special articles

Recommendations for Advancing the Diagnosis and Management of Hereditary Breast and Ovarian Cancer in Brazil

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abstract

PURPOSE The objective of this review was to address the barriers limiting access to genetic cancer risk assessment and genetic testing for individuals with suspected hereditary breast and ovarian cancer (HBOC) through a review of the diagnosis and management steps of HBOC.

METHODS A selected panel of Brazilian experts in fields related to HBOC was provided with a series of relevant questions to address before the multiday conference. During this conference, each narrative was discussed and edited by the entire group, through numerous drafts and rounds of discussion, until a consensus was achieved.

RESULTS The authors propose specific and realistic recommendations for improving access to early diagnosis, risk management, and cancer care of HBOC specific to Brazil. Moreover, in creating these recommendations, the authors strived to address all the barriers and impediments mentioned in this article.

CONCLUSION There is a great need to expand hereditary cancer testing and counseling in Brazil, and changing current policies is essential to accomplishing this goal. Increased knowledge and awareness, together with regulatory actions to increase access to this technology, have the potential to improve patient care and prevention and treatment efforts for patients with cancer across the country.

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INTRODUCTION

Approximately 10% and 25% of all breast (BC) and ovarian cancers (OC), respectively, are hereditary.[1] Identification of pathogenic germline variants in high-/moderate-penetrance cancer-predisposing genes allows the implementation of strategies for cancer risk reduction and early detection. In Brazil, there is limited access to cancer risk assessment and genetic testing for individuals with suspected hereditary cancer, as well as limited information on its burden in the country. Therefore, the objective of this study was to make harmonized recommendations for improving early detection, risk management, and cancer care of patients with hereditary breast and ovarian cancer (HBOC).

METHODOLOGY

The Americas Health Foundation convened a 6-member panel of clinical and scientific experts in oncology, gynecology, genetics, and applied genomics from Brazil. PubMed and Embase were used to conduct a literature review and to identify Brazilian experts who have published in the field of HBOC since 2012. To better focus the discussion, Americas Health Foundation staff developed specific questions for the panel to address. A written response to each question was drafted by each expert and was discussed during a multiday meeting. Questions were edited by the entire group, through numerous drafts and rounds of discussion, until complete consensus was obtained.

BURDEN AND EPIDEMIOLOGY OF, AND RISK FACTORS FOR, HBOC

HBOC is a highly penetrant, autosomal dominant disorder mostly caused by pathogenic and likely pathogenic germline variants in *BRCA1* and *BRCA2* genes.[1] *BRCA1* and *BRCA2* are tumor suppressor genes that repair double-stranded DNA breaks through homologous recombination (HR).[2] Individuals harboring germline pathogenic variants in *BRCA1* and *BRCA2* are predisposed to BC (lifetime risk up to 85% and 45%, respectively) and OC (lifetime risk up to 39% and 11%, respectively), as well as other malignancies.[3-5]

The population prevalence of *BRCA1* and *BRCA2* pathogenic variants is 1:150-1:200 individuals in North American and European populations.[6] Mutation prevalence varies according to ethnicity, the genetic testing criteria used, age at cancer diagnosis, and family history. The catalog of germline variants in

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

How can the diagnosis and management of hereditary breast and ovarian cancer be improved in Brazil? A panel of Brazilian experts proposes recommendations for improving access to early diagnosis, risk management, and cancer care of hereditary breast and ovarian cancer.

Knowledge Generated

Understanding Brazil's unique social and structural barriers is crucial to expanding access to genetic cancer risk assessment. Government, medical societies, patient organizations, academic centers, and the private sector should collaborate to create a multistakeholder commission to develop and promote the incorporation of genetic cancer risk assessment.

Relevance

Increased knowledge and awareness, together with regulatory actions to expand hereditary cancer testing and counseling in Brazil, have the potential to improve the care of patients with cancer and reduce the cancer burden across the country.

BRCA genes in different populations should be expanded and made available in public databases such as ClinVar and *BRCA* Challenge.

BC and OC risks may be increased by pathogenic variants in other high-penetrance (*TP53*, *PTEN*, *STK11*, *CDH1*, and *PALB2*) and moderate-penetrance (*CHEK2*, *ATM*, *NF1*, *RAD51C*, *RAD51D*, and *BRIP1)* genes. The American College of Medical Genetics has recognized 25 actionable genes for which there is enough evidence to implement an effective cancer risk-reduction strategy.[7] Cancer risk management has been implemented in *BRCA1* and *BRCA2* pathogenic carriers, whereas knowledge about the appropriate management of carriers with moderate-penetrance genes is still limited.[8]

Multigene panel testing, including actionable genes related to BC and OC, may be considered for patients who fulfill the clinical criteria for HBOC.[9] Testing only *BRCA* genes may miss approximately one-half of the pathogenic germline variants involved in HBOC risk,[10] and next-generation sequencing allows testing genes with clinical usefulness at an affordable cost.[9,11,12] Panel testing should be recommended only by trained physicians to ensure adequate genetic counseling and management. There is no added value of exome and whole-genome testing in HBOC families, and this should not be recommended. Treatment-focused genetic testing (TFGT) and genomic tumor profiling are currently the gold standard in defining better treatment strategies for tumors such as ovarian serous carcinomas. This generates an urgent need to provide more effective, timely, and adequate pre- and post-test genetic counseling.[13]

Several genetic and environmental factors can modulate the penetrance of germline *BRCA1* and *BRCA2* pathogenic variants. Variant location, with the identification of clusters of mutations with differential cancer risks, may be associated with higher BC or OC risks.[14] In addition, several genetic variants have been identified in coding and noncoding regions, which may modulate the penetrance of germline *BRCA1/2* variants, such as those described by the Consortium of Investigators of Modifiers of *BRCA1/2*.[15] Risk-protecting factors (eg, breast feeding in *BRCA1* carriers) and risk-enhancing factors (eg, obesity) have been identified (Appendix Table A1). Studies on cancer risk modifiers in Brazilian patients with HBOC are not currently available. Such studies are needed to verify whether these cancer risk modifiers have a role in risk management strategies tailored to Brazil's admixed population.

MOLECULAR EPIDEMIOLOGY OF HBOC

In the mutational landscape of *BRCA1* and *BRCA2* variants in > 29,000 families[16] substantial variation in mutation type and frequency by geographical region and race/ethnicity was observed. Recurrent germline *BRCA* variants have been described in specific populations or geographic regions, and some are caused by founder effects (Table 1). In these situations, mutation-specific screening strategies are efficient, such as the 3 *BRCA1* and *BRCA2* Ashkenazi founder mutations identified in 2.5% of this population.[13] Nine studies have performed comprehensive *BRCA* mutation testing in 2,090 individuals from high-risk cohorts in Brazil.[17-25] Mutation prevalence estimates in individuals with clinical criteria are 19%-22%.[26,27] Approximately 5% are large gene rearrangements. Certain variants are specific to Brazilian regions as a result of distinctive patterns of immigration in the past centuries.[28,29]

HEREDITARY BC RELATED TO *TP53* GENE

In Brazil, a significant percentage of BC burden is conferred by Li-Fraumeni syndrome (LFS), because of a founder mutation, *TP53* p.Arg337His (p.R337H)(NC_000017.9: c.1010G>A), present in 0.3% of the southern and southeastern populations. LFS has a wide tumor spectrum, predisposing to premenopausal BC, sarcomas, brain tumors, and adrenocortical carcinoma, among other cancers.[30] Strong evidence supports the association between the *TP53* germline variant and a worse overall and disease-free survival in BC.[31-33] In classic LFS, cancer risk

TABLE 1. Recurrent Pathogenic Variants in Hereditary Breast and Ovarian Cancer Syndrome Identified in Different Countries

Continent	Country	Gene	Mutation(s)	Confirmed Founder	Details	First Author
Africa	Algeria, Morocco, and Tunisia	*BRCA1*	c.798_799delTT	No	22% of *BRCA1* mutations in North African families	Laraqui[85]
	South Africa			No		
		BRCA1		No		
		BRCA2	c.1374delC c.2641G>T c.7934delG	No	77.8% of mutation carriers had one of the 3 Afrikaner founder mutations	Seymour[86]
Americas						
North	Mexico	*BRCA1*	Exon 9-12 del	Yes	35% and 29% of the *BRCA*-associated ovarian and breast cancer cases, respectively	Villareal-Garza[87]
	Canada	*BRCA1*	c.4327C > T c.8537_8538del c.5266dupC	Yes		
		BRCA2		Yes		Cavallone[88]
South	Brazil	*BRCA1*		Yes		Fernandes[19]
Asia	Israel	*BRCA1*	c.5266dup	Yes		Manchanda[89]
			c.68_69del	Yes		
		BRCA2	c.5946del	Yes		
Europe	Portugal	*BRCA2*	c.156_157insAlu	Yes	37.9% of *BRCA2* pathogenic variants in Portuguese families	Peixoto[90]
	Iceland	*BRCA2*	c.771_775del	Yes		Rafnar[91]
	Hungary	*BRCA2*	c.9097dup	Yes		Van der Looij[92]
Australia/Oceania	Australia	*BRCA1*	c.3331_3334del	No	Also recurrent in Hispanic populations, Europe, USA, and the UK	Rebbeck[16]
	Australia	*BRCA2*	c.6275_6276del	No	Also recurrent in the UK, Belgium, Spain, the Netherlands, and North America	Rebbeck[16]

by age 60 years is 90% in women and 73% in men, with an overall cumulative incidence of 50% by age 40 years.[34,35] The p.R337H *TP53* variant confers a lifetime cancer risk that differs from typical DNA-biding domain TP53 pathogenic variants. Carriers have a lifetime cancer risk of 80% in females, and 47% in males.[36] BC is the most common malignancy diagnosed in LFS. In p.R337H carriers, the mean age is 40 years, and in classic LFS, 32 years.[37] In a cohort of 815 women affected by BC in southern Brazil who developed the disease before age 45 years, the result was a high prevalence of the p.R337H (12.1%).[38] These results suggest that inheritance of p.R337H may contribute to a significant number of BC cases in Brazil.

Currently, in Brazil, genetic testing for *TP53* mutation is for families who fulfill certain criteria, which may include all cases of BC below age 35 years, regardless of family history.[27,39] Recent studies suggested that all women with premenopausal BC in Brazil should be tested for p.R337H.[40,41] Effective screening strategies for LFS represent a major challenge because of the wide spectrum of tumors and the variable ages of onset. Given the suspected high population prevalence of the founder mutation in Brazil, and the public health issue it may constitute, a better knowledge of its country-wide prevalence, as well as the effective management of cost-effective strategies dedicated to the Brazilian population, are urgently required.

DIAGNOSIS, MANAGEMENT, COST EFFECTIVENESS, AND TREATMENT OPTIONS IN HBOC IN BRAZIL

Genetic cancer risk assessment (GCRA) is an interdisciplinary medical practice that identifies, counsels, and manages individuals and families at high risk of an inherited cancer syndrome.[42] In Brazil, access to GCRA and consequent management options according to established risk are limited. Improving access is essential to increase health and improve cancer outcomes.

Although genetic testing is not available in the Brazilian public health care system, in the private system, coverage is available for molecular testing in individuals who fulfill criteria established by the Agencia Nacional de Saude.[27] Agencia Nacional de Saude guidelines include risk-reducing interventions for carriers of a pathogenic germline variant (eg, risk-reducing surgeries, breast reconstruction, and access to follow-up breast magnetic resonance imaging [MRI] in patients who decline surgery). Meeting the need for adequate post-test counseling is a challenge. Regulatory actions and policy recommendations are urgently needed to address these issues. Table 2 lists the recommendations of this panel in defining criteria for genetic testing for individuals with HBOC in Brazil.

Women diagnosed with BC or OC may be offered TFGT, with targeted therapies for *BRCA* carriers. As the demand for TFGT increases, alternative models of providing information to patients before genetic testing should be sought, because there is a limited number of genetic risk assessment providers. A streamlined approach may be an effective solution. It relies on substituting traditional pretest genetic counseling with providing information, the graphic/visual information to the patient, or focused counseling by the treating physician.[43-45]

UNDERSTANDING GENETIC TESTING RESULTS

In the presence of germline *BRCA1*/*BRCA2* and *TP53* variants, current options for risk reduction and early detection include surveillance and risk-reducing surgeries. In individuals without a previously identified pathogenic variant, the absence of a pathogenic variant cannot definitively exclude hereditary cancer, because some individuals may still harbor an elevated risk of HBOC caused by unknown/unidentified genetic risk factors. In this scenario, models estimating cancer risk on the basis of family history and individual risk factors should be communicated to the patient. It is important to investigate both maternal and paternal lineages to prevent missing additional cancer risk.

Whenever a variant of uncertain significance (VUS) is identified, this result must be considered inconclusive and no clinical action is justified. The Brazilian population is highly admixed, and there is likely an increased prevalence of VUS. Nevertheless, preliminary data have shown a prevalence similar to those of North American and European populations.[23] The majority (> 90%) of VUS will be reclassified to benign or likely benign categories.[46] Nevertheless, VUS should always be reported and periodically reassessed. Reaching back to patients regarding new, updated testing options or techniques should also be ensured.[42,46-49]

MANAGEMENT OPTIONS

Because of a lack of local studies, all recommendations for Brazil are based on international data. Although surveillance strategies for moderate-penetrance genes have limited data, some screening strategies must be encouraged (Table 3).

Intensive Surveillance for *BRCA1* and *BRCA2* Carriers

An annual breast MRI in conjunction with annual mammography screening in *BRCA1* and *BRCA2* carriers from the age of 30 years is more sensitive than annual mammography alone, detecting BC at an earlier stage.[50-54] MRI screening every 6 months has shown optimal performance for women at risk of *BRCA1*-associated BC.[55] Although in Brazil these resources are not sufficiently well distributed, breast MRI is fully covered for patients who carry a *BRCA* pathogenic variant.[27] Additional studies to determine the combination of screening modalities, potential harms of exposure to mammography radiation, cost effectiveness, and survival are needed.[56,57] Future perspectives in this field include the adoption of abbreviated MRI protocols and

TABLE 2. Recommendations for Testing Individuals With Hereditary Breast and Ovarian Cancer

Individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing
Individual from a family with a known BRCA1/2 pathogenic/likely pathogenic variant in a cancer predisposition gene
Personal history of breast cancer and one of the following:
Diagnosed at ≤ 45 years of age
Diagnosed at 46-50 years of age with
An additional breast cancer primary at any age
≥ 1 close blood relative with breast cancer at any age
≥ 1 close blood relative with high-grade (Gleason score ≥ 7) prostate cancer at any age
An unknown or limited family history
Diagnosed at ≤ 60 years of age with triple-negative breast cancer
Diagnosed at any age with
≥ 1 close blood relative with
Breast cancer diagnosed at ≤ 50 years of age; or
Ovarian carcinoma, or
Male breast cancer, or
Metastatic prostate cancer, or
Pancreatic cancer
≥ 2 additional diagnoses of breast cancer at any age in patient and/or in close blood relatives
Personal history of male breast cancer
Ashkenazi Jewish ancestry
Personal history of ovarian carcinoma
Personal history of pancreatic cancer
Personal history of metastatic prostate cancer
Personal history of high-grade prostate cancer (Gleason score ≥ 7) at any age with
≥ 1 close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer at any age, or breast cancer at < 50 years of age
≥ 2 close blood relatives with breast or prostate cancer (any grade) at any age, or Ashkenazi Jewish ancestry
BRCA1/2 pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic/likely pathogenic variant analysis
Regardless of family history, some individuals with a *BRCA*-related cancer may benefit from genetic testing to determine eligibility for targeted treatment
An individual who does not meet the other criteria but with ≥ 1 first- or second-degree blood relative meeting any of the previously mentioned criteria; the significant limitations of interpreting test results for an unaffected individual should be discussed

the use of less contrast to reduce costs.[58,59] OC screening is not recommended. However, in patients who decline risk-reducing salpingo-oophorectomy, transvaginal ultrasound and serum CA-125 may be considered, at the clinician's discretion.

Risk-Reducing Bilateral Mastectomy for *BRCA1* and *BRCA2* Carriers

Bilateral mastectomy is associated with > 90% risk reduction in BC.[60] In *BRCA1* and *BRCA2* carriers, nipple-sparing mastectomy is associated with a low rate of complications.[61,62] Surveillance strategies after risk-reducing mastectomy are not well established and should be addressed on a case-by-case basis. A recent study showed that bilateral risk-reducing mastectomy in mutation carriers had an impact on mortality in *BRCA1* carriers, although the impact in *BRCA2* carriers was less evident.[63]

Contralateral Risk-Reducing Mastectomy for *BRCA1* and *BRCA2* Carriers

Cumulative contralateral BC risk 20 years after a first primary BC is 40% for *BRCA1* and 26% for *BRCA2* carriers. Current evidence suggests that contralateral risk-reducing mastectomy is effective for *BRCA1* carriers, reducing mortality.[64-67]

Risk-Reducing Bilateral Salpingo-Oophorectomy for *BRCA1* and *BRCA2* Carriers

Bilateral salpingo-oophorectomy (BSO) confers a 72%-88% risk reduction in OC and fallopian tubal cancer. It is associated with a reduction in OC-specific and all-cause mortality in *BRCA* carriers.[60,68] Therefore, BSO is recommended for *BRCA* carriers who have completed childbearing, and it should be performed by age 35-40 years in *BRCA1* carriers, by age 40-45 years in *BRCA2* carriers, or

TABLE 3. Cancer Risk and Management in Non-BRCA Hereditary Breast and Ovarian Cancer–Related Genes

Gene	Breast Cancer Risk	Breast Cancer Management	Ovarian Cancer Risk	Ovarian Cancer Management	Other Cancer Risks
ATM	Increased risk	Annual mammogram with consideration of tomosynthesis, and consider breast MRI with contrast starting at age 40 years RRM: evidence insufficient, manage on the basis of family history	Potentially increased risk	Insufficient evidence for recommending RRSO	Insufficient evidence for pancreas or prostate cancer
BARD1	Potentially increased risk	Insufficient evidence, manage on the basis of family history	Unknown	Insufficient evidence for management recommendations	Unknown
BRIP1	Unknown	Insufficient evidence, manage on the basis of family history	Increased risk	Consider RRSO at age 45-50 years	N/A
CDH1	Increased risk[a]	Annual mammogram with consideration of tomosynthesis, and consider breast MRI with contrast starting at age 30 years RRM: evidence insufficient, manage on the basis of family history	No increased risk	N/A	Diffuse gastric cancer
CHEK2	Increased risk	Annual mammogram with consideration of tomosynthesis, and consider breast MRI with contrast starting at age 40 years RRM: evidence insufficient, manage on the basis of family history	No increased risk	N/A	Colon cancer
MLH1, MSH2	Unknown	Insufficient evidence, manage on the basis of family history	Increased risk[b]	Consider RRSO on completion of childbearing	Colon, endometrial, and other cancers
NBN	Increased risk	Annual mammogram with consideration of tomosynthesis, and consider breast MRI with contrast starting at age 40 years RRM: evidence insufficient, manage on the basis of family history	Unknown	N/A	Unknown
NF1	Increased risk	Annual mammogram with consideration of tomosynthesis starting at age 30 years, and consider breast MRI with contrast from ages 30-50 years RRM: evidence insufficient, manage on the basis of family history	No increased risk	N/A	GIST, malignant peripheral nerve sheath tumors, others
PALB2	Increased risk	Annual mammogram with consideration of tomosynthesis starting at age 30 years, and consider breast MRI at age 30 years RRM: evidence insufficient, manage on the basis of family history	Unknown	N/A	Unknown

(Continued on following page)

TABLE 3. Cancer Risk and Management in Non-BRCA Hereditary Breast and Ovarian Cancer–Related Genes (Continued)

Gene	Breast Cancer Risk	Breast Cancer Management	Ovarian Cancer Risk	Ovarian Cancer Management	Other Cancer Risks
PTEN	Increased risk	Annual mammogram with consideration of tomosynthesis starting at age 30 years, and consider breast MRI at age 30 years RRM: evidence insufficient, manage on the basis of family history	No increased risk	N/A	Thyroid, endometrial, renal, and colon cancer
RAD51C, RAD51D	Unknown	Insufficient evidence, manage on the basis of family history	Increased risk	Consider RRSO at age 45-50 years	Unknown
STK11	Increased risk	Annual mammogram with consideration of tomosynthesis, and consider breast MRI with contrast starting at age 40 years RRM: evidence insufficient, manage on the basis of family history	Increased risk	Insufficient evidence for management recommendations	GI tumors
TP53	Increased risk	Annual mammogram with consideration of tomosynthesis, and consider breast MRI with contrast starting at age 25 years RRM: discuss option of risk-reducing mastectomy	No increased risk	N/A	Sarcomas, adrenocortical carcinoma, brain tumors, and others

NOTE. Adapted from National Comprehensive Cancer Network.[26]

Abbreviations: GIST, gastrointestinal stromal tumor; MRI, magnet resonance imaging; N/A, not available; RRM, risk-reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy.

[a]Predisposes to lobular breast cancer.

[b]Mucinous ovarian cancer.

TABLE 4. Recommendations for Overcoming Barriers to Adequate Diagnosis and Management of Hereditary Breast and Ovarian Cancer in Brazil

Access Barriers	Education Barriers	Quality Assurance Barriers
Lack of a structured referral network in both public and private health care systems	Limited public awareness of genetic risk and of the benefits of GCRA	Lack of regulatory guidelines governing quality control of laboratories and genetic tests
Insufficient number of trained professionals who are able to recognize and provide genetic counseling to patients with a higher cancer risk	Incomplete/incorrect counseling provided by professionals with limited knowledge in the field	Lack of continued assessment of the quality of the clinical services provided in cancer genetics
Absence of genetic testing in the public system and limited access for coverage in the private setting[a]	Limited knowledge of HBOC syndrome and tests among health care professionals at all levels of care	Lack of adequate research budget for epidemiologic studies to delineate hereditary cancer in the country
Limited availability to genetic counseling in both public and private systems	Reluctance of at-risk patients and family members to seek genetic testing and counseling	Lack of funding to develop innovative solutions to overcome local barriers
High cost of genetic tests	Cultural and religious barriers	
Lack of inclusion of GCRA and surveillance of patients in the national cancer policy	Patient and family fears and misconceptions	

Abbreviations: GCRA, genetic cancer risk assessment; HBOC, hereditary breast and ovarian cancer.

[a]Patients must fulfill Agencia Nacional de Saude criteria, including the need for a prescription from a board-certified clinical geneticist to qualify for reimbursement.

individualized, on the basis of the age of onset of OC in the family. Detailed sectioning and microscopic examination of ovaries and fallopian tubes from BSO in high-risk populations led to the identification of occult carcinomas in up to 1.9%-9.1% of cases.[60] After risk-reducing surgery, there is a 10% risk of recurrence after detection of an occult carcinoma and a 1% risk of developing a primary peritoneal tumor.[69]

Early surgical castration causes early menopause and increases the risk of cardiovascular disease and osteoporosis. On the basis of available data from observational studies, hormone replacement therapy after BSO should not be performed in patients affected by BC, but it has not shown an increased risk of BC among cancer-free *BRCA* carriers who have undergone risk-reduction bilateral mastectomy.[70]

Chemoprevention for *BRCA1* and *BRCA2* Carriers

Large primary prevention trials with tamoxifen, 20 mg once per day for 5 years, have demonstrated that BC risk can be reduced by 40%-50% in women at high risk, although not necessarily in pathogenic variant carriers.[71] Limited data are available regarding the benefit of tamoxifen in *BRCA* carriers, but it may be considered for patients who do not want to undergo risk-reducing surgery.[72,73] There are no data on the benefit of raloxifene or aromatase inhibitors in *BRCA* carriers.

PolyADP-Ribose Polymerases in *BRCA*-Associated OC for *BRCA1* and *BRCA2* Carriers

PolyADP-ribose polymerases (PARP) inhibitor is a targeted therapy that acts on a deficiency in the HR pathway. In OC, 2 randomized phase III trials (SOLO-2 and NOVA) demonstrated improved progression-free survival with monotherapy PARP inhibitor as maintenance therapy in patients with recurrent, platinum-sensitive *BRCA*-associated OC and HR-deficient tumors.[74,75] In first-line treatment, SOLO-1 showed better progression-free survival with PARP inhibitor (olaparib) maintenance treatment after usual chemotherapy in *BRCA*-associated stage III-IV high-grade serous or endometrial OC.[76] Agência Nacional de Vigilância Sanitária has approved olaparib for relapsed high-grade OC and for first-line *BRCA*-associated serous and endometrioid high-grade OC, but it is not yet available to the public or in the private health system.

PARP Inhibitor in *BRCA*-Associated BC for *BRCA1* and *BRCA2* Carriers

Two phase III trials (OlympiAD and EMBRACA) randomly assigned patients after chemotherapy in HER2-negative, *BRCA*-associated metastatic BC and showed longer progression-free survival with PARP inhibitor. The Food and Drug Administration has approved 2 PARP inhibitors (olaparib[77] and talazoparib[78]) for germline *BRCA*-associated metastatic BC. In Brazil, olaparib was approved in this setting by Agência Nacional de Vigilância Sanitária in 2018.

MANAGEMENT OPTIONS FOR *TP53* GERMLINE PATHOGENIC VARIANT CARRIERS

All carriers of a *TP53* pathogenic variant should receive intensive surveillance. In Brazil, because of the founder variant present in a significant part of the population, management is a public health situation that remains unresolved. Nevertheless, breast MRI should be offered annually from age 20 years and mammography annually after age 30 years. Risk-reducing bilateral mastectomy and contralateral risk-reducing mastectomy should be suggested. Whole-body MRI and brain MRI should be performed yearly from birth in carriers because of the high risk of sarcomas and CNS, adrenocortical, and other tumors.

COST-EFFECTIVENESS OF GENETIC TESTING

BRCA testing is cost effective in BC and OC. It is associated with reduced risk and improved survival in female carriers, with benefits when testing is extended to family members (cascade testing).[79,80] Presymptomatic cancer surveillance is cost effective for patients with germline pathogenic variants in *TP53*.[81]

Risk-reduction surgery and intensive breast screening were cost effective in models of *BRCA* carrier risk management.[82] In Brazil, *BRCA1*/*BRCA2* diagnostic and management strategies for patients with OC were considered cost effective but only when cancer-unaffected relatives of OC mutation carriers were included in the model.[83]

CURRENT BARRIERS AND RECOMMENDATIONS FOR OVERCOMING BARRIERS TO ADEQUATE DIAGNOSIS AND MANAGEMENT OF HBOC IN BRAZIL

Despite evidence of the benefits of genetic counseling, testing, and adequate risk management,[42] access is limited in Brazil and in most Latin American countries (Table 4). To address these limitations, strategies related to public awareness, education, integrated services, implementation, and monitoring are needed. Government, medical societies, patient organizations, academic centers, and the private sector should create a multistakeholder commission to develop and promote the incorporation of GCRA and management into the public and private health care systems. Such a plan should include the following:

1. Establishment of genetic health benefits, including genetic testing, counseling, and long-term management, accessible to patients in both public and private health care systems:
   - The Brazilian National Cancer Control Policy should be updated to include essential genetic health benefits.
   - Regulatory agencies in the Brazilian Ministry of Health should prioritize the incorporation of policies related to hereditary cancer.

- Guidelines that ensure coverage for genetic services in private health care should be updated on an annual basis and should include genetic testing coverage for cancer-unaffected individuals when first- and second-degree relatives fulfill criteria.

2. Development of a 3-tiered training program for health professionals.
   - Tier 1: Basic genetics education and continued medical education should be provided to all health care professionals to enable recognition and referral of at-risk patients;
   - Tier 2: A minimum curriculum on hereditary cancer should be included in training programs in specialties related to cancer care, and continuing medical education should be required;
   - Tier 3: Specialty training programs should be developed and expanded for health care professionals seeking to conduct GCRA.
3. In TFGT, a streamlined approach should be implemented. Traditional GCRA should be available whenever indicated. Research studies should be conducted to validate whether a streamlined approach is effective in Brazil.
4. Genetic counseling and risk assessment should be offered in a multidisciplinary setting involving multiple health care professionals to ensure the most appropriate management of patients and their families.
5. Public health officials should be educated on the importance of GCRA, guaranteeing access to genetic health benefits as part of the strategic national cancer control plan.
6. A Brazilian network of reference centers should be expanded and the insertion of GCRA and genetic testing should be championed in both public and private health care systems.
7. Continuing professional education and periodic recertification should be implemented to guarantee clinical and laboratory services. Professional societies should oversee these efforts.
8. Government, medical societies, health care professionals, and patient organizations should support education programs to promote public awareness of the importance of understanding personal and family genetic risk factors and their influence on cancer management.
9. Politicians should be encouraged to pass laws protecting individuals against genetic discrimination by employers and insurance companies.
10. Systematic reporting should be encouraged. Results from clinical and research-focused genetic testing should be made available in public databases on human genomic variations.

There is a great need to expand hereditary cancer testing and counseling in Brazil. Understanding Brazil's unique social and structural barriers and mounting a strong, timely response to this public health problem is crucial. Increased knowledge and awareness of HBOC among nongenetic health care professionals, as well as the general population, public health officials, and patient organizations, would advance translational efforts to improve cancer care and outcomes.[84]

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APPENDIX

TABLE A1. Breast Cancer Risk and Protective Factors

Nongenetic Exposures Variable	Hereditary Ovarian Cancer Risk Factor[a]
Late age at menarche	**BRCA1:** Null results[b] or borderline protective effect[c]
	BRCA2: null results[b,d]
Alcohol consumption	Three studies reported on alcohol use,[e] all of which reported **null results**
Smoking	**BRCA1:** One article studied coffee intake and smoking with **null results** in each category[c]
	BRCA2: A pooled estimate of 2 studies[f,g] showed an **increased risk** for more than 4 years of smoking *v* never, whereas an ever *v* never meta-analysis of smoking produced **null results**
Coffee/caffeine intake	**BRCA1:** One article studied coffee intake and smoking, with **null results** in each category[c]
Oral contraceptive use	**BRCA1:** Studies reported a **decreased risk** of ovarian cancer for BRCA1 mutation carriers with ever *v* never use; when the oral contraceptive use occurred for > 1 year, there was a statistically significant decreased risk, ranging from a 33% to a 80% reduction[b,c,h,i]
	BRCA2: Use of oral contraceptives **reduced the risk** of ovarian cancer in carriers of BRCA2 mutations (0.39 [0.23-0.66]; $P = .0004$)[h-j]
Age at first live birth	**BRCA1/2:** The meta-analysis results were **largely null**[b,k,l]
Parity	**BRCA1/2:** Studies reported on trend per birth, and a meta-analysis showed statistically **significant risk reduction** only seen in women with > 4 live births[b,c,i,l]
Breastfeeding	**BRCA1:** A study reported a **statistically significant reduction** in ovarian cancer risk with ever *v* never breastfeeding.[c]
	BRCA2: Two studies reported **no association** for ever *v* never, ≤ 1 year *v* never, and > 1 year *v* never[b,j]
Combined HRT exposure	**BRCA1:** Hormone replacement therapy was examined, with **null effects reported**[i,m]
Tamoxifen (contralateral breast cancer)	**BRCA1:** One study reported a **null effect** of tamoxifen[i]
	BRCA2: Studies reported a **null effect**[i,n]
Tubal ligation	**BRCA1**: Studies that evaluated tubal ligation[b,h,j] reported a **reduction in risk** for ever having a tubal ligation
	BRCA2: No protective effect of tubal ligation was seen among carriers of the mutation[b,h,j]

NOTE. Boldface indicates significance.

Abbreviation: HRT, hormone replacement therapy.

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