



# How Should Genetic Counseling for Ovarian Cancer Be Implemented in a Middle-Income Country? An Insight Based on the Brazilian Scenario

Our aim is to focus attention on epithelial ovarian cancer (EOC), a serious health problem and a burden for women in Brazil. Ovarian cancer is the seventh most common cancer among Brazilian women and one of the deadliest, with 3,320 deaths in 2014 and estimates of 6,150 new cases in 2016.<sup>1</sup> Unfortunately, in most parts of the world, 5-year survival for patients with ovarian cancer is dismal, in the range of 30% to 40%,<sup>2</sup> mainly because the disease has already reached an advanced stage at first diagnosis.

One of the main risk factors for EOC is a germline mutation in the *BRCA1* or *BRCA2* genes, which account for approximately 6% to 24% of EOC cases worldwide.<sup>3</sup> In two recent studies performed among Brazilian patients with EOC, about one fifth were *BRCA1* or *BRCA2* mutation carriers.<sup>4,5</sup> Women harboring *BRCA1/2* germ line mutations have an increased lifetime risk of EOC, with risk estimates of up to 59% for *BRCA1* carriers and 35% for *BRCA2* carriers.<sup>6</sup> Patients with EOC who are *BRCA1* or *BRCA2* mutation carriers may benefit from targeted therapies. Their healthy family members who are *BRCA1* or *BRCA2* mutation carriers may also benefit from early detection measures for breast cancer as well as from preventive measures for both ovarian and breast cancer. An additional 6% of unselected patients with ovarian cancer may have mutations in other cancer-predisposing genes such as *BARD1*, *CHEK2*, *MRE11A*, *MSH6*, *NBN*, *PALB2*, *RAD50*, *RAD51C*, *RAD51*, and *TP53*. For these reasons, a diagnosis of EOC should be considered an indication for multi-gene testing.<sup>7</sup>

In Brazil, there is a dual composite system of public and private health care, and even though one fourth of the population contributes to private health care insurance,<sup>8</sup> the remaining three

fourths depends exclusively on the public health care system, Sistema Único de Saúde (SUS). SUS was instituted in the 7th Brazilian Federal Constitution in 1988, which states that health is a right of each citizen and the duty of the state, which should guarantee universal access to health promotion, health protection, and health care. There are approximately 207,700,000 people in Brazil, which makes SUS one of the biggest public health care systems in the world. In Brazil in the twenty-first century, despite the benefits stated before, it is not common practice in the public health care system to screen women who have a diagnosis of EOC for the presence of germ line mutations, mainly because there are no facilities to perform this genetic testing.

We believe a public testing facility should be made available to offer genetic testing to all women with a recent diagnosis of EOC and we propose a model for a centralized facility dedicated to next-generation sequencing (NGS) to process samples. We think this is feasible because the costs of multigene testing by NGS are rapidly decreasing. In this model, physicians would invite all women diagnosed with EOC to have genetic testing. After obtaining a signed informed consent, the women would complete a questionnaire regarding demographic information, clinical data, and family history of cancer. A sample provided via oral swab would then be collected. All this material (accompanied by the histopathologic report) would be sent by express mail to the central facility, where a first triage would be made by health professionals to confirm the histopathology diagnosis and the indication for mutation testing. DNA would be extracted from the oral swab and analyzed through NGS by using a multigene panel to identify gene variants and also through multiplex ligation-dependent probe amplification to detect

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**Table 1. Model for a Gene Testing Facility**

Factors	Proposal and Cost Estimates
The team	We propose a dedicated team that includes seven health professionals: four biomedical or biologists or pharmacists, one oncogeneticist, and two laboratory technicians.
The facility	We propose a facility with one automated DNA extraction system, one fluorometer for DNA quantitation, one automated system for DNA quality control, one NGS system capable of analyzing at least 24 samples per day, and one capillary sequencing instrument (for MLPA and for capillary sequencing of an identified pathogenic mutation in family members).
Estimated costs	We estimate \$142.00 (USD) per patient for multigene testing: a gene panel sequencing assay (approximately \$52.00 per sample) plus reagents and flow cell (approximately \$32.00 per sample) and MLPA kit and reagents (approximately \$58.00 per sample), which adds up to \$284.00. These values do not include Brazilian import taxes or staff wages and facility maintenance.

Abbreviations: MLPA, multiplex ligation-dependent probe amplification; NGS, next-generation sequencing.

major rearrangements. A consulting oncogeneticist would review the sequencing reports and the results would be sent to the assisting physicians. Patients who are *BRCA1* or *BRCA2* mutation carriers would be referred for genetic counseling. In this model, one facility and one dedicated team specializing in molecular biology and genetics would suffice. We propose to apply a gene panel sequencing assay featuring genes that might be altered in ovarian cancer and we consider the cost of our plan to be reasonable (Table 1).

In summary, a diagnosis of EOC is strongly associated with germ line mutations. Although it is still expensive for our health care system (for comparison, the minimum monthly wage in Brazil was \$371.00 [USD] in 2016),<sup>9</sup> multigene testing of patients with EOC might greatly benefit healthy family members who carry the same gene mutation and who might adopt preventive measures to avoid cancer.

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#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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