Adv Ther (2023) 40:331–348
https://doi.org/10.1007/s12325-022-02302-2

ORIGINAL RESEARCH

Real-World Study of Regional Differences in Patient Demographics, Clinical Characteristics, and *BRCA1/2* Mutation Testing in Patients with Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer in the United States, Europe, and Israel

Reshma Mahtani · Alexander Niyazov · Katie Lewis · Alex Rider · Lucy Massey · Bhakti Arondekar · Michael P. Lux

Received: July 13, 2022 / Accepted: August 10, 2022 / Published online: October 28, 2022

ABSTRACT

Introduction: Genetic mutations in breast cancer susceptibility gene 1 or 2 (*BRCA1/2*) confer a high risk for developing breast cancer; however, at least 50% of women with *BRCA1/2* mutations go undiagnosed. This study evaluated differences in patient demographics, clinical characteristics, and *BRCA1/2* mutation testing in the USA, European Union (EU4), and Israel in a real-world population of patients with human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC).

Methods: This study was a retrospective analysis of data from the Adelphi Real World ABC Disease Specific Programme in the USA, EU4, and Israel. Medical oncologists completed a patient record form, which included detailed questions on demographics, clinical assessments and outcomes, and treatment history. Eligible patients were at least 18 years of age and receiving therapy for stage IIIb–IV ABC.

Results: Among the 2527 study patients, 407 were from the USA, 1926 were from the EU4, and 194 were from Israel; 86% had hormone receptor–positive (HR+)/HER2− ABC and 14% had triple-negative breast cancer (TNBC). Israeli

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-022-02302-2.

R. Mahtani (✉)
Miami Cancer Institute, Plantation, FL, USA
e-mail: rmahtani@baptisthealth.net

A. Niyazov
Patient Health and Impact, Pfizer Inc, New York, NY, USA
e-mail: Alexander.Niyazov@pfizer.com

K. Lewis · A. Rider
Oncology Franchise, Adelphi Real World, Adelphi Mill, Bollington SK10 5JB, UK

K. Lewis
e-mail: katie.lewis@adelphigroup.com

A. Rider
e-mail: Alex.Rider@adelphigroup.com

L. Massey
Department of Statistics and Data Analytics, Adelphi Real World, Bollington, UK
e-mail: lucy.massey@adelphigroup.com

B. Arondekar
Patient Health and Impact, Pfizer Inc, Collegeville, PA, USA
e-mail: Bhakti.Arondekar@pfizer.com

M. P. Lux
Klinik für Gynäkologie und Geburtshilfe Frauenklinik St. Louise, Paderborn, Frauenklinik St. Josefs-Krankenhaus, Salzkotten, St. Vincenz Kliniken, Paderborn, Germany
e-mail: M.Lux@vincenz.de

patients had a higher rate of family history of *BRCA*-related cancer (69%) compared with patients in the EU4 (18%; $p < 0.0001$) and USA (18%; $p < 0.0001$). Among patients with HR+/HER2− ABC, the *BRCA1/2* testing rate was 99% in Israel, 37% in the EU4, and 68% in the USA ($p < 0.0001$ vs Israel and the EU4). The age of tested patients was significantly younger in Israel (56 years) compared with the EU4 (59 years; $p = 0.016$ vs Israel) and USA (64 years; $p < 0.0001$ vs Israel and the EU4). Among patients with TNBC, the *BRCA1/2* testing rate was 100% in Israel, 78% in the EU4 ($p < 0.0001$ vs Israel), and 93% in the USA ($p < 0.002$ vs the EU4). Among tested patients, genetic counseling rates were also higher in Israel (98%) compared with the EU4 (40%; $p < 0.0001$) and USA (38%; $p < 0.0001$).

Conclusions: Testing and genetic counseling rates for *BRCA1/2* mutations were very high in Israel, potentially due to the high rate of family history of *BRCA*-related cancer in this population and higher general awareness of genetic testing. In the EU4 and USA, overall rates of testing for *BRCA1/2* mutations and genetic counseling were significantly lower compared with Israel. Given the high risk of breast cancer in *BRCA1/2* mutation carriers and the efficacy of new therapies in treating ABC with a *BRCA1/2* mutation, efforts should be made to improve *BRCA1/2* testing rates in Europe and the USA.

Keywords: Breast cancer susceptibility gene 1 or 2; Genetic testing; Human epidermal growth factor receptor 2–negative advanced breast cancer; Real-world

Key Summary Points

National and international guidelines recommend testing patients with advanced breast cancer (ABC) for germline breast cancer susceptibility gene 1 or 2 (*BRCA1/2*) mutations.

This real-world study evaluated *BRCA1/2* mutation testing rates in patients with human epidermal growth factor receptor 2–negative (HER2−) ABC in the USA, the European Union 4 (EU4; France, Germany, Italy, and Spain), and Israel.

Among patients with hormone receptor–positive/HER2− ABC, the *BRCA1/2* testing rate was 99% in Israel, 37% in the EU4, and 68% in the USA.

Among patients with triple-negative breast cancer, the *BRCA1/2* testing rate was 100% in Israel, 78% in the EU4, and 93% in the USA.

Given the high risk of breast cancer in *BRCA1/2* mutation carriers and the efficacy of new therapies in treating ABC with a *BRCA1/2* mutation, efforts should be made to improve *BRCA1/2* testing in Europe and the USA.

INTRODUCTION

Women in the general population have an approximately 13% risk of developing breast cancer in their lifetime [1]. By contrast, women with genetic mutations in breast cancer susceptibility gene 1 or 2 (*BRCA1/2*) have a 45–90% risk for developing breast cancer [1, 2]. Approximately 3–6% of all breast cancer cases are caused by *BRCA1/2* mutations [3–6]. Importantly, a recent study found that *BRCA1/2* mutations in over 50% of individuals would have gone undetected when using traditional clinical criteria (e.g., family history) for genetic testing [7].

Higher risk populations have also been identified. As a result of the founder effect, *BRCA1/2* mutations occur at higher rates in some countries with populations that arise from a small number of individuals and a more

homogeneous gene pool. In Israel, for example, 12% of Ashkenazi Jewish women with breast cancer have a *BRCA1/2* mutation [8]. Also, *BRCA1/2* mutation-related breast cancers are more likely to be triple-negative breast cancer (TNBC), which has a worse prognosis, often a higher stage, and therefore may require more intensive therapies [9].

The poly(adenosine diphosphate-ribose) polymerase inhibitors (PARPi) olaparib and talazoparib are approved by the US Food and Drug Administration, the European Medicines Agency, and in Israel for the treatment of patients with germline *BRCA1/2* (g*BRCA1/2*)–mutated, human epidermal growth factor receptor 2–negative (HER2−) advanced breast cancer (ABC) [10, 11]. These approvals were based on findings from the OlympiAD [12] and EMBRACA [13] studies, both of which demonstrated improved progression-free survival outcomes in patients with HER2− g*BRCA1/2*-mutated ABC who received olaparib or talazoparib, respectively, compared with patients who received physician's choice of chemotherapy (OlympiAD: capecitabine, vinorelbine, or eribulin; EMBRACA: capecitabine, vinorelbine, eribulin, or gemcitabine). In the OlympiA trial, olaparib also significantly prolonged invasive disease-free survival, compared with placebo, when taken as an adjuvant therapy in patients with HER2– early breast cancer who had a g*BRCA1/2* mutation [14]. On the basis of these findings, the US Food and Drug Administration recently approved olaparib as an adjuvant treatment for patients with deleterious or suspected deleterious g*BRCA1/2* mutation and HER2– high-risk early breast cancer [15]. These findings underscore that, in addition to hormone receptor (HR) status, HER2 status, and programmed death ligand 1 (PD-L1) status in TNBC, *BRCA1/2* germline status should also be available for a therapy decision before the start of therapy.

With the approval of the PARPi olaparib and talazoparib and the potential for effective therapeutic intervention in patients with *BRCA1/2* mutations, eligibility criteria have broadened for g*BRCA1/2* mutation testing, as recommended in national and international guidelines [16, 17]. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) now recommend that all patients with locally advanced or metastatic breast cancer be tested for *BRCA1/2* mutation [18]. In addition, identifying carriers of germline *BRCA1/2* mutations affords the opportunity for testing of family members, who can then access risk-reducing interventions [19, 20]. The present analysis evaluated differences in patient demographics, clinical characteristics, and genetic counseling in a real-world population of adult patients who have been diagnosed with locally advanced or metastatic HER2− breast cancer, and who underwent *BRCA1/2* mutation testing, across different regions: the USA, the European Union 4 (EU4; France, Germany, Italy, and Spain), and Israel.

METHODS

Study Design

Data were drawn from the Adelphi Real World ABC Disease Specific Programme (DSP™) from October 2019 through March 2020 in the USA, EU4, and Israel. DSPs are large, multinational, point-in-time surveys conducted in clinical practices, the results of which help describe disease burden, disease management strategies, and responses to treatment as assessed by treating physicians [21].

Participating physicians, recruited by local fieldwork teams, were medical oncologists evaluating at least five patients with ABC per month and were personally responsible for making their treatment decisions. Eligible patients were at least 18 years of age with stage IIIb–IV breast cancer and receiving therapy for ABC at the time of data collection. Patients with an unknown HR status and those participating in a clinical trial at the time of data collection were excluded.

Physicians provided patient record forms (PRFs) for the next eight eligible consulting patients: four patients receiving first-line advanced treatment and four patients receiving second- or later-line advanced treatment. The PRFs included detailed questions on patient demographics, clinical assessments, diagnosis

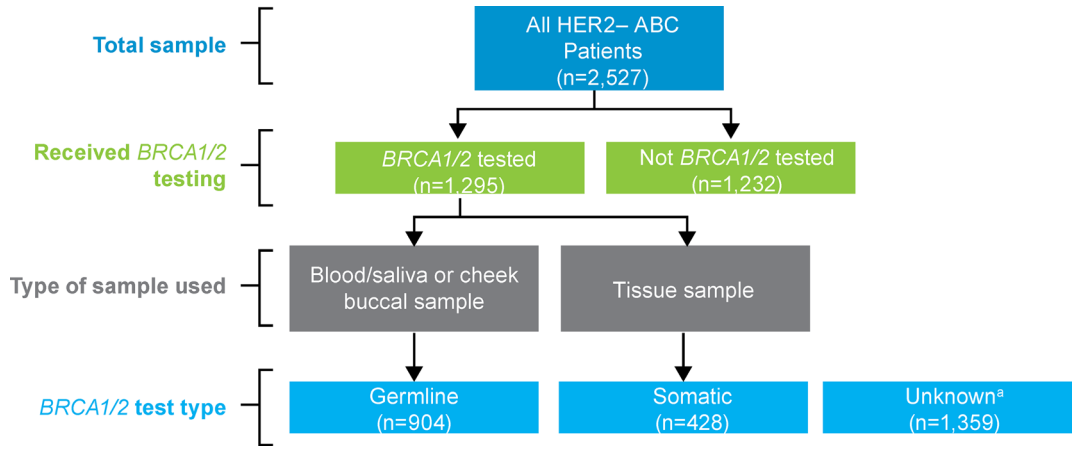

Fig. 1 *BRCA1/2* mutation status. *ABC* advanced breast cancer, *BRCA1/2* breast cancer susceptibility gene 1 or 2, *HER2−* human epidermal growth factor receptor 2–negative. [a]Includes not tested; not known to have a *BRCA1/2* germline mutation test result; not known to have *BRCA1/2* germline and somatic wild-type test results

patterns, comorbidities and symptoms, treatment history and pathways, reasons behind current treatment choice and areas of improvement, current treatment side effects, compliance and satisfaction with current treatment, current treatment goal, future treatment choices and patient life expectancy, resource utilization, market access, and physician satisfaction with treatment. Physicians also reported on tumor and biomarker testing, including, but not limited to, estrogen and progesterone receptor, HER2, PD-L1, progesterone and estrogen receptor, PIK3CA, homologous recombination repair genes, and were asked the proportion of patients tested and the proportion returning a positive result. No guidance was provided on *BRCA1/2* testing; therefore physicians were invited to report any patient regardless of *BRCA1/2* status to prevent any bias in patient selection. *BRCA1/2* mutation testing was focused on in depth, with physicians asked to report patient characteristics for those tested, the type of test used to determine *BRCA1/2* status, cancer stage of patient during the tests, and whether the results were somatic or germline. Patient age at time of data collection, but not at genetic testing, was reported. The treating physicians abstracted data using patient medical records as well as their clinical judgement and diagnostic skills consistent with their decision-making process during routine clinical practice.

All patients provided informed consent for use of their anonymized and aggregated data for research and in scientific publications. Data were aggregated and de-identified before receipt by Adelphi Real World. This research was approved by the Western Institutional Review Board (study protocol AG8643). Data collection was undertaken in line with European Pharmaceutical Marketing Research Association guidelines [22] and as such did not require ethics committee approval. Each survey was administered in full accordance with relevant legislation at the time of data collection, including the US Health Insurance Portability and Accountability Act of 1996 [23] and the Health Information Technology for Economic and Clinical Health Act [24].

Outcomes and Measures

BRCA1/2 mutation testing rates and the characteristics of patients undergoing these tests were stratified by the type of test performed: testing for all *BRCA1/2* mutations, testing for a g*BRCA1/2* mutation with or without testing for a somatic *BRCA1/2* (s*BRCA1/2*) mutation, testing for a s*BRCA1/2* mutation only, unknown *BRCA1/2* mutation test (i.e., the physician was

not aware of testing results or it could not be verified if mutations were somatic or germline), or no *BRCA1/2* mutation test. Results were also stratified by region (i.e., USA, EU4, Israel) and HR status (i.e., HR+/HER2−, TNBC). Characteristics of patients who did and did not receive a *BRCA1/2* mutation test were compared to identify possible factors that may have contributed to the decision to test these patients. Physicians also reported whether patients had undergone genetic counseling before, during, or after *BRCA1/2* mutation testing.

Physicians were asked to designate the sample used for testing and if reported as done on blood, saliva, and buccal samples, this information was used to confirm that *BRCA1/2*mut testing was germline; for USA-based patients, this was also verified by inquiring the name of the laboratory where the testing was performed, whereas data for laboratory confirmation of test type was not available for the EU4 and Israel. For g*BRCA1/2* mutation testing, tissue-only samples were used for s*BRCA1/2* mutation testing (Fig. 1). For USA-based patients, this was verified by the laboratory where the testing was performed; data for laboratory confirmation of test type was not available for the EU4 or Israel.

Statistical Analyses

Descriptive statistics were calculated for intergroup comparisons. For the *BRCA1/2* mutation tested and untested subgroups, differences in demographic and/or clinical characteristics and *BRCA1/2* mutation testing rates were analyzed using Student's *t* tests and Fisher's exact tests. Missing data were not imputed; thus, the sample size varied among variables assessed and is reported separately for each analysis.

RESULTS

Physicians and Patients

Physicians (305) completed PRFs for 2527 patients: 407 in the USA, 1926 in the EU4, and 194 in Israel. Among all patients, 56% (n = 1421) were undergoing treatment at academic medical centers and 44% (n = 1106) were undergoing treatment at community-based centers. All Israeli patients were treated at academic medical centers. A larger percentage of US versus EU4 patients was treated at community-based centers (62% vs 44%; $p < 0.001$).

Patient demographic and clinical characteristics are summarized in Table 1. There were statistically significant regional differences in many of these characteristics, particularly for Israeli patients compared with those in the USA and EU4. Overall, mean (SD) age was 63 (12) years: 57 (13) years in Israel, 63 (11) years in the EU4 ($p < 0.0001$ vs Israel), and 64 (11) years in the USA ($p < 0.0001$ vs Israel). The vast majority of EU4 patients (94%) were White, compared with 65% in the USA and none in Israel. In Israel, 41% of patients (n = 80) were of Ashkenazi Jewish heritage. All Black patients were from the USA. Overall, 18% of patients (n = 458) had full- or part-time employment, ranging from 5% in Israel ($p < 0.0001$ vs USA and EU4) to 17% in the EU4 and 29% in the USA ($p < 0.0001$ vs EU4). A significantly larger percentage of patients in the EU4 was retired (43%) compared with in the USA (35%; $p = 0.003$) and Israel (13%; $p < 0.0001$). Overall, a family history of *BRCA*-related cancer was recorded for 21% of patients (n = 531); the percentage was significantly larger in Israel (69%) compared with the USA (18%; $p < 0.0001$) and EU4 (18%; $p < 0.0001$). Eighty-six percent of patients (n = 2169) had HR+/HER2− ABC and 14% (n = 358) had TNBC. Eighty-eight percent of patients (n = 2214) had stage IV breast cancer, and 78% (n = 1969) had an Eastern Cooperative Oncology Group performance status score of 0 or 1.

BRCA1/2 Testing

BRCA1/2 mutation testing rates overall and by type differed across regions and are listed in Table 2. Overall, 51% of patients (n = 1295/2527) underwent *BRCA1/2* mutation testing. Of these, 70% of patients (n = 904) had g*BRCA1/2* mutation testing with or without s*BRCA1/2* mutation testing and 20% (n = 264) had s*BRCA1/2* mutation–only testing. Test type was

Table 1 Patient demographic and clinical characteristics

Characteristic	Overall *N* = 2527	Region			*p* value		
		USA *n* = 407	EU4 *n* = 1926	Israel *n* = 194	EU4 vs USA	Israel vs USA	EU4 vs Israel
Mean age[a] (SD), year	63 (12)	64 (11)	63 (11)	57 (13)	0.0557	< 0.0001	< 0.0001
Race							
White[b]	2081 (82)	266 (65)	1815 (94)	0	< 0.0001	< 0.0001	< 0.0001
Ashkenazi Jewish	80 (3)	0	0	80 (41)	–	< 0.0001	< 0.0001
Black	101 (4)	101 (25)	0	0	< 0.0001	< 0.0001	–
Other[c]	265 (10)	40 (10)	111 (6)	114 (59)	0.0038	< 0.0001	< 0.0001
Employment status							
Working full/part time	458 (18)	119 (29)	330 (17)	9 (5)	< 0.0001	< 0.0001	< 0.0001
Retired	993 (39)	142 (35)	826 (43)	25 (13)	0.0033	< 0.0001	< 0.0001
Homemaker	570 (23)	80 (20)	396 (21)	94 (49)	0.7351	< 0.0001	< 0.0001
On long-term sick leave	298 (12)	12 (3)	253 (13)	33 (17)	< 0.0001	< 0.0001	0.1508
Unemployed	123 (5)	16 (4)	80 (4)	27 (14)	1	< 0.0001	< 0.0001
Other	85 (3)	38 (9)	41 (2)	6 (3)	< 0.0001	0.0066	0.4365
Premenopausal	229 (9)	26 (7)	151 (8)	52 (27)	0.3544	< 0.0001	< 0.0001
Family history of *BRCA*-related cancer	531 (21)	63 (18)	337 (18)	131 (69)	0.8806	< 0.0001	< 0.0001
HR status							
HR+/HER2−	2169 (86)	325 (80)	1703 (88)	141 (73)	< 0.0001	0.0596	< 0.0001
TNBC	358 (14)	82 (20)	223 (12)	53 (27)			
Current disease stage							
IIIb	182 (7)	27 (7)	146 (8)	9 (5)	0.6025	0.3655	0.1488
IIIc	131 (5)	11 (3)	88 (5)	32 (17)	0.1037	< 0.0001	< 0.0001
IV	2214 (88)	369 (91)	1692 (88)	153 (79)	0.1256	0.0001	0.001
ECOG PS score							
0/1	1969 (78)	324 (80)	1526 (79)	119 (61)	0.8931	< 0.0001	< 0.0001
2+	555 (22)	83 (20)	398 (21)	74 (38)	0.9463	< 0.0001	< 0.0001
Unknown	3 (< 1)	0	2 (< 1)	1 (< 1)	1	0.3228	0.2503
Medical practice setting							
Academic	1421 (56)	153 (38)	1074 (56)	194 (100)	< 0.0001	< 0.0001	< 0.0001
Community	1106 (44)	254 (62)	852 (44)	0 (0)			

Data are *n* (%) unless noted otherwise

BRCA breast cancer susceptibility gene, *ECOG PS* Eastern Cooperative Oncology Group performance status, *EU4* European Union 4 (France, Germany, Italy, Spain), *HR+/HER2*– hormone receptor positive/human epidermal growth factor receptor 2 negative, *TNBC* triple-negative breast cancer

[a]Age at time of data collection

[b]Non-Israeli

[c]Other included but was not limited to Native American, Asian-Indian subcontinent, Asian, Chinese, Hispanic/Latino, Middle Eastern, and mixed race in the USA; Asian-Indian subcontinent, Asian, Chinese, Hispanic/Latino, Middle Eastern, Afro-Caribbean, and mixed race in the EU4; and Maronite, Arab, Druze, and Christian in Israel

Table 2 *BRCA1/2* mutation testing across regions according to HR status

Test performed	Region			*p* value		
	USA	EU4	Israel	USA vs EU4	USA vs Israel	EU4 vs Israel
HR+/HER2−	***n* = 325**	***n* = 1703**	***n* = 141**			
Any *BRCA1/2* mutation	222 (68)	631 (37)	139 (99)	< 0.0001	< 0.0001	< 0.0001
g*BRCA1/2* with or without s*BRCA1/2*	140 (43)	401 (24)	135 (96)	< 0.0001	< 0.0001	< 0.0001
s*BRCA1/2* only	59 (18)	155 (9)	1 (1)	< 0.0001	< 0.0001	< 0.0001
Unknown *BRCA1/2*	23 (7)	75 (4)	3 (2)	0.0474	0.0454	0.2473
No *BRCA1/2* test	103 (32)	1072 (63)	2 (1)	< 0.0001	< 0.0001	< 0.0001
TNBC	***n* = 82**	***n* = 223**	***n* = 53**			
Any *BRCA1/2* mutation	76 (93)	174 (78)	53 (100)	0.0024	0.081	< 0.0001
g*BRCA1/2* with or without s*BRCA1/2*	50 (61)	127 (57)	51 (96)	0.601	< 0.0001	< 0.0001
s*BRCA1/2* only	16 (20)	31 (14)	2 (4)	0.2825	0.0089	0.0564
Unknown *BRCA1/2*	10 (12)	16 (7)	0	0.1706	0.0064	0.0479
No *BRCA1/2* test	6 (7)	49 (22)	0	0.0024	0.081	< 0.0001

Data are *n* (%) unless noted otherwise

BRCA breast cancer susceptibility gene, *g* germline, *HR+/HER2−* hormone receptor positive/human epidermal growth factor receptor 2 negative, *s* somatic, *TNBC* triple-negative breast cancer

unknown for 10% of patients (*n* = 127). Testing rates were significantly higher in Israel compared with other regions. In patients with HR+/HER2− ABC, 99% (*n* = 139/141) underwent testing in Israel, compared with 68% (*n* = 222/325) in the USA ($p < 0.0001$) and 37% (*n* = 631/1703) in the EU4 ($p < 0.0001$). Significantly more patients with HR+/HER2− ABC in the USA underwent s*BRCA1/2* mutation-only testing (18%) compared with patients in the EU4 (9%; $p < 0.0001$) and Israel (1%; $p < 0.0001$). In patients with TNBC, 100% (*n* = 53/53) underwent testing in Israel, compared with 93% (*n* = 76/82) in the USA ($p < 0.081$) and 78% (*n* = 174/223) in the EU4 ($p < 0.0001$). Regardless of cancer type, nearly all testing in Israel was for a g*BRCA1/2* mutation with or without an s*BRCA1/2* mutation versus for an s*BRCA1/2* mutation only (HR+/HER2− breast cancer, 99% vs 1%; TNBC, 96% vs 4%). In the USA, testing rates were 68% (*n* = 222/325) and 93% (*n* = 76/82) for patients with HR+/HER2− breast cancer and TNBC, respectively. Testing rates were lowest in the EU4 (37% [*n* = 631/1703] and 78% [*n* = 174/223] for patients with HR+/HER2− breast cancer and TNBC, respectively). In both the USA and EU4, larger percentages of patients, regardless of cancer type, underwent g*BRCA1/2* mutation testing with or without s*BRCA1/2* mutation testing versus s*BRCA1/2* mutation–only testing (HR+/HER2− breast cancer, 43% vs 18% in the USA and 24% vs 9% in the EU4; TNBC, 61% vs 20% in the USA and 57% vs 14% in the EU4; Table 2).

BRCA1/2 Testing and Patient Characteristics

Tested Versus Not Tested

Overall rates of any type of *BRCA1/2* mutation testing were significantly higher in Israel (99%) compared with the USA (73%; $p < 0.0001$) and EU4 (42%; $p < 0.0001$). The rate of testing was

Table 3 Demographic and clinical characteristics of patients with ABC who did and did not receive *BRCA1/2* testing

	Tested				Not tested			
	Overall	USA	EU4	Israel	Overall	USA	EU4	Israel
HR+/HER2−	***n* = 992**	***n* = 222**	***n* = 631**	***n* = 139**	***n* = 1177**	***n* = 103**	***n* = 1072**	***n* = 2**
Mean age[j] (SD), year	60 (12)	64 (11)[a]	59 (11)[h]	56 (13)[b]	67 (10)	69 (8)[g]	67 (10)	68 (2)
Ethnicity								
White[i]	739 (74)	154 (69)[a]	585 (93)[c]	0[b]	1084 (92)	64 (62)[a]	1020 (95)[h]	0
Black	47 (5)	47 (21)[a]	0	0[b]	26 (2)	26 (25)[a]	0	0
Ashkenazi Jewish	56 (6)	0	0[c]	56 (40)[b]	2 (< 1)	0	0[c]	2 (100)[e]
Other	150 (15)	21 (9)	46 (7)[c]	83 (60)[b]	65 (6)	13 (13)[g]	52 (5)	0
Employment status								
Working full/part time	231 (23)	69 (31)	155 (25)[c]	7 (5)[b]	135 (11)	18 (17)	116 (11)	1 (50)
On long-term sick leave	123 (12)	4 (2)[a]	94 (15)	25 (18)[b]	114 (10)	4 (4)[g]	110 (10)	0
Premenopausal	137 (14)	11 (5)[d]	88 (14)[f]	38 (28)[b]	32 (3)	2 (2)	30 (3)	0
Family history of *BRCA*-related cancer	309 (31)	36 (16)[d]	173 (27)[c]	100 (72)[b]	115 (10)	7 (7)	107 (10)	1 (50)
Treated at academic medical center	616 (62)	91 (41)[a]	386 (61)[c]	139 (100)[b]	597 (51)	30 (29)[a]	565 (53)	2 (100)
TNBC	***n* = 303**	***n* = 76**	***n* = 174**	***n* = 53**	***n* = 55**	***n* = 6**	***n* = 49**	***n* = 0**
Mean age (SD), year	57 (11)	58 (11)	56 (11)	58 (12)	63 (10)	67 (4)	62 (10)	–
Ethnicity								
White[i]	213 (70)	46 (61)[a]	167 (96)[c]	0[b]	45 (82)	2 (33)[g]	43 (88)	–
African American	24 (8)	24 (32)[a]	0	0[b]	4 (7)	4 (67)[a]	0	–
Ashkenazi Jewish	22 (7)	0	0[c]	22 (42)[b]	0	0	0	–
Other	44 (15)	6 (8)	7 (4)[c]	31 (58)[b]	6 (11)	0	6 (12)	–
Employment status								
Working full/part time	82 (27)	30 (39)	51 (29)[c]	1 (2)[b]	10 (18)	2 (33)	8 (16)	–
On long-term sick leave	54 (18)	4 (5)[d]	42 (24)	8 (15)	7 (13)	0	7 (14)	–
Premenopausal	57 (19)	13 (17)	30 (18)	14 (26)	3 (6)	0	3 (6)	–
Family history of *BRCA*-related cancer	101 (33)	20 (26)	51 (29)[f]	30 (57)[e]	6 (11)	0	6 (12)	–
Treated at academic medical center	193 (64)	31 (41)[g]	109 (63)[c]	53 (100)[b]	15 (27)	1 (17)	14 (29)	–

Data are *n* (%) unless noted otherwise

ABC advanced breast cancer, *BRCA1/2* breast cancer susceptibility gene 1 or 2, *HR+/HER2−* hormone receptor positive/human epidermal growth factor receptor 2–negative, *TNBC* triple-negative breast cancer

The type of test was unknown in 127 patients

[a]USA vs EU4, $p < 0.0001$

[b]USA vs Israel, $p < 0.0001$

[c]EU4 vs Israel, $p < 0.0001$

[d]USA vs EU4, $p < 0.001$

[e]USA vs Israel, $p < 0.001$

[f]EU4 vs Israel, $p < 0.001$

[g]USA vs EU4, $p < 0.05$

[h]EU4 vs Israel, $p < 0.05$

[i]Non-Israeli

[j]Age at time of data collection

also significantly lower in the EU4 compared with the USA ($p < 0.0001$).

HR+/HER2− ABC

In patients with HR+/HER2− ABC, the mean age of tested USA-based patients was significantly higher than that of EU4-based patients (64 vs 59 years; $p < 0.0001$; Table 3). The mean age of Israeli patients was significantly lower (56 years) compared with patients in the USA ($p < 0.0001$) and EU4 ($p = 0.016$). Of the patients with HR+/HER2− ABC that were tested for any *BRCA1/2* mutation, the majority in the USA (55%) were 65 years of age or older, whereas in the EU4 and Israel, 35% and 31% of these patients, respectively, were 65 years of age or older (Fig. 2a). A significantly larger percentage of patients in the EU4 versus the USA was White (93% vs 69%; $p < 0.0001$); there were no Black patients in the EU4 or Israel. Forty percent of Israeli patients were of Ashkenazi Jewish descent.

With regard to employment status, similar percentages of tested patients in the USA and EU4 were working full or part time (31% and 25%, respectively). In Israel, significantly fewer patients were working full or part time (5%) compared with the USA (31%; $p < 0.0001$) or EU4 (25%; $p < 0.0001$), and significantly larger percentages of patients were on long-term sick leave in the EU4 (15%; $p < 0.0001$) and Israel (18%; $p < 0.0001$) compared with patients in the USA (2%). According to the age distribution, the largest percentage of premenopausal patients was in Israel (28%), followed by the EU4 (14%) and USA (5%).

The largest percentage of tested patients with a family history of *BRCA1/2* mutation–related cancer was in Israel (72%), followed by the EU4 (27%; $p < 0.0001$ vs Israel) and USA (16%; $p < 0.0001$ vs Israel). Furthermore, for only 1% of patients in Israel tested for any type of *BRCA1/2* mutation was it unknown if the patient had a family history of *BRCA1/2* mutation–related cancer, whereas in the EU4 and USA, 3% and 14% of tested patients, respectively, had an unknown family history of *BRCA1/2* mutation–related cancer (Fig. 2c). Also, a similar pattern of family history of *BRCA1/2* mutation–related cancer was observed in the subgroup of patients who had a g*BRCA1/2* mutation test with or without an s*BRCA1/2* mutation test; 73%, 30%, and 16% of patients in Israel, the EU4, and the USA, respectively, had a family history of *BRCA1/2* mutation–related cancer, and in those who had s*BRCA1/2* mutation testing only, 100%, 21%, and 19% of patients in Israel, the EU4, and the USA, respectively, had a family history of *BRCA1/2* mutation–related cancer (Table 4).

Rates of testing, any *BRCA1/2* mutation tested, g*BRCA1/2*+/− s*BRCA1/2* tested, and s*BRCA1/2*-only tested, among patients with HR+/HER2− ABC by demographic and clinical characteristics in the individual EU4 countries are show in Supplementary Tables 1 and 2. Among patients with *BRCA1/2* mutation–tested HR+/HER2− ABC in the four individual EU4 countries evaluated (France, Germany, Italy, and Spain), the mean ages and percentages of patients with a family history of *BRCA1/2* mutation–related cancer were generally similar, although the percentage of patients treated in academic medical centers was relatively small in Germany (26%) compared with France (79%), Italy (69%), and Spain (77%; Supplementary Table 1).

Triple-Negative Breast Cancer

For patients with TNBC who were tested for any *BRCA1/2* mutation, there were fewer significant regional differences in patient characteristics. In contrast to patients with HR+/HER2− ABC, there were no significant differences in mean age (Table 3). Of the patients with TNBC who were tested for any *BRCA1/2* mutation, 37% in the USA, 25% in the EU4, and 40% in Israel were 65 years of age or older (Fig. 2b). Consistent with patients with HR+/HER2− ABC, a significantly larger percentage of patients in the EU4 versus the USA was White (96% vs 61%; $p < 0.0001$). Forty-two percent of Israeli patients with TNBC were of Ashkenazi Jewish descent (Table 3).

In Israel, significantly fewer tested patients were working full or part time (2%) compared with the USA (39%; $p < 0.0001$) or EU4 (29%; $p < 0.0001$). The largest percentage of patients on long-term sick leave was in the EU4 (24%), followed by Israel (15%) and the USA (5%); only

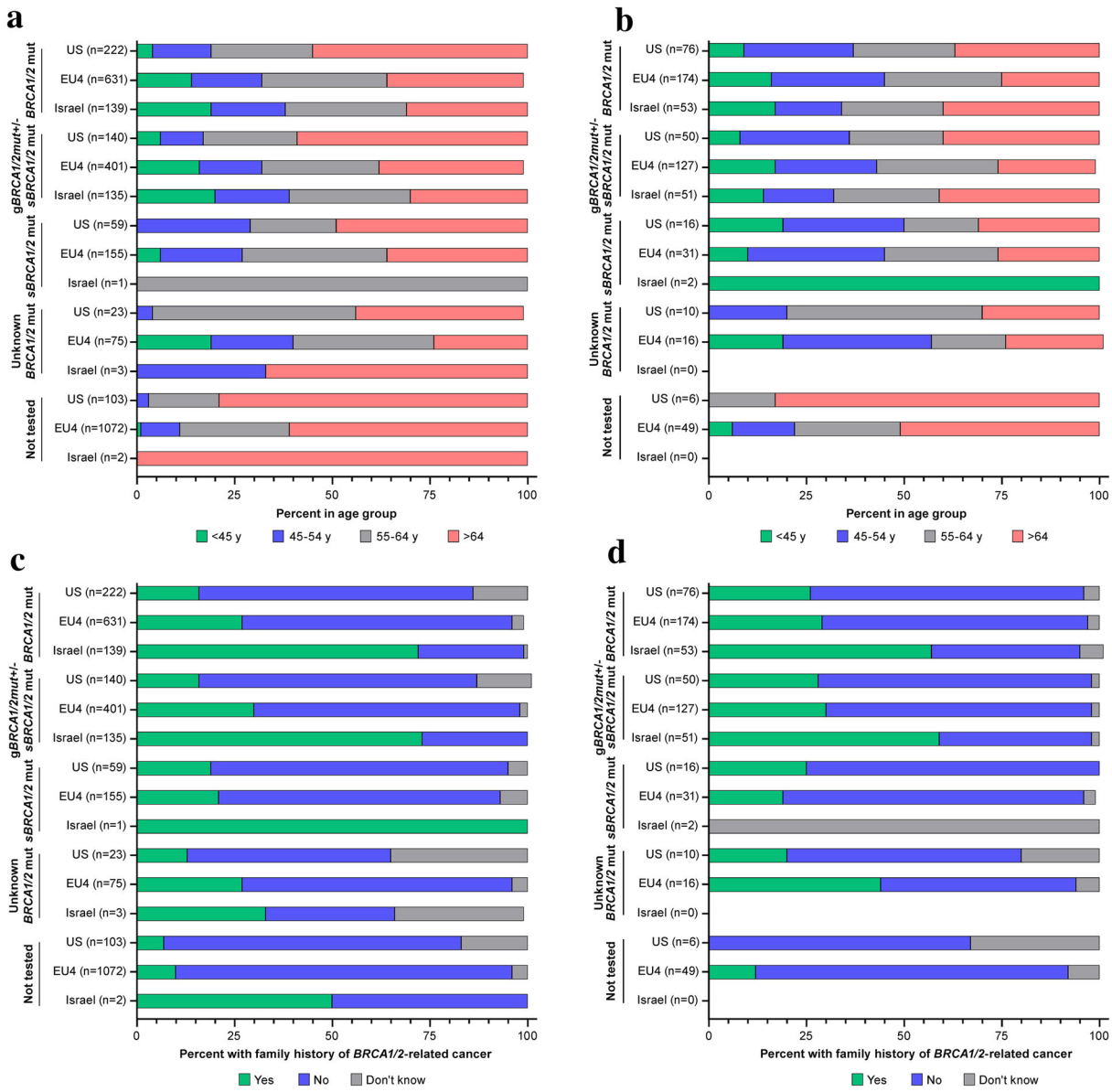

Fig. 2 Testing patterns across regions according to age group and family history of *BRCA*-related cancers. *BRCA1/2* mutation status of patients with HR+/HER2− breast cancer (**a**, **c**) and TNBC (**b**, **d**) stratified into four different age groups (**a**, **b**) and stratified by family history of *BRCA*-related cancer (**c**, **d**). *BRCA1/2mut* breast cancer susceptibility gene 1 or 2 mutation, *HR+/HER2−* hormone receptor–positive/human epidermal growth factor receptor 2–negative, *TNBC* triple-negative breast cancer

the difference between the USA and EU4 reached statistical significance ($p < 0.001$).

The largest percentage of tested patients with a family history of *BRCA1/2* mutation–related cancer was in Israel (57%), which was significantly larger than the percentages for both the EU4 (29%; $p < 0.001$) and USA (26%; $p < 0.001$). Among patients with TNBC who were tested, 4%, 3%, and 6% in the USA, EU4, and Israel, respectively, had an unknown family history of *BRCA1/2* mutation–related cancer (Fig. 2d). A similar pattern of family history of

Table 4 Demographic and clinical characteristics of patients with ABC who received g*BRCA1/2* and/or s*BRCA1/2* testing and those who received s*BRCA1/2* only testing

	g*BRCA1/2* ± s*BRCA1/2* testing				s*BRCA1/2* only testing			
	Overall	**USA**	**EU4**	**Israel**	**Overall**	**USA**	**EU4**	**Israel**
HR+/HER2−	***n* = 676**	***nn* = 140**	***n* = 401**	***n* = 135**	***n* = 215**	***n*0 = 59**	***n* = 59**	***n* = 59**
Mean age[j] (SD), year	59 (12)	64 (12)[a]	59 (12)[g]	56 (13)[b]	61 (10)	62 (9)	60 (10)	56 (0)
Ethnicity								
White[i]	462 (68)	94 (67)[a]	368 (92)[c]	0[b]	194 (90)	44 (75)[a]	150 (97)[g]	0
Black	26 (4)	26 (19)[a]	0	0 [b]	14 (7)	14 (24)[a]	0	0
Ashkenazi Jewish	55 (8)	0	0[c]	55 (41)[b]	0	0	0	0
Other	133 (20)	20 (14)[f]	33 (8)[c]	80 (59)[b]	7 (3)	1 (2)	5 (3)[g]	1 (100)[h]
Employment status								
Working full/part time	142 (21)	45 (32)[f]	90 (22)[c]	7 (5)[b]	59 (27)	18 (31)	41 (26)	0
On long-term sick leave	80 (12)	4 (3)[d]	52 (13)	24 (18)[b]	34 (16)	0[a]	34 (22)	0
Premenopausal	99 (15)	6 (4)[f]	55 (14)[e]	38 (28)[b]	22 (10)	5 (9)	17 (11)	0
Family history of *BRCA*-related cancer	240 (36)	22 (16)[f]	120 (30)[c]	98 (73)[b]	45 (21)	11 (19)	33 (21)	1 (100)
Treated at academic medical center	436 (64)	65 (46)[f]	236 (59)[c]	135 (100)[b]	125 (58)	15 (25)[a]	109 (70)	1 (100)
TNBC	***n* = 228**	***n* = 50**	***n* = 127**	***n* = 51**	***n* = 49**	***n* = 16**	***n* = 31**	***n* = 2**
Mean age (SD), year	57 (11)	59 (11)	55 (11)	59 (11)	55 (12)	54 (14)	57 (9)[g]	34 (13)
Ethnicity								
White[i]	153 (67)	32 (64)[a]	121 (95)[c]	0[b]	36 (73)	6 (38)[a]	30 (97)[g]	0
Black	14 (6)	14 (28)[a]	0	0[b]	8 (16)	8 (50)[a]	0	0
Ashkenazi Jewish	21 (9)	0	0[c]	21 (41)[b]	1 (2)	0	0	1 (50)
Other	40 (18)	4 (8)	6 (5)[c]	30 (59)[b]	4 (8)	2 (13)	1 (3)	1 (50)
Employment status								
Working full/part time	52 (23)	17 (34)	34 (27)[c]	1 (2)[b]	19 (39)	9 (56)	10 (32)	0
On long-term sick leave	46 (20)	4 (8)[f]	34 (27)	8 (16)	7 (14)	0	7 (23)	0
Premenopausal	39 (17)	7 (14)	20 (16)	12 (24)	15 (31)	5 (31)	8 (27)	2 (100)
Family history of *BRCA*-related cancer	82 (36)	14 (28)	38 (30)[c]	30 (59)[h]	10 (20)	4 (25)	6 (19)	0
Treated at academic medical center	152 (67)	24 (48)	77 (61)[c]	51 (100)[b]	31 (63)	4 (25)[d]	25 (81)	2 (100)

Data are *n* (%) unless noted otherwise

ABC advanced breast cancer, *BRCA1/2* breast cancer susceptibility gene 1 or 2, *g* germline, *HR+/HER2−* hormone receptor positive/human epidermal growth factor receptor 2 negative, *s* somatic, *TNBC* triple-negative breast cancer

The type of test was unknown in 127 patients

[a]USA vs EU4, $p < 0.0001$

[b]USA vs Israel, $p < 0.0001$

[c]EU4 vs Israel, $p < 0.0001$

[d]USA vs EU4, $p < 0.001$

[e]EU4 vs Israel, $p < 0.001$

[f]USA vs EU4, $p < 0.05$

[g]EU4 vs Israel, $p < 0.05$

[h]USA vs Israel, $p < 0.05$

[i]Non-Israeli

[j]Age at time of data collection

BRCA1/2 mutation–related cancer was observed in the subgroup of patients who had g*BRCA1/2* mutation testing with or without s*BRCA1/2* mutation testing; 59%, 30%, and 28% of patients in Israel, the EU4, and the USA, respectively, had a family history of *BRCA1/2* mutation–related cancer, and in those who had s*BRCA1/2* mutation testing only, 0%, 19%, and 25% of patients in Israel, the EU4, and the USA, respectively, had a family history of *BRCA1/2* mutation–related cancer (Table 4).

Rates of testing, any *BRCA1/2* mutation tested, g*BRCA1/2*+/− s*BRCA1/2* tested, and s*BRCA1/2*-only tested, among patients with TNBC by demographic and clinical characteristics in the individual EU4 countries are show in Supplementary Tables 3 and 4. Among patients with *BRCA1/2* mutation–tested TNBC in the four individual EU4 countries evaluated (France, Germany, Italy, and Spain), the mean ages were generally similar. As with patients with HR+/HER2− ABC, the percentage of patients treated in academic medical centers was relatively small in Germany (42%) compared with France (69%), Italy (61%), and Spain (70%; Supplementary Table 3).

Genetic Counseling

Overall, genetic counseling was more common in Israel than in the USA or EU4. Among tested patients, counseling rates were 38% (n = 114/298) in the USA, 40% (n = 321/805) in the EU4, and 98% (n = 188/192) in Israel ($p < 0.0001$ vs USA and EU4; Fig. 3). Among patients receiving genetic counseling in the USA, the rates of patients receiving pre-*BRCA1/2* mutation testing only, post-*BRCA1/2* mutation testing only, and pre- and post-*BRCA1/2* mutation testing only were similar (13%, 13%, and 10%, respectively; Fig. 3). In the EU4, 24% of patients received pretest counseling only, 11% received posttest counseling only, and 4% received both pretest and posttest counseling (Fig. 3). In Israel, 16% received pretest counseling only; however, a large percentage of patients (81%) received posttest counseling only (Fig. 3). No patients in Israel received both pretest and posttest counseling. Genetic counseling was provided by the patient's oncologist for 11% of patients in the USA, 25% of patients in the EU4, and none of the patients in Israel. Across all regions, genetic counseling was face to face for the vast majority of patients (Israel, 99%; EU4, 95%; and USA, 92%).

When genetic counseling rates were compared in the individual European countries, receipt of genetic counseling was higher in Spain (60%) relative to France (46%), Germany (29%), and Italy (30%; Supplementary Table 5). These patients also received pre-genetic testing only at a higher rate in Spain (36%) compared with France (29%), Germany (16%), and Italy (17%; Supplementary Table 5).

DISCUSSION

In this retrospective analysis of data drawn from the Adelphi Real World ABC DSP, we evaluated potential differences in patient demographics, clinical characteristics, and genetic counseling for different *BRCA1/2* mutation testing subgroups in the USA, EU4, and Israel in a real-world population of patients with HER2− ABC. By design, DSPs are large, multinational, point-in-time surveys conducted in clinical practices, and the results contribute to our understanding of disease burden, treatment strategies, and responses to treatment as assessed by treating physicians [21].

BRCA1/2 Testing

International guidelines for genetic testing of patients with breast cancer are generally similar across regions (Supplementary Table 6); however, we found significant differences in *BRCA1/2* testing rates across regions. The most striking finding is that 99% of patients with HR+/HER2− ABC and 100% of patients with TNBC had undergone any type of *BRCA1/2* mutation testing in Israel. Corresponding percentages were 68% and 93% in the USA and 37% and 78% in the EU4. A significantly larger percentage of Israeli patients (69%) had a family history of *BRCA1/2*-related cancer compared with the USA (18%) and EU4 (18%), likely due to a founder effect among Ashkenazi Jews from Israel. This founder effect in Ashkenazi Jews may contribute to an increased awareness of

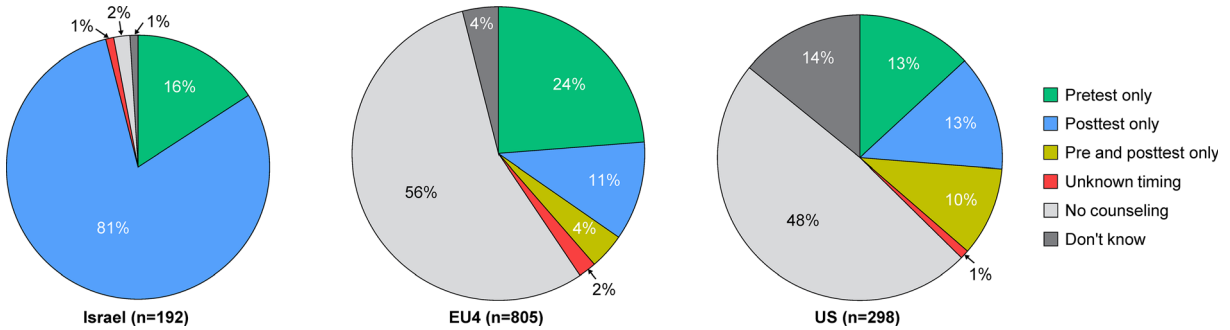

Fig. 3 Genetic counseling in the USA, EU4, and Israel in patients with HER2− breast cancer. The figure shows the rates and timing of counseling. *EU4* European Union 4 (France, Germany, Italy, Spain)

genetic predispositions to cancer and, hence, the high rate of genetic testing in Israel. Across regions, larger percentages of patients had g*BRCA1/2* mutation testing with or without s*BRCA1/2* mutation testing compared with s*BRCA1/2* mutation testing only. There were many more statistically significant between-region differences in *BRCA1/2* mutation testing and testing type for patients with HR+/HER2− ABC compared with patients with TNBC. Israel was one of the first countries to enact legislation to protect the confidentiality of genetic data and prohibit discrimination by employers and health insurance companies based on genetic information. As a result of patient organizations such as BRACHA, public awareness of *BRCA1/2* mutations is increasing; however, eligibility criteria for publicly funded testing need to be expanded so that more high-risk patients can be tested [25]. Although Israel has the infrastructure for free genetic testing and care for *BRCA1/2* mutation carriers, waiting times can be long.

Our results for testing rates in the USA were higher than those reported by Katz et al. for nearly 2000 USA-based patients with early-stage breast cancer surveyed between 2013 and 2015, of which 53% received some form of genetic testing [26]. The difference may be due, at least in part, to the earlier time frame for testing and a lower clinical impact at this time, as genetic testing rates are increasing rapidly. Also, patients in the study by Katz et al. had early-stage breast cancer versus ABC in the current study.

In our study, patients from France, Germany, Italy, and Spain were included in the results for the EU4. In a 2019 report of genetic testing for *BRCA1/2* mutations, individual country profiles were detailed for France, Germany, and Italy; Spain was not included in the report [25]. Briefly, in France, prevention of genetic cancers is a strategic priority, and legislation has been enacted to prevent genetic discrimination by employers or insurers. France has well-defined and up-to-date referral and diagnostic systems and a nationally coordinated system for testing and monitoring those with *BRCA1/2* mutations. In 2015, BRCA-France was established as the only patient organization focused on people with or at risk for *BRCA1/2* mutations. Their work includes advocacy to expand genetic testing criteria. Genetic testing and consultation are available in every region, but utilization is not equal. Thus, efforts are needed to ensure that patients at high risk of *BRCA1/2*-related breast cancer throughout the country can access *BRCA1/2* testing and timely genetic counseling. As of 2019, waiting times were 12 and 22 weeks for a genetic consultation and testing, respectively. France is one of two countries in Europe to have a legal framework for the profession of genetic counseling, and the country offers standardized training for genetic counseling. Despite this, France has a relatively low number of genetic counselors compared with other European countries. Although genetic counseling is not mandatory, it is recommended and prioritized. Between 2003 and 2017, the

number of genetic consultations increased more than sixfold, which is promising [25].

In Germany, guidelines are in place that significantly advance the provision of care for women who have or are at risk for hereditary breast cancers [25]. The current national cancer plan is designed to improve upon the risk-adjusted early detection of people at high risk of cancer, which includes women who may carry a *BRCA1/2* mutation. Nevertheless, more attention is needed to ensure that *BRCA1/2* mutation carriers and those at risk for carrying a mutation can access comprehensive and affordable care. This would address the geographic barriers and differences in insurance coverage that have resulted in disparities in access to comprehensive *BRCA1/2*-related care. Although Germany has several hereditary tumor and cancer registries that collect information on *BRCA1/2* carriers, the data are not aggregated, which limits the potential to support policymakers, clinicians, and researchers. Finally, efforts to increase awareness of *BRCA1/2* mutations, understanding of genetic testing, and the importance of interdisciplinary care among the general population of Germany should be undertaken [25].

In Italy, the prevention of hereditary breast cancer is a stated priority; however, several challenges exist. First, comprehensive national clinical guidelines are not available, and thus there are wide regional variations and inconsistencies in the implementation and provision of comprehensive care pathways. There is a geographic imbalance in the location of testing facilities and insufficient information about these facilities, which present significant barriers for patient access. Awareness among the general public and health care professionals is low but appears to be improving, due at least in part to the efforts of active national organizations that support patients. To address these challenges and to improve the prevention of *BRCA1/2*-related breast cancer, policymakers should consider several priorities: improving equal, consistent, and timely access to *BRCA1/2* testing and genetic counseling for women at high risk of *BRCA1/2*-related breast cancer; establishing a national registry for *BRCA1/2* mutation carriers to support evidence-based policymaking and programming; increasing knowledge about *BRCA1/2*-related cancers among health care professionals; and reducing the cost of testing and ongoing management of asymptomatic *BRCA1/2* mutation carriers to mitigate the real and significant financial barriers for some people with *BRCA1/2* mutations across the country [25].

We also note that at the time of data collection, Italy and Spain did not have reimbursement for use of PARPi to treat *BRCA1/2*-associated ABC and thus had limited access to PARPi. This potentially impacted the rates of *BRCA1/2* mutation testing and counseling in the EU4. In addition, we infer that as a result of the limited access to PARPi, *BRCA1/2* mutation testing in Italy and Spain was predominantly for diagnostic use (i.e., clarification of risk), not for therapeutic testing.

Genetic Counseling

Overall, genetic counseling rates for patients who had any type of *BRCA1*/2 mutation testing were significantly higher in Israel (98%) than in the USA (38%) or EU4 (40%). Although, when provided, counseling was given most often by a genetics counselor (100% of Israeli patients, 90% of USA-based patients, and 78% of EU4-based patients) across regions. Globally, Israel has one of the highest ratios of genetic counselors to patients [27]. Under Israel Ministry of Health policies, pretest and posttest genetic counseling is supposed to be offered to all patients who undergo *BRCA1/2* mutation testing [28]. These factors likely contribute to the reason that rates of genetic counseling and testing in Israel are higher than in the USA and EU4 and are consistent with guidelines. Our results for the USA were similar to those reported by Katz et al., where 61–68% of tested patients received formal counseling [26]. However, our results may not be directly comparable to the study by Katz et al. because, as indicated earlier, the patients in the study by Katz and colleagues had early-stage breast cancer versus ABC in the current study [26]. Furthermore, statutory differences in genetic testing must also be taken into account. For example, for

therapeutic testing (e.g., to check whether a drug is suitable) in Germany, advice from a human geneticist is not mandatory but is recommended in the event of a positive result. However, the oncologists need to be better informed in this case so that they can initiate the test themselves. Thus, on a legal basis, the hurdle for testing is lower, but awareness is still lacking.

In general, other reported barriers for patients to receive genetic counseling include limited knowledge among health care providers about genetic counseling; misperception about its relevance and utility; and concerns among patients about the genetic counseling process, costs, and insurance coverage [29]. Others have reported lack of referral by an oncologist as the most significant barrier among patients meeting the National Comprehensive Cancer Network's criteria for genetic testing and counseling [30].

BRCA1/2 mutations substantially increase the risk of development of breast cancer. Therefore, women who know they carry a *BRCA1/2* mutation after genetic testing and counseling may reduce their risk of developing the disease by undergoing chemoprevention and/or preventive surgery [20], and they may reduce their risk of breast cancer-related mortality by being evaluated on an intensified basis. For health care providers, knowing the *BRCA1/2* mutation status of women with breast cancer can help inform their decisions about disease management. Finally, identifying carriers of *BRCA1/2* mutations affords the opportunity for testing of family members, who can then access risk-reducing interventions themselves [20].

Several limitations should be considered with regard to the evaluation of our findings. First, the survey participants may not be representative of the general ABC population. Because these patients were visiting their physicians, they may be more severely affected by their disease and/or treatment than those who have not consulted with their physicians. The DSP is not based on a true random sample of physicians or patients. Although minimal inclusion criteria were used to select the physicians, participation is influenced by willingness to complete the survey. Physicians were asked to provide data for a consecutive series of patients to avoid selection bias; however, no formal patient selection verification procedures were applied. Identification of the target patient group was based on physician judgement rather than a formalized diagnostic checklist. Nevertheless, this process is representative of physicians' real-world classification of their patients. The point-in-time design of DSPs prevents any conclusions about causal relationships, although the identification of some associations was certainly possible. Recall bias may have affected physician responses to the questionnaires, which is a common limitation of surveys. However, the data for these analyses were collected at the time of the patient's appointment, which is expected to reduce the likelihood of recall bias. Furthermore, it is possible that influences of the individual countries on the testing rates that may not be known were not taken into account (differences in accounting, legal regulations, and guidelines). In addition, the exact time of genetic testing is not known. The high testing rate in Israel may also be due to tests occurring earlier, before the illness or during the initial breast cancer diagnosis. Finally, physician-reported mutation testing in blood was used as a proxy for germline *BRCA1/2*mut testing. As blood is used as a source material for testing of circulating tumor DNA, it cannot be verified that all testing done on blood samples was germline testing only.

Despite such limitations, real-world studies play an important part in highlighting areas of concern that are not addressed in clinical trials. Patients treated in the real-world setting may be less likely to be adherent to medication and more representative of the general population than those included in clinical trials [31]. As a result, data from real-world studies can complement clinical trials.

CONCLUSIONS

In this retrospective analysis of demographic and clinical variables of patients with ABC in Israel, the EU4, and the USA, rates of any type of testing for *BRCA1/2* mutation and genetic counseling were found to be consistent with guidelines in Israel and much higher than rates

in the EU4 and USA. The rate of a family history of *BRCA1/2*-related cancer was significantly higher in Israel (68%) compared with the EU4 (17%) and USA (15%). Additionally, compared with the EU4 and USA, Israeli patients had a higher rate of TNBC and, among those with HR+/HER2− ABC, were significantly younger. Such demographic and clinical variables, in addition to proactive national policies for genetic testing, may contribute to the high rates of *BRCA1/2* mutation testing and counseling in Israel. Among patients with TNBC, in the EU4 and USA, *BRCA1/2* testing rates were much higher among patients with TNBC (78% and 93%, respectively) compared with testing rates in patients with HR+/HER2− ABC (37% and 68% in the EU4 and USA, respectively). Genetic counseling rates were also lower in the EU4 (40%) and USA (38%) compared with Israel (98%). Given the high risk of breast cancer in *BRCA1/2* mutation carriers and the efficacy of recently developed PARPi in treating patients with HER2− ABC with a *BRCA1/2* mutation, efforts should be made to improve *BRCA1/2* testing rates and genetic counseling in Europe and the USA, particularly in patients with HR+/HER2− ABC. Also, as population sizes in this study were relatively small, additional studies of germline *BRCA1/2* mutation and genetic counseling rates in larger populations and in different countries are warranted.

ACKNOWLEDGEMENTS

We thank the participants of the study.

Funding. This study was sponsored by Pfizer Inc. and Adelphi Real World in accordance with Good Publication Practice (GPP3) guidelines. The journal's Rapid Service and Open Access fees were funded by Pfizer. Pfizer was involved in study design; data interpretation of data; writing the report, and the decision to submit the report for publication.

Medical Writing Assistance. Medical writing support was provided by John Teiber, PhD, of ICON (Blue Bell, PA) and funded by Pfizer.

Author Contributions. Conceptualization: Alex Rider, Katie Lewis, Michael P. Lux, Alex Niyazov, Reshma Mahtani, Bhakti Arondekar. Methodology: Alex Rider, Katie Lewis, Michael P. Lux, Alex Niyazov, Reshma Mahtani, Bhakti Arondekar. Formal analysis and investigation: Katie Lewis, Lucy Massey, Michael P. Lux, Alex Niyazov, Reshma Mahtani, Bhakti Arondekar. Writing - review and editing: Alex Rider, Katie Lewis, Lucy Massey, Michael P. Lux, Alex Niyazov, Reshma Mahtani, Bhakti Arondekar. Provision of resources: Alex Rider, Katie Lewis, Alex Niyazov, Bhakti Arondekar. Supervision of team or personnel: Alex Rider, Katie Lewis, Alex Niyazov, Bhakti Arondekar.

Disclosures. Reshma Mahtani has acted as consultant for AstraZeneca, Amgen, Biotheranostics, Daiichi-Sankyo, Genentech, Immunomedics, Eli Lilly, Merck, Novartis, Pfizer, Puma, Sanofi, and SeaGen. Alex Niyazov, Bhakti Arondekar are employees of and own stock in Pfizer Inc. Katie Lewis, Alex Rider, and Lucy Massey are employees of Adelphi Real World. Michael P Lux has received honoraria for lectures, consulting or working in an advisory role for Eli Lilly, AstraZeneca, MSD, Novartis, Pfizer, Eisai, Exact Sciences, Daiichi-Sankyo, Grünenthal, Gilead, Pierre Fabre, PharmaMar, Onkowissen, and Roche; received fees for travel, accommodations, expenses from Roche and Pfizer; and acted as editorial board member of Medac.

Compliance with Ethics Guidelines. Patients provided informed consent for use of their anonymized and aggregated data for research and in scientific publications. Data were aggregated and de-identified before receipt. This research was approved by the Western Institutional Review Board (study protocol AG8643). Data collection was undertaken in line with European Pharmaceutical Marketing Research Association guidelines, and as such did not require ethics committee approval.

Data Availability. Data collection was undertaken by Adelphi Real World as part of an Adelphi Disease Specific Programmes™ independent survey subscribed by multiple

pharmaceutical companies, one of which was Pfizer Inc. Pfizer did not influence the original survey through either contribution to the design of questionnaires or data collection. The survey described here using data from the Adelphi Disease Specific Programmes was funded by Pfizer. Publication of study results was not contingent on the subscriber's approval or censorship of the manuscript. All data that support the findings of this study are the intellectual property of Adelphi Real World. All requests for access should be addressed directly to Katie Lewis at katie.lewis@adelphigroup.com.

REFERENCES

1. National Cancer Institute. *BRCA1* and *BRCA2*: cancer risk and genetic testing. https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet. Accessed 23 May 2022.

2. The Royal Marsden. A beginner's guide to *BRCA1* and *BRCA2*. London: The Royal Marsden NHS Foundation Trust; 2016.

3. Fasching PA, Hu C, Hart SN, et al. Cancer predisposition genes in metastatic breast cancer—association with metastatic pattern, prognosis, patient and tumor characteristics [Abstract PD1-02]. Presented at: San Antonio Breast Cancer Symposium; December 5–9, 2017; San Antonio.

4. Meynard G, Villanueva C, Thiery-Vuillemin A, et al. Real-life study of *BRCA* genetic screening in metastatic breast cancer [Abstract 284P]. Ann Oncol. 2017;28:94.

5. Nelson HD, Pappas M, Zakher B, Mitchell JP, Okinaka-Hu L, Fu R. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: a systematic review to update the U.S. Preventive Services Task Force recommendation. Ann Intern Med. 2014;160:255–66.

6. Tung N, Lin NU, Kidd J, et al. Frequency of germline mutations in 25 cancer susceptibility genes in a sequential series of patients with breast cancer. J Clin Oncol. 2016;34:1460–8.

7. Manchanda R, Loggenberg K, Sanderson S, et al. Population testing for cancer predisposing *BRCA1*/*BRCA2* mutations in the Ashkenazi-Jewish community: a randomized controlled trial. J Natl Cancer Inst. 2015;107:379.

8. Rennert G, Bisland-Naggan S, Barnett-Griness O, et al. Clinical outcomes of breast cancer in carriers of *BRCA1* and *BRCA2* mutations. N Engl J Med. 2007;357:115–23.

9. Bayraktar S, Gutierrez-Barrera AM, Liu D, et al. Outcome of triple-negative breast cancer in patients with or without deleterious *BRCA* mutations. Breast Cancer Res Treat. 2011;130:145–53.

10. US Food and Drug Administration. FDA approves olaparib for germline *BRCA*-mutated metastatic breast cancer. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-germline-brca-mutated-metastatic-breast-cancer. Accessed 31 Jan 2022.

11. US Food and Drug Administration. FDA approves talazoparib for g*BRCA*m HER2-negative locally advanced or metastatic breast cancer. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-talazoparib-gbrcam-her2-negative-locally-advanced-or-metastatic-breast-cancer. Accessed 31 Jan 2022.

12. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline *BRCA* mutation. N Engl J Med. 2017;377:523–33.

13. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline *BRCA* mutation. N Engl J Med. 2018;379:753–63.

14. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant olaparib for patients with BRCA1- or BRCA2-

mutated breast cancer. N Engl J Med. 2021;384:2394–405.

15. US Food and Drug Administration. FDA approves olaparib for adjuvant treatment of high-risk early breast cancer. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-adjuvant-treatment-high-risk-early-breast-cancer. Accessed 1 June 2022.

16. Daly MB, Pal T, Berry MP, et al. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic, version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw. 2021;19:77–102.

17. Gonzalez-Santiago S, Ramon YCT, Aguirre E, et al. SEOM clinical guidelines in hereditary breast and ovarian cancer (2019). Clin Transl Oncol. 2020;22:193–200.

18. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.4.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed July 5, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way

19. Hoogerbrugge N, Jongmans MC. Finding all BRCA pathogenic mutation carriers: best practice models. Eur J Hum Genet. 2016;24(Suppl 1):S19-26.

20. McCarthy AM, Armstrong K. The role of testing for *BRCA1* and *BRCA2* mutations in cancer prevention. JAMA Intern Med. 2014;174:1023–4.

21. Anderson P, Benford M, Harris N, Karavali M, Piercy J. Real-world physician and patient behaviour across countries: Disease-Specific Programmes—a means to understand. Curr Med Res Opin. 2008;24:3063–72.

22. European Pharmaceutical Marketing Research Association. EphMRA Code of Conduct 2022. https://www.ephmra.org/sites/default/files/2022-08/EPHMRA%202022%20Code%20of%20Conduct.pdf. Accessed 28 Sept 2022.

23. Atlantic.net. HIPAA compliance: important fundamentals you need to know. https://www.hipaajournal.com/wp-content/uploads/2020/02/HIPAA-Compliance-Fundamentals-Atlantic-Net-Whitepaper-2018.pdf. Accessed 28 Apr 2022.

24. Office for Civil Rights. OCR privacy brief: summary of the HIPAA privacy rule. https://www.hhs.gov/sites/default/files/ocr/privacy/hipaa/understanding/summary/privacysummary.pdf. Accessed 28 Apr 2022.

25. The Health Policy Partnership. Genetic testing for *BRCA* mutations: a policy paper. https://www.healthpolicypartnership.com/app/uploads/Genetic-testing-for-BRCA-mutations-a-policy-paper.pdf. Accessed 23 May 2022.

26. Katz SJ, Ward KC, Hamilton AS, et al. Gaps in receipt of clinically indicated genetic counseling after diagnosis of breast cancer. J Clin Oncol. 2018;36:1218–24.

27. Abacan M, Alsubaie L, Barlow-Stewart K, et al. The global state of the genetic counseling profession. Eur J Hum Genet. 2019;27:183–97.

28. Rosner G, Rosner S, Orr-Urtreger A. Genetic testing in Israel: an overview. Annu Rev Genomics Hum Genet. 2009;10:175–92.

29. Kne A, Zierhut H, Baldinger S, et al. Why is cancer genetic counseling underutilized by women identified as at risk for hereditary breast cancer? Patient perceptions of barriers following a referral letter. J Genet Couns. 2017;26:697–715.

30. Swink A, Nair A, Hoof P, et al. Barriers to the utilization of genetic testing and genetic counseling in patients with suspected hereditary breast and ovarian cancers. Proc (Bayl Univ Med Cent). 2019;32:340–4.

31. Hubbard TE, Paradis R. Real world evidence: a new era for health care innovation. The Network for Excellence in Health Innovation (NEHI). https://www.nehi-us.org/publications/66-real-world-evidence-a-new-era-for-health-care-innovation/view. Accessed 23 May 2022.