Germline Genetic Testing in Breast Cancer: Utilization and Disparities in a Middle-Income Country

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ABSTRACT

PURPOSE Low rates of germline genetic testing (GGT) for breast cancer (BC) have been reported globally, with limited data from low- and middle-income countries (LMICs). In this study, we used real-world data to assess the GGT rate for BC in an LMIC and identified barriers to its use.

METHODS We analyzed 2,974 newly diagnosed patients with BC from the AMAZONA III study, the largest Brazilian multicenter, prospective BC cohort. GGT rates were determined for the entire cohort and the high-risk hereditary BC group (HR), defined by the National Comprehensive Cancer Network criteria, between 2019 and 2020. Barriers to GGT performance associated with patient characteristics and health care systems were identified using multivariable Poisson regression model. Values of $P < .05$ were considered significant.

RESULTS In the AMAZONA III cohort, 1,476 (49%) were classified as HR. Genetic counseling was recommended for 521 patients (35% of HR), and 282 (19%) underwent GGT. Notably, 97% of patients with HR treated within the public health care systems and 56% in the private system did not undergo GGT. Age, education, occupation, monthly income, availability of onsite genetic counseling, and treatment at a teaching center were factors associated with GGT uptake ($P < .05$). Of those tested, 50 (17%) harbored a germline pathogenic or likely pathogenic variant.

CONCLUSION Only 9% of this robust Brazilian BC cohort underwent GGT, highlighting a considerable gap from the current recommendation to test all patients with BC under age 65 years. GGT is underused by patients with HR in both public and private health care systems, with those in the public system being more affected. The disparities and barriers identified emphasize the need for educational interventions and enhanced access to GGT. Prioritizing GGT is critical to improving BC outcomes in LMICs.

ACCOMPANYING CONTENT

Data Supplement

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INTRODUCTION

Breast cancer (BC) is the leading cause of cancer-related death in women worldwide, with more than two million new cases annually.[1] Approximately 5%-10% of all BC cases are associated with high-risk and moderate-risk BC genes.[2,3] Identifying this small proportion of patients with hereditary BC using germline genetic testing (GGT) is critical as it affects decisions on treatment management.[4] Currently, numerous guidelines recommend GGT in patients at risk of hereditary BC.[5-8] Until 2021, GGT results were used in discussions of risk-reducing surgery, decisions regarding surveillance, and family counseling. Recent reports suggest that this information may also affect systemic treatment for early-stage and advanced BC.[9]

The OlympiA trial reported a significant benefit in overall survival with adjuvant poly (ADP-ribose) polymerase inhibitors in patients with high-risk human epidermal growth factor receptor 2 (HER2)–negative BC with a germline BRCA mutation. This finding was considered practice-changing[9] and provided a rationale for offering GGT to all patients with

CONTEXT

Key Objective

What percentage of patients with breast cancer (BC) undergo germline genetic testing (GGT) in a middle-income country (MIC), and what factors represent barriers to its performance?

Knowledge Generated

In the AMAZONA III trial, 1,476 (49%) of 2,974 patients with BC met the National Comprehensive Cancer Network criteria for GGT and were classified as high-risk for hereditary BC. Of this group, alarmingly, 97% in the public health care system and 56% in the private sector did not receive GGT, underscoring a disparity in health care access. Only 9% of the total cohort underwent GGT. Factors associated with lower testing rates include socioeconomic conditions, the availability of on-site genetic counseling, and whether patients were treated at a teaching center, emphasizing the need for better education and access to genetic counseling.

Relevance

This study highlights a critical gap: GGT for BC is rarely performed in an MIC, with serious implications for global efforts to improve GGT practices.

BC.[10,11] Although GGT is widely recommended, a limited number of mutation carriers have been identified. GGT is offered even less frequently in deprived populations such as racial minorities and developing countries.[12-16] In low-resource countries, the cost of testing and nonavailability of genetic counseling represent significant barriers to BC genetic testing, meaning that universal testing is far from being achieved in low- and middle-income countries (LMICs).[15]

Brazil is a large, heterogeneous, upper middle-income country (MIC) with 74,000 new BC cases expected annually.[17] Regional socioeconomic differences and variability in the quality of health care services affect diagnosis, treatment, and clinical outcomes. Although low rates of GGT have been reported in high-income countries (HICs), the prevalence of hereditary BC and the rate of GGT in LMICs are unknown.[12,13]

The different health system structures in Brazil make the present complex multicenter cohort an important source of data on BC. This study evaluated the use of GGT in an MIC in which the comprehensive public health care program does not offer GGT for BC and the private health care system only provides it in certain specific cases.[18] Approximately 75% of the Brazilian population depends exclusively on the public health care system; therefore, identifying barriers to testing rather than simply noting the failure to provide GGT is essential for devising strategies to improve testing rates. This study aimed to determine the GGT rate in women with BC enrolled in a large Brazilian cohort and the potential barriers that affect GGT performance.

METHODS

AMAZONA III Cohort

This study consisted of an analysis of the AMAZONA III study (GBECAM 0115/ClinicalTrials.gov identifier: NCT02669373), a prospective multicenter study involving approximately 3,000 women in Brazil age ≥18 years who had been diagnosed with newly invasive BC. Twenty-two sites participated in the study between January 2016 and March 2018, including patients treated in public and private health care systems. Although previous studies on this cohort analyzed 2,950 women using valid data for specific objectives, the current analysis included 2,974 patients.[19-21]

Sociodemographic, clinical, and pathology data were collected during the AMAZONA III study, including family history of cancer. Patient medical records were reviewed yearly for 5 years to collect follow-up data regarding treatment patterns, disease recurrence, disease progression, and survival outcomes. The internal review board of each participating institution approved the study protocol, which was conducted according to good clinical practice guidelines and those of the International Council of Harmonization for human research. All participants provided signed informed consent before inclusion in the study.

Variables Evaluated

Patients meeting the criteria for hereditary BC testing according to the 2019 National Comprehensive Cancer Network (NCCN) criteria[7] were defined as having an high-risk hereditary BC (HR). The following characteristics were analyzed: age ≤45 years at diagnosis, triple-negative BC before age 60 years, bilateral BC, personal history of ovarian cancer, any family member with ovarian cancer, and patients age <50 years at diagnosis with a family history or previous personal history of BC. Some of the more than 20 NCCN criteria for recommending GGT could not be assessed due to unavailable information in the AMAZONA III database, including a history of other types of cancer, such as prostate or pancreatic cancer in the family, Ashkenazi Jewish descent, or unknown family history.

Genetic Data Collection

During the 2019 and 2020 patient reviews, the investigators collected data on GGT, including referrals for genetic evaluation, performance of GGT, results of genetic testing (variants of uncertain significance, pathogenic or likely pathogenic variants, or negative for variants), and type of genetic testing (panel or individual gene test; Data Supplement, Fig S1).

Health Center Characteristics

The 22 centers involved in the study provided information on whether professional genetic counseling was available, whether it was available within the public health care system, whether the health care center was located in a teaching hospital, and which health care systems were accepted.

Statistical Analyses

All patients with available data were included in this analysis. Quantitative variables are presented as means and standard deviations. Categorical variables are expressed as frequency percentages, and differences were evaluated using a *t*-test. Qualitative variables are presented as absolute and relative frequencies, and differences were evaluated using the chi-square test. Adjusted residuals were calculated whenever necessary. $P < .05$ was considered statistically significant.

Univariable and multivariable Poisson regression analyses with robust variance were adjusted to assess the characteristics associated with GGT rate. Variables in the multivariable analysis were selected by backward elimination. Variables with $P < .2$ remained in the final model. All analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC).

The primary outcome measure was the proportion of patients who underwent GGT. The secondary outcome measure was identification of the variables associated with undergoing GGT.

This analysis followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for cross-sectional studies.[22]

RESULTS

Patients' Characteristics

Entire Cohort

Overall, 2,974 patients were enrolled in the AMAZONA III cohort study. Table 1 shows the patients' sociodemographic characteristics and baseline tumor characteristics. Briefly, the median age at diagnosis was 53.9 years, and 63.01% of the patients were treated in the public health care system. The majority of the patients were White (58.72%), postmenopausal (59.35%), either illiterate or had completed only elementary school (46.47%), unemployed (56.84%), and had a family history of ovarian or BC (62.37%). Data were previously published on young patients and health care systems from the AMAZONA III cohort.[19,21]

High-risk Group

Of the 2,974 patients enrolled in the original cohort, 49% (n = 1,476) met the 2019 NCCN criteria for genetic testing for hereditary BC, constituting the HR group (Figure 1).

In the HR group, the median age at diagnosis was 44.0 years; 60% of patients (n = 874) were treated within the public health care system, 40% (n = 588) in the private health care system (data missing for the remaining cases), 64% had no more than a high school education, 83% earned a monthly salary of less than five minimum wages, and 52.34% reported being employed. The majority of the patients were White (58.70%), premenopausal (65.53%), and had a family history of ovarian cancer or BC (69.91%; Table 1). According to the NCCN criteria used to identify the 1,426 patients with HR in the cohort, the oncology teams at each institution classified 826 patients (55.96%) as HR, whereas 289 (19.58%) as not HR and 361 (24.46%) as unknown.

GGT in the Entire Sample Population and in the HR Group

Overall, 17% of the patients in the entire cohort (n = 521) were referred for genetic counseling, and 9% (n = 282) actually underwent GGT (Fig 1; Data Supplement, Table S1). In the HR group, 64% of patients (n = 955) were not offered genetic evaluation, and of those referred for genetic counseling, only 54% underwent GGT.

Only 3% of patients with HR treated in the public health care system and 43.2% treated in the private health care system underwent GGT (Table 2). Of the 282 patients tested, 9% (n = 26) were treated in the public health care system. Genetic panel testing was performed in 63% (n = 175) of patients, irrespective of the health care system. In the tested group, 17% (n = 50) of women had a germline pathogenic variant, including 35 with a variant in *BRCA1* or *BRCA2* and 15 with a variant in other BC-related genes (Table 3).

Of the participating centers, 40% did not employ qualified professionals to provide genetic counseling. Of those offering this service, only 30% provided it to the public health care system. Approximately 55% of the centers were affiliated with teaching institutes. Only 18% of the centers received patients exclusively within the public health care system (Data Supplement, Table S2).

Clinical and Pathologic Characteristics and Likelihood of Undergoing GGT

Patients under age 40 years had a significantly greater chance of undergoing GGT (relative risk [RR], 6.82; 95% CI, 4.13 to 11.27; $P < .0001$) compared with those over age 50 years. Patients with lower education level, including

TABLE 1. Characteristics of the Patients, Treatment Centers, and Tumors in the AMAZONA III Cohort

Patient Characteristic	All Patients (N = 2,974)	HR (n = 1,476)	Tested (n = 282)
Age, years			
≤35	237 (8.61)	237 (17.10)	76 (29.46)
35-45	546 (19.83)	546 (39.39)	91 (35.27)
45-50	423 (15.36)	229 (16.52)	32 (12.40)
50-65	1,000 (36.31)	287 (20.71)	52 (20.16)
>65	548 (19.90)	87 (6.28)	7 (2.71)
Health care system			
Public	1,855 (63.01)	874 (59.78)	26 (9.29)
Private	1,089 (36.99)	588 (40.22)	254 (90.71)
Menopausal status			
Premenopausal/perimenopausal	1,122 (40.65)	886 (65.53)	179 (75.85)
Postmenopausal	1,638 (59.35)	466 (34.47)	57 (24.15)
Ethnicity/skin color			
White	1,701 (58.72)	847 (58.70)	233 (85.35)
Non-White	1,196 (41.28)	596 (41.30)	40 (14.65)
Education level			
Illiterate—completed elementary school	1,245 (46.47)	469 (35.29)	17 (7.23)
Completed high school	679 (25.35)	384 (28.89)	48 (20.43)
University or postgraduate degree	755 (28.18)	476 (35.82)	170 (72.34)
Monthly household income			
No income—two minimum wages (R$ 880-R$ 1,760)	959 (46.44)	443 (44.70)	6 (5.56)
Two to five minimum wages (R$ 2,640-R$ 4,400)	801 (38.79)	388 (39.15)	59 (54.63)
5-10 minimum wages (R$ 4,400-R$ 8,800)	198 (9.59)	97 (9.79)	28 (25.93)
>10 minimum wages (over R$ 8,800)	107 (5.18)	63 (6.36)	15 (13.89)
Employment status			
Employed	1,240 (43.16)	749 (52.34)	221 (81.85)
Unemployed	1,633 (56.84)	682 (47.66)	49 (18.15)
Marital status			
Yes	1,699 (58.79)	931 (64.34)	194 (70.55)
No	1,191 (41.21)	516 (35.66)	81 (29.45)
Family history of cancer[a]			
Yes	2,757 (92.77)	1,379 (93.49)	253 (89.72)
No	215 (7.23)	96 (6.51)	29 (10.28)
Family history of breast and ovarian cancer			
Yes	1,855 (62.37)	1,032 (69.91)	216 (76.59)
Children			
Yes	2,386 (85.43)	1,146 (83.22)	188 (74.90)
No	407 (14.57)	231 (16.78)	63 (25.10)
Type of surgery performed			
Breast-conserving surgery	791 (44.97)	339 (35.72)	46 (33.09)
Mastectomy, NSM, SSM	800 (45.48)	390 (41.10)	78 (56.12)
Other	168 (9.55)	81 (8.54)	15 (10.79)
Neoadjuvant treatment			
Yes	1,045 (38.01)	613 (45.11)	105 (42.68)
No	1,704 (61.99)	746 (54.89)	141 (57.32)
Region of the country			
South	1,002 (34.12)	501 (34.50)	142 (51.45)
Southeastern	615 (20.94)	328 (22.59)	101 (36.59)
Midwest	568 (19.34)	235 (16.18)	13 (4.71)
North	6 (0.20)	2 (0.14)	1 (0.36)

(continued on following page)

TABLE 1. Characteristics of the Patients, Treatment Centers, and Tumors in the AMAZONA III Cohort (continued)

Patient Characteristic	All Patients (N = 2,974)	HR (n = 1,476)	Tested (n = 282)
Northeast	746 (25.40)	386 (26.58)	19 (6.88)
Characteristics of the treatment center			
Teaching hospital			
Yes	1,060 (38.45)	490 (36.00)	112 (39.72)
No	1,697 (61.55)	871 (64.00)	170 (60.28)
Health care sector covered at the institution			
Both (public and private)	1,606 (58.25)	795 (58.41)	86 (30.50)
Private	845 (30.65)	444 (32.62)	181 (64.18)
Public health care system	306 (11.10)	122 (8.96)	15 (5.32)
Genetic counseling availability			
Yes	1,441 (52.27)	760 (55.84)	261 (92.55)
No	1,316 (47.73)	601 (44.16)	21 (7.45)
Tumor characteristics			
ECOG performance status			
0	1,671 (75.92)	881 (80.90)	193 (93.69)
1	471 (21.40)	195 (17.91)	12 (5.83)
2	48 (2.18)	12 (1.10)	0
3	8 (0.36)	1 (0.09)	1 (0.49)
4	3 (0.14)	0	0
Clinical stage of cancer at initial diagnosis			
I	500 (24.27)	217 (21.11)	50 (26.32)
II	859 (41.70)	439 (42.70)	90 (47.37)
III	630 (30.58)	325 (31.61)	40 (21.05)
IV	71 (3.45)	47 (4.57)	10 (5.26)
Molecular subtype—surgery			
Luminal A	1,062 (48.05)	533 (47.04)	99 (47.14)
Luminal B—HER2-negative	267 (12.08)	115 (10.15)	27 (12.86)
Luminal B—HER2-positive	377 (17.06)	167 (14.74)	40 (19.05)
HER2-positive	161 (7.29)	77 (6.80)	16 (7.62)
Triple-negative	343 (15.52)	241 (21.27)	28 (13.33)
Tumor grade (biopsy)			
1	398 (17.87)	166 (15.16)	28 (12.50)
2	1,190 (53.44)	566 (51.69)	101 (45.09)
3	639 (28.69)	363 (33.15)	95 (42.41)
Moment of breast cancer detection			
At screening	941 (34.01)	445 (32.36)	113 (44.84)
From symptoms	1,826 (65.99)	930 (67.64)	139 (55.16)
Molecular subtype—biopsy			
Luminal A	1,062 (48.05)	533 (47.04)	99 (47.14)
Luminal B—HER2-negative	267 (12.08)	115 (10.15)	27 (12.86)
Luminal B—HER2-positive	377 (17.06)	167 (14.74)	40 (19.05)
HER2-positive	161 (7.29)	77 (6.80)	16 (7.62)
Triple-negative	343 (15.52)	241 (21.27)	28 (13.33)
Molecular subtype—biopsy			
Hormone receptor–positive	1,329 (60.14)	648 (57.19)	126 (60.00)
HER2-positive	538 (24.34)	244 (21.54)	56 (26.67)
Triple-negative	343 (15.52)	241 (21.27)	28 (13.33)

NOTE. Data were missing in some cases.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HR, high-risk hereditary BC; NSM, nipple-sparing mastectomy; R$, Brazilian Real; SSM, skin-sparing mastectomy.

[a]Family history included all tumor types in first-, second-, or third-degree relatives.

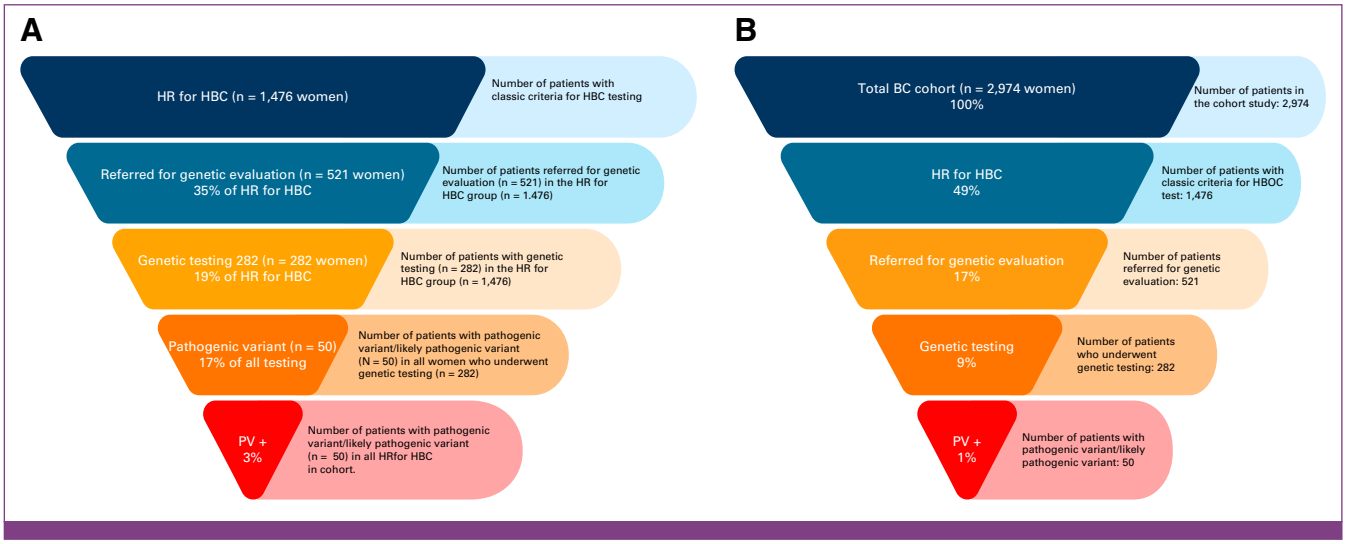

FIG 1. (A) Number of patients in the HR group who were referred for genetic evaluation, underwent genetic testing, and tested positive. (B) Number of patients in the total cohort who were referred for genetic evaluation, underwent genetic testing, and tested positive. All percentages are relative to the total number of patients in the HR group (A) or total cohort (B). This graph highlights the gaps in genetic testing for BC and missed cases through failure to identify patients with HR who would ultimately require genetic counseling and testing. Figure created in BioRender.com (Borba A, 2024). BC, breast cancer; HBC, hereditary BC; HBOC, hereditary breast and ovarian cancer; HR, high-risk hereditary BC; PV, pathogenic variant.

illiterate patients and those with only elementary school education, were less likely to undergo GGT than those with a university degree (RR, 0.47; 95% CI, 0.22 to 0.96; $P = .0379$). Patients earning two to five minimum wages had a significantly higher chance of undergoing GGT compared with those earning zero to two minimum wages (RR, 2.22; 95% CI, 1.30 to 3.75; $P = .0002$).

No association was found between undergoing GGT and tumor characteristics, type of surgery, menopausal status, or ethnicity. Being treated in a teaching center and having access to genetic counseling were significantly associated with a greater likelihood of undergoing GGT (RR, 1.64; 95% CI, 1.02 to 2.64; $P = .0406$ and RR, 2.27; 95% CI, 1.34 to 3.83; $P = .0022$, respectively). The results of univariable and multivariable analyses of all factors are shown in Table 4.

DISCUSSION

This study highlights the worrisome observation that GGT is rarely performed in this large cohort of patients with BC, and significant disparities were found in the management of patients within the same country. To some degree, a low GGT level was expected, as this test is not offered by the public health system. However, less than half of patients with HR in the private health care system were tested, which is notable, as the testing is offered and covered in that setting. Although low rates of GGT have been reported in HICs, data for LMICs remain very limited.[12,13,23-25] To our knowledge, this is the first prospective, multicenter cohort data regarding the accessibility and performance of genetic testing in an LMIC.

Genetic testing is highly important for patients with BC.[3,4,9,13] Clearly, rates of *BRCA1/2* testing in patients with BC remain suboptimal. According to Kurian et al,[13] only 24.1% of patients with BC diagnosed in 2013-2014 in California and Georgia underwent GGT. Another US study estimated GGT rates using pooled cross-sectional data from three Cancer Control Modules. Although 35.6% of women with BC met one or more of the eligibility criteria for testing, only 20.2% were advised to undergo testing, and only 15.3% were actually tested.[25] Recently reported real-world data for 2,527 patients with advanced BC showed that in patients with estrogen receptor positive (ER+)/HER2-, the *BRCA* testing rate was 99% in Israel, 68% in the United States, and 37% in the European Union. In patients with advanced triple-negative BC, the testing rate was 100% in Israel, 93% in the United States, and 78% in the EU.[26] However, another recent multicountry study (France, Germany, Italy, Spain, the United Kingdom, and the United States) reported that only 28% of patients with advanced HER2-BC underwent *BRCA* testing.[27]

In Latin America, China, India, and other LMICs, different retrospective single-center or single-laboratory analyses have been published, with 9%-30% of patients being found to harbor a pathogenic variant in BC genes.[28-34] However, data from these countries regarding GGT rate remain scarce. A recent retrospective report from Chile involving 3,955 patients with BC from the public and private health care systems reported results similar to those found in the present study. Although 48.3% of patients met the NCCN HR criteria, only 15.7% were tested: 19.6% in the private health care network versus 10.3% in the public health care service.[35] In our study, although the testing rate was expected to be low

TABLE 2. Missed Opportunity for Germline Genetic Testing in Patients With HR According to the Health Care System

Health Care System	Total Number of Patients With HR (n = 1,462)	Total Number of Tested Patients (n = 280)	Proportion of Patients With HR Not Tested (%)
Public[a]	874	26	97
Private[b]	588	254	56.8

NOTE. Data were missing in some cases.
Abbreviation: HR, high-risk hereditary BC.
[a]The public health care system does not offer coverage for germline genetic testing.
[b]The private health care system covers germline genetic testing.

in the public health care system, which does not cover GGT, fewer than half of the patients with HR treated in the private health care system underwent testing, which is disappointing, as the test is available in that setting.

AMAZONA III is a multicenter trial with data from 22 centers in 14 cities in Brazil (Data Supplement, Fig S2), including patients from the public and private health care sectors. Most patients were treated within the public health care system, and the small number of patients in these groups who were tested either paid for the test themselves (19%) or were tested through research programs (38%). This is consistent with some of the barriers experienced by Latin American women living in the United States, including the high cost of testing, lack of awareness, and competing life concerns.[36]

Surprisingly, we found that a considerable proportion of patients with HR treated within the private health care system failed to undergo GGT, and as these patients had access to testing, lack of information regarding its importance or a lack of formal genetic counseling could be the primary reason for the low rates of GGT. In 2016, the Brazilian National Health Agency made *BRCA1/2* testing available for some patients with HR cancer. In 2018, an expanded-panel test was also authorized.[37] The present findings highlight a missed opportunity to recognize patients with hereditary BC who could benefit from risk-reducing surgery and the identification of asymptomatic carrier family members. Reported barriers to testing patients with HR include inadequate physician education and lack of awareness that genetic testing is available.[38] Dusic et al[39] proposed solutions at the provider level that included education regarding genetics, communication with genetic counselors, and training to identify patients with HR. At the individual level, the perceived cost and preconceived ideas about GGT were cited as barriers that need to be addressed.[39] Our findings consistently showed that patient-related socioeconomic factors such as high educational level, high family income, and young age were significantly associated with a greater likelihood of undergoing testing. Concomitantly, factors related to where a patient received care (ie, in a teaching hospital) and the availability of genetic counseling increased the likelihood of identifying HR characteristics and referrals for testing.

TABLE 3. Number of Patients With Pathogenic Variant or Likely Pathogenic Variant in Genetic Test Results and Proportion of Genes With Pathogenic Variant/Likely Pathogenic Variant in the Group of Patients With Positive Results

Genes	Patients With Pathogenic Variant/Likely Pathogenic Variant (n)	Percent
BRCA1	22	44
BRCA2	13	26
ATM	4	8
PALB2	3	6
TP53	2	4
BRIP1	2	4
MUTHY	2	4
PTEN	1	2
MSH6	1	2
Total	50	100

Genetic risk assessment is one of the many challenges in health care systems in Brazil and other LMICs. Fragmented health care systems with insufficient resources, ineffective payment systems and services, inconsistent quality of care, and lack of integration among health specialties produce significant discrepancies in outcomes.[22] Lourenção et al[40] evaluated a Brazilian cohort and reported data on *BRCA* pathogenic mutations in 275 index cases and in 356 carriers who were relatives of the index patients. The analysis was conducted from a payer's perspective, considering the Brazilian public health care system. *BRCA1/2* testing and preventive strategies were shown to be cost effective for the health care system.[40] Although it is difficult to draw definitive conclusions regarding the use of limited resources in the context of a specific country, GGT for patients meeting HR criteria seems to be a reasonable option. However, it should be taken into account that approximately 30% of pathogenic variants in high and moderate BC gene carriers are missed when these criteria are used to evaluate hereditariness.[41]

Strategies to identify these patients, including the use of the FHS-7 questionnaire, need to be addressed. The FHS-7 is a simple instrument for identifying the most common hereditary BC syndrome phenotypes, and it was validated in southern Brazil as a family history screening tool in primary care settings to refer at-risk individuals for genetic evaluation.[42] To integrate GGT into routine medical care, barriers must be addressed at the individual, provider, clinical, and

TABLE 4. Univariable and Multivariable Regression Analyses to Evaluate Factors Associated With Undergoing Germline Genetic Testing

		Univariable Analysis			Multivariable Analysis		
Parameter	Tested (%)	Relative Risk	95% CI	*P*	Relative Risk	95% CI	*P*
Health care sector				<.0001			
Public	26 (1.45)	0.05	0.03 to 0.08				
Private	254 (27.88)	1.00	—				
Menopausal status				<.0001			
Premenopausal/perimenopausal	179 (17.33)	1.00	—				
Postmenopausal	57 (3.74)	0.22	0.16 to 0.29				
Ethnicity/skin color				<.0001			
White	233 (15.45)	4.5	3.25 to 6.24				
Non-White	40 (3.43)	1.00	—				
Education level				<.0001			.0379
Illiterate—completed elementary school	17 (1.44)	0.06	0.03 to 0.09		0.47	0.22 to 0.96	
Completed high school	48 (7.43)	0.29	0.21 to 0.39		0.58	0.36 to 0.94	
Graduate or postgraduate degree	170 (26.07)	1.00	—		1.00	—	
Employment				<.0001			.0546
Yes	221 (19.84)	6.19	4.59 to 8.36		1.61	0.99 to 2.63	
No	49 (3.20)	1.00	—		1.00	—	
Age, years				<.0001			<.0001
≤40	128 (28.64)	6.93	5.18 to 9.26		6.82	4.13 to 11.27	
40-50	71 (10.60)	2.56	1.83 to 3.58		2.92	1.71 to 4.97	
≥50	59 (4.13)	1.00	—		1.00	—	
Region of the country				<.0001			
South	142 (16.47)	0.88	0.69 to 1.11				
Southeast	101 (18.70)	1.00	—				
Midwest	13 (2.31)	0.12	0.07 to 0.22				
North	1 (20.00)	1.07	0.18 to 6.23				
Northeast	19 (2.60)	0.14	0.08 to 0.23				
Molecular subtype				.5403			
Hormone receptor–positive	126 (10.31)	1.16	0.78 to 0.72				
HER2-positive	56 (11.22)	1.27	0.82 to 1.95				
Triple-negative	28 (8.86)	1.00	—				
Monthly household income				<.0001			.0002
No income—two minimum wages (R$ 880-R$ 1,760)	6 (0.65)	0.04	0.01 to 0.11		0.56	0.20 to 1.52	
Two to five minimum wages (R$ 2,640-R$ 4,400)	59 (7.87)	0.52	0.30 to 0.88		2.22	1.30 to 3.75	
5-10 minimum wages (R$ 4,400-R$ 8,800)	28 (14.97)	0.99	0.55 to 1.77		1.92	1.10 to 3.32	
More than 10 (>R$ 8,800)	15 (15.15)	1.00	—		1.00	—	
Clinical stage of cancer at initial diagnosis				.0098			
I	50 (11.55)	1.12	0.58 to 2.13				
II	90 (11.28)	1.09	0.58 to 2.04				
III	40 (6.75)	0.65	0.33 to 1.27				
IV	10 (10.31)	1.00	—				
Family history of cancer				.0243			
Yes	253 (9.90)	0.60	0.42 to 0.86				
No	29 (16.38)	1.00	—				
Children				<.0001			
Yes	188 (8.45)	0.49	0.37 to 0.64				
No	63 (17.40)	1.00	—				
Type of surgery				.0141			

(continued on following page)

TABLE 4. Univariable and Multivariable Regression Analyses to Evaluate Factors Associated With Undergoing Germline Genetic Testing (continued)

Parameter	Tested (%)	Univariable Analysis			Multivariable Analysis		
		Relative Risk	95% CI	*P*	Relative Risk	95% CI	*P*
Mastectomy, nipple-sparing mastectomy, skin-sparing mastectomy	78 (10.58)	1.00	—				
Breast-conserving surgery	46 (6.43)	0.61	0.42 to 0.87				
Other	15 (9.80)	0.93	0.54 to 1.57				
Neoadjuvant treatment				.2755			
Yes	105 (10.45)	1.14	0.90 to 1.46				
No	141 (9.13)	1.00	—				
Marital status				<.0001			
Yes	194 (12.54)	1.72	1.34 to 2.21				
No	81 (7.30)	1.00	—				
Health care sector covered at the institution				<.0001			.0003
Private and public	86 (5.87)	1.18	0.69 to 2.02		0.76	0.31 to 1.84	
Private	181 (23.94)	4.82	2.89 to 8.03		3.99	1.91 to 8.32	
Public	15 (4.97)	1.00	—		1.00	—	
Genetic counseling availability in the institution				<.0001			.0022
Yes	261 (21.10)	12.91	8.33 to 20.00		2.27	1.34 to 3.83	
No	21 (1.63)	1.00	—		1.00	—	
Institution providing care is a teaching center				.2746			.0406
Yes	112 (12.10)	1.14	0.90 to 1.43		1.64	1.02 to 2.64	
No	170 (10.65)	1.00	—		1.00	—	

Abbreviations: HER2, human epidermal growth factor receptor 2; R$, Brazilian Real.

societal levels using tailored approaches.[12,13,39] Achatz et al[43] proposed realistic strategies for improving genetic counseling, testing, and the management of hereditary breast and ovarian cancers in Brazil, including regulatory actions. This is certainly a complex issue, however, with multiple context-dependent dimensions.

The strengths of this national, multicenter, real-world study include the large number of patients recruited and the fact that data were collected prospectively. The large, heterogeneous cohort of this study is representative of MICs. Nevertheless, some limitations need to be considered, including missing sociodemographic and clinical data, which precluded conducting a full analysis of the entire set of NCCN criteria.

In conclusion, a very low rate of GGT was found in this large, prospective, multicenter Brazilian cohort, and the disparities between the public and private health care systems were clear. Older age, low education level, and low monthly income were significantly associated with low GGT uptake. Failure to recognize individuals with pathogenic variants in high-risk genes for BC through GGT represents a lost opportunity to prevent cancer-related deaths in mutation carriers and members of their families. In addition, the low GGT uptake at this MIC represents a lost opportunity to advance the understanding of cancer-related genetic features in such a miscegenated population. Beyond addressing the controversy over universal testing, offering *BRCA* testing and testing of other high and moderate BC risk genes to all women identified as having HR criteria represents a critical first step toward improving BC care, with possible implications affecting global efforts to improve GGT in LMICs.

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DISCLAIMER

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DATA SHARING STATEMENT

The data sets analyzed during this study are available from the corresponding author upon reasonable request.

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