Awareness and Availability of Routine Germline BRCA1/2 Mutation Testing in Patients with Advanced Breast Cancer in Germany

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Abstract
Introduction: Diagnostic testing of germline mutations in breast cancer susceptibility genes 1 or 2 (gBRCA1/2) in patients with human epidermal growth factor receptor 2 negative (HER2–) advanced breast cancer (ABC; locally advanced or metastatic breast cancer) is necessary to assess eligibility for poly(ADP-ribose) polymerase inhibitors (PARPi). We investigated awareness, clinical practice, and the availability of gBRCA1/2 mutation testing in the German outpatient oncology setting. Methods: Office-based oncologists completed a 23-item online survey. Responses were evaluated collectively and by center type. Results: Of 50 oncologists, 33 and 17 were medical and gynecological oncologists, respectively. Oncologists treated a median of 65 (range 14–350) patients with ABC per year. The strongest decision factors to initiate gBRCA1/2 mutation testing were: patient’s known family history of gBRCA1/2 mutation-related cancer(s), guideline recommendations, and triple-negative breast cancer (TNBC). In routine practice, 86% of oncologists tested for gBRCA1/2 mutations. Most oncologists (76–98%) reported testing patients with a known family history of gBRCA1/2 mutation-related cancer(s) irrespective of receptor status. For unknown family history, 92% of oncologists reported testing patients with advanced TNBC versus 30% for HR+/HER2– ABC. Oncologists (66%) rated the awareness of therapeutic relevance of gBRCA1/2 mutation testing for targeted treatment selection as good to satisfactory; 22% rated awareness as poor to insufficient. Conclusion: Diagnostic gBRCA1/2 mutation testing in patients with HER2– ABC is available and routinely performed in Germany’s outpatient oncology setting. However, specific patient subgroups were not routinely tested despite therapeutic indications. Given PARPi availability, opportunities exist to improve testing rates especially for patients with HR+/HER2– ABC without a known family history of gBRCA1/2 mutation-related cancer(s). © 2021 The Author(s) Published by S. Karger AG, Basel

Introduction
Germline mutations in breast cancer susceptibility genes 1 or 2 (gBRCA1/2) are associated with approximately 20–25% of hereditary breast cancers [1–4] and found in approximately 5–10% of all patients with breast cancer [1]. Individuals carrying a gBRCA1/2 mutation have an increased lifetime risk for development of certain cancers, including breast cancer [5, 6], and are commonly up to 25 R.G.W.Q. was an employee of Pfizer at the time of the analyses.

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years younger at diagnosis than the total breast cancer population [7]. Predictive testing in individuals with a familial predisposition to a known or likely pathogenic gBRCA1/2 mutation is well established in Western countries [6]. Identified carriers of gBRCA1/2 mutations also have access to intensified surveillance programs to ensure a prompt diagnosis if cancer develops [8].

The poly(ADP-ribose) polymerase inhibitors (PARPi) talazoparib and olaparib are the first approved targeted treatment options specifically for adult patients with human epidermal growth factor receptor 2 negative (HER2–) advanced breast cancer (ABC) and a gBRCA1/2 mutation [9–12]. Olaparib and talazoparib are available and have been reimbursed in Germany since July 2019 and June 2020, respectively [13, 14]. The pivotal randomized phase 3 studies EMBRACA [15] and OlympiaAD [16] compared talazoparib and olaparib, respectively, with a single-agent chemotherapy of the physician’s choice (eribulin, vinorelbine, capcitabine, or as a fourth option in EMBRACA only, gemcitabine). In both studies, treatment significantly improved progression-free survival and improved objective response rates, but not overall survival in the full intent-to-treat population [15–19]. Both PARPi exhibited a manageable safety profile, and significantly improved patient-reported quality-of-life versus chemotherapy [15, 16, 20–22]. Based on clinical evidence, PARPi are recommended treatments for patients with HER2– ABC and proven gBRCA1/2 mutations [23–25]. Consequently, international and national evidence-based consensus guidelines extended their recommendation for early and broad diagnostic gBRCA1/2 testing when therapeutically relevant [23–26]; NCCN broadened their guidelines to test any breast cancer subtype associated with a gBRCA1/2 mutation [24]. Despite these recommendations, testing rates of patients with ABC vary among countries and are still not part of the clinical routine even in most countries with access to PARPi [27]. This survey evaluated awareness, clinical practice, and availability of routine diagnostic gBRCA1/2 mutation testing in the outpatient oncology setting in Germany, particularly for patients with HER2– ABC.

Materials and Methods

A multicentric, 23-item multiple-choice online survey (www.limesurvey.org) was completed by office-based oncologists across Germany from October 23, 2019 to February 3, 2020. Only oncologists treating patients with ABC were eligible. Clinicians practicing in hospitals, clinics, and direct members of the German Consortium for Hereditary Breast and Ovarian Cancer [28] were excluded. The German Consortium for Hereditary Breast and Ovarian Cancer, which currently consists of more than 20 university centers with multiple cooperation partners, was established to provide structured interdisciplinary care of individuals with a family history of breast and ovarian cancer in Germany [28].

Eligibility screening was conducted based on described criteria. All data were anonymized and analyzed descriptively as a whole and stratified by center type.

Results

Participant Demographics

Of 173 practices contacted, 53 agreed to participate, 21 declined, and 99 did not respond. Of the 53 practices who agreed to participate, 50 office-based oncologists completed the survey; around two-thirds were medical oncologists (n = 33) and one-third gynecological oncologists (n = 17). To our knowledge, this reflects the approximate proportion of medical and gynecological oncologists treating patients with ABC in an outpatient oncology setting in Germany. Most practices (n = 36) were associated with a breast cancer center certified by the German Cancer Society (Deutsche Krebsgesellschaft e.V.) and 5 were cooperation partners of the German Consortium for Hereditary Breast and Ovarian Cancer. Oncologists treated a median of 65 patients with ABC per year (range 14–350); this was consistent across medical and gynecological oncologists.

gBRCA1/2 Testing Decision Factors and Testing Rates

A known family history of gBRCA1/2 mutation-related cancer(s) (defined by the Arbeitsgemeinschaft Gynäkologische Onkologie e.V. [AGO] 2020 recommendations [23]), guideline recommendations, and triple-negative breast cancer (TNBC) were the strongest factors influencing an oncologist’s decision to initiate gBRCA1/2 mutation testing (Fig. 1). Health economic factors such as therapy/test costs, and a patient’s insurance type, as well as clinico-pathological factors such as localization of metastases, a patient’s general condition, histological grade, or medullary morphology, were considered but did not play a leading role in decision making.

In a routine outpatient oncology setting, 86% of oncologists reported testing patients with ABC for a gBRCA1/2 mutation. The selection of patients for mutation testing was strongly dependent on a known familial history of gBRCA1/2 mutation-related cancer(s) and type of breast cancer. In patients with a known familial history, testing was conducted in 98%, 82%, 82%, and 76% of patients with advanced TNBC, HR+/HER2– ABC, HR–/HER2+ ABC, and HR+/HER2+ ABC, respectively. Notably, if the predisposition of a patient’s family to a gBRCA1/2 mutation-related cancer was unknown, only 30% of oncologists routinely tested patients with HR+/HER2– ABC. In the absence of a known familial history, 92% of oncologists reported routinely testing patients with TNBC (Fig. 2).
Routine gBRCA1/2 Mutation Testing

In an outpatient cancer setting, gBRCA1/2 mutation testing was carried out by various facilities. While 68% of surveyed oncologists confirmed their laboratory is accredited for gBRCA1/2 testing, 30% were not aware of the accreditation status of their testing facility; 1 oncologist (2%) did not answer. No physician ordered testing from a facility known to be non-accredited. Time from the initiation of testing to receipt of results ranged from 1 to 21 weeks with a median of 4 weeks; only 24% of oncologists received a test result within 2 weeks. This was comparable with sites that cooperated with the German Consortium for Hereditary Breast and Ovarian Cancer (n = 5; median of 4 weeks; range 3–8 weeks).
Given the therapeutic relevance of gBRCA1/2 mutations for patients with HER2- ABC, genetic counseling is neither required to initiate gBRCA1/2 testing for these patients, nor to initiate PARPi therapy. However, oncologists must offer genetic counseling to patients where a (potentially) deleterious gBRCA1/2 mutation has been detected (GenDG §10). In this survey, 94% of oncologists routinely advised patients to receive genetic counseling if a gBRCA1/2 mutation was detected. Most commonly, oncologists referred patients with a positive gBRCA1/2 mutation test result for genetic counseling to the German Consortium for Hereditary Breast and Ovarian Cancer (44%); however, 28% of oncologists surveyed had qualified for genetic counseling according to the German Genetic Diagnostics Act (GenDG §7) and provided counseling to their patients. For those oncologists who did not collaborate with the German Consortium for Hereditary Breast and Ovarian Cancer (n = 43; 86%), 93% informed patients about the option of genetic counseling if a (potentially) deleterious gBRCA1/2 mutation was detected. If the patient opted to receive genetic counseling, most oncologists referred their patient to an associated human geneticist (60%) and/or counselled the patient themselves (42%).

Approximately one-third (30%) of oncologists received notification from their pathologists about potential familial breast cancer if the tumor tissue displayed typical histopathological features of BRCA1-associated breast cancer (invasive mammary carcinoma with medullary features and grade 3 morphology) [29]. Of the 15 oncologists who received this information, 73% routinely initiated testing for gBRCA1/2 mutations.

**Awareness and Access to gBRCA1/2 Testing**

General access to gBRCA1/2 testing in clinical practice was rated as very good or good by 54% of oncologists, while 10% rated access as poor or insufficient. Access was perceived as slightly better among medical oncologists (61% rated very good or good) than gynecological oncologists (41% rated very good or good; Fig. 3). All 5 centers cooperating with the German Consortium for Hereditary Breast and Ovarian Cancer perceived access to gBRCA1/2 mutation testing as at least sufficient.

A total of 66% of oncologists rated awareness among oncologists of the therapeutic relevance of gBRCA1/2 mutation testing to identify patients with ABC eligible for treatment with a PARPi as good or satisfactory. Notably, 22% of oncologists rated awareness as poor or insufficient.

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**Fig. 3.** Oncologists’ evaluation of access to germline BRCA1/2 testing for patients with ABC and awareness of therapeutic relevance of germline BRCA1/2 testing for patients with ABC (numbers may not add to 100 due to rounding). ABC, advanced breast cancer; gBRCA1/2, germline breast cancer susceptibility genes 1 or 2.
(Fig. 3). Only 6% of oncologists rated awareness of the therapeutic relevance of gBRCA1/2 mutation testing among patients as very good or good; most oncologists considered awareness as poor (26%), sufficient (20%), or satisfactory (34%).

**PARPi and Chemotherapy**

When asked about the potential advantages of PARPi over chemotherapy, oncologists considered the following partially, largely, or fully applicable: proven efficacy and safety profile (100%), patient’s quality of life (100%), flexibility of oral administration (92%), efficacy in patients with a history of central nervous system metastasis (90%), and fear of chemotherapy among patients (78%; Fig. 4).

**Discussion**

The results from this survey describe the real-world practice of gBRCA1/2 mutation testing among community oncologists across Germany. Participating oncologists represented a broad range of office-based medical and gynecological oncologists who treated 14–350 patients with ABC per year.

Diagnostic gBRCA1/2 mutation testing of patients with ABC was routinely performed in Germany’s outpatient oncology setting. This aligns with previous reports, which indicated higher testing rates in countries with access to treatment with PARPi [27]. However, diagnostic gBRCA1/2 mutation testing was carried out with greatest frequency when a familial predisposition to gBRCA1/2 mutation-related cancer(s) was known, and/or when a patient presented with advanced TNBC. While this aligns with reported factors that influence an oncologist’s decision to initiate gBRCA1/2 mutation testing in this survey, it does not fully align with current guideline recommendations [23, 25]. This is notable as only one-third of oncologists reported routinely testing patients with HR+/HER2– ABC without a known familial predisposition, despite PARPi being effective alternatives to chemotherapy in patients with HR+ disease [15, 16]. Of note, about 1 in 20 patients with HR+/HER2– breast cancer have a gBRCA1/2 mutation regardless of a known family history [2, 30]. gBRCA1/2 mutations are more frequent in patients with TNBC than those with HR+ disease [1]. However, since HR+ breast cancer accounts for approximately 80% of all breast cancers [31], increasing gBRCA testing in this population is an important and clinically meaningful consideration.

One quarter of oncologists who do not routinely test patients with HR+/HER2– ABC confirmed reimbursement difficulties as a contributing cause. Before January 2020 in Germany, there was no health insurance billing code number available for patients to undergo diagnostic testing.

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**Fig. 4.** Oncologists’ opinions on the advantages of PARPi over conventional chemotherapy. *In the EMBRACA study, efficacy in terms of progression-free survival and tumor response was shown for patients with a known history of CNS metastasis [15, 19]. CNS, central nervous system; PARPi, poly(ADP-ribose) polymerase inhibitors; QoL, quality of life.
gBRCA1/2 mutation testing in the absence of an identified familial risk. Now, inclusion of a new doctor’s fee scale also facilitates the reimbursement of diagnostic gBRCA1/2 testing in patients with HER2− ABC without a known familial risk [32]. This may increase therapeutically relevant diagnostic gBRCA1/2 mutation testing of all patients with advanced HER2− breast cancer in Germany.

While the majority of physicians rated awareness of the therapeutic relevance of gBRCA1/2 mutation testing among oncologists as good or satisfactory, actual testing rates were low in certain subgroups, for example patients with HR+ ABC without a known familial predisposition. Thus, there is a need to increase oncologists’ awareness of the therapeutic relevance of gBRCA1/2 mutation testing, similar to other European countries [27]. Three pillars are essential to increase awareness of the diagnostic relevance of gBRCA1/2 testing. First, it is important to ensure and maintain awareness among treating physicians; this includes comprehensive sector-wide educational and training programs delivered by academia and medical societies, as well as guideline committees and industry. In today’s digital age, access to advanced training should also remain available virtually. Second, it is necessary to closely collaborate with patient advocacy groups and increase patient awareness; this includes patient-oriented educational materials and lay language presentations of scientific research findings. Third, it is important to effectively plan the country-wide dissemination of research findings and educational programs, support local activities, and thus eventually reach a country-wide awareness of the therapeutic relevance of gBRCA1/2 testing.

Thus, in the age of precision medicine, broad, fast, and informed access to diagnostic testing is of paramount importance to guide treatment decisions. In Germany, gBRCA1/2 mutation testing in patients with HER2− ABC is considered routinely available and feasible in the outpatient oncology setting across center types. However, there is a need to improve therapeutically relevant gBRCA1/2 mutation testing. This holds true especially for patients with HR+/HER2− ABC without a known family history of gBRCA1/2 mutation-related cancer(s) to evaluate eligibility for targeted treatment with a PARPi.

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Statement of Ethics

As no patients were involved in this survey, no ethical approval was required.

Conflict of Interest Statement

M.P.L. reports honoraria for lectures, consulting, or an advisory role for Eli Lilly, AstraZeneca, MSD, Novartis, Pfizer, Eisai, Genomic Health, Roche, Hexal, and Medac; travel, accommodations, expenses from Roche and Pfizer; editorial board member of Medac; fees for non-CME services from Eli Lilly, Roche, Novartis, Pfizer, Genomic Health, AstraZeneca, MSD, and Eisai. T.D. reports advisory/consultancy fees for Novartis and Eli Lilly. E.D.R. and A.N. are employees of Pfizer and report ownership interest in Pfizer. R.G.W.Q. was an employee of Pfizer at the time of the analyses and reported ownership interest in Pfizer and Amgen. N.M. reports ownership and a leading position within iOMEDICO, and research grants from Pfizer in the last 3 years. N.H. reports honoraria from Pfizer, AstraZeneca, and MSD.

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The authors had full access to the data and take responsibility for the integrity of the data and accuracy of the analysis. E.D.R., A.N., and R.G.W.Q.: survey concept and design. N.M.: acquisition of data and statistical analysis (iOMEDICO AG, Freiburg, Germany). M.P.L., T.D., E.D.R., A.N., R.G.W.Q., N.M., and N.H.: analysis and interpretation of data. E.D.R.: drafting of the manuscript. M.P.L., T.D., A.N., R.G.W.Q., N.M., and N.H.: critical revision of the manuscript for important intellectual content. E.D.R.: obtaining funding.

Availability of Data

Data are available for bona fide researchers who request it from the authors.

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