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Editorial

Precision medicine in ovarian cancer: disparities and inequities in access to predictive biomarkers

Massimo Barberis[1], Nicoletta Colombo[2,3], Nicoletta Cerana[4]

[1] Advanced Molecular Diagnostics, Istituto Europeo di Oncologia, IRCCS, Milano, Italy; [2] Department of Medicine and Surgery, Milano-Bicocca University, [3] Oncological Gynecology Program Istituto Europeo Oncologia, IRCCS, Milano, Italy; [4] Chief Executive Officer of ACTO Italia ETS (Alliance against Ovarian Tumors)

In 2020 the Global Cancer Statistics reported that ovarian cancers are the eight most-common malignancy in females, accounting for 3.4% of all new cancer diagnoses in women worldwide [1].

High-grade serous carcinoma (HGSC) remains the most-common histotype of all ovarian cancers [2]. Unfortunately, HGSC cancer continues to be a disease that is diagnosed at an advanced stage and less than 50% of patients survive for 5 years after diagnosis in spite of improvements in treatment.

The introduction of PARP inhibitors (PARPi) in first-line therapeutic regimens of women with platinum-sensitive ovarian cancers has dramatically changed clinical outcomes, both in terms of progression free and overall survival [3-6]. Except for BRCA1/2 mutated cancers, which present the higher magnitude of clinical benefit for PARPi, this class of drugs show great efficacy also in BRCA wild type tumors with Homologous Recombination Repair deficiency (HRD). Clinically meaningful improvements reported in recent trials [5,6] have lead to the approval of PARPi alone or in combination with antiangiogenetic therapy for the maintenance treatment of patients with HRD-positive advanced ovarian cancer (Food and Drug Administration [7] in 2020, European Medicines Agency [8] in 2020, and Agenzia Italiana del Farmaco [9] in 2022).

As recently reported in European expert consensus recommendations [10] BRCA1/2 tumor assessment should be associated with the evaluation of Homologous Recombination Repair (HRR) status, as a pivotal step to extend effective PARPi treatment to the largest number of patients, considering that about 20-25% of HGSCs harbor BRCA1/2 alterations and approximately 50% are characterized by HRD [11].

With the publication of ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer HRD testing officially entered in precision medicine programs for solid tumors [11].

Since BRCA1 and 2 evaluation (alone or in combination of other genes involved in Homologous Recombination Repair) is comprised in HRD assays, it is possible to study the family history of patients carrying BRCA mutations and to identify healthy carriers of the mutation who, in 70-75% of cases, have the possibility of developing this tumor during their lifetime. From this point of view, therefore, HRD testing also represents a concrete possibility of prevention.

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Correspondence
Massimo Barberis
E-mail: massimo.barberis@ieo.it

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The Myriad MyChoice CDx assay, widely used in clinical trials [4,5] is considered the gold standard test to obtain an HRD score and candidate the patients to PARPi. Recently different studies [12-15] demonstrated the feasibility and robustness of in-house testing, showing high concordances with Myriad MyChoice CDx in terms of overall, positive and negative percent agreement.

The access to HRD testing which comprises BRCA1 and BRCA2 evaluation is the only suitable tool to prevent and improve the conditions of women with ovarian cancer. However, in Europe there are differences in the delivery of the two tests. BRCA testing is provided by the National Health Services with access criteria and reimbursement and pricing regimes that are not homogeneous in European countries.

Recently Normanno et al. reported a survey on the access on biomarker testing proposed by the International Quality Network for Pathology, the European Cancer Patient Coalition and the European Federation of Pharmaceuticals Industries and Associations; the study evaluated the access to and quality of biomarker testing across Europe [16]. The authors stated that the access to precision medicine is higher in countries with public national reimbursement processes in place. Lack of diagnostic laboratory infrastructure, inefficient organization and/or insufficient public reimbursement narrow the access to single biomarker tests in many European countries. In countries with limited public reimbursement, pharma and patients' out of pocket expenses were the primary funding sources for testing. Uptake of multi-biomarker Next Generation Sequencing (NGS) is highly varied, ranging from 0% to > 50%. Financial constraints, a lack of NGS testing capabilities and the failure to include NGS testing in the guidelines represent the main barriers to NGS implementation.

HRD testing requires high-throughput platforms combined with softwares generating complex algorithms, which are currently present only in few specialized centers. This creates a major barrier to access to these assays which, in turn, limits the potential benefits of PARPi that can only be prescribed according to the results of these tests.

To avoid inequality and limitations the National or Regional Health Care Officers should identify the laboratories suitable to perform HRD tests, depending on the type of accreditation, the performances of the instrumentations, the staff capacity and the presence of verifiable Quality Assistance and Quality Control programs.

Only a wide network of laboratories that meet pre-defined structural, organizational and operative parameters can guarantee equitable access to predictive tests throughout the European countries. The transition to ISO 15189:2022 accreditation could offer an important qualitative parameter shared among laboratories. ISO15189:22 provides for the assessment of the managerial and technical adequacy of the laboratory with respect to the entire cycle of its activities: from the request of the clinician to the verification of the impact of the laboratory in the process of prevention, diagnosis and monitoring of a specific treatment. The concept of the "Total Testing Process" is applied to verify the competence of the staff and the adequacy of the diagnostic processes in all its phases.

This is not a novelty; there is a prior clinical experience.

ESGO (the European Society of Gynaecological Oncology) has prepared a set of indicators for advanced ovarian cancer surgery and a consequent certification of hospital centers that offer optimal levels of surgical care. The certification is based on adherence to 10 quality indicators with a scoring evaluation system designed and validated by international experts [18].

To be eligible for subspecialty training a center should comply with qualitative and quantitative criteria, as defined in the ESGO Curriculum that enable the fellows to be exposed to all aspects of care of patients with gynecological malignancies (diagnostics, planning of treatment, surgical treatment, systemic treatment, radiologic treatment, follow-up, supportive and palliative care, publications and research).

Recently we collaborated with the initiative of the European Union to implement "Cancer Diagnostic and Treatment for All" [19].

Two main barriers to access to tumor biomarkers have been identified:

1 Low awareness of the benefits of biomarker testing.
   This represent a cultural problem related to difficulties of some Gynecologists, Oncologists and Pathologists in approaching precision medicine.
2 Inadequate infrastructure compounded by workforce shortage.
   Shortage of the primary care workforce represents in many European countries the most formidable challenge of the near future. The complexity of the shortage of doctors and other healthcare professionals in European primary care necessitates an urgent approach [20].

   In conclusion, we tried to demonstrate that the lesson of HRD testing and its barriers is part of the lesson of precision medicine based on biomarkers. The community of patients with ovarian cancer need optimal infrastructures to produce the test, development of specialized knowledge in personalized medicine, mobilization of resources to promote equal access to high quality assays.

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