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EDITORIAL

No more disparities among regions in Italy: recent approval of genomic test reimbursability for early breast cancer patients in the country

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Abstract
There are five BC gene-profiling tests commercially available namely Prosigna®(PAM50), Mammaprint®, Oncotype DX®, Breast Cancer Index®, and Endopredict®. The use of these tests emerge to be different among the various countries because of the disparity in clinical criterion of genomic test recommendation (e.g., presence of axillary lymph nodes involvement or not), and test reimbursement. This implies that the country where a patient lives can be a discriminant for him to be eligible for the molecular test execution. Several time ago, the Italian Ministry of Health signed the approval for genomic test reimbursability for breast cancer patients who need the evaluation of gene profile in order to establish the risk of disease recurrence within 10 years. This means less toxicities for patients and to save money avoiding inappropriate treatments. In Italy, the diagnostic workflow requires that the clinicians ask to perform the molecular test to the reference laboratory. Unfortunately, not all laboratories are equipped to perform this type of test given that specific instruments are necessary as well as specialized personnel. The establishment of criteria used to perform molecular tests in BC patients needs to be standardized, and the tests should be performed in specialized laboratories. Test centralization and reimbursement are fundamental to be able to compare the outcome of patients treated or not with chemotherapy in addition to hormone therapy to verify data from clinical randomized studies in a real-world setting.

Keywords Breast cancer · Genetic testing · Health policy

Main body

Breast cancer is by the most frequent tumor in Italy. In 2020, nearly 55,000 new cases (54,976) are estimated, in front of the colorectal (43,702) and lung (40,882) cancer. The new diagnoses of breast cancer in Italy increased 14% in 5 years, from 47,900 in 2015 to almost 55,000 in 2020 [1, 2].

834,000 women live after diagnosis, with a 5-year survival reaching 87%. However, it should be considered that breast cancer (BC) recurrence can occur up to twenty years after the initial diagnosis, especially in women with hormone-receptor-positive carcinoma. Adjuvant chemotherapy treatment, i.e., performed after surgery, reduces the risk of relapse, and the decision about whether or not to carry it out is traditionally based on the characteristics of the patient and the tumor.

Up to know, the prognosis of BC patients is defined by the use of molecular tests only on specific cases. There are five BC gene-profiling tests commercially available namely Prosigna®(PAM50), Mammaprint®, Oncotype DX®, Breast Cancer Index®, and Endopredict®. The Prosigna BC Prognostic Gene Signature Assay is based on advanced genomic technology to inform next steps for patients with early-stage BC, based on the genomic make-up of their disease. The test analyzes 50 genes known as the PAM50 gene signature, together with clinical-pathological features, to have a prognostic score indicating the probability of cancer recurrence during the next 10 years for hormone-receptor-positive early BC patients [3]. Prosigna is used to help guide therapeutic decisions so that patients receive therapeutic interventions, such as chemotherapy, only if clinically warranted. The in vitro diagnostic test is indicated in postmenopausal women with hormone-receptor-positive,

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node-negative (Stage I or II) or node-positive (Stage II or IIIA) early-stage BC to be treated with adjuvant endocrine therapy. The 70-gene signature (70-GS, MammaPrint) is a microarray-based, FDA-cleared, molecular diagnostic assay that assigns tumors into categories of high or low risk of metastasis based on the combined expression of 70 genes [4]. The 70-GS was developed independently of clinical pathology by interrogating about 25,000 genes representing the entire human genome for a gene expression signature associated with disease outcome[4] and validated in the prospective, randomized 'Microarray in Node-negative and 1 to 3 positive lymph node Disease may Avoid Chemotherapy' (MINDACT) trial. The 21-gene recurrence score (RS) assay (Oncotype DX; Genomic Health, Redwood City, CA, USA) is used to assess the BC genes related to proliferation and invasion. The 21-gene RS assay can also provide information on the risk of distant recurrence as well as the benefit of adjuvant chemotherapy [5]. The BC Index test analyzes the activity of seven genes to help predict the risk of node-negative, hormone-receptor-positive BC coming back 5 to 10 years after diagnosis. The test can help women and their clinicians to decide if extending hormonal therapy 5 more years (for a total of 10 years of hormonal therapy) would be beneficial. The BC Index reports how likely the cancer is to come back 5 to 10 years after diagnosis and if a woman is likely to benefit from taking hormonal therapy for a total of 10 years Endopredict. Endopredict is a test that based on the analyses of RNA expression of 8 target genes, 6 normalization genes, 1 control gene to provide a 12 genes molecular score which is combined with clinical features of the tumor to predict the 10 year distant recurrence rate [6]. All tests are feasible from paraffinized tissue, including Mammaprint originally developed on RNA extracted from fresh-frozen tissue. Prosigna® and Mammaprint® have been approved in the USA by the FDA. When genomic signatures, including PAM50, MammaPrint, and Oncotype DX, were tested on the same patient cohort, each test had significant prognostic value but individual risk assignments were often discordant [7]. In 2016, ASCO/CAP produced recommendations for the use of molecular gene expression profiling (GEP) tests in guiding the addition of adjuvant chemotherapy to endocrine therapy in patients with breast tumors positive for hormone receptors and negative for HER2, also considering the lymph nodal status. While for BC that express the HER2 protein and triple-negative ones, which do not have any of the receptors (estrogen, progesterone, HER2) the use of the adjuvant chemotherapy is often essential and benefit is evident, in tumors that express estrogen receptors but not the HER2 protein (ER+/HER2−), however, the advantage of adding adjuvant chemotherapy to hormone therapy is in some cases controversial. Genomic tests are an important tool for the clinician in the choice of treatment for women who, based on their pathological and clinical characteristics, are in a sort of 'gray zone,' in which chemotherapy cannot be included or excluded with certainty to hormone therapy alone. In particular, in US, the Oncotype DX® and PAM50-Prosigna® are recommendable with a high degree of evidence in ER/PgR-positive, HER2-negative BC and in tumors without lymph node metastases, while for the European guidelines, the use of tests is still discussed in tumors with 1–3 lymph node metastases and not in HER2+ or triple-negative tumors [8]. The terms of use of molecular tests were re-discussed at the 16th St Gallen conference in 2019 [6]. In particular, the Panel of Experts, based on the recent results of prospective trials, supported the value of genomic tests as a useful tool in the decision to recommend or not adjuvant chemotherapy in case of T1/T2 N0, T3 N0 tumors (1–3 positive lymph nodes). The panel noted that there is no benefit from adding chemotherapy to hormone therapy in postmenopausal patients with node-negative cancer or with limited lymph node involvement (1–3 lymph nodes) in the case of a low-risk genomic signature. This means that the use of these tests emerges to be different among the different countries because of the lack of specific and unique guidelines and the different clinical criterion of test recommendation (e.g., presence of axillary lymph nodes metastasis or not), type of genomic test used. This implies that the country where a patient lives can be a discriminant for her to be eligible for the molecular test execution. The conduction of follow-up trials is necessary and even if these trials will be performed, they will take 9 years or more to complete [9]. The most important thing is to know the follow-up of the patient after the indication of the test. However, considering that the recurrence risk among women with ER-positive BC who received Tamoxifen for 5 years or more, even a 9-year trial would not be informative. In 2017, the Superior Health Council of the Ministry of Health wrote a document "The Prescription of Multigenic Molecular Tests for BC (TMMP)," which specifies that in Italy, TMMPs are not currently included among the Essential Levels of Assistance (LEA) and, therefore, are non-refundable. They are used without specific institutional rules, but on the basis of clinical needs on individual cases and the possibility of patients to provide directly to cover the cost.

Few months ago, the Italian Ministry of Health signed the approval for genomic test reimbursability for breast cancer patients who need the evaluation of gene profile in order to establish the risk of disease recurrence within 10 years. This means less toxicities for patients and to save money avoiding inappropriate treatments for women at low risk of disease recurrence.

However, for its introduction into clinical practice as a service offered by the National Health System (NHS), it is necessary to regulate its execution, quality, and application for the protection of patients, as well as an analysis of costs with a view to an effective economic health policy efficient.

Up to now in Italy, TMMPs are available to patients in several regions (for example Emilia- Romagna, Lombardy, in the Autonomous Province of Bolzano, Tuscany etc.) and in some point-like areas. Despite the recent approval of BC genomic test reimbursement, several months are necessary to render the tests available for patients in all Italian regions. This implies that if a clinician needs to perform the genetic test in other regions or the institute or the patient has to pay.

This means that if the genetic test is not performed, the patient could receive a chemotherapy improperly with costs and toxicity that can be avoided. In Italy, the diagnostic workflow requires that the clinicians ask to perform the molecular test to the reference laboratory (with the exception of Oncotype Dx that is normally performed in US). Unfortunately, not all laboratories can perform this type of test given that specific instruments are needed as well as specialized personnel. The approval of the genetic test is an important goal, but each region must be able to perform the tests by reimbursement.

Future directions

The establishment of criteria used to perform testing in BC patients needs to be defined, and the tests should be performed in specialized laboratories with specific instruments and personnel expertise.

The accredited centers should be able to guarantee the possibility of the test execution for the whole population and with appropriate time to avoid to start the oncologic treatment with delay.

The cost of the test should include also the use of quality control (inter and intra laboratory) for the same test.

Then disparities among countries and regions on the possibility to perform tests are evident and need to be resolved.

Test centralization and reimbursement are fundamental to be able to compare the outcome of patients treated or not with chemotherapy in addition to hormone therapy and to verify data from clinical randomized studies in a real-world setting.

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