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**Article — Published Version**

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Applied Health Economics and Health Policy

**Provided in Cooperation with:**

Springer Nature

*Suggested Citation:* Simoes Correa-Galendi, Julia; del Pilar Estevez Diz, Maria; Stock, Stephanie; Müller, Dirk (2020) : Economic Modelling of Screen-and-Treat Strategies for Brazilian Women at Risk of Hereditary Breast and Ovarian Cancer, Applied Health Economics and Health Policy, ISSN 1179-1896, Springer International Publishing, Cham, Vol. 19, Iss. 1, pp. 97-109, <https://doi.org/10.1007/s40258-020-00599-0>

This Version is available at:

<https://hdl.handle.net/10419/286710>

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# Economic Modelling of Screen-and-Treat Strategies for Brazilian Women at Risk of Hereditary Breast and Ovarian Cancer

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Published online: 15 June 2020  
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## Abstract

**Background** Clinical evidence supports the use of genetic counselling and *BRCA1/2* testing for women at risk for hereditary breast and ovarian cancer. Currently, screen-and-treat strategies are not reimbursed in the Brazilian Unified Healthcare System (SUS). The aim of this modelling study was to evaluate the cost effectiveness of a gene-based screen-and-treat strategy for *BRCA1/2* in women with a high familial risk followed by preventive interventions compared with no screening.

**Methods** Adopting the SUS perspective, a Markov model with a lifelong time horizon was developed for a cohort of healthy women aged 30 years that fulfilled the criteria for *BRCA1/2* testing according to the National Comprehensive Cancer Network (NCCN) guideline. For women who tested positive, preventive options included intensified surveillance, risk-reducing bilateral mastectomy and bilateral salpingo-oophorectomy. The Markov model comprised the health states ‘well’, ‘breast cancer’, ‘death’ and two post-cancer states. Outcomes were the incremental costs per quality-adjusted life-year (QALY) and the incremental costs per life-year gained (LYG). Data were mainly obtained by a literature review. Deterministic and probabilistic sensitivity analyses were performed to assess the robustness of the results.

**Results** In the base case, the screen-and-treat strategy resulted in additional costs of 3515 Brazilian reais (R\$) (US\$1698) and a gain of 0.145 QALYs, compared with no screening. The incremental cost-effectiveness ratio (ICER) was R\$24,263 (US\$21,724) per QALY and R\$27,258 (US\$24,405) per LYG. Applying deterministic sensitivity analyses, the ICER was most sensitive to the probability of a positive test result and the discount rate. In the probabilistic sensitivity analysis, a willingness to pay of R\$25,000 per QALY gained for the screen-and-treat strategy resulted in a probability of cost effectiveness of 80%.

**Conclusion** Although there is no rigorous cost-effectiveness threshold in Brazil, the result of this cost-effectiveness analysis may support the inclusion of *BRCA1/2* testing for women at high-risk of cancer in the SUS. The ICER calculated for the provision of genetic testing for *BRCA1/2* approximates the cost-effectiveness threshold proposed by the World Health Organization (WHO) for low- and middle-income countries.

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s40258-020-00599-0>) contains supplementary material, which is available to authorized users.

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## Key Points for Decision Makers

Genetic testing for *BRCA1/2* for healthy women with high familial risk results in more quality-adjusted life years at a moderately higher cost.

This economic modelling shows that a screen-and-treat strategy for women at risk for hereditary breast and ovarian cancer might be cost-effective from the perspective of the Brazilian Unified Healthcare System (SUS).

## 1 Introduction

Breast cancer is the main cause of cancer-related death in Brazilian women [1]. According to the Brazilian National Cancer Institute, in 2018, the incidence of breast cancer amounted to 56 cases per 100,000 women, resulting in 59,700 new cases annually [1]. Additionally, 6150 incident cases of ovarian cancer were diagnosed in Brazil in 2018 [1]. Although there has been a trend toward stabilization in female breast cancer mortality rates in Brazil, the state-specific mortality rates show considerable inequalities that may indicate disparities in healthcare availability [2].

The risk of breast cancer or ovarian cancer increases with the number of affected relatives in the family and the closeness of the relationship (i.e. first- or second-degree relative). Additionally, the younger a woman is diagnosed with cancer, the more likely a genetic component will be found [3]. Hereditary breast and ovarian cancer (HBOC) are mainly associated with germline mutations in the genes *BRCA1* and *BRCA2* (collectively named *BRCA* hereafter). Pathogenic variants in the *BRCA* genes are important predictors of breast and ovarian cancer, with a 40–80% lifetime risk of breast cancer and an 11–50% lifetime risk of ovarian cancer, respectively [4]. In case of a *BRCA* mutation, a non-directive counselling session should be provided to inform women of their absolute individual risk. For women who have tested positive, different preventive options are recommended. According to published evidence, risk-reducing surgery (bilateral mastectomy or bilateral salpingo-oophorectomy), chemoprevention and enhanced surveillance are effective for reducing the incidence and mortality of cancer [5, 6]. However, the decision between the available risk-reducing strategies is highly preference-sensitive [7, 8].

In order to identify high-risk women for genetic testing and counselling, the National Comprehensive Cancer Network (NCCN) guideline proposes to select women based on their personal and familial history of cancer [7]. These criteria are currently applied to reimburse genetic testing for privately insured women in Brazil [9]. Whereas private insurance offers supplementary coverage, about 70% of the population is exclusively insured within the Brazilian Unified Healthcare System (SUS). The SUS is organized according to three levels of complexity of care. In the primary level, general practitioners are responsible for basic care. If further laboratory testing and imaging is required, patients are referred to high complexity centres. Cancer care in Brazil is performed on the third level (i.e. specialized care units and hospital complexes), which is largely financed by the federal government and reimbursed according to disease-related package sums. Among the high-complexity oncology centres, only a few

with research motivation offer genetic counselling and testing [10]. As a result, in Brazil there is limited access to genetic counselling and *BRCA* testing for women at increased familial risk.

Recently, a Markov model for screen-and-treat strategies offered to Brazilian women at risk for *BRCA* mutation revealed an incremental cost-effectiveness ratio of R\$910 (Brazilian reais) per cancer case avoided. However, the cohort simulated in this study represented only first-degree relatives of women with ovarian cancer and aspects of health-related quality of life were not reflected [11].

The aim of this modelling study was to evaluate the costs and effects of a genetic-based screen-and-treat strategy compared with standard care. The screen-and-treat strategy will be provided to healthy women with a first- or second-degree relative affected by *BRCA*-associated cancer (i.e. breast, ovarian, pancreatic and prostate cancer) [7]. The prophylactic treatments considered in this model were intensified surveillance, risk-reducing bilateral mastectomy or risk-reducing bilateral salpingo-oophorectomy.

## 2 Methods

Using TreeAge Pro (TreeAge® ProSuite 2018), a Markov model was developed to assess the cost and effectiveness of a screen-and-treat strategy for women with a first- or second-degree relative affected by *BRCA*-associated cancer compared with no screening (i.e. no prophylactic treatment). To reflect long-term consequences of breast and ovarian cancer, the model had a time horizon of 70 years. Using a 1-year cycle length, the analysis was performed from the perspective of the SUS.

The selection of the model population was based on the clinical criteria for *BRCA* testing established by the NCCN. The NCCN guideline criteria (version 2.2017) consider several aspects of a woman's personal and family history including different HBOC-related tumours (i.e. prostate and pancreatic cancers) (Table A1, appendix—see electronic supplementary material [ESM]). Thus, the model population reflects Brazilian women still unaffected by breast or ovarian cancer with first- or second-degree relatives who have *BRCA*-related cancer [7]. Due to the low incidence of breast and ovarian cancer at younger ages, all women enter the model at the age of 30 years.

### 2.1 Strategies for the Comparison

The intervention is defined as a stepwise process that starts by the identification of women at high risk of HBOC due to familial or personal history. The three main components are genetic counselling by a trained health professional (i.e. evaluation of individual risk and patient education of

risk-reducing alternatives), genetic testing and different surgical/non-surgical preventive options [12]. The preventive options for women testing positive were (i) intensified surveillance, defined as yearly breast examination by physicians and alternate mammography and magnetic resonance imaging (MRI) every 6 months, (ii) salpingo-oophorectomy and (iii) bilateral mastectomy. For women choosing (ii) or (iii), it was possible to delay the preventive surgery for 5–10 years for the purpose of childbearing and other personal reasons. Women who postpone the preventive surgery were assumed to receive intensified surveillance. Women in the intervention group who test negative and women in the control group are treated in accordance with the standard breast-cancer—screening programme provided by the SUS, which does not include intensive surveillance for familial syndromes (i.e. biennial mammography between 50 and 69 years) (Fig. 1).

### 2.2 Model Overview

The structure of the Markov model was based on a previous publication and on consultancy with Brazilian oncologists [13, 14]. The Markov model comprised the health states

‘well’, ‘breast cancer’, ‘ovarian cancer’, ‘death’ and two-post cancer states. Women diagnosed with breast cancer were assumed to undergo either unilateral mastectomy (i.e. simple and radical) or breast-conserving surgery in the same proportion [15]. Women with contralateral breast cancer returned to the initial breast cancer state, with treatment costs and utilities assumed to be the same as for their first breast cancer. The state ‘death’ was modelled as an absorbing state. Transition from ovarian cancer to breast cancer was not included, considering the low incidence of ovarian cancer and its high rates of recurrence and mortality [16] (Fig. 2).

### 2.3 Input Parameters

Several systematic literature searches in Medline and BIREME (a Latin American health database) were performed to identify input data on clinical efficacy of surgical treatment options, transition probabilities and utilities. If possible, data reflecting the Brazilian context were preferred. Quality of studies was assessed following the recommendations of the Cochrane non-Randomized Studies

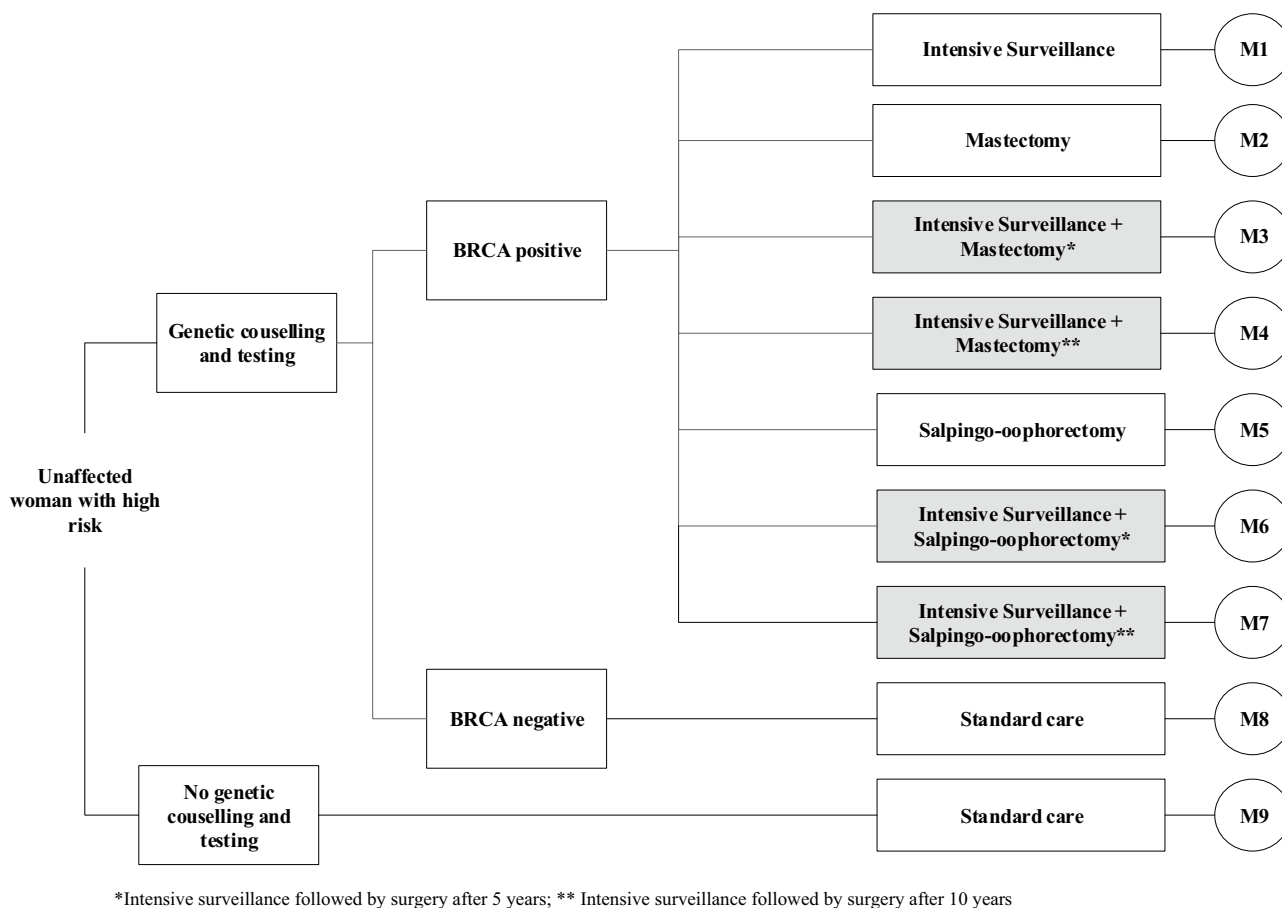


Fig. 1 Decision model that shows the test/no-test strategies and risk-reduction options depending on the test result

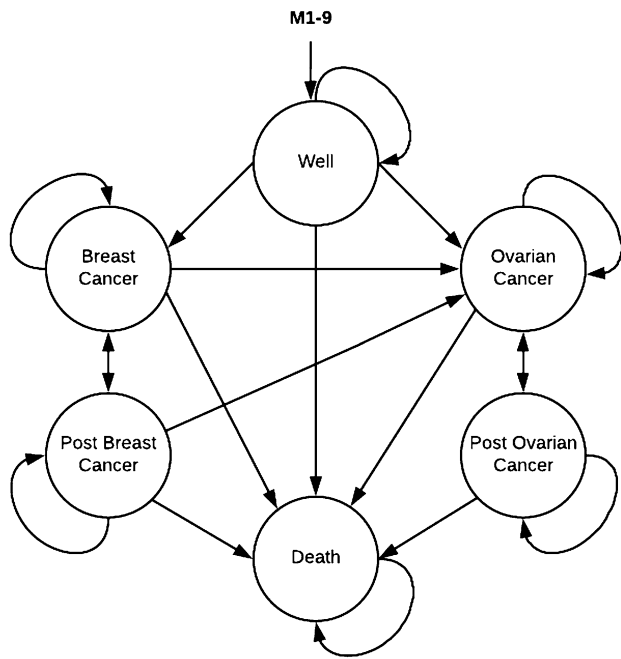


Fig. 2 Markov model overview

Methods Group [17]. In addition, clinical experts were asked about the suitability of data in the specific clinical context. Table 1 summarizes all input data and data sources, whereas Table A2 (Appendix, see ESM) provides additional information on the way the literature review was conducted.

## 2.4 Probabilities

Data on the prevalence of *BRCA* variants among the at-risk population were extracted from a cohort of healthy women that fulfilled the HBOC testing criteria in Southern Brazil according to the NCCN. This reference study applied next-generation sequencing or Sanger sequencing to analyse the coding region of the *BRCA* genes and intron–exon junctions [18].

For women who tested *BRCA* positive, the probabilities of moving from the ‘well’ state to the states ‘breast cancer’ or ‘ovarian cancer’ and data on the recurrence of breast cancer were derived from a retrospective study including 7666 female mutation-carriers from the United Kingdom, Netherlands, France, Australia, New Zealand, United States and Canada [19]. For women who tested *BRCA* negative and for the control group, we applied the breast and ovarian cancer risk of the general Brazilian population [20–22]. Similarly, the probability of recurrent cancer (for both breast and ovarian) was assumed to be equal to that of the general Brazilian population [23, 24]. Mortality data on breast and ovarian cancer were obtained from a Southwest Brazilian cohort and a national registry [25], 26.

## 2.5 Risk Reduction Strategies

The uptake of risk-reducing surgery for our model was based on data from a prospective cohort from the United States and the United Kingdom with a sample of 1499 *BRCA* carriers [27]. Because randomization was not possible due the nature of the intervention, data on effectiveness of risk-reducing mastectomy (breast cancer incidence) and salpingo-oophorectomy (both breast and ovarian cancer incidence) were taken from systematic reviews from observational trials. These studies included only women who tested positive for *BRCA* [5, 6, 28, 29].

## 2.6 Utilities

In the model, utilities decreased as a result of a positive genetic test, prophylactic surgery and breast or ovarian cancer. Utilities for the prophylactic strategies were obtained from Grann et al. [30]. In that study, a Time Trade-Off instrument (TTO) was applied to 83 female Canadian *BRCA* carriers to reflect health states such as tested gene-positive, breast cancer and ovarian cancer. In this survey, women were asked how many years of their life expectancy they would trade to be free of these states. In accordance with assumptions of other modelling studies and based on findings from a retrospective cohort, decreased utilities following preventive surgery and a positive test result were assumed to increase in a linear manner for 5 years to regain the age-specific utility of an otherwise healthy woman carrying a mutation [13, 31, 32]. To women with contralateral breast cancer, recurrent ipsilateral breast cancer or recurrent ovarian cancer, the utilities and costs of the first year of disease were once more applied. Although metastatic breast cancer was not included as a separated health state, an additional decrease of utilities due to metastasis was reflected in a proportion (i.e. 8.4%) of patients within the breast cancer state [33]. Similarly, lower utility values due to end-stage ovarian cancer were applied to the proportion of women in the ‘ovarian cancer’ state, whose survival was expected to be < 1 year (i.e. proportional to the age-adjusted mortality applied to each cycle).

Data on utility in case of breast cancer or metastatic breast cancer were obtained from a meta-regression of studies eliciting utilities with the Standard Gamble (SG) approach [34]. It was assumed that a woman’s utility declines as a result of breast cancer and then increases linearly for 5 years to regain the age-specific utility of a post-cancer state as determined by Grann et al. [30]. Utilities for ovarian cancer were taken from a single study based on the SG approach. The utility values in that study were associated with five clusters of patients with different levels of toxicity and symptoms [35]. To ensure a consistent set of utilities, these were combined and age-adjusted using the multiplicative method [36].

**Table 1** Input data

Variable	Input parameter	References
Probabilities, value (SD)		
Positive testing	0.1216 (0.09)	[18]
Positive testing (at least 10% pretest probability)	0.225	[18]
Uptake of prophylactic surgeries <sup>a</sup>		[27]
Mastectomy	30–34 y: 0.104 (0.083, 0.93); 35–39 y: 0.112 (0.089, 0.100); ≥ 40 y: 0.070 (0.056, 0.063)	
Salpingo-oophorectomy	30–34 y: 0.274 (0.219, 0.246); 35–39 y: 0.233 (0.186, 0.209); ≥ 40 y: 0.168 (0.134, 0.51)	
<i>BRCA</i> -positive women		
Well—breast cancer	30–39 y: 0.019 (0.0044); 40–49 y: 0.028 (0.0053); 50–59 y: 0.027 (0.0051); 60–69 y: 0.024 (0.0050); ≥ 70 y: 0.018 (0.0045)	[19]
Well—ovarian cancer	30–39 y: 0.001 (0.0060); 40–49 y: 0.005 (0.0083); 50–59 y: 0.011 (0.0162); 60–69 y: 0.022 (0.0226); ≥ 70 y: 0.004 (0.0135)	
Breast cancer—contralateral breast cancer	30–39 y: 0.03 (0.0469); 40–49 y: 0.02 (0.0339); 50–59 y: 0.024 (0.0369); 60–69 y: 0.017 (0.0308); ≥ 70 y: 0.011 (0.0282)	
<i>BRCA</i> -negative women		
Well—breast cancer	30–39 y: 0.0005; 40–49 y: 0.0014; 50–59 y: 0.0021; 60–69 y: 0.0027; 70–79 y: 0.0029; ≥ 80 y: 0.0028	[67]
Well—ovarian cancer	30–39 y: 0.00004; 40–49 y: 0.0001; 50–59 y: 0.0002; 60–69 y: 0.0003; 70–79 y: 0.0003; ≥ 80 y: 0.0001	[67]
Breast cancer—contralateral breast cancer	0.065	[68]
Breast cancer—death	30–39 y: 0.0509 (0.1054); 40–49 y: 0.0386 (0.0900); 50–59 y: 0.0546 (0.1082); 60–69 y: 0.0576 (0.1115); ≥ 70y: 0.0675 (0.1228)	[69]
Ovarian cancer—death	0.1898 (0.445)	[26]
Breast cancer—ovarian cancer	0.00112	[70]
Well—death	35 y: 0.0010; 40 y: 0.0015; 50 y: 0.0035; 60 y: 0.0077; 70 y: 0.0186	[38]
Relative risk, value (95% CI)		
Breast cancer		
Mastectomy	0.06 (0.01–0.41)	[5]
Salpingo-oophorectomy	0.64 (0.43–0.96)	
Contralateral breast cancer		
Mastectomy	0.48 (0.19–1.14)	[29]
Salpingo-oophorectomy	0.46 (0.27–0.78)	[29]
Ovarian cancer		
Salpingo-oophorectomy non-prior breast cancer	0.28 (0.12–0.69)	[6]
Salpingo-oophorectomy prior breast cancer	0.14 (0.04–0.59)	[6]
Utilities, value (SD)		
Well at the age of 30 y, annual decrease due to age	0.92 (0.002), 0.00029	[71]
Positive test result, linear increase year 2–5	0.887 (0.16), 0.006	[30]
Prophylactic mastectomy, linear increase year 2–5 <sup>b</sup>	0.880 (0.17), 0.007	[30]
Prophylactic oophorectomy, linear increase year 2–5 <sup>b</sup>	0.917 (0.14), 0.001	[30]
Ovarian cancer, post-cancer year 1–5	0.694 (0.221), 0.788 (0.189), 0.817 (0.175), 0.866 (0.139), 0.93 (0.071), 0.977 (0.044)	[35]
Ovarian cancer—end stage	0.55 (0.29)	[72]
Breast cancer, metastatic breast cancer linear increase year 2–5 <sup>b</sup>	0.663 (0.14 <sup>c</sup> ), 0.640 (0.12 <sup>c</sup> ), 0.0374	[34]
Costs <sup>d</sup> , value in R\$ (US\$)		
BRCA testing	2950 (1480)	

**Table 1** (continued)

Variable	Input parameter	References
Genetic counselling	200 (100)	[38]
Intensive screening (yearly MRI and mammography)	314 (157)	[38]
Standard screening (yearly mammography)	27 (13)	[38]
Prophylactic mastectomy	3158 (1584)	[38]
Prophylactic salpingo-oophorectomy	542 (272)	[38]

*CI* confidence interval, *MRI* magnetic resonance imaging, *SD* standard deviation

<sup>a</sup>For sensitivity analysis, we assumed a 10% and 20% lower uptake of prophylactic surgeries

<sup>b</sup>Assumption of a linear increase from year 2 to 5 was made, considering the combined utilities for breast cancer and metastatic breast cancer

<sup>c</sup>Because data were not available, an assumption of 20% standard deviation was made

<sup>d</sup>For sensitivity analysis, an assumption of 50% standard deviation was made

## 2.7 Costs

Cost data were mainly expressed in Brazilian currency (Reais, R\$), as suggested by the Brazilian guideline of economic evaluations [37]. Costs of preventive strategies for the year 2019 (i.e. genetic counselling, mammography, breast MRI, prophylactic mastectomy and prophylactic oophorectomy) were obtained from the Table of Procedures, Medications and Ortheses, Prostheses, and Special Materials for the National Health System (*DATASUS Tabnet*) [38]. The prices for genetic testing were based on commercial proposals from local distributors, which were similar to the costs currently applied in the private sector.

All other cost data were extracted from a recent analysis that used a macro costing approach to estimate the mean reimbursement per case of breast and ovarian cancer to a hospital in Sao Paulo [11]. In that study, data on costs were collected from a cohort of 100 patients during a mean follow-up of 3.3 years. The mean costs of treatment for ovarian cancer amounted to R\$12,958 for the first year, and decreased from R\$3960 in year 2 to R\$3508 in year 5 (breast cancer: R\$9120 in the first year, R\$4059 to R\$1278 in years 2 to 5). These costs include the costs of palliative care, adjuvant and neo-adjuvant chemotherapy, radiotherapy, diagnostic and surgical procedures. (Table 2 and Table A3 in the Appendix, see ESM) Because in this study estimates of resource consumption and costs were made for the year 2014, these were adjusted to unitary prices established by the SUS for 2019 [38]. For women in the post-cancer states, the costs associated with cancer treatment decreased yearly up to year 5. From the fifth year on, no additional costs were considered.

In order to allow comparisons with other settings, conversion to United States dollars (US\$) was performed by using a web-based tool for adjusting for currency and inflation. This web tool adjusts estimates of costs for currency and/or price year using a two-stage computation. Stage one adjusts the original estimate of cost from the original price year to

a target price year, using a Gross Domestic Product deflator index ('GDPD values'). Stage two converts the price-year-adjusted cost estimate from the original currency to a target currency, using rates based on Purchasing Power Parities for GDP ('PPP values') [39].

## 2.8 Model Outcomes

The model outputs were measured as an incremental cost-effectiveness ratio (ICER) and expressed in R\$ per quality-adjusted life-year (QALY) and R\$ per life-year gained (LYG). In line with recommendations from the Brazilian guideline for economic evaluations, costs and benefits were discounted at 5% and a half-cycle correction was applied [37].

## 2.9 Model Validation and Sensitivity Analyses

In order to explore sources of uncertainty and heterogeneity, several one-way deterministic sensitivity analyses were applied. In addition, the following structural sensitivity analyses were performed: (i) women in the control group received standard care whereas 50% of women in the intervention group who tested negative for BRCA received intensive surveillance and 50% standard care; (ii) the target group was limited to women fulfilling the NCCN criteria and a pre-test probability of BRCA mutation of 10% (according to the Manchester tool) [40]; and (iii) a higher cancer risk for women who tested negative, due to family history of cancer. The Manchester tool is a manual scoring system that can be easily applied in counselling sessions to quantify the likelihood of identifying a *BRCA1* or *BRCA2* mutation. In order to assess how a simultaneous change of several variables affected the cost-effectiveness ratio, a probabilistic sensitivity analysis (10,000 iterations) was conducted. Gamma distributions were used for modelling cost parameters, while probabilities and utilities were assumed to be beta-distributed.

**Table 2** Costs of breast and ovarian cancer (R\$)<sup>a</sup> (Adapted from Ramos et al. [11] with permission)

	First year	Second year	Third year	Fourth year	Fifth year
<b>Breast cancer</b>					
Mean (SD)	9120 (7408.05)	4059 (6466.35)	3247 (5396.12)	2328 (4018.88)	1278 (1757.77)
Costs per procedure group (%)					
Clinical procedures <sup>b</sup> (%)	6714 (73.6)	3187 (78.5)	2335 (71.9)	1503 (64.6)	807 (63.1)
Neoadjuvant chemotherapy (%)	2085 (31.1)	33 (1)			
Adjuvant chemotherapy (%)	1681 (25)	847 (26.6)	495 (21.2)	624 (41.5)	429 (53.1)
Palliative chemotherapy (%)	1164 (17.3)	1443 (45.3)	1256 (53.8)	381 (25.4)	159 (19.8)
Radiotherapy (%)	745 (11)	167 (5.2)		104 (6.9)	
Other clinical procedures	727 (10.8)	391 (12.3)	382 (16.4)	234 (15.6)	125 (15.5)
Surgical procedures (%)	942 (10.3)	242 (6)	316 (9.7)	148 (6.4)	84 (6.6)
Diagnostic (%)	1887 (13)	565 (13.9)	497(15.3)	433 (18.6)	271 (21.2)
Other (%)	276 (3.1)	65 (1.6)	99 (3.1)	243 (10.4)	116 (9.1)
<b>Ovarian cancer</b>					
Mean (SD)	12,958 (7418.81)	3960 (5786.85)	4861 (5731.54)	4168 (5073.04)	3508 (5007.76)
Costs per procedure group (%)					
Clinical procedures <sup>b</sup> (%)	7195 (55.5)	2414(61)	3382 (69.6)	2696 (64.7)	1582 (45.1)
Neoadjuvant chemotherapy (%)	1385 (19.2)	31 (1.3)			
Adjuvant chemotherapy (%)	2035 (28.3)	161 (6.7)	385 (11.4)	178 (6.6)	103 (6.5)
Palliative chemotherapy (%)	3013 (41.9)	1918 (79.4)	2573 (76.1)	2186 (81.1)	1104 (69.8)
Radiotherapy (%)	40 (0.6)	27 (1.1)	64 (1.9)		127 (8.1)
Other clinical procedures (%)	649 (9)	277 (11.5)	359 (10.6)	325 (12)	225 (14.2)
Surgical procedures (%)	3472 (26.8)	410 (10.3)	378 (7.8)	298 (7.2)	469 (13.4)
Diagnostic (%)	1761 (13.6)	912 (23)	1011 (20.8)	1023 (24.5)	963 (27.4)
Other (%)	531 (4.1)	224 (5.7)	90 (1.8)	150 (3.6)	494 (14.1)

SD standard deviation, % percentage shares of total costs

<sup>a</sup>In brackets: percentage share of costs according to procedure group

<sup>b</sup>Clinical procedures' costs refer to costs of neoadjuvant, adjuvant, palliative chemotherapy, radiotherapy and other clinical procedures

In order to validate the model, we consulted experts on the adequacy of input data and the conceptual appropriateness of the model. Technical accuracy was checked regarding data entry and potential programming errors (computerized model validation). For cross-model validation, we assessed the extent to which other models for breast cancer prevention came to different conclusions. To make our model more comparable to others, we increased the starting age (i.e. all women underwent surgery at the age of 35). The 'Assessment of the Validation Status of Health-Economic decision models' (AdViSHE) was used to provide structured information regarding the validation status of this model [41] (Table A5, appendix, see ESM).

### 3 Results

#### 3.1 Base-Case Analysis

The screen-and-treat strategy costs R\$5995 for the base-case scenario, resulting in an incremental cost of R\$3515

(US\$1698) compared with the no-testing strategy. Correspondingly, women that were offered the genetic screening strategy had an incremental gain of 0.145 QALYs. The ICER for the base-case analysis was R\$24,263 (US\$11,726) per QALY. The costs per LYG amount to R\$27,258 (US\$13,174). Base-case results are described in Table 3.

#### 3.2 Sensitivity Analyses

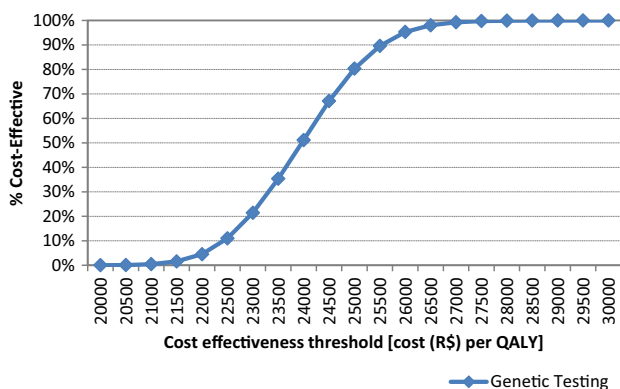
The probability of a positive test result and the discounting rate were the variables with the largest impact on the ICER. In a scenario where the probability of a positive test result was 50% lower, the ICER increased to R\$40,715/QALY (US\$19,678). In contrast, if the probability of a positive test result was 50% higher, the ICER would decrease to R\$17,228/QALY (US\$8326). A discount rate of zero would reduce the ICER to R\$3459/QALY (US\$1672), while a discount rate of 10% would result in an ICER of R\$101,857/QALY (US\$49,230). The cost-effectiveness ratio was also sensitive to data on effectiveness of prophylactic surgical procedures. Assuming a



**Table 3** Base case results

Strategy	Costs (R\$)	Incremental costs (R\$)	QALYs	Incremental QALYs	LYG	Incremental LYG	ICER (R\$)	
							Costs/QALY	Costs/LYG
No testing	2480		16.3774		18.0457			
Testing	5995	3515	16.5223	0.1449	18.1747	0.1290	24,264	27,258

ICER incremental cost-effectiveness ratio, LYG life-years gained, QALY quality-adjusted life-years



**Fig. 3** Cost-effectiveness acceptability curve for genetic screen-and-treat strategy provided to Brazilian women. QALY quality-adjusted life-years

higher impact on incidence of breast cancer (i.e. a hazard ratio [HR] of 0.01 for mastectomy and of 0.04 for salpingo-oophorectomy), the ICER would decrease by 48%. Assuming a higher impact on incidence of ovarian cancer by salpingo-oophorectomy (HR of ovarian cancer = 0.12), the ICER would drop by 20% (Table 4A and Fig. 1a Tornado Diagram, appendix [ESM]).

If all women underwent surgical prevention at the age of 35 years, the ICER would decrease by 6%. If the provision of genetic testing were restricted to women with a 10% pre-test probability or more, the ICER would decrease by 40% (R\$14,467 or US\$10,489 per QALY). If the risk of breast and ovarian cancer in BRCA-negative women were considered two-fold the risk of the general population, the ICER would decrease by only 2%. The ICER almost doubled in the scenario where patients in the intervention group that tested negative would be followed with intensive surveillance instead of intensive surveillance (Table 5A, appendix [see ESM]).

In the probabilistic sensitivity analysis, all 10,000 iterations fell in the northeast quadrant, indicating that the screen-and-treat strategy is certainly more expensive and generates more QALYs (Fig. 2a, appendix [see ESM]). The cost-effectiveness acceptability curve showed a probability of genetic testing being cost effective of 21%, 80% and 99% at a willingness to pay (WTP) of R\$23,000, R\$25,000 and R\$27,000/QALY, respectively. Figure 3 shows the

cost-effectiveness acceptability curve for the genetic screen-and-treat strategy provided to Brazilian women.

## 4 Discussion

Currently, within the Brazilian SUS, genetic testing is exclusively provided in the context of scientific research (e.g. clinical trials). Because risk-reducing strategies for BRCA carriers are clinically established and adopted by international guidelines [7, 42], the objective of this modelling study was to evaluate the costs and effects of a genetic-based screen-and-treat strategy provided to healthy women at risk for HBOC, as defined by the NCCN criteria, from the perspective of the SUS. The analysis revealed that the provision of genetic testing for BRCA in Brazilian woman with a high familial risk would result in both additional benefits and costs.

The calculated cost-effectiveness ratio in this analysis is below the cost-effectiveness threshold proposed by the World Health Organization (WHO) recommended for middle-income countries (i.e. 1 to 3 of the Gross Domestic Product [GDP] per capita) [43]. Because the ICER of our analysis is 1.04 times the GDP per capita, a genetic-based screen-and-treat strategy for Brazilian women at increased risk of cancer might be considered cost effective. Nonetheless, a reliable threshold for Brazil is yet to be defined.

The cost-effectiveness threshold from the WHO has been discredited, as have other estimates. One estimate based on per capita health expenditures and life expectancy at birth suggested a threshold for Brazil between 0.62 and 1.05 GDP per capita per QALY [44]. Using data from several low- and middle-income countries combined with several assumptions, an opportunity-cost-based threshold was proposed to lay between 0.18 and 0.71 of the GDP per capita [45]. Based on these thresholds, the genetic-based screen-and-treat strategy for Brazilian women at risk for hereditary breast and ovarian cancer would not be cost effective. However, a systematic review of health economic evaluations in Brazil showed that many interventions with an ICER above the upper limit of these two thresholds still received supporting decisions [46]. Therefore, decision making concerning health interventions in Brazil appears to be based on factors including but not limited to thresholds (e.g. budgetary

impact, magnitude of clinical effectiveness, epidemiological relevance, among others).

Because data on utilities specific to the Brazilian population is not available, it is perceived that decision-making agencies in Brazil prefer to take into account additional measures of clinical benefit (e.g. life-years gained, deaths averted, or new cases of cancer averted) [47]. Therefore, the ICER calculated as cost per LYG may contribute to allocation decisions (R\$27,258 per LYG).

The structure of the model had a number of strengths. First, unlike previous modelling studies, this model considered the women's option to postpone the surgery by 5 or 10 years after genetic counselling and testing. As many women might prefer to delay a prophylactic surgery to allow for childbearing or for aesthetic or other personal reasons, the adopted structure reflects women's options more accurately. Second, data on costs were based on a reference case (DATASUS Tabnet) that corresponds to the main components of health financing in Brazil (including geographic discrepancies). In addition, most utility data applied to the model were generated using the SG approach, resulting in homogeneous parameters on quality of life. However, utilities on prophylactic surgeries and end-stage ovarian cancer had to be based on TTO.

Finally, data on reimbursement for oncological procedures and medications in the SUS were in accordance with the disease-related package of standard reimbursement sums. Although the prices used for this analysis do not cover the costs of all available chemotherapy regimens, they were assumed to adequately reflect the additional burden for the SUS [48].

A limitation of the model is in the unknown risk of *BRCA*-negative tested women with a family history of cancer compared with cancer risks observed in the general population. Two studies found an increased risk only for relatives of *BRCA2* [49] or *BRCA1* [50] carriers, while more recent studies based on larger cohorts showed that noncarriers of either genetic mutation did not show an increased risk for HBOC [20–22]. Due to this uncertainty, we followed the guideline recommendation by assuming standard care for women who tested negative [7]. However, the uncertainty of the risk in women testing negative can lead to a more conservative approach by the physician where the decision between standard care and intensified surveillance is concerned. Therefore, an unknown proportion of *BRCA*-negative tested women may receive intensive surveillance, which would increase the cost-effectiveness ratio. Assuming a scenario of intensive surveillance for 50% of negative tested women (which would reflect a more cautious treatment attitude of physicians), this would increase the ICER to R\$38,968 per QALY. A structural sensitivity analysis reflecting a higher cancer risk in *BRCA*-negative tested women did not affect the cost-effectiveness ratio.

A further limitation of the present model might be the lack of Brazilian data on penetrance of *BRCA*. Whereas the variability on penetrance was similar between the United States, the United Kingdom, Spain, Australia and New Zealand [19, 51–57], a cohort of Colombian mutation carriers appeared to be associated with lower penetrance [58]. Nevertheless, studies that reflect the genetic profile of the Latin American population are limited and their application to the Brazilian population is difficult. The reason is that the Hispanic influence on the Brazilian population structure is considerably lower than that on neighbour countries [59]. In order to account for the heterogeneity and variability of *BRCA* penetrance, the data applied to this model were selected from a retrospective international cohort. Although we cannot rule out having misjudged the risk profile of Brazilian women, several sensitivity analyses showed similar results.

In addition, the rates of uptake of prophylactic procedures used for the model could not be obtained from the Brazilian population. Although this choice of prophylactic strategies by women at risk is contingent on personal beliefs and physician recommendations, a healthcare system's structure and access to service are the main determinants for the surgical uptake rates of different countries [60]. Given the lack of Brazilian data, we relied on data from the United Kingdom, as the structure of the healthcare system is similar to that of the Brazilian system [27]. Furthermore, a sensitivity analysis simulating a lower uptake of prophylactic surgeries (20%) than that applied to the base case resulted in only a slight change of the ICER.

A further limitation is the exclusion of a transition from ovarian cancer to breast cancer. The rationale for this omission was (i) the low incidence of ovarian cancer [25, 26] and (ii) high rates of mortality and recurrence of ovarian cancer [27]. Thus, an impact of breast cancer in women with ovarian cancer on the overall results of the model is not expected.

Among the previous Markov models that evaluated the cost effectiveness of genetic *BRCA* testing for breast or ovarian cancer in high-risk women, Ramos et al. concluded *BRCA* testing to be cost effective from the perspective of the SUS. This conclusion was drawn from the comparison of the ICER of R\$908 per case of cancer prevented with the usual sums typically spent on treatment of breast and ovarian cancer in Brazil. Data on costs used for that analysis were the same as were applied to our model, while the model structure differed to some extent, compromising comparability of results. In detail, the population analysed in the model was restricted to only first-degree relatives of patients affected by ovarian cancer. Additionally, women at risk were offered surgical procedures at the age of 35 years (i.e. a delayed prophylactic procedure was not considered) and the time horizon was shorter (i.e. 40 years) [11]. Hence, the comparability of the results

of our study with those of Ramos et al. might be limited. Different methodological approaches were also observed for models developed for other countries. Holland et al. assessed a cost-effectiveness evaluation of *BRCA* testing for US women from the societal perspective. In that model, a long-term decrease of utility due to prophylactic surgeries was assumed (i.e. 60 years) and a combined state of breast and ovarian cancer was considered. The results of that model were most sensitive to a utility decrease due to a *BRCA* mutation or a prophylactic mastectomy and a utility gain from a negative test result [61]. In the model designed by Müller et al., the option to undergo both procedures simultaneously was provided and a separate state for metastatic breast cancer was included [13]. These and other methodological discrepancies affect the comparability of the results. However, most analyses showed similar results with a tendency in favour of genetic screening being cost effective.

Gene mutations are detectable by standard methods such as Sanger Sequencing of polymerase chain reaction, amplified DNA sequencing or alternative assays. For the last decades, few facilities in Brazil have offered genetic testing, motivated either by research purposes or by reimbursement for privately insured women [62]. For low- and middle-income countries, multigene panels that incorporate recurrent mutations are an alternative to more expensive standard techniques. A panel assay designed for recurrent Hispanic *BRCA* mutations (HISPANEL) was already implemented throughout Latin America [63, 64]. In a sample of 193 Brazilian women, however, the panel assay showed a sensitivity of only 27% for detecting a *BRCA* mutation [65]. Nevertheless, the development of a genetic panel that accounts for the heterogeneous structure of the Brazilian population has the potential to be a cost-effective alternative and should be further investigated in future studies [66].

## 5 Conclusion

The present model showed that a screen-and-treat strategy for healthy women at risk for HBOC results in additional QALYs/LYG and moderately more costs, with an ICER of R\$24,264 per QALY gained. The cost effectiveness of the screen-and-treat intervention depends on a still undecided cost-effectiveness threshold for Brazil. Further studies should assess the cost effectiveness of multigene test strategies, which are a viable and promising option for preventing breast and ovarian cancer in low- and middle-income countries. Although the choice of a risk-reducing surgery depends on the woman's preferences and her current personal situation, increased accessibility of genetic testing should support her decision.

**Acknowledgements** Open Access funding provided by Projekt DEAL. The model used in this study was provided to the journal's peer reviewers for their reference when reviewing the manuscript.

**Author Contributions** Conception and design: JC-G, DM, SS, MPED. Collection and assembly of data: JC-G, MPED. Data analysis and interpretation: JC-G, DM. Manuscript writing: JC-G, DM, SS. Final approval of manuscript: JC-G, DM, MPED, SS.

**Funding** The German Chancellor Fellowship from the Alexander von Humboldt Foundation supported Julia Correa-Galendi during the development of this research. Project funded by the German Chancellor Fellowship from the Alexander von Humboldt Foundation.

**Data Availability** The model used in the current study can be made available to researchers upon request.

## Compliance with Ethical Standards

**Conflict of Interest** The authors confirm that they have no conflicts of interest to declare.

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