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ORIGINAL RESEARCH

Clinical Outcomes, Treatment Patterns, and Health Resource Utilization Among Metastatic Breast Cancer Patients with Germline *BRCA1/2* Mutation: A Real-World Retrospective Study

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ABSTRACT

Introduction: With evolving treatment guidelines for germline *BRCA1/2* mutation (g*BRCA*m) in breast cancer, we present the latest g*BRCA* testing rates among metastatic breast cancer (mBC) patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) or triple-negative breast cancer (TNBC). Among these patients with g*BRCA*m, we analyzed clinical outcomes, treatment patterns, and health resource utilization (HRU).

Methods: The Flatiron Health electronic health record database was used to assess g*BRCA* testing rates in a real-world retrospective analysis of US patients at least 18 years old with HR+/HER2− or TNBC, and with mBC diagnosed from January 2011 to February 2018. Outcomes were compared between g*BRCA*m patients with HR+/HER2− vs TNBC, adjusting for imbalances utilizing inverse probability treatment weighting; effects of HR+/HER2− vs TNBC on overall survival (OS) were assessed, antineoplastic treatments summarized, and HRU analyzed using *t* tests.

Results: The study included 12,021 mBC patients (HR+/HER2−, 10,291; TNBC, 1730). Results for g*BRCA* testing were available for 2005 (16.7%) patients (HR+/HER2−, 1587; TNBC, 418). A total of 229 (1.9%) patients (HR+/HER2−, 165; TNBC, 64) had g*BRCA*m. Significantly worse OS in g*BRCA*m mBC was observed in TNBC vs HR+/HER2− [hazard ratio (95% confidence interval), 0.45 (0.27–0.74); $p = 0.002$]. Estimated median and 4-year OS rates for g*BRCA*m mBC patients with either HR+/HER2− or TNBC were 38.0 months, 23.4 months and 35.6%, 21.2% respectively. The most common first-line treatment post diagnosis for g*BRCA*m HR+/HER2− was letrozole (8%) vs capecitabine (14%) for g*BRCA*m TNBC. The number of HRU treatment visits per patient per year was significantly ($p < 0.05$) higher among g*BRCA*m mBC patients with TNBC vs HR+/HER2−.

Conclusion: Among HER2− mBC patients, g*BRCA* testing rates are low. Among gBRCAm HER2− mBC patients, the poor OS and HRU burden observed, especially in patients with TNBC, demonstrate an unmet need for more efficacious, targeted, and less HRU-intensive treatment options.

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INTRODUCTION

In the USA, breast cancer (BC) is one of the most common cancers (an estimated 268,670 new cases diagnosed in 2018 among women and men) and the second leading cause of cancer death in women (an estimated 40,920 deaths in 2018) [1]. BC comprises multiple subtypes that are commonly classified using tumor biomarkers for hormone receptor (HR) and human epidermal growth factor receptor-2 (HER2) expression, with approximately 85% of new incident BC being either HR-positive/HER2-negative (HR+/HER2−) or triple-negative BC (TNBC) [2]. Genetic predisposition to BC may be associated with mutation of gene(s) including key tumor suppressor genes, i.e., the BC susceptibility genes 1 or 2 (*BRCA1/2*) [3]. Carriers of *BRCA1/2* mutations have an increased lifetime risk for BC, which varies from 65% to 85% with *BRCA1* and 40% to 85% with *BRCA2* [4]. *BRCA* mutations may be inherited [germline (g*BRCA*)] or arise de novo (somatic) as a result of combinatorial genetic and environmental factors [3]. Specific population subgroups have been identified as having a higher proportion of individuals who carry g*BRCA* mutation, including those who have been diagnosed with TNBC [5].

Testing for g*BRCA* in patients newly diagnosed with BC has the potential to reduce disease burden through secondary prevention and targeted therapies. It is therefore important to understand how frequent g*BRCA* testing is integrated into clinical practice for patients newly diagnosed with BC and the impact g*BRCA* test results have on treatment patterns and health resource utilization (HRU). Recent US clinical practice guidelines, including those from the National Comprehensive Cancer Network (NCCN), recommend strong consideration of g*BRCA1/2* testing among patients with recurrent/metastatic BC (mBC) and HER2− disease (i.e., HR+/HER2− or TNBC) who are eligible for single-agent therapy [6].

In light of evolving guidelines for g*BRCA* testing and management of g*BRCA*-mutated BC, a large real-world electronic health record (EHR) database was used to study the latest g*BRCA* testing rates among mBC patients with HR+/HER2− or TNBC in the USA. Clinical outcomes, antineoplastic treatment patterns, and HRU in patients with g*BRCA* mutation were also compared between those with HR+/HER2− vs TNBC subtypes; findings from this study will aid clinicians' understanding regarding current disease burden and treatment landscape while optimizing future clinical decisions to improve patient outcomes.

METHODS

Database Description

De-identified patient-level data from the Flatiron Health longitudinal EHR database were used. At the time of study, the database represented a diverse group of approximately 265 predominantly community cancer clinics, ranging from small practices to large multicenter practices, with more than 2 million active cancer patients. Data compliant with the Health Insurance Portability and Accountability Act of 1996 and agnostic to the source EHR were gathered, processed, harmonized centrally, and stored securely by Flatiron Health. Patients were selected based on the review of unstructured data, which resulted in a more accurate cohort selection approach compared with traditional ICD-code-based methods [7]. Details on how the EHR database was prepared for analysis and how aggregate records were processed are as follows: structured data (e.g., laboratory test results, information on prescribed drugs) were harmonized and normalized to a standard ontology [8]; unstructured data (e.g., radiology reports, pathology reports, medical care notes, some biomarker tests) were extracted from EHR-based digital documents via technology-enabled chart abstraction. Every data point sourced from unstructured documents was manually reviewed by trained chart abstractors (clinical oncology nurses and tumor registrars, with oversight from oncologists). These

processed data were de-identified with third-party statistical verification and stored in a separate analytic database. Rigorous data quality control procedures conducted on the EHR database have been described previously [8].

Patients

Adult patients, aged at least 18 years old, confirmed via review of unstructured data, including pathology reports, to have been diagnosed with mBC of HR+/HER2− or TNBC subtypes from January 1, 2011, to February 28, 2018, with at least two visits to a cancer clinic in the Flatiron Health network, were included in this study. When the clinical outcomes, antineoplastic treatment patterns, and HRU were analyzed, mBC patients with g*BRCA* mutation were also required to have at least one visit post mBC diagnosis.

g*BRCA* Testing

g*BRCA* testing data were abstracted from EHR biomarker testing reports, pathology reports, and oncology clinic visit notes by trained chart abstractors, with full traceability back to source documentation. Abstractors collected relevant testing dates and g*BRCA* mutation result data for each g*BRCA* testing event. Data were abstracted exactly as reported in each chart; abstractors did not derive or interpret test results when the laboratory did not provide a clear interpretation. g*BRCA* testing results (including *BRCA1*- and/or *BRCA2*-specific information wherever specified) were recorded as positive, negative, genetic variant favor polymorphism, genetic variant of unknown significance, other, results pending, unknown, or unsuccessful/indeterminate test. Hence, documentation of "positive" on a g*BRCA* mutation expression assay was according to the final results presented in the test report and considered deleterious or suspected deleterious g*BRCA* mutation and signaled the information on which the treating clinician acted. The documentation of "positive" on a g*BRCA* mutation expression assay can occur before and/or after mBC diagnosis.

Antineoplastic Lines of Therapy and HRU Specification

Antineoplastic lines of therapy (LOTs) were derived on the basis of prespecified algorithms according to antineoplastic usage recorded in the EHR and indexed to the date of metastatic diagnosis [8]. Administration of therapy was defined as uncancelled medication orders and documented administrations. A "regimen" was defined as the name of a particular combination of drugs given in a single line and included all the drugs administered in that line. A line started with the initiation of a new regimen and ended when the patient switched to a subsequent treatment regimen or the end of follow-up also signaled the end of a LOT. The first treatment regimen was designated as the first LOT, and each subsequent change to a new treatment for any reason led to an incrementally ordered increase in the LOT (e.g., second).

HRU in the form of visits that included interactions with the oncology clinic, specifically treatment, laboratory, and vital signs visits, were derived from the EHR.

Our study covered the period before and after US Food and Drug Administration (FDA) approvals of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors indicated for patients with HR+/HER2− mBC. As part of a sensitivity analysis, we analyzed antineoplastic treatment patterns before and after February 3, 2015 (the FDA approval date for the first CDK4/6 inhibitor) for the HR+/HER2− g*BRCA*-mutated mBC subgroup.

Statistical Analysis

Descriptive statistics were used to summarize patient demographic and clinical characteristics that were collected from structured and unstructured data. Characteristics included age at mBC diagnosis, sex, race/ethnicity, US region, stage at BC diagnosis, hormonal subtypes (i.e., HR+/HER2−, TNBC), Eastern Cooperative Oncology Group (ECOG) performance status, payer category, healthcare practice setting, g*BRCA* testing, duration of follow-up, and HRU visit types. Categorical variables were

reported as frequency and percentage, and continuous variables were reported as median and interquartile range. g*BRCA* testing rates were compared among mBC patients with HR+/HER2− vs TNBC.

Among mBC patients tested positive with g*BRCA* mutation, inverse probability of treatment weighting (IPTW) [9], adjusted for age at mBC diagnosis, sex, baseline ECOG performance status, time between initial BC diagnosis to mBC diagnosis, and BC stage at diagnosis, was used to compare the following outcomes between HR+/HER2− vs TNBC subtypes: median overall survival (OS) and 1- through 4-year post-mBC diagnosis product limit OS estimates; effects of HR+/HER2− vs TNBC on OS estimated by a weighted Kaplan–Meier method (all OS data were based on a starting date of when mBC was diagnosed); the most common first and second antineoplastic LOTs; mean and median duration of collective first and second antineoplastic LOTs; and number of HRU visits (treatment, laboratory, vital signs) per patient per year (compared using IPTW-adjusted *t* tests) [9].

Compliance with Ethics Guidelines

Institutional review board (IRB) approval is not required because the study does not involve the collection, use, or transmittal of individual identifiable data. Both the datasets and the security of the offices where the analysis was completed (and where the datasets are kept) meet the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

The study included 12,021 mBC patients (HR+/HER2−, 10,291; TNBC, 1730) (Fig. 1). Results for g*BRCA* testing were available for 2005 (16.7%) patients (HR+/HER2−,1587; TNBC, 418). A total of 229 (1.9%) patients (HR+/HER2−, 165; TNBC, 64) tested positive for g*BRCA* mutation. Of these patients, 225 (HR+/HER2−, 161; TNBC, 64) had at least one visit to a cancer clinic post mBC diagnosis; their demographic and clinical characteristics are summarized in Table 1. The mean follow-up duration from mBC diagnosis was 27.7 months for 161 patients with metastatic HR+/HER2− and 17.5 months for 64 patients with metastatic TNBC (mTNBC).

OS of Patients with mBC and g*BRCA* Mutation (HR+/HER2− vs TNBC)

For patients with HR+/HER2− mBC and g*BRCA* mutation, estimated median OS post mBC diagnosis [95% confidence interval (CI)] was 38.0 (30.8–42.9) months; patients with mTNBC and g*BRCA* mutation had an estimated median OS (95% CI) of 23.4 (14.9–34.5) months.

Among patients with mBC and g*BRCA* mutation, significantly worse OS was observed among patients with mTNBC vs HR+/HER2− [hazard ratio (95% CI) 0.45 (0.27–0.74); $p = 0.002$] (Fig. 2).

One- to 4-year post-mBC diagnosis OS rates for patients with HR+/HER2− mBC and g*BRCA* mutation ranged from 92.2% to 35.6%; for patients with mTNBC and g*BRCA* mutation 1- to 4-year post-mBC diagnosis OS rates ranged from 73.6% to 21.2% (Table 2).

Antineoplastic Treatment Patterns of Patients with mBC and g*BRCA* Mutation (HR+/HER2− vs TNBC)

The most common first- and second-line antineoplastic treatments (post mBC diagnosis) for patients with mBC and g*BRCA* mutation (HR+/HER2− vs TNBC) are found in Table 3. Across both HR+/HER2− and TNBC groups, antineoplastic treatment patterns post mBC diagnosis were fragmented; 34 patients did not have a first-line antineoplastic prescription recorded in the EHR, and 87 patients did not have a second-line antineoplastic prescription recorded in the EHR. A complete list of first- and second-line antineoplastic treatments recorded in EHRs can be found in the supplementary appendix.

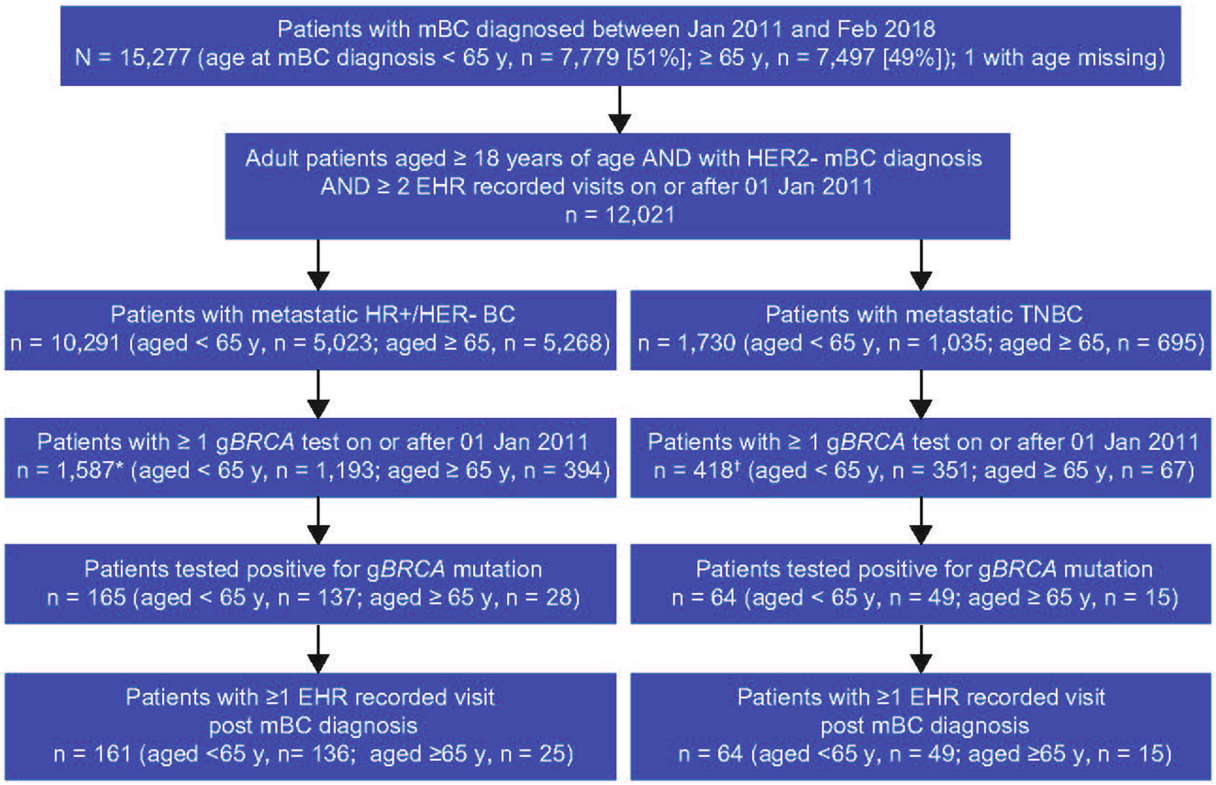

Fig. 1 Patient selection diagram. *1345 patients did not test positive for g*BRCA1/2* mutations; g*BRCA* test results for 77 patients were marked as genetic variant favor polymorphism, genetic variant of unknown significance, other, results pending, unknown, or unsuccessful/indeterminate test. †328 patients did not test positive for g*BRCA1/2* mutations; g*BRCA* test results for 26 patients were marked as genetic variant favor polymorphism, genetic variant of unknown significance, other, results pending, unknown, or unsuccessful/indeterminate test. EHR electronic health record, HER2− human epidermal growth factor receptor 2 negative, HR+ hormone receptor positive, g*BRCA* germline breast cancer susceptibility gene, mBC metastatic breast cancer, TNBC triple-negative breast cancer

Collectively, across both HR+/HER2− and TNBC groups, among those with first and second lines of antineoplastic prescriptions recorded after mBC diagnosis, median duration of treatment for each line was at most 5.7 months (Table 3).

As part of a sensitivity analysis to account for the availability of CDK4/6 inhibitors among patients with HR+/HER2− mBC and g*BRCA* mutation (with at least one line of antineoplastic treatment post mBC diagnosis), after February 3, 2015 (n = 89), the most common first-line antineoplastic treatment after mBC diagnosis was letrozole/palbociclib (n = 9) and fulvestrant/palbociclib (n = 8); the most common second-line antineoplastic treatment after mBC diagnosis was letrozole/palbociclib (n = 5), fulvestrant/palbociclib (n = 4), and capecitabine (n = 4).

Among patients with HR+/HER2− g*BRCA*-mutated mBC (with at least one line of antineoplastic treatment post mBC diagnosis), before February 3, 2015 (n = 56), the most common first-line antineoplastic treatment post mBC diagnosis was anastrozole (n = 7); the most common second-line antineoplastic treatment post mBC diagnosis was letrozole (n = 6).

HRU Among Patients with mBC and g*BRCA* Mutation

The mean number of HRU visits per patient per year (for all visits) among patients with HER2−

Table 1 Baseline characteristics among patients with mBC and g*BRCA* mutation (HR+/HER2− vs TNBC)

	HR+/HER2− mBC with g*BRCA* mutation (*n* = 161)	**mTNBC with g*BRCA* mutation (*n* = 64)**	**HER2− mBC with g*BRCA* mutation (*n* = 225)**
Demographics			
Age at mBC diagnosis, years			
Mean (SD)	51.6 (13.1)	51.7 (15.2)	51.6 (13.7)
Median	51.0	47.5	51.0
Q1, Q3	42.0, 59.0	39.5, 63.0	41.0, 59.0
18–54, *n* (%)	99 (61.5)	39 (60.9)	138 (61.3)
55–64, *n* (%)	37 (23.0)	10 (15.6)	47 (20.9)
65–74, *n* (%)	16 (9.9)	8 (12.5)	24 (10.7)
75+, *n* (%)	9 (5.6)	7 (10.9)	16 (7.1)
Female, *n* (%)	156 (96.9)	63 (98.4)	219 (97.3)
Race/ethnicity, *n* (%)			
Non-Hispanic/Latino White	100 (62.1)	33 (51.6)	133 (59.1)
Non-Hispanic/Latino Black or African American	16 (9.9)	7 (10.9)	23 (10.2)
Non-Hispanic/Latino Asian	4 (2.5)	2 (3.1)	6 (2.7)
Hispanic/Latino only	7 (4.3)	2 (3.1)	9 (4.0)
Other/unknown	34 (21.1)	20 (31.3)	54 (24.0)
US region, *n* (%)			
South	61 (37.9)	22 (34.4)	83 (36.9)
Northeast	26 (16.1)	8 (12.5)	34 (15.1)
Midwest	21 (13.0)	10 (15.6)	31 (13.8)
West	37 (23.0)	16 (25.0)	53 (23.6)
Unknown	16 (9.9)	8 (12.5)	24 (10.7)
Clinical characteristics			
BC stage at initial diagnosis, *n* (%)			
I	14 (8.7)	8 (12.5)	22 (9.8)
II	42 (26.1)	24 (37.5)	66 (29.3)
III	35 (21.7)	16 (25.0)	51 (22.7)
IV	59 (36.6)	14 (21.9)	73 (32.4)
Not documented	11 (6.8)	2 (3.1)	13 (5.8)

Table 1 continued

	HR+/HER2− mBC with g*BRCA* mutation (*n* = 161)	mTNBC with g*BRCA* mutation (*n* = 64)	HER2− mBC with g*BRCA* mutation (*n* = 225)
ECOG performance status, *n* (%)			
Missing	111 (68.9)	40 (62.5)	151 (67.1)
0	39 (24.2)	11 (17.2)	50 (22.2)
1	9 (5.6)	12 (18.8)	21 (9.3)
2	2 (1.2)	0 (0.0)	2 (0.9)
3	0 (0.0)	1 (1.6)	1 (0.4)
Germline *BRCA* status, *n* (%)			
BRCA1 mutation identified	38 (23.6)	42 (65.6)	80 (35.6)
BRCA2 mutation identified	99 (61.5)	15 (23.4)	114 (50.7)
BRCA mutation NOS	18 (11.2)	5 (7.8)	23 (10.2)
Both *BRCA1* and *BRCA2* mutations identified	6 (3.7)	2 (3.1)	8 (3.6)
Payer type[a]*/healthcare setting*			
Commercial health plan, *n* (%)			
No	55 (34.2)	24 (37.5)	79 (35.1)
Yes	106 (65.8)	40 (62.5)	146 (64.9)
Medicare, *n* (%)			
No	126 (78.3)	51 (79.7)	177 (78.7)
Yes	35 (21.7)	13 (20.3)	48 (21.3)
Enrolled in patient assistance program, *n* (%)			
No	123 (76.4)	53 (82.8)	176 (78.2)
Yes	38 (23.6)	11 (17.2)	49 (21.8)
Medicaid, *n* (%)			
No	138 (85.7)	54 (84.4)	192 (85.3)
Yes	23 (14.3)	10 (15.6)	33 (14.7)
Healthcare practice setting, *n* (%)			
Academic	13 (8.1)	8 (12.5)	21 (9.3)
Community	148 (91.9)	56 (87.5)	204 (90.7)

BC breast cancer, *BRCA1/BRCA2* breast cancer susceptibility gene 1 or 2, *ECOG* Eastern Cooperative Oncology Group, *HER2−* human epidermal growth factor receptor 2 negative, *HR+* hormone receptor positive, *mBC* metastatic breast cancer, *mTNBC* metastatic triple-negative breast cancer, *NOS* not otherwise specified, *Q* quartile, *SD* standard deviation

[a] Patients may have multiple payer coverage

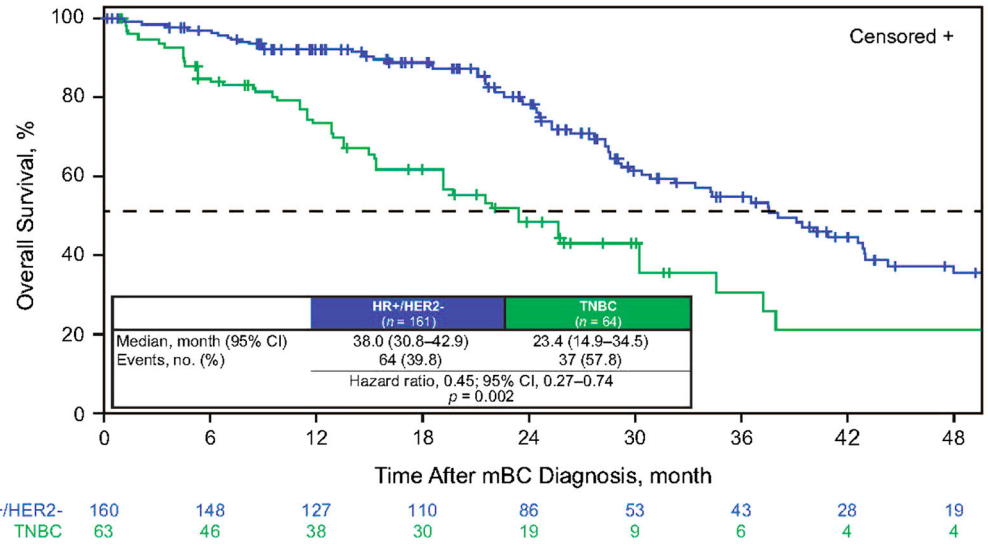

Fig. 2 Overall survival* from mBC diagnosis with mBC and g*BRCA* mutation (HR+/HER2− vs TNBC). *IPTW-adjusted numbers of patients at risk are shown. The study covered the period before and after US FDA approvals of CDK4/6 inhibitors; hence, results do not solely reflect OS post availability of CDK4/6 inhibitors, especially for patients with HR+/HER2− mBC. *CDK4/6* cyclin-dependent kinase 4/6, FDA Food and Drug Administration, g*BRCA* germline breast cancer susceptibility gene, HER2− human epidermal growth factor receptor 2 negative, HR+ hormone receptor positive, IPTW inverse probability of treatment weighting, mBC metastatic breast cancer, OS overall survival, TNBC triple-negative breast cancer

mBC and g*BRCA* mutation was 34.2 [standard error (SE): 2.4]; the mean number of HRU visits per patient per year (for all visits) among patients treated in the academic healthcare practice setting was higher (54.7, SE: 18.4) than those treated within the community setting (32.2, SE: 1.9).

The number of HRU visits per patient per year, across all types of HRU, were higher for patients with mTNBC and g*BRCA* mutation vs patients with HR+/HER2− mBC and g*BRCA* mutation (Table 4). In particular, the number of treatment visits per patient per year was significantly higher for patients with mTNBC and g*BRCA* mutation vs patients with HR+/HER2− mBC and g*BRCA* mutation (Table 4).

DISCUSSION

To the best of our knowledge, this study is the largest EHR database study to report g*BRCA* testing rates among mBC patients (stratified by HR+/HER2− and TNBC subtypes) predominantly from US community cancer clinics. The low overall g*BRCA* testing rates (16.7%) observed in this study are similar to those previously published (15.3%) from the pooled 2005–2015 US National Health Interview Survey of high-risk BC patients [10]. These low g*BRCA* testing rates are in light of growing evidence that supports the expansion of g*BRCA* testing to the general population, beyond the use following high-risk family history assessment criteria [11, 12]. The latest US NCCN 2018 genetic/familial high-risk assessment guidelines specifically state that "regardless of family history, some individuals with a *BRCA*-related cancer may benefit from genetic testing to determine eligibility for targeted treatment". Similarly, other international guidelines have started to recommend that genetic testing be considered as early as possible in the advanced BC setting, "especially since germline mutations in *BRCA1/2* have proven clinical utility and therapeutic impact" [13]. Future studies are required to understand g*BRCA* testing barriers and to recommend strategies to improve awareness of and adherence to these new guidelines in order to

Table 2 Overall survival of patients with mBC and g*BRCA* mutation (HR+/HER2− vs TNBC)

	HR+/HER2− mBC and g*BRCA* mutation (*n* = 161)	mTNBC and g*BRCA* mutation (*n* = 64)	HER2− mBC and g*BRCA* mutation (*n* = 225)
Overall survival from mBC diagnosis			
Mean, months (SE)	34.9 (1.3)	22.9 (2.0)	32.2 (1.2)
Median, months	38.0	23.4	34.3
95% CI	30.8–42.9	14.9–34.5	28.5–39.4
% alive at 1 year after mBC diagnosis (SE)	92.2 (2.2)	73.6 (6.6)	87.1 (2.4)
% alive at 2 years after mBC diagnosis (SE)	78.3 (3.7)	48.4 (7.9)	70.0 (3.6)
% alive at 3 years after mBC diagnosis (SE)	54.8 (5.0)	30.5 (9.3)	48.5 (4.4)
% alive at 4 years after mBC diagnosis (SE)	35.6 (5.5)	21.2 (9.3)	31.9 (4.7)

The study covered the period before and after the US FDA approvals of CDK4/6 inhibitors; hence, results do not solely reflect OS post availability of CDK4/6 inhibitors, especially for patients with HR+/HER2− mBC

CDK4/6 cyclin-dependent kinase 4/6, *CI* confidence interval, *FDA* Food and Drug Administration, g*BRCA* germline breast cancer susceptibility gene, *HER2-* human epidermal growth factor receptor 2 negative, *HR+* hormone receptor positive, *mBC* metastatic breast cancer, *OS* overall survival, *SE* standard error, *mTNBC* metastatic triple-negative breast cancer

improve the g*BRCA* testing rates among mBC patients.

Our study also highlighted the fragmented antineoplastic treatment patterns in patients with g*BRCA*-mutated mBC in both the HR+/HER2− and TNBC subtypes. Especially in patients with g*BRCA*-mutated mTNBC, the most frequent first and second LOTs consist of chemotherapy infusions and therefore would require clinical visits. This may explain the significantly greater HRU burden among these patients vs those with the HR+/HER2− subtype; future studies should investigate if similar HRU results are also observed among early BC patients. The generally short duration (at most 5.7 months) of first and second lines of antineoplastic treatment post mBC diagnosis coupled with the poor OS prognosis (4-year OS rates less than 36%) observed in both the HR+/HER2− and TNBC patients with g*BRCA*-mutated mBC further underscore the need for more efficacious and increased use of g*BRCA* mutation-targeted therapy.

Multiple international guidelines, including from the USA, have recently recommended targeted therapies for patients with advanced BC and g*BRCA* mutation [6, 13, 14]. Since October 2018, two orally administered poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors (olaparib [AstraZeneca Pharmaceuticals LP] and talazoparib [Pfizer Inc.]) specifically indicated for g*BRCA*-mutated HER2– advanced BC have been approved by the US FDA [15, 16]. Future EHR studies are warranted to understand the effects of these new treatment guidelines and newly available PARP inhibitors on the potential improvements in clinical outcomes, changes in antineoplastic treatment patterns, and HRU among patients with mBC and g*BRCA* mutation.

Because the Flatiron Health EHR database does not include information on surgery or radiation therapy, we are unable to account for prior treatment received by patients across these modalities. Tumor progression data was also not available within the EHR database, and as such

Table 3 Antineoplastic treatment patterns and duration of antineoplastic treatment of patients with mBC and g*BRCA* mutation

	HR+/HER2− mBC with g*BRCA* mutation (*n* = 161)	mTNBC with g*BRCA* mutation (*n* = 64)
Antineoplastic treatment pattern[a]		
First-line post mBC diagnosis, *n* (%)[b]	*n* = 145 (90)	*n* = 46 (72)
Most common antineoplastic prescribed	Letrozole 13 (8)	Capecitabine 9 (14)
	Fulvestrant 10 (6)	Carboplatin, gemcitabine 7 (11)
	Anastrozole 10 (6)	Cyclophosphamide, doxorubicin 6 (9)
Second-line post mBC diagnosis, *n* (%)[c]	*n* = 111 (69)	*n* = 27 (42)
Most common antineoplastic prescribed	Letrozole 8 (5)	Eribulin 4 (6)
	Fulvestrant 7 (4)	
	Paclitaxel 7 (4)	
Duration of antineoplastic treatment, months		
First-line post mBC diagnosis[b]		
Mean (SD)	8.5 (9.5)	8.5 (11.3)
Median	5.7	4.6
Q1, Q3	2.6, 11.3	2.5, 9.4
Second-line post mBC diagnosis[c]		
Mean (SD)	6.9 (6.7)	7.5 (6.5)
Median	4.3	4.6
Q1, Q3	2.5, 9.9	2.1, 10.5

CDK4/6 cyclin-dependent kinase 4/6, *FDA* Food and Drug Administration, g*BRCA* germline breast cancer susceptibility gene 1 or 2, *HER2*− human epidermal growth factor receptor 2 negative, *HR*+ hormone receptor positive, *mBC* metastatic breast cancer, *mTNBC* metastatic triple-negative breast cancer, *Q* quartile, *SD* standard deviation

[a] The study covered the period before and after US FDA approvals of CDK4/6 inhibitors; hence, results do not solely reflect the latest antineoplastic treatment pattern and duration of antineoplastic treatment post availability of CDK4/6 inhibitors, especially for patients with HR+/HER2− mBC

[b] 16 and 18 patients in the respective HR+/HER2 and TNBC groups had no antineoplastic prescription recorded

[c] 50 and 37 patients in the respective HR+/HER2− and TNBC groups had no antineoplastic prescription recorded

we were unable to ascertain or assign antineoplastic therapy changes due to disease progression. These real-world EHR data lacked complete information on ECOG performance status and comorbidities (i.e., information that is not typically and routinely documented during all clinical visits). In addition, accurate assignment of lines of antineoplastic therapy was contingent on the availability of appropriate underlying EHR data supporting prespecified LOT definitions. As a large majority of patients (more than 87%) were from the community oncology setting, results summarized in this study may not reflect those observed in academic settings. As a result of the limitation of the Flatiron Health EHR database, we are

Table 4 Healthcare resource visits among mBC patients with g*BRCA* mutation (HR+/HER2− vs TNBC)

Visits per patient per year	HR+/HER2− mBC and g*BRCA* mutation (*n* = 161)	mTNBC and g*BRCA* mutation (*n* = 64)	*P* value[a]	HER2− mBC and g*BRCA* mutation (*n* = 225)
Treatment visits, mean (SE)	15.1 (1.7)	21.9 (3.5)	0.048	17.0 (1.6)
Laboratory visits, mean (SE)	21.5 (2.6)	23.4 (2.2)	0.65	22.1 (1.9)
Vitals visits, mean (SE)	25.6 (2.9)	31.1 (3.0)	0.27	27.2 (2.2)
All visits, mean (SE)	32.0 (3.0)	39.8 (3.9)	0.15	34.2 (2.4)

CDK4/6 cyclin-dependent kinase 4/6, *FDA* Food and Drug Administration, g*BRCA* germline breast cancer susceptibility gene, *HER2*− human epidermal growth factor receptor 2 negative, *HR*+ hormone receptor positive, *IPTW* inverse probability treatment weighting, *mBC* metastatic breast cancer, *mTNBC* metastatic triple-negative breast cancer, *SE* standard error

The study covered the period before and after US FDA approvals of CDK4/6 inhibitors; hence, results do not solely reflect HRU post availability of CDK4/6 inhibitors, especially for patients with HR+/HER2− mBC

[a] Student *t* test using IPTW for statistical difference between g*BRCA*-mutated mBC patients with HR+/HER2− vs TNBC

unable to ascertain the guidelines used by physicians to recommend their patients for g*BRCA* testing and are unable to determine the family history of patients; therefore, we are unable to analyze g*BRCA* testing guideline concordance in this study.

CONCLUSIONS

In this real-world study of US adult mBC patients diagnosed between January 2011 and February 2018 with HR+/HER2− or TNBC, g*BRCA* testing rates were low. Future studies are required to understand the effects of the changes in the latest guidelines on g*BRCA* testing rates.

Among mBC patients with g*BRCA* mutation, poor OS (4-year OS rates less than 36%) was observed for HR+/HER2− and TNBC subtypes. Patients with mTNBC and g*BRCA* mutation also faced significantly worse OS and greater HRU burden vs mBC patients with HR+/HER2− and g*BRCA* mutation. Poor prognosis and greater HRU burden demonstrate a significant unmet need for more efficacious, targeted, and less HRU-intensive treatment options among these patients.

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On October 16, 2018, Pfizer Inc. received approval from the US Food and Drug Administration regarding talazoparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, for patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m), HER2− negative locally advanced or metastatic breast cancer. We thank the participants whose data contributed to this study.

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Compliance with Ethics Guidelines. IRB approval is not required because the study does not involve the collection, use, or transmittal of individual identifiable data. Both the datasets and the security of the offices where the analysis was completed (and where the datasets are kept) meet the requirements of the HIPAA of 1996. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated and analyzed during the current study are not publicly available based on the licensing agreement between Flatiron Health and Pfizer Inc.

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