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FLABRA, frontline approach for *BRCA* testing in an ovarian cancer population: a Latin America epidemiologic study

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Aim: FLABRA evaluated the prevalence of *BRCA* mutations, genetic counseling and management approaches in patients with ovarian cancer in Latin America. **Patients & methods:** Patients with ovarian cancer from six Latin–American countries were enrolled. Tumor samples were tested for *BRCA* mutations (*BRCA^{mut}*). In cases with *BRCA^{mut}*, blood samples were analyzed to determine germline versus somatic mutations. Medical records were reviewed for counseling approach and treatment plan. **Results:** From 472 patients enrolled, 406 samples yielded conclusive results: 282 were *BRCA* wild-type (*BRCA^{wt}*), 115 were *BRCA^{mut}* and nine were variants of uncertain significance. In total, 110/115 were tested for germline mutations (77 germline and 33 somatic). **Conclusion:** Tumor testing to identify mutations in *BRCA1/2* in ovarian cancer can help optimize treatment choices, meaning fewer patients require germline testing and genetic counseling, a scant resource in Latin America.

Clinical trial registration: NCT02984423 (ClinicalTrials.gov)

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Keywords: *BRCA* • Latin America • mutation testing • ovarian cancer

Although the vast majority of ovarian cancers are sporadic in origin, it is estimated that approximately 20% of ovarian cancers have mutations in *BRCA* [1]. BRCA mutation (*BRCA^{mut}*) ovarian cancer has distinct clinical characteristics, being associated with better prognosis in terms of increased overall survival compared with ovarian cancer without *BRCA* mutations and increased sensitivity to both platinum- and non-platinum-based chemotherapy regimens [2–4]. Moreover, patients with *BRCA^{mut}* ovarian cancer appear to particularly improve their outcome from maintenance therapy with PARPi, regardless of the type of previous surgery, level of resection or depth of response to chemotherapy [5,6]. Therefore, identifying those with *BRCA^{mut}* ovarian cancer as early as possible is important to optimize treatment strategies.

In ovarian cancer, *BRCA1* or *BRCA2* mutation carriers often do not have a family history of ovarian cancer and 30% are older than 60 years old [7–9]. Therefore, it is important to test for *BRCA* mutations in ovarian cancer at the earliest opportunity, at the lowest possible cost, to be able to make informed decisions on treatment course. Testing for *BRCA* mutational status can identify not only potentially inherited germline *BRCA* mutations (*gBRCA^{mut}*) but also non-inherited mutations that arise in the tumor (somatic *BRCA* mutations; *sBRCA^{mut}*). This can inform the

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need for further genetic testing and counseling within families, in addition to supporting treatment decisions, such as identifying those who would benefit from the use of PARP inhibitors.

The Latin-American (LATAM) population is a paradigm of poly-ethnicity, with a mixture of native, Spanish, Italian, Portuguese, African and Jewish ancestries leading to high genetic diversity, which complicates the ability for robust overall population-based genetic analyses [10]. The prevalence of *gBRCA*^{mut} variants in patients with ovarian cancer varies depending on the ethnicity of the population analyzed. In Latin America, the prevalence of *BRCA* mutations has not been well characterized compared with other regions [10], potentially due to limited access to affordable genetic testing [11,12]. Furthermore, there is a lack of data on the prevalence of *BRCA* variants of somatic versus germline origin [13–17]. The approach of initial tumor mutational testing may provide a cost-effective way of testing for *BRCA* mutations.

Here we report data on the prevalence of *BRCA* mutations in patients with newly diagnosed high-grade serous ovarian cancer in Latin America and describe the management of ovarian cancer, as these data are currently limited due to the lack of systematic ovarian cancer registries in these countries.

Patients & methods

The FLABRA study (ClinicalTrials.gov: NCT02984423) was a cross-sectional, multicenter, prospective, observational epidemiological study designed to evaluate the prevalence of *BRCA* mutations in newly diagnosed high-grade serous ovarian cancer patients across understudied ethnic groups in Latin America. Secondary objectives of the study were to evaluate the prevalence of somatic versus germline *BRCA1/2* mutations in newly diagnosed high-grade serous ovarian cancer patients who were identified as having *BRCA*^{mut} tumors, overall and by ethnic subgroup, and to describe current ovarian cancer counseling and treatment approach patterns (including stage at diagnosis, outcome from primary surgery and first-line treatment) in the frontline setting across Latin America.

Inclusion criteria were females >18 years old with recent (within 120 days of informed consent for the study) diagnosis of Federation of Gynecology and Obstetrics (FIGO) stage III or IV high-grade serous ovarian, primary peritoneal or fallopian tube cancer, with at least twenty 10 µm slides or paraffin-embedded blocks available that were <8 weeks old. Exclusion criteria included unwillingness to sign the informed consent form, lack of reliable clinical records or biopsies and personal history of cancer other than basal cell/squamous carcinoma.

In the screening visit, consecutive eligible patients were invited to participate, and after providing informed consent, provided ethnicity and cancer family history information. Patients were assigned to one or more defined broad ethnic groups: native American, Afro-Caribbean, European and its combinations (including 'Mestizos', meaning that they neither identify fully with any indigenous culture or with a particular non-indigenous heritage, but rather identify as having cultural traits and heritage that is mixed by elements from indigenous and European traditions; and 'Mulatos', meaning that they identify with a mixture of European and African heritage), based on self-reported ancestry information. Archived tumor blocks or twenty 10 µm sections from eligible patients were requested from the local pathology lab and used for *BRCA* mutation testing.

The algorithm used in this study first determined *BRCA1* and *BRCA2* mutational status in tumor tissue (*tBRCA*). Testing for *BRCA1/2* mutations was performed at Myriad Genetics Laboratories, Martinsried, Germany, using a fully validated method, approved by the US FDA for *BRCA* breast cancer analysis (Myriad Tumor *BRCA* Analysis). Mutational status of *BRCA1* and *BRCA2* was determined using next generation sequencing, preceded by a target-enrichment strategy to sequence coding exons (22 in *BRCA1* and 26 in *BRCA2*) plus adjacent regions. Upon receipt of the laboratory tumor test results for *BRCA*, patients were assigned to either the tumor *BRCA* mutant (*tBRCA*^{mut}) or wild-type BRCA (*tBRCA*^{wt}) cohorts. For those patients where a pathogenic or likely pathogenic variant was found in tumor tissue, the result was considered *tBRCA*^{mut} and a confirmation in blood was performed using 'single-site' *BCRA* testing confirming whether the variant was from germline or somatic origin.

During the follow-up visit, results of the tumor *BRCA* test were communicated to the patient, and information about counseling approach and surgical outcomes and treatment plan was recorded. For patients with *BRCA*^{wt} ovarian cancer, this was the last visit for this study. For patients for whom a *BRCA* mutation was identified in tumor samples, a further visit was scheduled to inform them of their germline mutation results (Figure 1).

It was expected that the median prevalence of *BRCA*^{mut} in newly diagnosed ovarian cancer patients would be between 15 and 25%, with 20% considered most likely *a priori*. A total sample size of approximately 480 patients was therefore calculated to provide 20% prevalence with accuracy of 95% for the primary objective and analyses in ethnic subgroups. Therefore, approximately 480 patients were planned to be screened for this study, across approximately 50 sites in Argentina, Brazil, Colombia, Mexico, Peru and Panama (with Panama and Peru

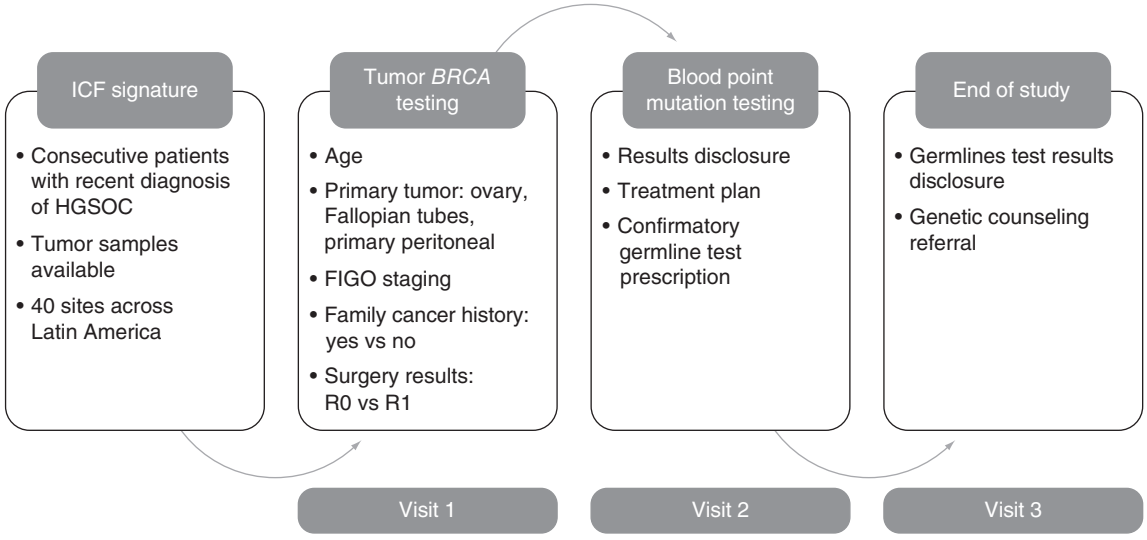

Figure 1. Study design.
FIGO: Federation of Gynecology and Obstetrics; HGSOC: High-grade serous ovarian cancer; ICF: Informed consent form.

considered a cluster). The study was performed in accordance with Declaration of Helsinki principles and all local ethics guidelines were adhered to.

Statistical analyses

For CIs, 95% was set using the Wilson/Brown method. Nonparametric, one-tailed *t*-tests with Wilcoxon's sub-analysis were performed to study the association of family history and pathogenicity analysis. One-way ANOVA for repeated measures without assuming normal distribution was used for inter-country comparison. Statistical analysis was performed using GraphPad Prism version 8.0.1 for Windows (GraphPad Software, CA, USA).

Results

Demographics & patient disposition

From January 2016 to April 2019, 472 patients with a recent diagnosis of high-grade serous ovarian cancer were enrolled in this trial from 40 sites from six different countries in Latin America. Data from 471 patients were used for this analysis, following exclusion of one patient due to endometrioid histology. Mean age at diagnosis was 57.8 years (standard deviation: 12.1; Table 1). A total of 76% of patients presented with stage III disease, 60% had a family history of cancer and 7% had a personal history of cancer. Nine patients were excluded from the analysis because their samples did not meet the histologic criteria (one endometrioid carcinoma and eight undifferentiated adenocarcinoma not otherwise specified). A further 52 were rejected due to poor DNA load (<20% tumor nuclei).

Prevalence of *BRCA* mutations in tumors

Out of 411 tumor samples tested for $tBRCA^{mut}$, the results from five were considered as inconclusive while 406 yielded a conclusive result. Of these conclusive results, 282 (69.4%) were wild-type or non-pathogenic variants ($tBRCA^{wt}$), 115 (28.3%) were pathogenic or likely pathogenic ($tBRCA^{mut}$) and nine (2.2%) were variants of uncertain significance (VUS) as shown in Figure 2 (stratified by country). Further information on mutation type by country and by ethnicity, and family history analysis by tumor mutation status is shown in the supplementary materials. Nomenclature of variants of uncertain significance is depicted in Supplementary Table 2.

Germline *BRCA* mutations

Of the 115 patients with pathogenic or likely pathogenic $tBRCA^{mut}$, 110 were tested at the germline level to confirm the germline origin of the specific variant found (a total of 5 patients did not complete germline testing due to lack of interest or loss of follow-up). Of those 110 patients, 77 had a germline mutation (19% of all evaluable samples) while in 33, mutations were not found at the germline level, so were identified as purely somatic in origin.

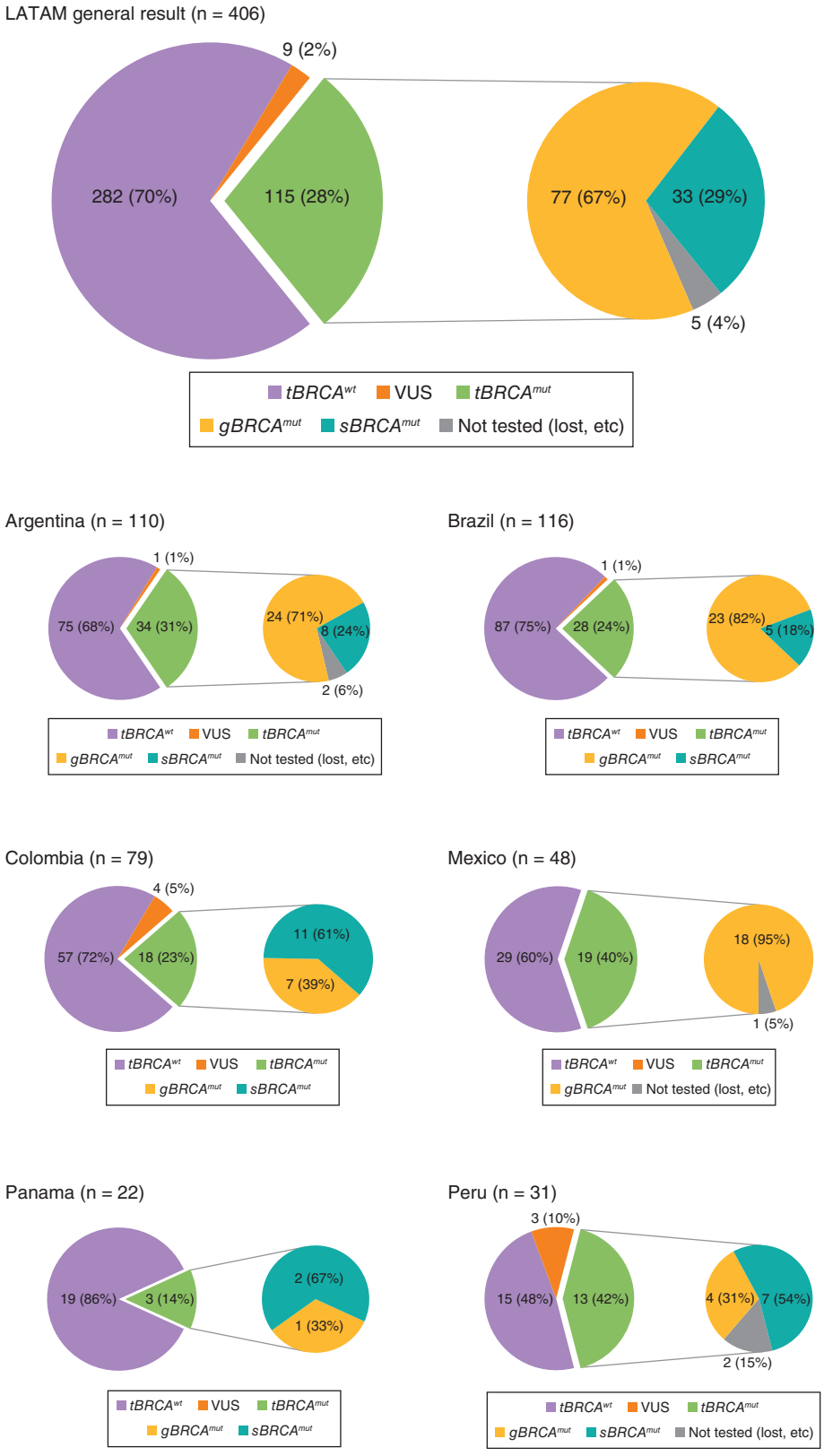

Figure 2. Prevalence of *BRCA* mutations in the total 406 evaluable patients and by country.
gBRCA^{mut}: Germline *BRCA* mutation; *sBRCA*^{mut}: Somatic *BRCA* mutation; *tBRCA*^{mut}: Tumor BRCA mutation; *tBRCA*^{wt}: Tumor BRCA wild-type; VUS: Variant of uncertain significance.

Table 1. Baseline characteristics.

Characteristic	Arg (n = 120)	Bra (n = 133)	Col (n = 97)	Mex (n = 56)	Pan (n = 27)	Per (n = 38)	Total (n = 471)
Age, mean (SD)	57.8 (12.2)	59.6 (12.1)	58.3 (11.9)	52.3 (10.9)	59.6 (11.4)	57.3 (12.3)	57.8 (12.1)
Ethnicity, n (%):							
– Afro-Caribbean or Black	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	3 (0.6)
– European or Caucasian	93 (77.5)	74 (55.6)	2 (2.1)	0 (0.0)	1 (3.7)	0 (0.0)	170 (36.1)
– Mestizo	24 (20.0)	22 (16.5)	78 (80.4)	55 (98.2)	24 (88.9)	35 (92.1)	238 (50.5)
– Mulato	1 (0.8)	14 (10.5)	13 (13.4)	0 (0.0)	0 (0.0)	2 (5.3)	30 (6.4)
– Native American	1 (0.8)	12 (9.0)	4 (4.1)	0 (0.0)	0 (0.0)	1 (2.6)	18 (3.8)
– Others	1 (0.8)	9 (6.8)	0 (0.0)	1 (1.8)	1 (3.7)	0 (0.0)	12 (2.5)
Histopathology, n (%):							
– HGSOC	116 (97)	133 (100)	92 (95)	56 (100)	27 (100)	37 (97)	461 (98)
– Other histology/missing	4 (3)	0 (0)	5 (5)	0 (0)	0 (0)	1 (3)	9 (2)
Surgery type, n (%):	n = 102	n = 90	n = 79	n = 29	n = 14	n = 33	n = 347
– Interval cytoreductive surgery	13 (12.7)	3 (3.3)	7 (8.9)	1 (3.4)	2 (14.3)	0 (0.0)	26 (7.5)
– Primary cytoreductive surgery	89 (87.3)	85 (94.4)	72 (91.1)	28 (96.6)	11 (78.6)	33 (100)	318 (91.6)
– Secondary cytoreductive surgery	0 (0.0)	2 (2.2)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	3 (0.9)
Cytoreductive surgery outcome, n (%):	n = 102	n = 84	n = 80	n = 29	n = 14	n = 33	n = 342
– No gross residual disease	44 (43.1)	29 (34.5)	28 (35.0)	7 (24.1)	6 (42.9)	9 (27.3)	123 (36)
– Residual disease <1 cm	18 (17.6)	17 (20.2)	8 (10.0)	3 (10.3)	2 (14.3)	5 (15.2)	53 (15.5)
– Residual disease ≥1 cm	40 (39.2)	38 (45.2)	44 (55.0)	19 (65.5)	6 (42.9)	19 (57.6)	166 (48.5)

Arg: Argentina; Bra: Brazil; Col: Colombia; HGSOC: High-grade serous ovarian cancer; Mex: Mexico; Pan: Panama; Per: Peru; SD: Standard deviation.

Table 2. Association between pathogenicity of germline *BRCA1/2* variants with family history of *BRCA*-related cancers.

Family history of cancer	No germline mutation	*gBRCA1/2* pathogenic variant	p-value	*gBRCA1* pathogenic variants	p-value	*gBRCA2* pathogenic variants	p-value
Family cancer history, n (%):	n = 303	n = 79		n = 56		n = 23	
– No	117 (39.0)	27 (34.2)		15 (26.8)		12 (52.2)	
– Yes	186 (61.4)	52 (65.8)	0.52	41 (73.2)	0.1	11 (47.8)	0.27
Family cancer group, n (%):	n = 186	n = 52		n = 41		n = 11	
– *BRCA*-related cancers	97 (52.7%)	37 (72.5%)	**0.03**	32 (78.0%)	**0.01**	5 (50.0%)	0.35
– Other	87 (47.3%)	14 (27.5%)		9 (22.0%)		5 (50.0%)	
– Missing/not reported†	2	1		–		1	

P-values are comparing *BRCA* data with no mutation data.
Bold values denote statistical significance.
†Percentages are of available samples, not including missing/not reported.

Results by country are shown in Figure 2. Figure 2 shows differences (no statistical differences) among countries regarding prevalence of $sBRCA^{mut}$. The percentage of $sBRCA^{mut}$ was particularly high in Colombia (61%) and Peru (54%), while no $sBRCA^{mut}$ samples were detected in Mexico. Results by ethnicity are shown in the Supplementary data. There were no statistically significant differences in the prevalence of germline mutations between patients with or without a family history of cancer in general; however, when considering specifically a family history of *BRCA*-related tumors (breast or ovarian cancer), significantly more patients with *BRCA* pathogenic variants had a positive family history, as would be expected (p = 0.03 overall, p = 0.01 *BRCA1* and p = 0.35 *BRCA2*; Table 2).

Approach to genetic counseling

The results of the tumor analysis were discussed with the patient by their treating physician in 89% of cases, and by a trained genetic counselor in 11% of cases. For germline testing results, 18% were informed by a genetic counselor; with the majority of cases (82%) being discussed by a physician not specialized in genetic counseling.

Treatment patterns

Surgical outcomes were reported in 342 patients; 123 (36%) had R0 as an outcome (no visible residual disease), 53 (15.6%) had R1 (residual disease ≤1 cm) and 166 (48.5%) had residual disease >1 cm. In terms of first-line treatment patterns, of 418 patients who received systemic treatment, most received platinum-based chemotherapy, while 21% received bevacizumab (Supplementary Table 4).

Discussion

In an era in which precision medicine is becoming the standard of care, the rapid detection of this particular group of patients with *BRCA*^{mut} ovarian cancer has never been more pertinent. The results of the SOLO1 trial with olaparib maintenance in the treatment of *BRCA*^{mut} ovarian cancer, showed a significant ($p < 0.001$) improvement in progression-free survival versus placebo [5]. Other first-line PARP inhibitor maintenance trials showed that this subgroup of ovarian cancer appears to benefit the most from PARP inhibitor treatment [18–20]. For this reason, it is important that initial diagnostic testing includes the determination of patients' *BRCA* mutational status at the somatic level and a confirmation at a germline level.

To our knowledge, this prospective, observational study is the first epidemiological study to test for *tBRCA* mutational status in a Latin–American population. We found that the prevalence of *tBRCA*^{mut} was 28%, slightly higher than the estimate that 20% of ovarian cancers have *BRCA1/2* mutations (14% germline and 6% somatic mutations) from The Cancer Genome Atlas data [1]; probably due to the mixed ancestry of the Latin–American population.

Moreover, by initially testing the tumor (*tBRCA*^{mut}), fewer patients will require a double round of testing (*gBRCA*^{mut} testing in case of *tBRCA*^{mut}) to confirm whether the mutation is germline or somatic in origin. Given the fact that most Latin–American countries suffer from a lack of resources in their healthcare system, both in terms of access to diagnostic testing facilities and genetic specialists (exemplified by only 18% of germline test results being delivered by a properly skilled genetic counselor), this pre-screening may provide a more cost-effective approach. In addition to the lack of genetic counselors, the 'guilt effect' of the *BRCA*^{mut} carrier is commonly seen in the Latin–American population [21]. This may delay testing for the *BRCA* mutation, resulting in a lost opportunity to use PARP inhibitors in first-line treatment. Starting by testing the tumor may allow the patient and their relatives to take their time to decide when and whether they want to be germline tested. Genetic counseling should be offered to every patient with a *tBRCA*^{mut} result that shows a germline origin confirmation (as in 80% of our *tBRCA*^{mut} cases) since this information may become more important to the patient's relatives. Since patients with *tBRCA*^{mut} seem to derive the same benefit from PARP inhibitors as patients with only a *gBRCA*^{mut}, not only as maintenance after first-line treatment but after platinum-sensitive relapse, this approach enlarges the population that would be eligible to receive PARP inhibitors by doing *tBRCA* compared with only doing *gBRCA* from 19% up to 28% [18–20].

Some may argue that tumor *BRCA* testing is inaccurate due to fixation artefacts, lack of enough mutational burden (lack of tumor DNA) and the inability to perform multiplex ligation-dependent probe amplification in tissue [22], but this is the technique that has been used in recent first-line PARP inhibitor maintenance Phase III trials (*tBRCA* testing, by the tumor Myriad® test). In our study, 11% of tumor samples had insufficient DNA load. In the PAOLA 1 study, only 4.6% of tumor samples were non-informative due to low cellularity and the level of discordance between somatic and germline *BRCA* testing (*gBRCA*^{mut}/*sBRCA*^{wt}) was only 0.4% [23]. Knowing the *BRCA* mutational status is a need right from the beginning of treatment for all ovarian cancer patients. In fact, more recent tests of homologous recombination deficiency include sequencing of *BRCA1* and *BRCA2* as part of the study and therefore *BRCA* mutational status remains recommended to allow treatment optimization [18–20,24].

The study also highlights some of the aspects we need to improve in order to optimize the management of ovarian cancer in Latin America, including the 36% of patients with R0 surgical outcomes and only 18% of germline tests being delivered by a genetic counselor. Additionally, this study was run in a centralized laboratory outside of the region due to the lack of validated laboratories performing validated *BRCA* sequencing in tumor tissue. We have to overcome these, among other hurdles, to provide patients with ovarian cancer with the best treatment choices available, by practicing biomarker-driven precision medicine. We did not find any difference regarding prevalence of *sBRCA*^{mut} versus *gBRCA*^{mut} between countries, potentially due to an insufficient sample size in some countries. There was also no association between personal/family history of cancer and presence of a *tBRCA* mutation, which reinforces the idea that every patient with ovarian cancer should be tested regardless of family history, personal history or age.

Conclusion

This approach of starting testing with analysis of tumoral *BRCA* status not only enlarges the population who might benefit the most from PARP inhibitor maintenance but also means fewer patients require germline testing and eventually genetic counseling, a resource that seems to be very scarce in Latin America. Therefore, this approach may result in a more cost-effective way to test and counsel our patients. As standardization of *tBRCA* testing technology and sample handling improves, this may become the standard way to test for *BRCA* mutation in recently diagnosed serous ovarian cancer patients in the coming years.

Summary points

- Around 20% of ovarian cancers are associated with *BRCA* mutations; these cases often have a better prognosis and particularly benefit from poly(ADP)-ribose polymerase inhibitors.
- Prevalence data of *BRCA* mutations in the Latin–American (LATAM) population are scarce.
- FLABRA evaluated the prevalence of *BRCA* mutations and the use of tumor testing followed by germline testing in $tBRCA^{mut}$ cases in Latin America.
- Patients' medical records were reviewed for data relevant to medical history, diagnosis, counseling approach and treatment plan.
- From December 2016 to April 2019, 472 patients from 40 centers across six different LATAM countries were enrolled.
- A total of 406 samples yielded conclusive results: 282 patients were $tBRCA^{wt}$, 115 were $tBRCA^{mut}$ (pathogenic or likely pathogenic) and nine were variants of uncertain significance.
- Of the 115 $tBRCA^{mut}$, 110 had blood tests for germline confirmation (77 germline and 33 somatic).
- Only in 18% of cases was the result of the germline *BRCA* test disclosed by a genetic counselor.
- As secondary objectives we found that overall: 125 (36%) and 268 (64%) were rendered R0 or R1 respectively after primary cytoreductive surgery. Adjuvant therapy was platinum-based chemotherapy in 92% of patients. Only 18% used bevacizumab as part of first-line treatment.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2020-1152

Author contributions

All authors contributed to the conception/design of the work or acquisition, analysis or interpretation of the work and reviewed and approved the manuscript.

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Financial & competing interests disclosure

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Ethical conduct of research

The study was performed in accordance with Declaration of Helsinki principles and all local ethics guidelines were adhered to.

Data sharing

Clinical trial registration number: NCT02984423. Individual, de-identified participant data is available, including data analyzed in tables as supplementary material (ethnicity, treatment) and the study protocol. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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