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Ovarian cancer and BRCA mutation genetic testing: the Brazilian reality

Câncer de ovário e teste genético de mutação BRCA: a realidade brasileira

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ABSTRACT

Introduction: Ovarian cancer (OC) is one of the leading causes of women's cancer deaths worldwide. Recent clinical trials with PARP inhibitors showed promising therapeutic opportunities for OC patients. The assessment of *BRCA* mutation is well established as relevant in the prevention, early diagnostic, and family counseling for OC, and recently *BRCA* gene mutation was associated as a prognosis for PARP inhibitors treatment. In this scenario, the assessment of the patient's mutation is proposed on Brazilian oncology guidelines and should be advised by health professionals that treat OC. **Objectives:** Inquire Brazilian oncologists about *BRCA* gene testing requesting time in the clinical practice for OC patients. **Material and Methods:** From May 2018 to June 2019, approximately 400 Brazilian oncologists received an online survey with questions related to the indication and challenges of *BRCA* gene testing. The survey was sent in 4 periods (waves); each wave received approximately 100 answers. **Results:** The compiled information showed that, on average, each oncologist treated 3 to 5 patients with ovarian cancer, they would recommend testing for three patients. Most respondents would indicate, *BRCA* testing during patients initial diagnostic period (w1=44%, w2=50%, w3=58%, and w4=64%). The sample of choice for testing would be blood/saliva assessing the germline mutational status (w1=35%, w2=43%, w3=46%, and w4=47%). The main reasons for oncologists to refrain from recommending *BRCA* testing were associated with cost and lack of reimbursement followed by lack of genetic counselors, among other factors. **Conclusion:** *BRCA* testing is restricted and not recommended for all ovarian cancer patients from the private health care sector. There is a lack of consensus on testing recommendations and discrepancies between coverage and national guidelines standardizing. There main difficulties associated with refraining testing were related to reimbursement and health plan coverage. Besides, the lack of genetic counseling was also pointed to as a bottleneck on oncologic patients' multidisciplinary treatment.

Keywords: Medical oncology; Clinical medicine; Ovarian diseases; Genetic counseling; Genes, Practice guideline.

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RESUMO

Introdução: O câncer de ovário (CO) é uma das principais causas de mortes por câncer de mulheres em todo o mundo. Ensaios clínicos recentes com inibidores de PARP mostraram oportunidades terapêuticas promissoras para pacientes com CO. A avaliação da mutação *BRCA* é bem estabelecida como relevante na prevenção, diagnóstico precoce e aconselhamento familiar para CO, e recentemente a mutação do gene *BRCA* foi associada como um prognóstico para o tratamento com inibidores de PARP. Nesse cenário, a avaliação da mutação do paciente é proposta nas diretrizes brasileiras de oncologia e deve ser orientada pelos profissionais de saúde que tratam da CO. **Objetivos:** Investigar oncologistas brasileiros sobre o teste do gene *BRCA*, questionando o momento da testagem na prática clinica para pacienets com CO. **Material e Métodos:** De maio de 2018 a junho de 2019, aproximadamente 400 oncologistas brasileiros receberam uma pesquisa online com perguntas relacionadas à indicação e desafios do teste do gene *BRCA*. A pesquisa foi enviada em 4 períodos (ondas); cada onda recebeu aproximadamente 100 respostas. **Resultados:** As informações compiladas mostraram que, em média, cada oncologista tratou de 3 a 5 pacientes com câncer de ovário, eles recomendariam o teste para três pacientes. A maioria dos entrevistados indicaria o teste *BRCA* durante o período inicial de diagnóstico dos pacientes (w1=44%, w2=50%, w3=58% e w4=64%). A amostra de escolha para teste seria sangue/saliva avaliando o status mutacional da linha germinativa (w1=35%, w2=43%, w3=46% e w4=47%). Os principais motivos pelos quais os oncologistas se abstiveram de recomendar o teste *BRCA* foram associados ao custo e à falta de reembolso, seguidos de falta de conselheiros genéticos, entre outros fatores. **Conclusão:** O teste *BRCA* é restrito e não recomendado para todas as pacientes com câncer de ovário do setor privado de saúde. Há uma falta de consenso sobre as recomendações de teste e discrepâncias entre a cobertura e a padronização das diretrizes nacionais. As principais dificuldades associadas ao teste de abstinência foram relacionadas ao reembolso e à cobertura do plano de saúde. Além disso, a falta de aconselhamento genético também foi apontada como um gargalo no tratamento multidisciplinar de pacientes oncológicos.

Descritores: Oncologia médica; Medicina Clínica; Doenças ovarianas; Aconselhamento genético; Genes; Diretriz prática de genes.

INTRODUCTION

In Brazil, ovarian cancer has a prevalence of 6,650 new cases every year, corresponding to the seventh cause of cancer mortality in women.[1] In the past few years, the primary treatment for advanced ovarian cancer (OC) consisted mainly of cytoreductive surgery and chemotherapy. Few new therapeutic approaches provide promising benefits for recently diagnosed patients, and unfortunately significant part of them endure relapses of this disease.[2] Increasingly advances in personalized medicine and new therapeutic proposals depend upon assessing genetic mutation status to provide an appropriate and assertive treatment decision. The necessity of understanding prognostic and predictive factors and assessing hereditarian information is well known, especially in light of new and promising target therapies for epithelial ovarian cancer (EOC).[3]

Oncology guidelines have been often revised to contemplate precision medicine advances and include genetic testing criteria (including *BRCA* gene testing) for ovarian cancer and genetic counseling recommendation in a movement to evaluate genetic risk assessment.[4,5] However, there are few accurate data about *BRCA* mutation testing recommendation in clinical practice for advanced OC patients. Recent clinical trials showed the importance of earlier treatment on OC *BRCA* mutated patients, bringing awareness about the right time of testing recommendation for better decisions concerning patients' treatment choices.[3,5]

Thus, assessing information about the genetic background in OC patients allows the medical community better to understand cancer risk and predictive and prognostic factors, leading to better decisions. In this context, understanding the mutation prevalence is critical. However, most of the available data about population genetic mutation come from clinical trials and epidemiologic researches, and few data are available showing real-world results from the clinical scenario. Nonetheless, few data are available showing the introduction of genetic testing as a biomarker during patient diagnostics in the context of clinical practice. In a scenario where everything is new, there is always missing some puzzle pieces.[2,7,8,10,11]

Thus, this work aimed to discuss genetic testing recommendations in Brazil's clinical practice, bringing information about the actual scenario of Brazilian clinical practice. Focusing on *BRCA 1/2* mutation testing for advanced OC patients, evidencing when the test is requested during the patient journey, discussing the implications of mutated patients, and the primary health care professionals that should be involved such as oncologists and where there is strong the patient history predictive of an inherited genetic mutation an oncogeneticist should be participating on this patient journey. We expect to bring to light the main concerns and barriers about genetic testing that may be guiding future medical and diagnostics education, providing a significant background to a transformation in oncology clinical practice hopping for better patient care.[12-14]

MATERIAL AND METHODS

The survey: AstraZeneca and Ipsos Brazil (a market research contractor) defined a survey to inquiry experienced Brazilian oncologists about their *BRCA* testing recommendation during OC patients' journey (Appendix I). Ipsos conducted this research upon request of AstraZeneca Brazil.

The questionnaire focused mainly on how frequently the oncologists recommended *BRCA* mutation testing when testing was requested and the main difficulties for the testing recommendation. The survey was built based on the expertise from AstraZeneca and Ipsos on oncology. Ipsos collected the answers after the physicians signed the informed consent to participate on the survey. Oncologists were randomly chosen from different regions of Brazil. The number of answers from each region was balanced. The criteria for respondent's selection included: time as oncology specialists and possible experience treating ovarian cancer, must spend at least 50% of the time in direct patient care, and must be chemotherapy prescriber.

The specialists chosen by Ipsos received an online questionnaire (duration of 30 minutes) in four different waves (wave 1: May 2018 | wave 2: September 2018 | wave 3: November October 2018 | wave 4: June 2019). Approximately 100 survey answers were expected in each wave, few physicians were kept in all waves, meaning that most of respondents were different across all waves. When this number was reached, Ipsos stopped contacting new respondents the total number of contacted physicians were not recorded. The sampling margin of error was 4.9 percentage points.

Demographic information and specific questions about the clinical practice related to *BRCA* testing for OC patients formed the questionnaire. The compiled answers were organized and described in the results section of this article and were the primary source of information for this article.

Statistical methodology: the results of time as oncologists (Table 1) is expressed in the average number of years, after medical residency, applied at the oncology specialty. The number of patients with ovarian cancer treated in the previous three months and the number of patients that received a *BRCA* testing recommendation in the private sector are expressed by the average number of reporter respondents ± standard deviation.

All other results are expressed by the percentage calculated based on the respondent's choice of answers.

Literature search: a literature search in the leading medical database, such as PubMed, Google Scholar, EMBASE, was conducted, using the combined terms, "ovarian cancer," "*BRCA* testing recommendation"; "guidelines," "treatment" "genetic counseling". The main articles and abstracts were selected and retrieved, and used as scientific background only for the discussion section.

Table 1. Respondents-demographic characteristics.

	Wave 1	Wave 2	Wave 3	Wave 4
Number of oncologists respondents	110	120	110	100
Gender-(male/female)	57/43%	54/46%	54/46%	57/43%
Time as oncologist (years)	9	10	9	9
Dedication of time (%)				
Public hospital	42	31	38	36
Private clinic	36	42	34	33
Private hospital	14	18	14	14
CACON**	8	8	13	15
University	0	1	1	1
Country region				
(Region, %*)		Southeast=56 South=26 Northeast=14 North and Center West=4		

The number of participants, percentage, the average number of years, percentage, respectively, represent the results. *Region of respondents from wave 4, missing data for w1, w2, w3. **CACON: High complexity health unity.

RESULTS

The results represent the compiled responses obtained in each wave (w), as described in the methods section. The compiled results are presented in Figure 1. The number of answers in each wave was w1=110, w2=120, w3=110, and w4=100. The oncologist's respondents were distributed in four regions of the country. Table 1 shows the demographic and gender data. The survey was answered exclusively by Brazilian oncologists, and the respondents perform their clinical practice in both the public and private health sectors. The compiled results showed that most of their time is dedicated to patients in the private care sector, including private clinics and hospitals (Table 1). Also, time dedicated in the public sector is lower, observed across all waves (Table 1).

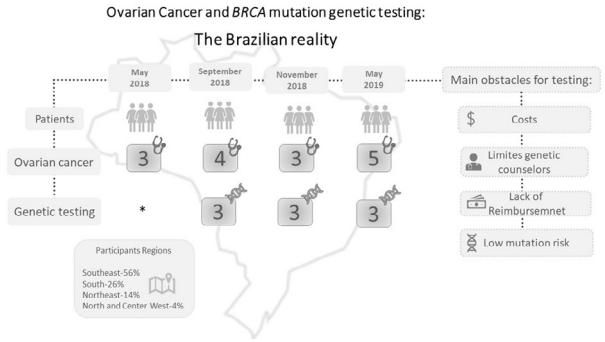

Figure 1. Main results obtained by survey responded Brazilian oncologists with the average number of patients with ovarian cancer, the average number of patients referred to BRCA mutation testing reported during the surveys, and the main obstacles pointed during the research.

Regarding OC patients, the oncologists interviewed reported that in the previous three months (starting from the moment they received the questionnaire), they were treating on average in w1=3, w2=4, w3=3, and w4=5 patients with OC. When inquired about *BRCA* testing recommendations related to their practice in the private sector, they indicated that this test was not recommended for all patients. In waves 2, 3, and 4, only an average of three patients in each wave respectively, received a testing recommendation from private institutions (wave 1 data not collected) (Table 2).

When inquired about the timing of testing recommendation, most specialists indicated that their central conduct would make the recommendation during the initial patient's diagnostic process w1=44%, w2=50%, w3=58% and there was an increase in the number of oncologists that requested the test early on initial diagnostics on w4=64%. Some respondents stated that testing recommendations would happen during the first line of treatment or chemotherapy. A reduction on wave 4 (4%) is noticeable in the *BRCA* testing recommendation later on, in a moment before the second line of OC treatment when compared to w1=9%, w2=5%, and w3=5% (Table 3).

Considering this, we went further and questioned the type of sample evaluated. The results showed that in wave 1, the first option pointed by the oncologists would be tumor testing (51%) followed by blood/saliva (35%), and only 14% would evaluate the tumor sample and check on blood/saliva to confirm mutation origin (somatic versus germline). In wave 2 (43%) of the participants pointed that they would refer patients to blood/saliva evaluation, and 43% would evaluate the tumor, and, likewise, in wave 1, 14% of answers pointed that they would recommend both blood/saliva and tumor testing.

In waves 3 and 4, most of the respondents pointed that the first option would be recommending blood/saliva testing (46% and 47%, respectively), and the second most frequent option would be tumor testing (37% and 38%, respectively). And, as observed in the previous waves, the less recommended option would be testing both blood/saliva and tumor samples (17% and 15%, respectively) (Table 4).

Considering the number of patients that received a test indication (Table 2), we inquired about the main reasons restrict *BRCA* testing for all OC patients. In a multiple-choice panel, they pointed the main barriers for testing (Table 5). The most frequent reasons for refrain *BRCA* testing recommendation in w1=36%, w2=26%, w3=18%, and w4=38% were cost associated with the exam and lack of patient's reimbursement. It is important to mention that this answer did not specify the sample type (blood/saliva or tumor tissue) (Table 5).

Another barrier associated with testing recommendation restriction was limited access to genetic counselors, 13%, 16%, 16%, and 19% in waves 1 to 4, respectively. This answer implies the oncologist recognizes the necessity of genetic counselors' involvement in OC patients' care. The time to obtain results versus the necessity for a prompt treatment decision was also mentioned as a reason not to recommend testing (w1=9%, w2=6%, w3=13 %, and w4=11%).

Some traits associated with the disease, such as low mutation risk, were also indicated as a reason for not recommending *BRCA* testing (w1=11%, w2=14%, w3=15%, and w4=11%). Patients' refusal due to family implications was also pointed as a reason for not testing patients (w1= 8%, w2=15%, w3=14%, and w4=10%) (Table 5).

DISCUSSION

In the past few decades, the main treatment for advanced epithelial ovarian cancer has been cytoreductive surgery and platinum-based chemotherapy, leaving patients with few options on this daunting disease and, consequently, very high recurrence rates.[15-17]

Table 2. Patients and *BRCA* testing recommendation.

	Wave 1	Wave 2	Wave 3	Wave 4
Average Number of patients with ovarian cancer treated in the previous three months (n)	3±4	4±3	3±4	5±5
Range (n)	1-19	1-11	1-19	1-16
Patients Distribution in Public/ private sector (%)	24%/76%	27%/73%	28%/72%	29%/71%
Average number of patients that received a BRCA testing recommendation in the private sector (n)	*	3±3	3±3	3±3
Range (n)	*	1-11	1-10	1-10

Results represent the average number of patients reported by respondents ± standard deviation. Percentage and the average number of patients reported by respondents, respectively. *Missing data for w1.

Table 3. Timing of ***BRCA*** testing recommendation for ovarian cancer patients (single choice) (%).

	Wave 1	Wave 2	Wave 3	Wave 4
During initial diagnostic (%)	44	50	58	64
After the first line of chemotherapy treatment (%)	22	30	19	19
After the beginning of treatment (%)	25	15	17	12
Before the second line of treatment (%)	9	5	5	4
Total	100%	100%	100%	100%

Percentage indicated by the sum of answers represents the results.

Table 4. Patients' proportion referred to different testing sample types (%).

	Wave 1	Wave 2	Wave 3	Wave 4
Blood/saliva (%)	35	43	46	47
Tumor (tissue) (%)	51	43	37	38
Blood/saliva and tumor (tissue) (%)	14	14	17	15
Total	100%	100%	100%	100%

Percentage indicated by the sum of answers represents the results.

Table 5. Main reason to restrict *BRCA* testing for all ovarian cancer patients (multiple choice) (%).

	Wave 1	Wave 2	Wave 3	Wave 4
The costs are restrictive	36	26	18	38
Limited genetic counselors	13	16	16	19
The test is not reimbursed	27	23	16	17
Low mutation risk	11	14	15	11
Timing for results versus the necessity of fast treatment decision	9	6	13	11
Patient does not want to know the results due to family implications	8	15	14	10

Sum of answers represents the results and respondents were allowed to choose more than one option.

The scientific and medical community is always in search of advances in cancer treatment. A recent proposal relying on genetic sequencing and target therapies allowed oncologists to be assertive about therapeutic choices. We cannot forget the importance of genetic testing. The inclusion of clinical practice is associated with preventive actions. In this scenario, the involvement of a scarce specialty, the oncogeneticist, is mandatory to compose a full therapeutic approach.[14] Since the description of *BRCA* gene mutation and the association with breast and ovarian cancers, the medical community has asked how to follow-up patients who have the mutation. In other words, the medical community miss specialists and guidance in oncogenetics.[18,19]

For a better-paved discussion on this matter, let us take a step back and refresh molecular biology concepts. Cell genetic content is susceptible to external and internal injury, leading to single and/or double-strand breaks. Double-strand breaks are rarer, nevertheless more dangerous, can lead to loss of genetic information, and are associated with

chromosomal instability on mitotic cells. *BRCA* genes (encode proteins) act on genes double-strand break repair, presenting antitumor growth properties.[20]

Homologous recombination repair (HRR) is a complex repair mechanism that prevents DNA double-strand breaks and counts on *BRCA* gene action.[21,22] Deficiency in (HRR) is one hallmark of cancer, and it is linked to some tumor types, including epithelial ovarian cancer.[23,24]

The poly (ADP-ribose) polymerase (PARP) enzymes also participate in mechanisms that maintain DNA integrity. New therapeutic approaches, with PARP inhibitors, provide an option for OC treatment. The mechanisms of action rely on inhibiting DNA repair, specifically single-strand breaks. Those defects will be accumulated and, in an environment where another genetic deficiency in homologous recombination repair is already present, such as observed in *BRCA* gene mutation, there is a lack of double-strand breaks repair. This sum of defects will lead to cell death and antitumor activity due to the accumulation of DNA defects (one basal and a second introduce). This mechanism is described as synthetic lethality.[24,25]

Enough of molecular biology. Let us explore new horizons. Recently, with the proposal of targeted therapies, such as PARP inhibitors, a new horizon for EOC treatment arose.[24,26] However, in some of those new targeted therapies, genetic testing can be required as a biomarker to identify those patients who would benefit from this treatment, introducing the necessity of genetic diagnostics, such as *BRCA 1/2* mutation testing, on the patient journey.[3]

Traditionally the assessment of *BRCA* mutation has been required in the clinical practice to identify patients' family members who are at higher risk of cancer development and can benefit from genetic counseling. Nonetheless, the medical community identified a difficulty associated with the limited number of genetic counselors, and some new methods are being proposed to fill out this gap.[13,14]

The sample type used to assess patients' *BRCA* status raises some implications and bring knowledge about the mutation origin. Testing the tumor will bring information only about the tumor environment, and this result will possibly guide the oncologist's treatment decision. On the other hand, testing the patient's blood/saliva (germline) will open a different knowledge level and bring implications to patients' families due to the hereditary associated with this genetic background.[5]

Do we need to test? Are there many patients that justify that?

A recent study evaluated the prevalence of *BRCA* mutation in the recently diagnosed OC Brazilian population. The results demonstrated that one in four patients (26,7%) had a *BRCA1 or BRCA2* gene mutation. They considered mutation found in the tumor and subsequently verified that 63% had a germline origin). Moreover, 14,8% had a somatic mutation. This data reinforces the importance of testing recommendations due to the frequency of *BRCA 1* and *2* gene mutation in the Brazilian population.[10,11]

Recent clinical trials have shown that patients with *BRCA* gene mutation may benefit from PARP inhibitor therapy, but some other trials bring data about other genes and diagnostics methodologies to identify patients.[6,24] Thus, the advances in medicine and diagnostics with gene sequencing allowed the adoption of *BRCA1* and *BRCA2* genes as a biomarker, beyond of assess family risks and bring relevant information for patients with breast cancer or OC. Testing allowing oncologists to predict patients that would benefit from PARP inhibitors therapy.[13,27]

Hence, in this work, we decided to inquiry oncologists, mapping the genetic testing recommendation in Brazil during a year, in four different periods referred to as waves.[12] This work's main objective was to report the *BRCA* gene testing recommendation in the context of Brazilian reality by oncologists, understand the sample of choice, and discuss the main concerns for *BRCA* gene testing, which may be guiding for future medical and diagnostic education.

What is being done from a clinical practice perspective?

The oncologist's respondents were well distributed in Brazil regions per previous studies showing medical and demographic distribution. Some criteria such as time as oncologist specialist, gender, experience in OC treatment, and dedication time in the public versus private health sector were considered. The number of answers distributed in each country's region reflects its medical demography.[28,29]

The data pooled from the four waves during a year showed that the oncologists' respondents reported that they treated in average 3 to 5 (range 1-19) patients with OC in the previous three months from the survey response and eventually only 3 (range 1-10) patients received their recommendation to testing *BRCA* mutation. In the meantime, concerning wave 3 and wave 4, there was a release and approval for a PARP inhibitor as maintenance therapy for patients recently diagnosed in the country; we did not notice an increase in testing recommendation due to this approval.

A survey conducted in Hong Kong showed that *BRCA* testing rates could be as low as 28% of the recommendation for OC patients, highlighting that the medical community should have a better agreement and consensus on *BRCA* genetic testing for those patients. Another recent work that analyzed retrospective data showed an increasing trend to refer patients with ovarian cancer to be tested, but it is consensus that the reality is far from ideal.[12,30]

Another critical subject is about the timing for testing. Genetic testing results can take few weeks to months to be released, being time-consuming. Considering the importance of this data to oncologist's treatment

decisions, we proceeded to inquire when the test recommendation was made, with a single choice answer about *BRCA* gene testing timing during OC patients' journey.

Surprisingly, most of the respondents acknowledged that they recommended *BRCA* gene testing during the initial diagnostic period, and an increase in wave 4 to 64% of respondents that made the testing recommendation in this period was noted when compared to the previous waves (w1=44%, w2=50%, and w3=58%). We believe that the positive result of clinical trials with maintenance PARP inhibition may have influenced their decision and changed their clinical practice, bringing a testing recommendation to an early period. Although we evidence this movement, it is clear that testing recommendations must be more homogeneous between specialists that treat OC.[3,17] However, many respondents have reported testing later during OC patients' journey, w1=25%, w2=15%, w3=17%, and w4=12%. This result would indicate testing after the beginning of OC treatment. In particular, these results let us question what might influence the oncologist's decision to delay patients testing. A recent study pointed to the lack of local evidence as a factor for broadening genetic testing, highlighting the absence of association of family history of pancreatic cancer, prostate cancer, and breast cancer in the local population as a predictor risk for OC. Thus, local epidemiologic data may convince local oncologists and influence guidelines for OC *BRCA* testing.[12]

Most respondents would recommend testing blood/saliva or tumor separately. In all waves, the sample of choice would be blood/saliva evaluating *BRCA* germline mutation. This kind of sample brings information about hereditary mutation and has an impact on information about family background. In this case, according to international guidelines, the involvement of a specialist in oncology and genetics would be required to make proper genetic counseling.[31]

Oncologists need to partner with specialists in oncogenetics. Inherited genetic alterations are associated with cancer are estimated in about 5% to 10% of all tumors. Considering this scenario, it a consensus that a genetic counselor's involvement in these cases has a crucial role in family at-risk evaluation, subsequently providing counseling on preventive actions. Thus, assessing germline mutations is mandatory to provide proper patients and families' assistance.[8]

The second most frequent option was testing the tumor (tissue) sample. When starting with a tumor (tissue) testing, both somatic and germline *BRCA* mutation can be detected. A growing body of evidence shows that starting testing by the tumor would be more cost-effective due to a possible improvement in efficiency by referring only patients with a tumor *BRCA* mutation to further blood/saliva testing to verify a possible germline mutation rather than all patients with OC.[12] It is essential to mention that this approach is a challenge due to the lack of coverage by the private health care providers for tumor testing in the Brazilian reality.[12,32]

Contrary to tumor testing, a recent guideline from ASCO (American Society of Clinical Oncology) stated that germline testing should be performed first, and only in negative mutation results, the tumor test should proceed, showing once more lack of consensus.[5]

The respondents were also asked why the oncologists would not recommend *BRCA* genetic testing in a multiple-choice questionnaire. In all waves, the answers related to patient's reimbursement and testing cost were the main concerns. In Brazil, two main initiatives govern health care: private and public. In the public sector, the Unified Health System or SUS (*Sistema* Único *de Saúde*) presents a very restrictive reality regarding new technologies and diagnostics assessment.[28]

In contrast, the private sector provides broader health access to the insured patients, and periodically the National Supplementary Health Agency (ANS) revises health procedures that should be covered by private health plans.[33]

For germline *BRCA* genetic testing, ANS has a statement declaring that all patients with EOC should have the *BRCA* testing covered in Brazil. Thus, in the private sector, the test should be covered by private health care plans, and the patients should receive genetic counseling as well. It is critical to mention that only approximately 25% of the Brazilian population has private health insurance coverage. Moreover, emerging data brought the discussion that testing ovarian cancer patients to detect BRCA mutation is cost-effective, and in a long-term perspective, it may reduce deaths and cancer treatment burden.[34,35]

Despite this advance from ANS regulation for the private health care sector, further steps are acknowledged as required for all patients to get the testing covered.[31]

The lack of genetic counselors was also mentioned as a reason for not recommending genetic testing. Some brazilian services are reference on genetic counseling, and a great effort is made to give proper genetic counseling. However, considering the country dimension, the number of professionals specializing in genetic counseling for oncologic patients is still deficient.[8]

In Brazil, genetic counselors are scarce, presenting as a bottleneck. The main reasons for this incipiency are the few medical specialization programs available in the country and the concentration of professionals in southeast and south regions of the country.[14]

There are numerous other obstacles to overcome. Some of them are associated with genetic testing, including the bureaucracy associated with reimbursement, from the moment of requesting

until getting the result report released. The entire process is time-consuming, and there is no clear description of patients on how to get tested. In high-income countries, the timing for schedule an appointment with a genetic counselor can be 12 to 15 weeks, showing that assess to this professional is a challenge in time and number of professionals to be overcome in our country and worldwide.[8,14,29,31] As *BRCA* testing has a significant predictive value for OC patients' treatment decisions, straightforward strategies should be studied parallel with genetic counselors' training in low and middle-income countries, in line with high-income countries' experience.[14] Low mutational risk and some patients' trait cancel testing necessity were less frequent options pointed as reasons not to recommend testing. The prevalence of *BRCA* mutation in the OC population is 14%, and more recent data revealed that in the Brazilian population with the prevalence in high serous ovarian cancer patients is 26%. Thus, the frequency of mutation is high and could be predictive of disease outcome and guide treatment decision, reinforcing that *BRCA* gene testing should be recommended to guide OC better treatment decision.[14]

These answers let us think that medical education and more effective guidelines would be required for professionals that treat OC once the recent data proved that the *BRCA* mutation frequency is high on our population and there is a better care option for treatment available.[10,11,36,37]

CONCLUSION

Our work showed that in the Brazilian reality, *BRCA* gene testing had not been recommended for all patients with advanced ovarian cancer in Brazil, and it has not improved within the study time frame. Despite new promising OC therapies and medical community efforts, our reality is far beyond ideal in genetic testing. There is a striking discrepancy in healthcare sectors and a lack of consensus in terms of genetic testing. Actions such as medical education, testing affordability, and new proposals for genetic counseling may gradually improve oncologists' clinical practice aiming for better care to ovarian cancer patients.

CONFLICT OF INTEREST

DCO, LM, ALM, GC, AA work for AstraZeneca Brazil.

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DECLARATIONS

ETHICS APPROVAL

No institutional ethics approval was required.

CONTRIBUTIONS

All authors approved the final manuscript version and organized the data, designed and analyzed the manuscript.

Ipsos do BRASIL conducted the survey. DCO was the medical writer.

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APPENDIX I. SURVEY QUESTIONS.

Survey questions – Table 1
1. What is your main medical specialty? Please indicate the one you invest most of your time in (single answer).
2. How long have you been practicing this specialty? (Single answer). Please indicate the number in years considering the residency period.
3. What is your gender? (Single answer). Female Male
4. Please indicate the % of the time you dedicate to each type of service below. Public hospital Private clinic Private hospital High complexity oncology service (CACON) University
5. In what region of the country do you provide your health assistance? Please choose one of the options below (single answer). Question included only in wave 4. Northeast South South East North and Center west

Survey questions – Table 2
1. In the previous three months, how many patients did you treat with ovarian cancer? Please indicate the number of patients.
2. Of those patients, how many were from the private/public health sector?
3. From those patients treated in the private sector, how many received BRCA testing recommendations? Please indicate the number of patients.

Survey question – Table 3
1. At what moment do you recommend BRCA Testing for ovarian cancer patients (primary conduct)? (Single answer). Please choose one of the option bellows. During initial diagnostic. After the first line of chemotherapy treatment. After the beginning of treatment. Before the second line of treatment.

Survey question – Table 4
1. Considering the patients that receive BRCA testing recommendation. What type of samples do you usually request? (Single answer). Blood/saliva Tumor (tissue) Blood/saliva AND tumor (tissue)

Survey question – Table 5
1. What is the main reason to restrict BRCA testing recommendation for ovarian cancer patients from diagnostic to any moment of treatment? Please choose the answer(s) that you agree most with. The costs are restrictive. Limited genetic counselors. The test is not reimbursed. Timing for results versus the necessity of fast decision on treatment decision. Some patients' traits cancel testing necessity in all patients. Patients do not want to know the results due to family implications.