Thieme

Breast Cancer and Genetic *BRCA1/2* Testing in Routine Clinical Practice: Why, When and For Whom?

Das Mammakarzinom und die genetische *BRCA1/2*-Testung in der klinischen Routine: warum, wann und für wen?

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ABSTRACT

Pathogenic variants of the tumor suppressor genes *BRCA1* and *BRCA2* are responsible for the majority of hereditary breast cancers; they are also becoming increasingly important to identify whether patients are suitable for targeted therapy with poly ADP-ribose polymerase inhibitors (PARPi).

Patients with HER2-negative breast cancer and *BRCA1/2* germline mutations can benefit significantly from PARPi therapy, and the findings of the OlympiAD and the EMBRACA phase III clinical trials for regulatory approval were recently expanded by the addition of the most recent OlympiA data on the treatment of patients with early disease and a high risk of recurrence.

This means that *BRCA1/2* germline testing to plan patient therapy is now also relevant for patients with early breast cancer and therefore has a direct impact on survival. Healthcare research data shows, however, that *BRCA1/2* testing rates are strongly affected by familial history, cancer subtype (particularly triple-negative subtypes), and patient age at onset of disease (especially with regards to younger patients with breast cancer), despite the existing clear recommendations for *BRCA1/2* germline testing to identify whether PARPi therapy is indicated.

This article presents the clinical implications of identifying *BRCA1/2* germline mutations in patients with breast cancer, the current recommendations on molecular diagnostics, and their implementation in practice. The treatment of patients with breast cancer has progressed greatly in recent years and now offers individual treatment concepts which can only be implemented after the targeted identification of individual parameters.

As detection of a *BRCA1/2* germline mutation is essential for planning individual therapy, where indicated, testing should be arranged as early as possible. It is the only way of identifying patients suitable for PARPi therapy and ensuring they receive the best possible treatment. This also applies to patients with a negative familial history, HR-positive disease, or who are older at onset of disease.

ZUSAMMENFASSUNG

Pathogene Varianten der Tumorsuppressorgene *BRCA1* und *BRCA2* sind für den Großteil der hereditären Mammakarzinome verantwortlich und gewinnen zunehmend an Bedeutung für die Bestimmung der Eignung einer zielgerichteten Therapie mit Inhibitoren der Poly-ADP-Ribose-Polymerasen (PARPi).

Patient*innen mit einem HER2-negativen Mammakarzinom und *BRCA1/2*-Keimbahnmutation können deutlich von einer PARPi-Therapie profitieren, und die Ergebnisse der Zulassungsstudien OlympiAD und EMBRACA aus der fortgeschrittenen Therapiesituation wurden kürzlich mit den aktuellen OlympiA-Daten für die Therapie von Patient*innen mit frühen Krankheitsstadien und hohem Rezidivrisiko erweitert.

Somit ist die *BRCA1/2*-Keimbahntestung zur Therapieplanung nun auch für Patient*innen mit Mammakarzinom im Frühstadium und damit direkt für das Überleben der Erkrankten relevant. Daten aus der Versorgungsforschung zeigen jedoch, dass die *BRCA1/2*-Testraten stark geprägt sind von Familienanamnese, Subtyp (insbesondere triple-negativ) und Erkrankungsalter (insbesondere jüngere Erkrankte) – trotz vorliegender klarer Empfehlungen für eine *BRCA1/2*-Keimbahntestung zur Indikationsstellung einer PARPi-Therapie.

Dieser Artikel beschreibt die klinischen Implikationen der Identifizierung einer *BRCA1/2*-Keimbahnmuation für Patient*innen mit einem Mammakarzinom, die aktuellen Empfehlungen zur molekularen Diagnostik sowie deren praktische Umsetzung. Die Behandlung der an einem Mammakarzinom Erkrankten hat in den letzten Jahren große Fortschritte erzielt und bietet nun individuelle Therapiekonzepte, welche nur durch die gezielte Identifikation von Einzelparametern zur Anwendung kommen können.

Da der Nachweis einer *BRCA1/2*-Keimbahnmutation für die individuelle Therapieplanung von entscheidender Bedeutung ist, ist diese bei entsprechender Indikation so früh wie möglich zu veranlassen. Nur so können für eine PARPi-Therapie geeignete Patient*innen identifiziert und eine bestmögliche Therapie garantiert werden. Dies gilt auch für Patient*innen mit negativer Familienanamnese, HR-positiver Erkrankung und höherem Erkrankungsalter.

Introduction

Breast cancer is a heterogeneous disease which requires individualized targeted therapy concepts. Biologically distinct subtypes correlate with genetic variants which are not just relevant for estimating the risk of developing breast cancer but are also increasingly predictive for drug therapy strategies. Pathogenic variants of the breast cancer susceptibility genes *BRCA1* and *BRCA2* (*BRCA1/2*) are mainly responsible for a predisposition to breast cancer and also the most important predictive factor for the patient's response to a targeted therapy with poly ADP-ribose polymerase (PARP) inhibitors [1, 2, 3].

The onus is on the treating oncologists and gynecologists to know when genetic testing is indicated and to offer and arrange for *BRCA1/2* germline testing when indicated.

This article focuses on the practical aspects of implementing *BRCA1/2* germline testing in patients with breast cancer to ensure the best possible therapy. Detection of a pathogenic *BRCA1/2* germline mutation is decisive for therapy with a PARP inhibitor (PARPi), and treatment with a PARPi is now no longer limited to advanced disease but, based on the recent expansion of the regulatory approval for PARPi, is also clinically relevant for early-stage disease [4, 5].

Hereditary Breast Cancer

Significance of risk genes

The lifetime risk of developing breast cancer for women is about 13 %. About 1 % of all new cases with disease are men [6, 7]. The lifetime risk increases if a pathogenic germline mutation of the high-risk genes *BRCA1* or *BRCA2* is present and is around 40–60%. *PALB2*, *CDH1*, *PTEN*, *TP53* and *STK11* are also associated with a high risk of developing breast cancer and *ATM*, *CHEK2*, *BARD1*, *RAD51C* and *RAD51D* with a moderate risk of breast cancer [1, 8, 9, 10].

Most mutations of established breast cancer predisposition genes affect *BRCA1/2*. It is estimated that about 5 % of all patients with breast cancer have a pathogenic *BRCA1/2* germline mutation [8, 11, 12, 13]. In the heterogeneous group of breast carcinomas, the mutation frequency varies according to subtype. In general, pathogenic mutations in *BRCA1/2* result in a more aggressive pathology (triple-negative subtype, higher grading). The strongest association is between *BRCA1* and triple-negative breast cancer (TNBC). As hormone receptor-positive (HR+) breast cancer, which is also negative for human epidermal growth factor receptor 2 (HER2−), is by far the most common subtype, numerically the majority of mutation carriers have an HR-positive pathology [11, 14]. Even though the cumulative familial occurrence of breast and/or ovarian cancer and/or early-age onset of disease are characteristic for hereditary breast cancers and the frequency of *BRCA1/2* mutations is greatest for TNBC, clinical parameters such as familial history, age, or tumor type are only associated with some of the mutations.

Special features in the treatment of tumors with *BRCA1/2* mutation

Many predisposition genes for breast and ovarian cancer play a role in homologous recombination, a key function for the repair of DNA double-strand breaks. Blocking DNA single-strand breaks through inhibition of PARP1 enzymes results in an accumulation of double-strand breaks which, in cells with homologous recombination deficiency, can only be repaired by less efficient and error-prone non-homologous recombination (non-homologous end joining, NHEJ). The biallelic inactivation of *BRCA1/2* genes in tumor cells and concurrent inhibition of PARP1 leads to the loss of

genomic integrity of tumor cells resulting in cell death (synthetic lethality) [15, 16].

Relevance of *BRCA1/2* Testing in Healthy Populations and Populations with Cancer

Identification of *BRCA1/2* germline mutations to estimate the risk of developing breast and/or ovarian cancer

A molecular diagnostic workup to identify mutations in the *BRCA1/2* genes offers the opportunity to estimate the risk of developing breast and/or ovarian cancer and includes, in addition to testing patients who have already developed cancer, the testing of healthy persons, particularly family members of patients with confirmed gene mutations, to detect genetic risks early on. Proof of pathogenic *BRCA1/2* variants permits intensified screening to be carried out of persons who have not yet developed disease and helps to detect emerging carcinomas in their very early stages (secondary prevention). Preventive measures such as surgery or drugs can also be used (primary prevention). For patients who have already developed cancer, testing offers the possibility of a more intensive follow-up and of risk-reducing interventions (surgery or drugs) because of the increased risk of secondary disease (contralateral breast and/or ovarian cancer) [1].

BRCA1/2 germline mutations as a predictive factor for therapy response

BRCA1/2 mutations influence the response to certain drugs and identifying them is therefore vitally important when planning individualized therapy concepts [1, 2, 3, 17]. Identification of a *BRCA1/2* germline mutation means that treatment with PARPi is possible, which contributes to longer term control of the disease. Since 2019, breast cancer patients with confirmed pathogenic *BRCA1/2* germline mutations can benefit from olaparib or talazoparib monotherapy to treat HER2-negative advanced disease, and, since August 2022, they may also benefit from (post-neo)adjuvant therapy with olaparib to treat early-stage HER2-negative disease with a high risk of recurrence [4, 5]. Moreover, *BRCA1/2* mutations are predictive of chemotherapy response in the neoadjuvant setting [18, 19, 20]. A higher sensitivity to platinum has also been reported for persons with *BRCA1/2* germline mutations and advanced triple-negative disease [21], although the addition of platinum agents is now standard in the treatment of triple-negative breast cancers in the neoadjuvant setting [22, 23].

Data on routine clinical care prior to the approval of PARPi to treat breast cancer show the need for targeted and well-tolerated therapies for patients with *BRCA1/2* mutated breast cancer. Despite the option of endocrine therapy, women with HR-positive disease had chemotherapy significantly more often in the metastatic setting if they had a *BRCA1/2* mutation. Adverse events were more common and the quality of life of *BRCA1/2* mutation carriers was lower compared to patients without *BRCA1/2* mutations [24, 25, 26].

Indications for PARP Inhibitors

The first PARPi, olaparib, was approved for use in Europe by the European Commission in December 2014 for the maintenance treatment of patients with relapsed ovarian cancer who had responded to previous platinum-based chemotherapy. This was followed by regulatory approval of niraparib and rucaparib for the same indication. Since 2019, olaparib as well as talazoparib have also been approved to treat HER2-negative locally advanced or metastatic breast cancer in patients with *BRCA1/2* germline mutations. The regulatory approval of olaparib was recently expanded (EU: August 2022, USA: March 2022) to include patients with early-stage HER2-negative breast cancer. More information on the indications for using PARPi is given in ▶ **Table 1**.

Approval for PARP Inhibitors to Treat Advanced and Early-stage Breast Cancer in Patients with *BRCA1/2* Germline Mutations: OlympiAD, EMBRACA and OlympiA Trials

Efficacy

For the PARPi substance class, monotherapy with olaparib (OlympiAD) or talazoparib (EMBRACA) resulted in a significantly longer progression-free survival (PFS) of about three months compared to standard chemotherapy in patients with HER2-negative locally advanced or metastatic breast cancer with confirmed *BRCA1/2* germline mutations. This corresponds to a reduction of the risk of progression of more than 40 %. The response rate in the group treated with a PARPi was about twice as high as in the group which received standard chemotherapy (▶ **Table 2**). The time to the onset of a response for olaparib or talazoparib was comparable to that for chemotherapy [28, 29]. The benefit of olaparib or talazoparib was independent of the site of metastasis and appeared to be consistent in patients with visceral as well as brain/CNS metastases [29, 30]. In the extended follow-up period of the OlympiAD trial, olaparib was not associated with a statistically significant improvement in overall survival (median OS: 19.3 vs. 17.1 months; HR 0.90; 95% CI: 0.66–1.23; p = 0.513). One possible OS benefit of olaparib vs. chemotherapy only became apparent when olaparib was administered as first-line therapy (median OS: 22.6 vs. 14.7 months; HR 0.51; 95% CI: 0.29–0.90; p = 0.02) [31].

▶**Table 1** Regulatory approval status of PARP inhibitors in Europe.

HER2-negative breast cancer	
Early-stage disease	
Monotherapy or in combination with endocrine therapy for the adjuvant treatment following neoadjuvant or adjuvant chemotherapy (CT) to treat patients with a high risk of recurrence	Olaparib for patients with *BRCA1/2* germline mutations
Advanced-stage disease	
Monotherapy	Olaparib and talazoparib for patients with *BRCA1/2* germline mutations
Advanced ovarian cancer	
First-line therapy	
First-line maintenance therapy (FIGO III/IV) for patients who have responded to platinum-based CT	Olaparib for patients with *BRCA1/2* mutations (germline and/or somatic); combined with bevacizumab for patients who are HRD-positive* Niraparib independent of *BRCA1/2* status
Recurrence therapy**	
Maintenance therapy for patients with platinum-sensitive recurrence who have responded to platinum-based CT	Olaparib, niraparib and rucaparib independent of *BRCA1/2* status
Metastatic pancreatic adenocarcinoma	
Maintenance therapy for patients who did not experience progression after at least 16 weeks of first-line platinum-based CT	Olaparib for *BRCA1/2* germline mutation
Metastatic castration-resistant prostate cancer	
Monotherapy for patients who have progressed following prior therapy with a new hormonal agent	Olaparib for patients with *BRCA1/2* mutation (germline and/or somatic)

For more details on indications, please refer to the respective specialist information.

* Positive status for homologous recombination deficiency (HRD) defined by *BRCA1/2* mutation and/or genomic instability.

** Rucaparib should no longer be used as monotherapy to treat patients with (germline and/or somatic) *BRCA1/2* mutated advanced ovarian cancer who have been treated with two or more prior lines of platinum-based CT and are unable to tolerate further platinum-based CT. The randomized controlled clinical post-approval study CO-338–043 (ARIEL4) reported adverse effects of rucaparib on overall survival (OS) compared to CT controls (HR 1.31; 95% CI: 1.00–1.73), which led to the issue of a Direct Healthcare Professional Communication (in Germany: Rote-Hand-Brief) [27].

▶**Table 2** OlympiAD and EMBRACA trials leading to the approval of PARP inhibitors to treat HER2-negative locally advanced or metastatic breast cancer in patients with confirmed *BRCA1/2* germline mutations.

	OlympiAD (olaparib vs. CT)	**EMBRACA (talazoparib vs. CT)**
Median PFS	7.0 vs. 4.2 months	8.6 vs. 5.6 months
HR (95% CI)	0.58 (0.43–0.80); p < 0.001	0.54 (0.41–0.71); p < 0.001
Response rate	59.9% vs. 28.8%	62.6% vs. 27.2%

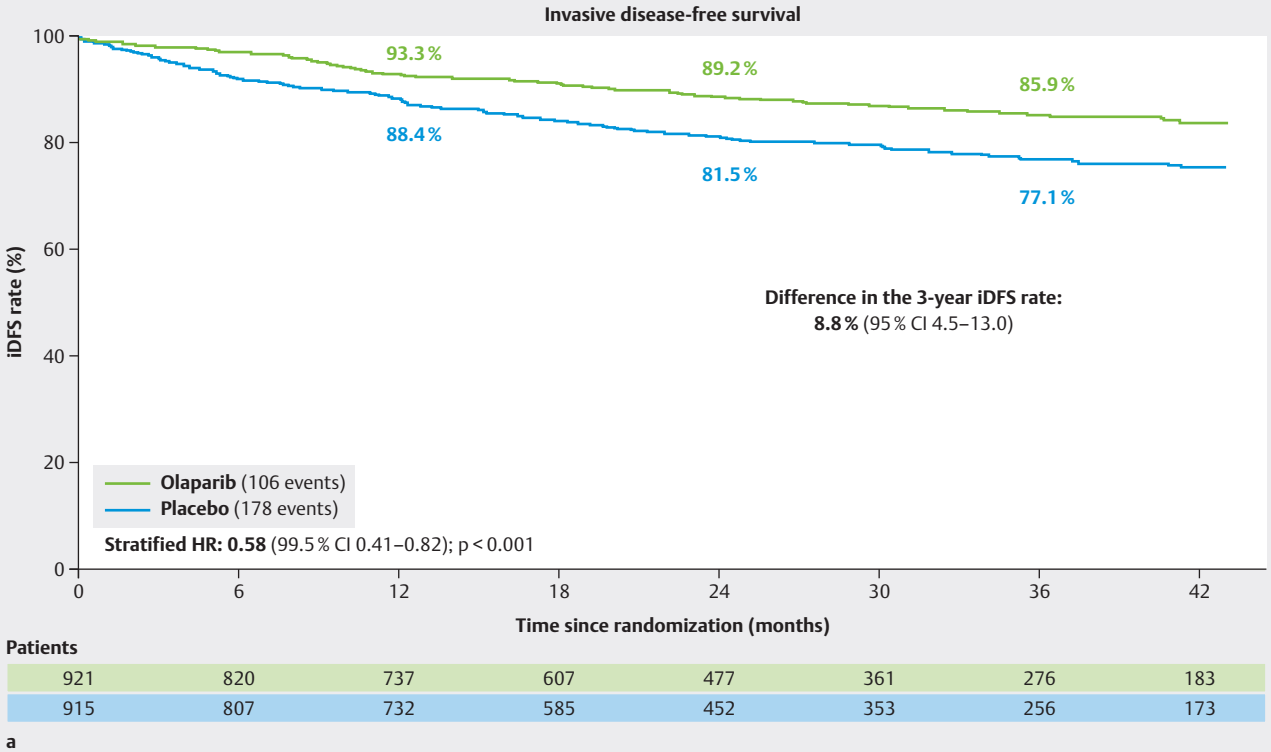
CT = standard chemotherapy; HR = hazard ratio; CI = confidence interval; PFS = progression-free survival

In the (post-neo)adjuvant setting, olaparib therapy resulted in a significant prolongation of invasive disease-free survival (iDFS) and distant disease-free survival (dDFS) as well as – according to the new 4-year data of the OlympiA trial – better overall survival (OS) in patients with early-stage HER2-negative breast cancer with a high risk of recurrence and confirmed *BRCA1/2* germline mutations compared to placebo. Olaparib therapy significantly reduced the risk of an iDFS event by 42% and the risk of death by 32% (▶ **Fig. 1**). Subgroup analyses (according to hormone receptor status, previous platinum-based therapy yes vs. no, previous chemotherapy adjuvant vs. neoadjuvant) showed no evidence for heterogeneity, even though the number of deaths was low in some of the subgroups. CNS recurrence was the first iDFS event for 2.4% of patients in the olaparib group vs. 3.9% in the placebo group [32, 33, 34]. ▶ **Fig. 2** shows the study design of the OlympiA trial.

The Breast Committee of the German Working Group for Gynecological Oncology (AGO) has therefore recommended olaparib for use as (post-neo)adjuvant treatment even prior to its approval by the European Commission for all HR+/HER2− and TNBC patients with *BRCA1/2* germline mutations based on the population in the OlympiA trial (for further information see chapter on **Guidelines and Recommendations on Molecular Diagnostics and Therapy**) [17].

Quality of life

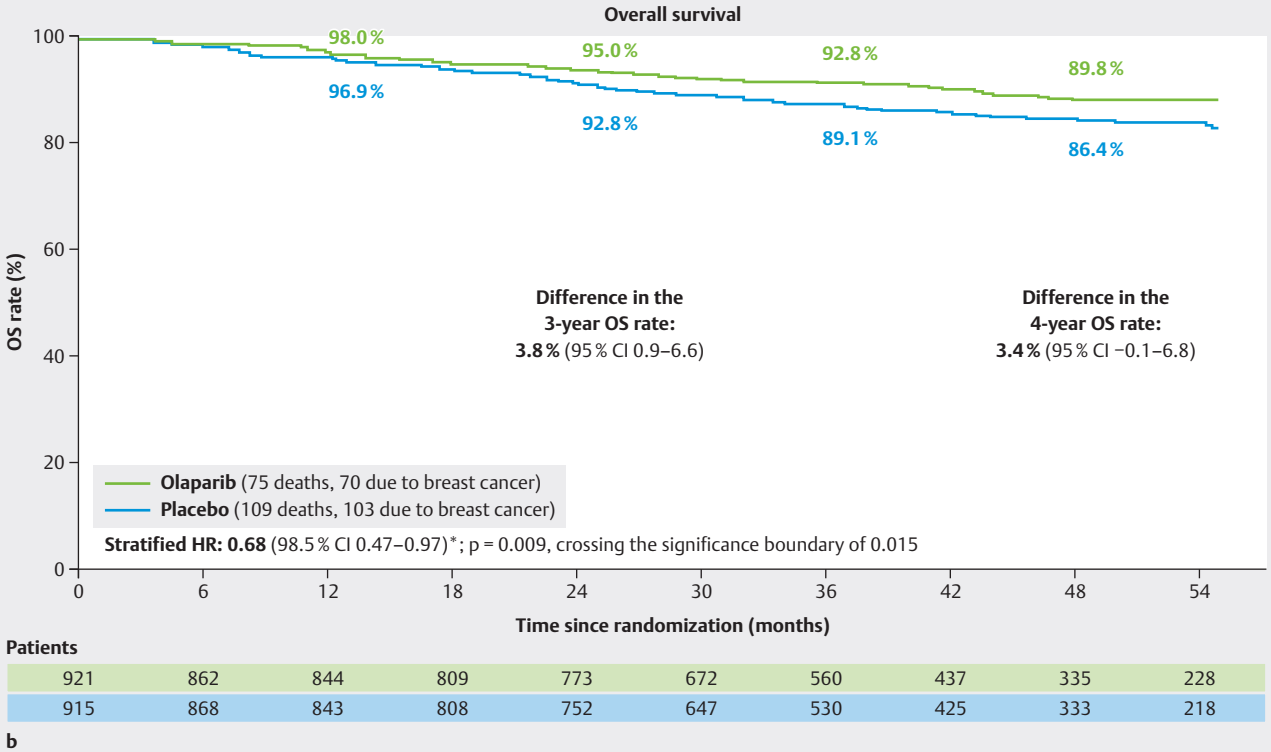
Efficacy benefits reported for PARPi include maintaining patients' quality of life. In contrast to chemotherapy, patients' quality of life in an advanced therapy setting improved with olaparib or talazoparib. Only gastrointestinal complaints, especially nausea and vomiting, were perceived as equally difficult or, particularly in the early stages of treatment, more burdensome under PARPi therapy compared to chemotherapy, which corresponds to the adverse events profile of PARPi. The study participants felt that other symptoms, particularly measured on the fatigue, pain, and appetite loss subscales, were less severe under PARPi therapy than under chemotherapy [36, 37]. The impact on quality of life based on both adverse events and the therapeutic effect is thus significantly lower with a PARPi versus chemotherapy.



Patients

921	820	737	607	477	361	276	183
915	807	732	585	452	353	256	173

a

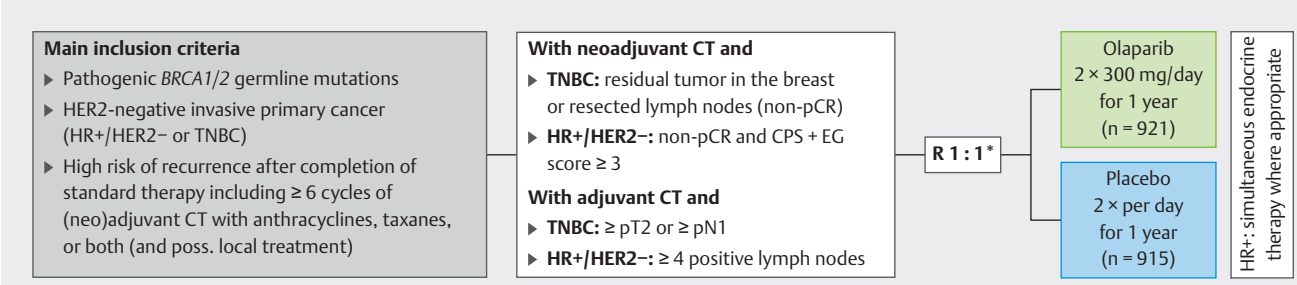


Patients

921	862	844	809	773	672	560	437	335	228
915	868	843	808	752	647	530	425	333	218

b

▶ **Fig. 1** OlympiA trial leading to the approval of olaparib to treat early-stage HER2-negative breast cancer with a high risk of recurrence in patients with confirmed *BRCA1/2* germline mutations (modified from [33, 35]): significant improvement of the 3-year iDFS rate ($p < 0.001$) (**a**) and the 4-year OS rate ($p = 0.009$) (**b**) after 1 year of (post-neo)adjuvant therapy with olaparib compared to placebo after (neo)adjuvant chemotherapy. HR = hazard ratio; iDFS = invasive disease-free survival; CI = confidence interval; OS = overall survival; * A 98.5% CI was used, as $p < 0.015$ was necessary for statistical significance.



▶ **Fig. 2** OlympiA patient cohort and study design. CPS + EG: prognostic score based on clinical staging prior to treatment (CS) and after neoadjuvant chemotherapy (PS), estrogen receptor status (E) and grading (G) to estimate the prognosis after neoadjuvant chemotherapy. * Stratified according to hormone receptor status (HR+/HER2− or TNBC), timing of previous CT (neoadjuvant or adjuvant) and use of previous platinum-based therapy for breast cancer (yes or no). Bisphosphonates and endocrine therapy in both treatment arms as adjuvant therapy according to institutional guidelines.

Quality of life remained largely unchanged during (post-neo)adjuvant olaparib therapy in the early-stage therapy setting. Although there was a statistically significant worsening of fatigue symptoms during olaparib therapy, the changes to FACIT Fatigue scores were below the clinically meaningful difference of 3 points [38]. A statistically and clinically significant but small worsening was shown for the symptom subscales Nausea and Vomiting during therapy [39]. The symptoms improved again directly after completion of therapy, meaning that the additional (post-neo)adjuvant therapy with olaparib did not meaningfully affect recovery after standard (neo)adjuvant treatment [40].

Routine Use of PARP Inhibitors to Treat Advanced Breast Cancer

Clinical routine data and real-world data have confirmed the efficacy and tolerability of olaparib and talazoparib in patients with HER2-negative advanced breast cancer and *BRCA1/2* germline mutations. In the phase IIIb LUCY trial, the median duration of olaparib treatment was 8 months. The median PFS was 8.2 months and the median OS was 24.9 months (27.4 months when olaparib was administered as first-line therapy vs. 22.7 months for later lines). Therapy discontinuation because of adverse events was rare (4.3 %) [41]. The initial results of the phase IV ViTAL trial report a median duration of talazoparib treatment of 9 months as well as a low discontinuation rate due to adverse events (8.0%) [42].

Guidelines and Recommendations on Molecular Diagnostics and Therapy

In the 2022 update of the recommendations for the diagnosis and treatment of patients with early and advanced breast cancer, the Breast Committee of the German Working Group for Gynecological Oncology (AGO) once again gave the highest level of recommendation to carrying out *BRCA1/2* gene testing in:

1. every case where it would be therapeutically relevant (e.g., PARPi), and
2. every patient with a possible hereditary predisposition for breast and/or ovarian cancer based on familial history and the patient's own medical history (including TNBC before the patient's 60 th birthday, and development of ovarian cancer) according to the checklist of the German Cancer Society [43]

Moreover, patients with a positive familial history and a suspicion of hereditary breast/ovarian cancer should receive testing for additional risk genes (e.g., gene panels, including *BRCA1/2*) [1].

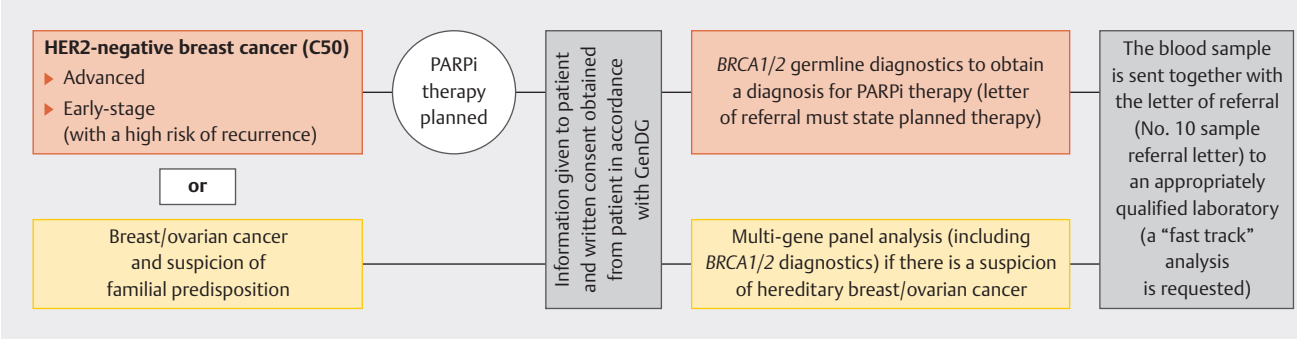
Use of a PARPi (olaparib or talazoparib) was again recommended for patients with confirmed *BRCA1/2* germline mutations and (HER2-negative) metastatic disease. In addition, (post-neo)adjuvant use of olaparib was recommended for the first time (since April 2022) for patients with confirmed *BRCA1/2* germline mutations and (HER2-negative) early-stage disease who have a high risk of recurrence after completion of standard treatment – even before the relevant expanded regulatory approval was granted [44].

Testing to allow therapy planning is therefore recommended, irrespective of the assessment of familial risk, for all patients who are eligible for PARPi therapy in accordance with the appropriate regulatory approval. This includes testing to plan:

1. systemic therapy with a PARPi (olaparib, talazoparib) to treat adult patients with HER2-negative locally advanced or metastatic breast cancer if indicated, and
2. adjuvant therapy with olaparib after (neo)adjuvant chemotherapy to treat adult patients with early-stage HER2-negative breast cancer and a high risk of recurrence

If treatment is curative and chemotherapy is indicated, neoadjuvant chemotherapy should be preferred, particularly in patients with triple-negative disease. In patients with *BRCA1/2* germline mutations, post-neoadjuvant treatment with olaparib is recommended if indicated, where appropriate with the addition of endocrine therapy (HR+) [17].

The ESMO guideline on metastatic breast cancer also recommends therapy planning based on *BRCA1/2* germline status in patients with HER2-negative disease. The most recent research results for early-stage therapy have, however, not yet been included in the ESMO guideline on early-stage breast cancer [45, 46]. The updated breast cancer guidelines of the *National Comprehensive Cancer Network* (NCCN) also support testing for therapy planning



▶ **Fig. 3** Arranging and implementing *BRCA1/2* germline diagnostics in Germany: *BRCA1/2* germline diagnostics for therapy planning is based on the regulatory approval of PARP inhibitors to treat HER2-negative breast cancer in cases with advanced or early-stage disease and can be arranged by the treating physicians for all patients for whom such treatment would be appropriate. If there is a suspicion that the patient may have a familial predisposition, multi-gene panel testing (including *BRCA1/2* diagnostics) instead of single tests may already be carried out at diagnosis. After the person who will be tested has been provided with the necessary information and has given their informed consent in accordance with the Genetic Diagnostics Act (GenDG), the blood sample is either sent to an approved human genetics laboratory or to a laboratory of a Consortium center together with a letter of referral ordering the laboratory tests (No. 10 sample referral letter). Since January 1 st, 2022, testing in patients with early-stage disease is also reimbursed through the *einheitlicher Bewertungsmaßstab* (EBM; a uniform assessment standard for doctors' fees used in Germany). Billing is done by the laboratory which carries out the testing.

in cases with advanced disease and, for the first time (since December 2021), in cases with early-stage breast cancer and a high risk of recurrence [3].

Outpatient *BRCA1/2* Germline Testing

Requirements for testing

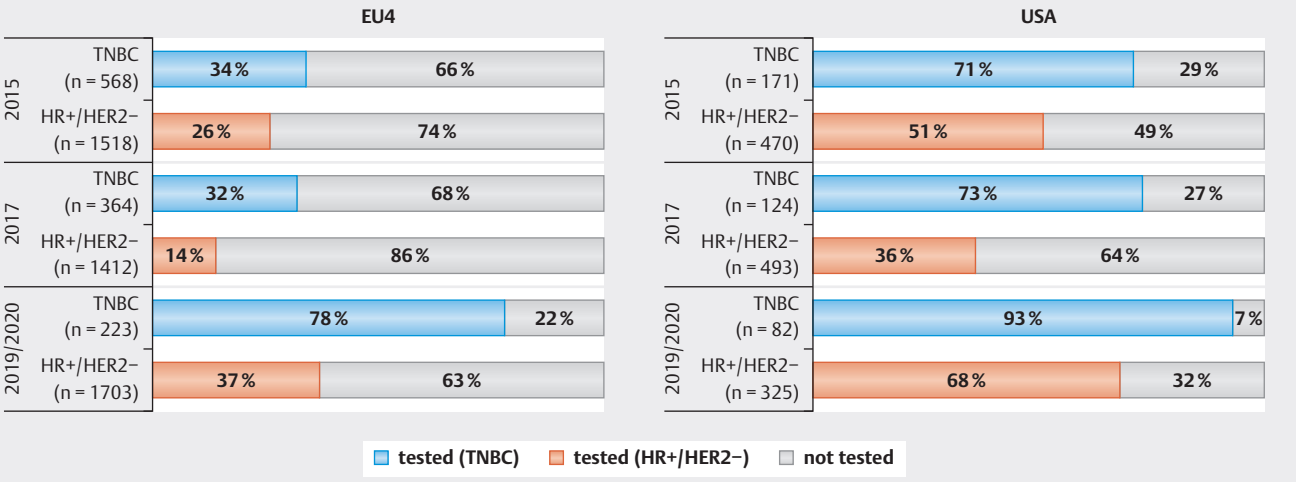
Blood samples are needed to detect *BRCA1/2* germline mutations as these mutations are present in all eukaryotic cells, whereas somatic mutations are only present in tumor cells and are therefore detected in tumor tissue (s. also ▶ **Table 1** on the regulatory approval status of PARPi with regards to *BRCA1/2* mutation status). In Germany, genetic analysis of a germline mutation is subject to the provisions of the German Genetic Diagnostics Act (GenDG, Sec. 2) which requires that the person who will undergo testing is given detailed information about the procedure as well as an analysis of their own/their familial medical history and provides written consent (§ 8 + 9). All registered physicians are permitted to arrange diagnostic testing for therapy planning. Treating physicians with the appropriate qualifications decide on the indications for testing at their own discretion. However, physicians who arrange to carry out predictive diagnostics in healthy at-risk persons must have a qualification in human genetics and must offer genetic counselling before and after testing (§ 7 + 10) [47]. The pathway to arrange for germline diagnostics in order to plan the therapy of persons who have developed disease or persons with a suspicion of hereditary breast cancer is shown in ▶ **Fig. 3**.

Communicating the findings

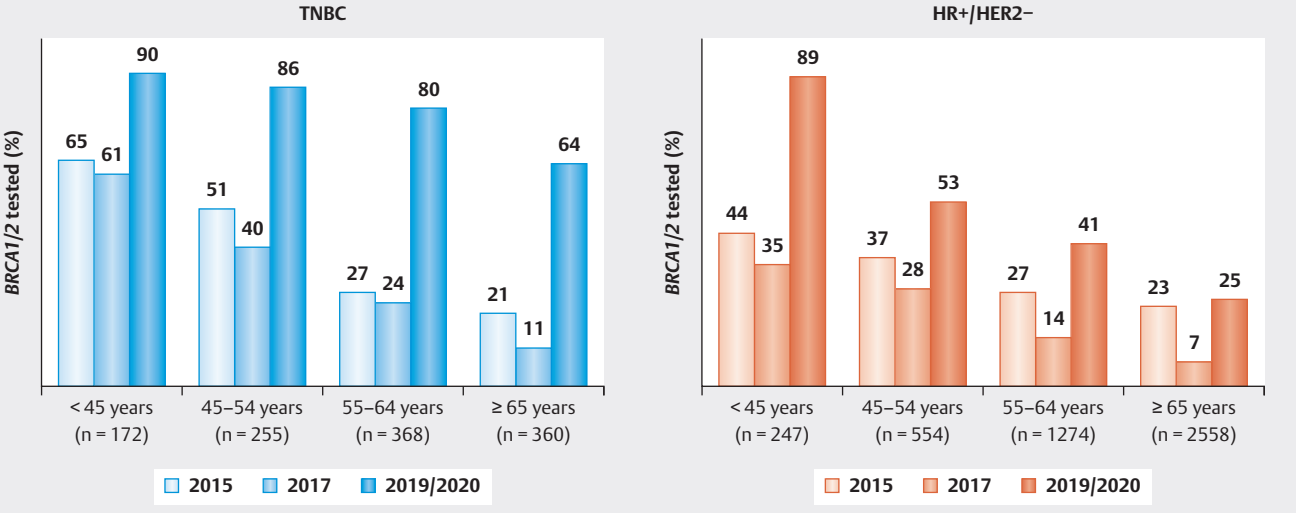
Test results should be available soon after initiation of the test. A German study on diagnostic testing found, however, that it took four weeks on average until the test results were available. Only 24 % of the physicians received a test result within two weeks [48]. The processes in the majority of laboratories clearly require optimization. The clinically relevant sequence variants are classified as pathogenic, likely pathogenic, or not pathogenic (or uncertain for variants of uncertain clinical significance) [49]. If a (likely) pathogenic variant is detected, the tested patient must be offered genetic counselling by physicians with the appropriate qualifications (§ 10 GenDG) [47].

Testing Behavior

Routine clinical care data show that, depending on the respective country, testing rates still vary greatly despite widespread clear recommendations in national and international guidelines supporting genetic testing for *BRCA1/2* in cases with possible hereditary predisposition and cases who have been diagnosed with HER2-negative breast cancer and metastatic disease irrespective of their familial history. The testing rates in routine clinical practice in most countries are low, even when PARPi are available. Studies on *BRCA1/2* testing rates in Europe and the USA before and after regulatory approval of PARPi for patients with HER2-negative advanced breast cancer show that testing rates in this setting were declining between 2015 and 2017, particularly for cases with HR-positive disease. This is possibly due to the availability of CDK4/6 inhibitors, which are used independent of *BRCA* status. As PARPi became available for patients with advanced breast cancer, testing rates increased again in 2019/2020, both for cases with triple-negative disease and cases with HR-positive disease, but rates were still too low, especially for patients with HR-positive disease and in Europe, where testing rates amounted to just 37 % (▶ **Fig. 4**). Patient age also affected testing rates: older women were tested significantly less often, and this was the case whether they had triple-negative disease or HR-positive disease. Testing rates were significantly lower for all age groups with HR-positive disease; in 2019/2020, the testing rates for women aged ≥ 65 years were only 25% compared to 64% for TNBC (▶ **Fig. 5**). Testing rates were also affected by patients' familial history: women with a positive familial history were tested significantly



▶ **Fig. 4** *BRCA1/2* testing rates according to region, hormone receptor status, and year for women with HER2-negative advanced breast cancer (modified from [50, 51]): the *BRCA1/2* testing rates for women with HER2-negative advanced breast cancer declined between 2015 and 2017 both in Europe (EU4: Germany, France, Italy, Spain) and the USA for HR-positive disease. When PARPi became available, testing rates increased again in 2019/2020 (both for cases with triple-negative disease and cases with HR-positive disease) but were still low, especially in patients with positive HR status and patients living in Europe. The data on testing rates was collected as part of three surveys carried out at different times (February to May 2015, March to July 2017 and September 2019 to April 2020). To obtain the information, oncologists consecutively extracted the relevant data from medical charts for the next 8–10 patients with HER2-negative advanced breast cancer. *BRCA1/2* mutation carriers were overrepresented in the 2019/2020 survey.



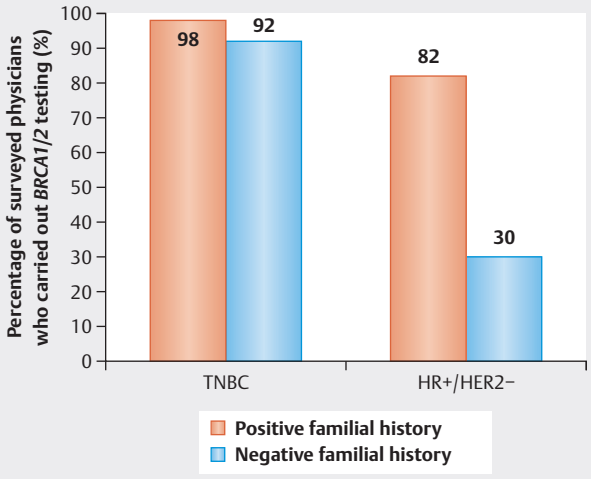
▶ **Fig. 5** *BRCA1/2* testing rates according to hormone receptor status, year, and age for women with HER2-negative advanced breast cancer in Europe (modified from [51]): *BRCA1/2* testing rates for women with HER2-negative advanced breast cancer before (2015 and 2017) and after (2019/2020) regulatory approval of PARPi in Europe (EU4: Germany, France, Italy, Spain) were strongly affected by patient age. Older women were tested significantly less often, irrespective of whether they had triple-negative disease or HR-positive disease. Women with HR-positive disease were less likely to be tested across all age groups than patients with TNBC. For details on how the data on testing rates was collected, see the caption to ▶ **Fig. 4**.

more often, irrespective of the subtype (whether it was triple-negative disease or HR-positive disease) and the patient's age (across all age groups) [50, 51].

A survey carried out in 2019/2020 on implementing *BRCA1/2* germline testing for patients with HER2-negative advanced breast cancer in Europe (EU4), the USA, und Israel revealed significant regional differences. Almost all (97 %) of the surveyed oncologists in Israel stated that they carried out *BRCA1/2* germline testing, demonstrating a greater willingness to carry out testing in high-risk groups [52]; in the USA, the percentage was 45% and in

Europe it was only 26%. In Israel, 90% of surveyed oncologists tested all patients with HER2-negative advanced breast cancer; 23% did so in the USA and only 5% in Europe. In the academic setting, testing was carried out more frequently across all regions. Testing was also carried out more often if PARPi were easily available [53].

According to a German study from 2019/2020, access to both *BRCA1/2* germline testing and PARPi therapy is considered feasible in the outpatient oncology setting. The majority (84%) of surveyed oncologists rated access to testing as very good, good, or satisfactory. The majority was aware of the therapeutic relevance of *BRCA1/2* germline testing, although 22% were not sufficiently aware of its importance. The surveyed oncologists also stated that a positive familial history continued to be the most important factor influencing their decision to perform *BRCA1/2* germline testing for patients with advanced disease, followed by guidelines, the presence of triple-negative disease, and patient age at onset of disease. Despite the available infrastructure and an awareness of the relevance of guidelines, only 30% of surveyed oncologists carried out genetic testing in patients with advanced HR+/HER2− disease if the patient had no positive familial history; in cases with advanced triple-negative disease the rate was 92% (▶ **Fig. 6**) [48].



▶ **Fig. 6** Testing rates for *BRCA1/2* germline testing according to receptor status and familial history in Germany (modified from [48]): the results of an online survey carried out between October 2019 and February 2020 of *BRCA1/2* germline testing (g*BRCA1/2* testing) in patients with advanced breast cancer show that the percentage of surveyed licensed oncologists (n = 50) who carry out testing in patients with HR-positive disease and a negative familial history is still very low. The main reasons cited by respondents why they did not test this patient population was the availability of other therapeutic options, followed by reimbursement difficulties.

Conclusion

The identification of molecular and predictive parameters in patients with breast cancer allows the probability of the effect of a given therapy to be predicted. Pathogenic *BRCA1/2* mutations are not only associated with a strongly increased risk of developing breast cancer, they are also vitally important for treatment planning. A treatment plan should be set up, which is usually done in an interdisciplinary tumor conference in a certified center, prior to initiating therapy, for which the relevant testing is required. Only genetic diagnostics will ensure that patients receive the appropriate individualized therapy, and genetic diagnostics are therefore the first step of any diagnostic workup. Patients should be fully informed as early as possible. All licensed physicians can initiate genetic testing for patients with breast cancer. If a pathogenic variant is identified, the patient must be offered genetic counselling.

Patients with HER2-negative advanced as well as early-stage breast cancer can benefit from PARPi therapy. In patients with metastatic disease, monotherapy with olaparib (OlympiAD) or talazoparib (EMBRACA) significantly prolonged progression-free survival compared with standard chemotherapy [28, 29]. In patients with early-stage disease and a high risk of recurrence (OlympiA), (post-neo)adjuvant olaparib therapy significantly improved not only invasive disease-free survival but also overall survival compared with placebo [33, 34]. Provided the therapy and adverse events are managed well, PARPi are tolerated well and PARPi-related adverse events do not lead to any meaningful impairment of patients' quality of life [36, 37, 40]. Therefore, genetic testing is not just relevant for prolonging progression-free survival and improving the quality of life in a metastatic setting but also has a direct impact on patient survival. For this reason, all breast cancer patients considered for PARPi treatment, if therapeutically relevant, should be routinely offered genetic *BRCA1/2* germline testing irrespective of HR status, familial history, and age at onset of disease. Patients qualify for testing if the results will be therapeutically relevant; from a legal standpoint, these patients should be informed about testing and its potential relevance.

Recent healthcare research analyses have shown, however, that even after PARPi were given regulatory approval the testing rates still depend on the patient's HR status, age, and familial history; cases with TNBC, young age at onset of disease, and a positive familial history are tested more frequently [50, 51].

Guidelines and recommendations (e.g., by AGO e. V.) support *BRCA1/2* germline testing as a basis for therapeutic decisions. Without confirmation of a *BRCA1/2* mutation, targeted therapy with PARPi to treat breast cancer is not possible. This should also be considered for patients with HR-positive breast cancer, patients who are older at onset of disease, and patients without a positive familial history. Once an appropriate diagnosis is made, there is no reason not to carry out testing as this would withhold the option of PARPi therapy from patients for whom it would be suitable, thereby denying them longer survival times.

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Conflict of Interest

MPL: Advisory Boards/Advisory for Lilly, AstraZeneca, MSD, Novartis, Pfizer, Eisai, Exact Sciences, Daiichi-Sankyo, Grünenthal, Gilead, Pierre Fabre, PharmaMar, Sysmex, Samantree, pfm, Hexal and Roche. Lectures for Boeringer-Ingelheim, Lilly, Roche, MSD, Novartis, Pfizer, Exact Sciences, Daiichi-Sankyo, Grünenthal, Gilead, AstraZeneca, Eisai and pfm. Travel expenses from Roche and Pfizer. Editorial Board for medac. PAF: Grants: BioNTech, Cepheid, Pfizer. Honoraria: Novartis, Pfizer, Roche, Daiichi-Sankyo, AstraZeneca, Lilly, Eisai, Merck Sharp & Dohme, Pierre Fabre, SeaGen, Agendia, Sanofi Aventis, Gilead, Mylan.

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