FLABRA, Frontline approach for BRCA testing in ovarian cancer (OC) treatment naïve population. A Latin America (LA) Epidemiologic Study

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Background: The majority of OC cases are sporadic, but it is estimated that in 17%, germline mutations in BRCA1 or BRCA2 genes can be identified. BRCA mutated OC has distinct clinical characteristics, increased sensibility to platinum and non-platinum agents, and to DNA damage repair (DDR) targeting agents like PARP inhibitors., which as maintenance therapy after platinum-sensitive relapse, have demonstrated the greatest benefit in this BRCA mutated population. Additionally, somatic BRCA mutations could be identified in patients not harboring germline mutations. The prevalence of germline BRCA mutations (gBRCAm) and somatic mutations (sBRCAm) has been well characterized in different populations, LA population is a paradigm of poly-ethnicity, with a mixture of native, Spanish, Italian, Portuguese and Jewish ancestries, where prevalence of germline, but especially somatic BRCA mutations in OC, has not been studied. Furthermore, somatic testing as first step may be a new option in BRCA testing algorithm that could avoid the necessity for double testing (gBRCA, then sBRCA testing) ,in case of gBRCAm negative result.

Methods:
FLABRA is a cross-sectional, multi-center, study designed to determine the prevalence of sBRCAm in newly diagnosed OC patients versus gBRCAm, and as secondary end points to describe different treatment approaches at front line in LA, and current OC genetic counselling. 480 patients from Argentina, Brazil, Colombia, Mexico, Peru and Panama, diagnosed with OC within the last 120 days will be invited to participate. Archived tumor blocks will be used for sBRCA testing (Myriad Tumor BRACAnalysis CDx™). In sBRCA positive patients, blood samples will be analyzed to determine wether the mutation is germline or somatic in origin. In gBRCAm, genetic counseling is advised. Patients medical records will be reviewed for data relevant to medical history, surgery results, treatment approach and genetic counseling.

Study Objectives
Primary objective of the study is:
- To estimate the prevalence of sBRCA 1 and 2 mutations identified in newly diagnosed ovarian cancer patients in LATAM population

Secondary objectives are:
- To estimate the prevalence of gBRCAm in newly diagnosed ovarian cancer patients who have a sBRCA mutation, in LATAM population
- To collect information about stage at diagnosis, outcome of primary surgery and first line treatment
- To describe genetic counseling approach in this group of patients

Study Design
Visit 1 (screening):
Eligible patients (HGSOC) will be invited to participate, and **after informed consent,** data will be collected regarding ethnicity and cancer family history. Medical records will be reviewed for data like stage at diagnosis, basic demographics, type of surgery and its results.
Tumor samples from the local pathology lab will be sent for s*BRCA*m testing providing standards of quality are met

Visit 2 (test results 1):
BRCA test results will be informed to the patient
Patient medical records will be reviewed for data relevant to **planned treatment strategy and surgery outcomes.** In case patients are sBRCA mutated, a blood sample will be used for gBRCA testing. gBRCA mutated patients will have an additional visit for genetic counselling
No- further study-related visits are required.

Somatic tissue testing
Archived 10-µm sections tumor blocks from the diagnostic biopsy sample of patients will be requested from the local pathology lab from all eligible patients who sign the ICF. Samples will be processed centrally for sBRCAm testing (Myriad Tumor BRACAnalysis). Genotypes of mutated samples tested will be compared to a list of known deleterious mutations. Testing for <u>sBRCA</u> mutations will be done at Myriad Genetics Laboratories

Germline BRCA testing
A blood sample will be collected from all eligible patients who were positive for sBRCA mutations and sent to Myriad central laboratory for testing the point mutation somatically identified to establish the germline vs somatic origin of the mutation. gBRCA mutated patients genotype will be compared to a list of known deleterious mutations

Results:
The estimated number of patients for the sample to be considered representative of LATAM population-is 480 subjects. We present the preliminary results with 170 patients tested (Argentina: 58, Brazil: 28 Colombia: 48, Mexico: 13, Panamá: 14 and Peru: 9**). For this first subset of patients 50/170 (29%) had BRCA mutation identified in their tumors.** From these 50 positive patients, 25 completed their germline test. 15/25 confirmed the germline origin of the mutations, while in 10 cases, the mutations were only somatic. These results are preliminary but confirm that starting with sBRCA testing enlarges the population eligible for PARP inhibitors, by detecting an additional patients that would be gBRCA negative.

	Argentina	Brazil	Colombia	Mexico	Panama	Peru
Total evaluated	58	28	48	13	14	9
Positive in tumor	21 (25%)	10 (36%)	11 (23%)	3 (23%)	1 (7%)	4 (44%)
Positive in blood gBRCA	13	3	2	1	0	
gBRCA in	13		2	1	0	
sBRCA in	2		7		1	2
negative in blood	2		7			2
Conclud-ed cases (g/s)	15 cases (13/2)		9 cases (2/7)		1 cases (0/1)	
Inconclusive/ pending blood test	6	7	2	2	0	2

Conclusions: Although preliminary, our data are in concordance with published literature (TCGA) of identifying additional patients with sBRCA mutations. This new approach may prove to be more cost effective, by avoiding a second round of gBRCA testing in–patients with sBRCA positive results. In this series preliminary analyiss we found that somatic BRCA mutations account for around 40% in LA population studied..