientinnen mit EOC eine genetische Testung anzubieten. Eine Optimierung der Checkliste mit eindeutiger Kennzeichnung der Testungsindikation in dieser Population ist daher anzustreben.

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**Introduction**

With 7350 new cases, ovarian cancer is the third most common gynaecological malignancy in Germany after breast and endometrial cancer [1]. Over 90% of these cases are tumours of epithelial origin — grouping together epithelial ovarian, fallopian tube and peritoneal cancer. Although the lifetime risk of developing ovarian cancer in the general population is rather low at around 1.5% [2], this risk of disease increases manifold if a pathogenic gene mutation is present, as, for example — in the case of a BRCA1 mutation — to 40–63%, or — in the case of a BRCA2 mutation — to 16–27% [3–7]. The prevalence of a BRCA1/2 mutation in the normal population is estimated to be 1:300–500 [8–13]. The prevalence is however clearly above 10% in persons where there is familial clustering of breast and ovarian cancers. In Germany, the indication for genetic germline testing for pathogenic mutations is indicated according to the criteria of the German Consortium for Hereditary Breast and Ovarian Cancer [14]. The genetic counselling and testing can be conducted by authorised persons (human geneticists and physicians with the appropriate additional qualification) within and outside of the German Consortium for Hereditary Breast and Ovarian Cancer. In addition, (following clarification of cost assumption by the cost-bearer), genetic counselling and testing can be conducted outside of these indications in justified cases (e.g. mutation probability ≥10% in women with triple negative breast cancer or singular ovarian cancer). The test criteria are based on considerations of capacity of supply and on costs, which, in the past, have led to in many countries a mutation prevalence requirement of at least 10% as inclusion criterion for being offered genetic testing. Nevertheless, country-specific differences exist such as in the USA with the recommendations of the NCCN (National Comprehensive Cancer Network). Here the criteria are much broader and include the recommendation for conducting genetic counselling and testing already in all persons with a mutation probability of 5%. This includes, for example, women with singular EOC regardless of family history, but also patients with prostate cancer, pancreatic cancer, and triple negative breast cancer up to 60 years of age [15]. With the introduction of high-throughput methods, which enable faster and more efficient genetic analysis, these boundaries are to be challenged in the future. Technological progress also enables genetic analyses to be extended to additional genes, which, if mutated, signify a marked increase in the lifetime risk of developing breast and/or ovarian cancer. Multi-gene panel analyses have already been in use and increasing in popularity in routine diagnostics for several years. At the same time, it is worth considering that the disease penetrances are also lower in patient cohorts with a low mutation prevalence.

Kast et al. [12] evaluated the prevalence of a pathogenic BRCA1/2 mutation based on the personal and family history of breast and/or ovarian cancer patients and were able to successfully define criteria for the clear identification of the at-risk population in Germany, assuming a mutation probability of ≥10%. For easy application, these were implemented in a user-friendly checklist [16], which records the personal and family history of healthy people seeking advice and those who have become ill, based on a three-generation family tree. Risk scores are assigned depending on the number and type of tumours in the family, but also on the individual age of initial manifestation of the disease. With a checklist score (CLS) of ≥3, a mutation probability of ≥10% is assumed, and affected persons are therefore offered ge-
nomic counselling and testing covered by the cost bearers. The user-friendly form of the checklist led to successful implementation in everyday clinical practice. The positive correlation of the checklist with a BRCA1/2 mutation could already be demonstrated in breast cancer patients [17]. In addition, recording of a hereditary predisposition based on this checklist is required as a quality criterion in the certification requirements of the German Cancer Society (DKG; [18,19]).

An aspect of criticism concerning the checklist, however, is that ovarian cancer patients with no other familial breast/ovarian cancer history (so-called "singular ovarian cancer") achieve a score (CLS) of 2 points and therefore do not receive an offer of genetic counselling and subsequent testing. Within the scope of the AGO-TR1 study [20], it was possible to show for the first time for Germany, in a large collective of EOC patients, that the prevalence for a pathogenic BRCA1/2 mutation is above the required 10% threshold even in women with singular ovarian cancer. Thanks to these study data, an expansion of the inclusion criteria of the German Consortium for Hereditary Breast and Ovarian Cancer has been achieved since 2016, although not across all health insurers, with the result that a genetic test is now also possible for women with singular ovarian cancer. Thanks to these study data, an expansion of the inclusion criteria of the German Consortium for Hereditary Breast and Ovarian Cancer has been achieved since 2016, although not across all health insurers, with the result that a genetic test is now also possible for women with singular ovarian cancer (regardless of family history and age of disease onset) about the risk of a hereditary disease and offering genetic testing (recommendation grade A, evidence level 2+).

Knowledge of the BRCA status in EOC patients is essential, among other things, for personalisation/optimisation of systematic therapy, but also for identification of family members who carry a relevant mutation and thus have a significantly higher risk of developing breast and/or ovarian cancer.

The objective of our work was to record the prevalence of a pathogenic BRCA1/2 mutation in unselected patients with epithelial ovarian cancer and to correlate this with the heritability checklist of the German Consortium for Hereditary Breast and Ovarian Cancer.

**Patients and Methods**

All patients with epithelial ovarian/fallopian tube/peritoneal cancer, who were treated between January 2011 and May 2019 in the Department for Gynaecology and Gynaecological Oncology of the Central Essen Clinics, were enrolled in this retrospective survey. Only patients who gave their written consent to the collection, processing and analysis of clinical data and the results of the genetic analyses were included in the evaluation. For the majority of patients, the indication for genetic counselling and testing was based on the inclusion criteria of the German Consortium for Hereditary Breast and Ovarian Cancer. Patients who had received genetic testing in the course of ongoing clinical studies were included, provided that the patient’s consent to the use of this data had been provided. The genetic analyses were carried out in accordance with the provisions of the German Genetic Diagnostics Act after extensive counselling and written consent of the affected persons within the scope of the cooperation agreement with the German Consortium for Hereditary Breast and Ovarian Cancer. Alternatively, where the analyses were carried out via other/external institutions, they were submitted to us for information by the patients themselves. The results of the analyses and the final human genetic categorisation were collected from the written
records. Patients who had received a genetic analysis within the German Consortium from 2015 onwards, were analysed with the TruRisk® gene panel, which contains other core genes (including ATM, BRRP1, CDH1, CHEK2, MLH1, MSH2, MSH6, PMS2, PALB2, RAD51C, RAD51D, TP53) in addition to the BRCA1/2 genes [22].

Recording of the checklist score took place within the scope of the genetic counselling on the basis of the individual patient medical history and family history. The principle of the checklist is based on the following: The purpose of the checklist is to identify patients and those seeking advice who could have a potential hereditary predisposition for breast and/or ovarian cancer. For this purpose, the checklist asks information about the patient, his/her children and siblings (A) as well as about other patients on the maternal side including the mother (B) and/or on the paternal side including the father (C), and rates this information with a corresponding point value. The highest total value (D) is obtained from the maternal/paternal line. The final checklist score is calculated from the sum of A and D. The model is based on a mathematical weighting, which has evaluated mutation prevalences in the aforementioned time period, 1206 patients with epithelial EOC of past malignancies (Table 1). The distribution of the checklist score (CLS) in the prevalence cohort (n = 545) was as follows: CLS 2 in 40.9% (n = 223), CLS 3 in 16.0% (n = 87), CLS 4 in 19.8% (n = 108), CLS 5 in 10.5% (n = 57), and CLS 6 in 6.8% (n = 37) and CLS ≥7 in 6.1% (n = 33) (Table 2). The prevalence (%), [95% confidence interval [CI]] for a pathogenic BRCA1/2 mutation based on the CLS point value of 2, 3, 4, 5, 6, and ≥7 was 10.8% (95% CI 7.0–15.6%), 17.2% (95% CI 10.0–

### Results

#### Patients and cancer characteristics

In the aforementioned time period, 1206 patients with epithelial ovarian cancer were treated. 45.2% (prevalence cohort, n = 545) of the patients had an evaluable BRCA1/2 gene result coupled with a pathogenic BRCA1/2 mutation in 23.3% (n = 127) of patients. This was based on a BRCA1 mutation in 16.9% (n = 92) and on a BRCA2 mutation in 6.4% (n = 35) of cases. One patient had a simultaneous pathogenic BRCA1 and BRCA2 mutation. Patients with a BRCA1/2 mutation differed significantly from those patients without a mutation in terms of median age (55 versus 59 years, p = 0.01), FIGO stage (FIGO III/IV: 92.2 versus 82.5%, p = 0.03) and histological sub-type (high-grade serous: 98.4 versus 74.2%, p ≤0.001) (Table 1). The median age in the prevalence cohort was 58 years (range 18–86), the disease was at FIGO stage III/IV in 84.8% (n = 462) and a high-grade serous histological subtype was present in 79.8% (Table 1). 84.4% of patients (n = 460) had no previous malignancy in their personal medical history, breast cancer was documented in 8.8% (n = 48) and another malignancy in 6.8% (n = 37). A pathogenic BRCA1/2 mutation was identified in 23.3% (n = 127) of patients. This was based on a BRCA1 mutation in 16.9% (n = 92) and on a BRCA2 mutation in 6.4% (n = 35) of cases. One patient had a simultaneous pathogenic BRCA1 and BRCA2 mutation. Patients with a BRCA1/2 mutation differed significantly from those patients without a mutation in terms of median age (55 versus 59 years, p = 0.01), FIGO stage (FIGO III/IV: 92.2 versus 82.5%, p = 0.03) and histological sub-type (high-grade serous: 98.4 versus 74.2%, p ≤0.001) (Table 1).

#### Heritability checklist

The distribution of the checklist score (CLS) in the prevalence cohort (n = 545) was as follows: CLS 2 in 40.9% (n = 223), CLS 3 in 16.0% (n = 87), CLS 4 in 19.8% (n = 108), CLS 5 in 10.5% (n = 57), and CLS 6 in 6.8% (n = 37) and CLS ≥7 in 6.1% (n = 33) (Table 2). The prevalence (%), [95% confidence interval [CI]] for a pathogenic BRCA1/2 mutation based on the CLS point value of 2, 3, 4, 5, 6, and ≥7 was 10.8% (95% CI 7.0–15.6%), 17.2% (95% CI 10.0–
26.8%), 25.0% (95% CI 17.2–34.2%), 35.1% (95% CI 22.9–48.9%), 51.4% (95% CI 34.4–68.1%) and 66.7% (95% CI 48.2–82.0%) (▶ Table 2, Fig. 2).

**Gene panel analysis**

The result of a gene panel analysis was available for 453 patients (83.1%). The rate of pathogenic *BRCA1/2* mutations in this collective was 19.6% (n = 89) (▶ Fig. 1). Furthermore, in 25 patients (5.5%) additional pathogenic mutations were detected in genes *RAD51C* (n = 7), *BRIIP* (n = 4), *MSH6* (n = 3), *PALB2* (n = 3), *RAD51D* (n = 2), *TP53* (n = 2), *CHEK2* (n = 2), *PMS2* (n = 1) and *ATM* (n = 1). In total, the prevalence for a pathogenic gene mutation was 15.9% for CLS 2, 16.4% for CLS 3, 28.2% for CLS 4, 40.4% for CLS 5, 44.8% for CLS 6 and 62.5% for CLS ≥ 7. If the prevalence of pathogenic mutations is considered depending on the checklist score value, there is still a clear correlation between the score value and the presence of a *BRCA1/2* mutation (10–63%), which, however, cannot be detected in patients with non-*BRCA* mutations (▶ Fig. 3).

**Discussion**

A pathogenic *BRCA1/2* mutation is present in around 15–22% of all ovarian cancer patients [20,23–25]. In our survey, the rate of *BRCA1/2* mutations was 23%. Accurate recording of *BRCA* status has in the meantime two important implications for women with ovarian cancer: on the one hand, the optimisation and individualisation of systematic therapy for patients with *BRCA* mutation (e.g. PARP-[Poly-ADP-Ribose-Polymerase]-inhibitor maintenance therapy [26–33]), on the other hand, the identification of as yet unaffected family members, where, with autosomal-dominant inheritance, 50% are transferred the pathogenic *BRCA* mutation. The clinically significant therapeutic benefit of maintenance therapy with PARP inhibitors was initially demonstrated in patients with relapsed high-grade serous/endometrioid ovarian cancer, and in this case especially where a *BRCA1/2* mutation was present [27, 29, 30]. The latest study data provide evidence that this effect can also be achieved in the primary situation with PARP-inhibitor maintenance therapy [26, 28, 31, 32].

<table>
<thead>
<tr>
<th>Checklist score</th>
<th>Total No <em>BRCA1/2</em> mutation</th>
<th>Pathogenic <em>BRCA1/2</em> mutation</th>
<th>Pathogenic <em>BRCA1</em> mutation</th>
<th>Pathogenic <em>BRCA2</em> mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>223 (40.9)</td>
<td>199 (47.6)</td>
<td>24 (18.9)</td>
<td>12 (13.0)</td>
</tr>
<tr>
<td>3</td>
<td>87 (16.0)</td>
<td>72 (17.2)</td>
<td>15 (11.8)</td>
<td>10 (10.9)</td>
</tr>
<tr>
<td>4</td>
<td>108 (19.8)</td>
<td>81 (19.4)</td>
<td>27 (21.3)</td>
<td>19 (20.7)</td>
</tr>
<tr>
<td>5</td>
<td>57 (10.5)</td>
<td>37 (8.9)</td>
<td>20 (15.7)</td>
<td>14 (15.2)</td>
</tr>
<tr>
<td>6</td>
<td>37 (6.8)</td>
<td>18 (4.3)</td>
<td>19 (15.0)</td>
<td>17 (18.5)</td>
</tr>
<tr>
<td>≥ 7</td>
<td>33 (6.1)</td>
<td>11 (2.6)</td>
<td>22 (17.3)</td>
<td>20 (21.7)</td>
</tr>
</tbody>
</table>

> Fig. 2 Prevalence of a pathogenic *BRCA1/2* mutation depending on the heritability checklist score (CLS) in the overall cohort (n = 545).

> Table 2 Distribution of patients depending on the heritability checklist score and detection of a *BRCA1/2* mutation.
Regardless of the success of the PARP inhibitors, the identification of healthy BRCA1/2 mutation carriers in the family, through testing the patient, is of clinical significance. Support and counselling of risk gene carriers should be performed in specialised centres in line with the consensus recommendations of the German Consortium [34].

Compared to the normal population and depending on the affected gene, healthy women with a pathogenic BRCA1/2 mutation have a significantly increased risk of breast (up to 70%) and/or ovarian cancer (up to 63%) [5–13]. Prevalence of BRCA1/2 gene mutations in the normal population is low, at 1:300–500 [8–12], and is currently not yet rated as sufficient justification for unselected population analysis. Therefore, in the past, different risk-assessment strategies were developed for the detection of risk groups with a substantially higher probability (≥10%) of BRCA1/2 mutation [17, 35–42]. All are based on a probability calculation for BRCA1/2 mutation being carried out for the affected person on the basis of personal/family history for breast/ovarian cancer and age at first diagnosis. In Germany, the German Consortium for Hereditary Breast and Ovarian Cancer established and validated inclusion criteria which have to be fulfilled before there is an indication for counselling and testing for a BRCA1/2 mutation. For easier, everyday use, a heritability checklist was drawn up [16], with the indication for genetic briefing/counselling and testing (≥3 points) based on the total point value. Rhiem et al. were able to show that the checklist was used successfully in breast cancer patients, with a positive correlation between the score value and prevalence of a BRCA1/2 mutation [17].

This analysis based on the checklist has, to date, not been carried out for patients with ovarian cancer. According to the heritability checklist, patients with singular ovarian cancer receive 2 points, and, on the basis of this survey, are not a priori identified as index patients for genetic briefing/counselling and testing, since historic study data suggested a prevalence of less than 10% for BRCA1/2 mutation in this constellation [43]. The predictive value of the family history (for breast and ovarian cancer) with regard to the prevalence of a pathogenic BRCA1/2 mutation is undisputed. 19–81% of ovarian cancer patients with other relatives with breast and/or ovarian cancer in their family, carry a BRCA1/2 mutation [12, 20, 44, 45]. Here, the prevalence correlates not only with the number of affected persons, but also with age at first diagnosis (the younger, the higher) and with the disease (higher prevalence with ovarian cancers). It is, however, known that a large proportion of ovarian cancer patients have no predisposition in the family history. In our collective, 41% of patients had no such predisposition. In the AGO-OVAR-TR1 study [20], the prevalence of gene mutation was analysed using the gene panel in 523 ovarian cancer patients with a first diagnosis or relapse. The prevalence for a pathogenic BRCA1/2 mutation was 21% in the overall cohort. In this study, 57% of patients had no positive family history, but the prevalence for a pathogenic mutation in this group was 11.4%. In patients with a positive family history, the prevalence was 31.6%. Specifically, this means that, in 33 (6.3% of the overall cohort) patients with singular ovarian cancer, a pathogenic BRCA mutation would not have been detected if the test criteria had been applied only according to the predisposing family history. In our collective, this rate was 4.4% (n = 24), other workgroups report 6.5–9% [43, 45]. This means that around ½ of BRCA1/2 germline mutations are overlooked if testing is decided solely on the basis of a positive family history. Critical consideration should be given to the fact that information on the medical history of family members harbours a high potential for sources of error and therefore the robustness should be viewed as limited. Furthermore, in the case of adoption or a lack of contact within a family, a sufficient family history of malignancies cannot be obtained.

Recent study results, however, show that both an unselected population analysis [46] and in particular genetic analysis in EOC...
patients [47] and first degree relatives [48] are not only cost effective, but can also contribute to the lowering of hereditary EOC. Since there exists neither a sufficiently reliable drug prevention option nor an adequate early detection measure for ovarian cancer, only prophylactic, risk-reducing bilateral salpingo-oophorectomy for mutation carriers offers a reduction in the disease and mortality risk by around 80% [49, 50].

Furthermore, the use of gene panel analyses demonstrates that other relevant pathogenic gene mutations can be detected regardless of the family disease situation [20]. In our collective, the rate of additional pathogenic mutation was 6.2%. This aspect is of particular significance, since this again allowed detection of healthy mutation carriers in the family circle, whose risk of developing malignancies is correspondingly increased.

The weaker aspects of our work are based on the one hand on the retrospective nature of the evaluation, where a selection bias cannot be excluded. On the other hand, a gene result was available to us in only 45% of our entire patient collective. This is due to the fact that, according to the Genetic Diagnostics Act, the genetic counselling must be “non-directive” and therefore conducted on a voluntary basis for the patient. Furthermore, there is no predefined time window after the initial diagnosis for performing a genetic analysis. This fact, coupled with the requirements of the Genetic Diagnostics Act, means that actively inquiring about genetic findings from EOC patients, who received their surgical therapy at our centre and afterwards continue their treatment close to home, is not permitted. The strengths of our work merit highlighting:
1. The data represent an unselected cohort of EOC patients with a primary diagnosis in a large clinic collective and thus optimally reflect the clinical reality;
2. Enquiries on the family history are carried out in a structured manner using the heritability checklist;
3. The proportion of EOC patients with a gene panel analysis is very high and therefore reflects reliable data.

In summary, our work allowed us to confirm that the prevalence of a pathogenic BRCA1/2 mutation in patients with singular ovarian cancer in our collective is 23.3% and thus clearly above the rate of additional pathogenic mutation was 6.2%. This aspect is of particular significance, since this again allowed detection of healthy mutation carriers in the family circle, whose risk of developing malignancies is correspondingly increased.

We therefore recommend genetic counselling and testing of patients with ovarian cancer regardless of their family history [15, 21, 51, 52] and argue in favour of clear identification of this indication in the heritability checklist used in Germany.

**Conflict of Interest**

BA (Consulting activities: Roche, Amgen, Tesaro; Advanced training/conferences/lecture honoraria: Roche, AstraZeneca, Tesaro, Clovis, Amgen, Celgene, PharmaMar).

DT No conflicts of interest.

KR (Consulting activities: AstraZeneca, Pfizer, Tesaro; Advanced training/conferences/lecture honoraria: AstraZeneca, Pfizer, Tesaro; Immaterial conflicts of interest/affiliation with scientific schools: German Consortium for Hereditary Breast and Ovarian Cancer).

PH (Consulting activities: AstraZeneca, Roche, Sitio, Tesaro, Lilly, Clovis, MSD, Merck; Author activity/expert reviewer activity: AstraZeneca; Advanced training/conferences/lecture honoraria: AstraZeneca, Roche, Tesaro, Stryker, Zailab, MSD/Merck; Scientific activities: AstraZeneca, Roche DFG, EU, Genmab).

STS (Consulting activities: Clovis, Tesaro; Advanced training/conferences/lecture honoraria: PharmaMar, Roche, Tesaro, Roche, AstraZeneca).

FH (Consulting activities: AstraZeneca, Tesaro, Clovis; Advanced training/conferences/lecture honoraria: AstraZeneca, Tesaro, Clovis, Roche, PharmaMar).

TB (Consulting activities: Tesaro; Advanced training/conferences/lecture honoraria: Roche, Amgen; Scientific activity: Amgen).

AT No conflicts of interest.

NP No conflicts of interest.

SE (Non-financial support: Tesaro).

HP No conflicts of interest.

RS (Consulting activities: AstraZeneca; Advanced training/conferences/lecture honoraria: AstraZeneca; Scientific activities: AGO study group; Immaterial conflict of interest/affiliation with scientific schools: German Consortium for Hereditary Breast and Ovarian Cancer).

AdB (Consulting activities: AstraZeneca, Clovis, Tesaro, Roche, Genmab, BIOCAD, Pfizer, MSD; Advanced training/conferences/lecture honoraria: AstraZeneca, Clovis, Tesaro; Scientific activities: AstraZeneca, Tesaro, Roche, Genmab, BIOCAD).

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