REVIEW

The Role of Multigene Assays in Adjuvant Treatment Decision for Early-Stage Breast Cancer

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Abstract

Multigene assays were developed to guide treatment in early-stage breast cancer and to evaluate the benefit of adjuvant chemotherapy. Patients with invasive breast carcinoma, either T1 or T2, N0 or N1 (one to three positive lymph nodes), with no invaded surgical margins (R0), positive for hormone receptors and negative for Her2 receptor derive benefit from these tests. The Food and Drug Administration (FDA) validated the use of the following tests: OncotypeDX (a 21 gene test), Mammaprint (70 ARN messenger genes), Predictor Analysis of Microarray 50-PAM50 (50 genes) also known as Prosigna and Endopredict (12 genes). These gene expression signatures have been increasingly used to evaluate the prognosis (such as Endopredict- that can predict outcomes more accurately than ki67 values in early-stage breast cancer) or the benefit of adjuvant chemotherapy (such as Oncotype DX). For the moment only two assays, the 70-gene signature (MammaPrint) and the 21-gene Recurrence Score (RS) assay (Oncotype DX), are supported by prospective randomized phase 3 trials. However, all multigene assays are important tools in the identification of low-risk, breast cancer patients, for whom chemotherapy could be avoided.

Keywords: breast cancer, multigene assays, OncotypeDX, Mammaprint, Prosigna, Endopredict.

Rezumat

Testele multigenice au fost dezvoltate pentru a ghida tratamentul cancerului mamar în stadiu incipient și pentru a evalua beneficiile chimioterapiei adjuvante. Pacienții cu carcinom mamar invaziv, T1, T2, N0 sau N1 (unul până la trei ganglioni limfatici pozitivi), fără margini chirurgicale invadate (R0), pozitivi pentru receptorii hormonali și negativi pentru receptorul Her2 sunt cei vizați de aceste teste. Food and Drug Administration (FDA) a validat utilizarea următoarelor teste: OncotypeDX (testează 21 de gene), Mammaprint (testează 70 de gene ARN messenger), Predictor Analysis of Microarray 50-PAM50 (testează 50 de gene) cunoscut, de asemenea, sub numele de Prosigna și Endopredict (testează 12 de gene). Acestea sunt utilizate din ce în ce mai des în evaluarea prognosticului (precum Endopredict - care poate prezice rezultate mai exact decât valorile ki67 în cancerul mamar în stadiu incipient) sau a beneficiului chimioterapiei adjuvante (Oncotype DX). În acest moment, două teste, MammaPrint și Oncotype DX, sunt susținute de studii prospective. Toate aceste teste genetice sunt instrumente importante în identificarea pacienților cu cancer de sân cu risc scăzut, pentru care chimioterapia ar putea fi evitată.

Cuvinte cheie: Cancer mamar, testări multigenice, OncotypeDX, Mammaprint, Prosigna, Endopredict.

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INTRODUCTION

Most breast cancer patients present with early-stage, hormone-receptor-positive tumors, and more than 65% receive adjuvant chemotherapy. Cytotoxic treatment can have important toxicities on both short and long-term: febrile neutropenia, cardiac toxicity, neurocognitive impairment, peripheral neuropathy. Undoubtedly, some of these patients derive little benefit from this aggressive approach. Therefore, selection methods by which physicians can select the subgroup with most benefits are necessary[1,2].

In an attempt for this selection, the genetic profiles of hormone-positive, Her2 negative, early-stage breast cancer have been analyzed and some genetic patterns were observed. To test these patterns, multigene assays were developed with the purpose to better predict individual risk. The *Food and Drug Administration* (FDA) validated the use of the following tests: OncotypeDX (a 21 gene test), Mammaprint (70 ARN messenger genes), Predictor Analysis of Microarray 50- PAM50 (50 genes) also known as Prosigna, Endopredict (12 genes)[3].

These tests are useful in patients with invasive breast carcinoma, either T1 or T2, N0 or N1 (one to three positive lymph nodes), with no invaded surgical margins (R0), positive for hormone receptors and negative for Her2 receptor[4]. MammaPrint is one exception, it can also be used for hormone negative early stage tumors.

MATERIALS AND METHODS

Relevant literature was identified by searching the PubMed database (https://www.ncbi.nlm. nih.gov/pubmed/). Search terms included: breast cancer, multigene assays, OncotypeDX, Mammaprint, Prosigna, Endopredict. Only articles written in English were included.

OncotypeDX

OncotypeDX is the first multigene assay approved by the FDA and the most used one. It consists of sixteen genes related to cancer and five reference genes. Their determination leads to the establishment of a recurrence score with certified predictive value[5].

Cancer-related genes, determined in the paraffin-embedded tissue, are related to the expression of the hormonal or Her2 receptors or are genes that encode proteins that active proliferation and invasion. After the data is collected a recurrence score is established with values from 0 to 100[6].

Several trials have assessed the predictive and prognostic value of OncotypeDX. Most of them have different primary endpoints. They were designed to predict both local and distant recurrence-free survival, survival free of invasive carcinoma, pathologic response to hormonal therapy, or time to disease progression of any kind[7,8,9].

OncotypeDX is the only multigene assay that has both predictive and prognostic significance, in comparison to the other prognostic only- tests. The test can predict response to adjuvant chemotherapy and this ability was tested in several retrospective trials and one prospective trial. Data from NSABP (*National Surgical Adjuvant Breast and Bowel Project*) B-20 trial was first used for this purpose. OncotypeDX was performed on all the paraffin-embedded samples in the trial. Patients included in this trial were early-stage breast cancer female patients, who received either CMF (cyclophosphamide, methotrexate, and fluorouracil or methotrexate and fluorouracil) and followed by tamoxifen or tamoxifen alone. The patients were then classified in low-risk with a recurrence score (RS) of <18, intermediate risk – RS between 18-31 and high risk -RS over 31. Only the high-risk patients had clear benefits from adjuvant chemotherapy. The low-risk group had no benefit from this approach. The intermediate-risk subgroup had a small, statistically insignificant benefit from chemotherapy[8].

The only prospective study involving OncotypeDX, or other any multigene assay, is the TAILORx trial, which enrolled 10273 women with early-stage, hormone-receptor-positive, Her2 receptor negative women and aimed to answer the question that was raised by all the previous, retrospective trials: is there any way to establish which subgroup of intermediate score patients has a benefit from adjuvant chemotherapy? Out of the enrolled women, 69%, n=6711 had the RS between 11 and 25 and were randomized to receive either chemotherapy or endocrine therapy. Chemotherapy regimens used included docetaxel and cyclophosphamide or anthracycline-based ones, whereas endocrine therapy consisted of aromatase inhibitors – for postmenopausal women and tamoxifen with or without ovarian suppression for premenopausal patients. The trial concluded that overall, adjuvant endocrine therapy was non-inferior to chemotherapy, but there was however a small benefit for cytotoxic therapy for women 50 years or younger, with RS between 16 and 25. This is the population where consideration for more aggressive therapy should be given[7].

The question of whether to offer adjuvant chemotherapy to patients with OncotypeDX scores between 11 and 25 remains debatable. There is however a randomized phase 3 trial that proved hormone therapy uninferior to chemo-endocrine adjuvant therapy in this setting and survival in both groups was similar (93.9% in the chemo-endocrine subgroup vs. 93.8% in the hormone therapy alone subgroup)[10].

Prosigna

Prosigna, a multigene assay based on the PAM50 risk of recurrence (ROR) score is indicated in postmenopausal patients with early-stage (T1 or T2, N1, or N1 tumors), hormone receptor-positive breast cancer. Data validating this test were derived from 2 major trials: TransATAC and ABCSG-8 that together included 1786 patients with no nodal involvement and 688 node-positive patients[11,12].

The purpose of the test was to determine the distant recurrence score at 10 years for this breast cancer population. To do this, subjects were stratified retrospectively for determining the risk cut-off. The risk was estimated for N0 patients as follows: low risk 0-40, intermediate risk 41-60, high risk 61-100. For N1 patients only 2 risk groups were developed: that used the ROR value of 40 as cut-off[13].

EndoPredict

EndoPredict is a multigene assay for early-stage breast cancer that aims to predict the risk of recurrence during the first 10 years after diagnosis. It includes 12 genes (3 proliferative genes, 5 related to hormonal receptors expression, and 4 control genes). It is slightly different from the other tests because it includes both molecular and clinical characteristics (tumor diameter, nodal status)[14].

The validation of this test was made using data from 3 trials: ABCSG-6, ABCSG-8, and TransATAC[15].

Endopredict can predict outcomes more accurately than ki67 values in early-stage breast cancer. This was demonstrated in a paper by Dubsly et al. which demonstrated that 29% of the patients with Luminal A immunohistochemical profile were reassessed as high risk after Endopredict testing and 34% with Luminal B profiles were reclassified as low risk.

The same was reported for tumor grade: 22% of patients with grade 1 tumors were reclassified as high risk and 19% of the patients with high-grade tumors were reclassified as low risk[14].

Another interesting aspect of the Endopredict assay is its presumed ability to guide the decision to prolong adjuvant endocrine therapy to 10 years. Because the patients assessed, using this multigene assay, were followed up for a long period, the prognostic value of this test can be reliable for 10-15 years. The distant recurrence-free survival rate for the patients classified as low risk was 95.7% for the first 10-15 years after diagnosis. Therefore it was extrapolated that 5 years only adjuvant hormone therapy can be safely offered to this subgroup. Longer periods of adjuvant endocrine therapy can be considered in the high-risk subgroup. These recommendations are suitable for node-positive patients as well[14,15,16,17].

Mammaprint

The 70 gene Mamma Print assay was developed to determine the risk of distant metastasis in early-stage breast cancer using gene expression analysis and was the first gene-expression signature approved by the FDA.

Mammaprint was enhanced by The Netherlands Cancer Institute, using DNA-microarray technology.

In contrast to the Oncotype DX assay, this test involves freshly frozen tumor samples or breast cancer tissues collected into an RNA preservative solution.

78 frozen tumor tissues from stage 1 or stage 2 breast cancer patients who had received standard treatment were tested at first. From the initial approximately 5000 genes included in the supervised analysis, a signature panel was created with 70 genes focused primarily on proliferation but also on invasion, metastasis, stromal integrity, and angiogenesis[18,19,20,21].

Analysis of the full genome (25 000 genes) was the first step in identifying the 70 relevant genes. This comprehensive analysis enabled the test to cover all six hallmarks of cancer and establish a link between a molecular signature and the underlying molecular mechanisms of tumor cell progression and metastasis. These six capabilities (evading apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, limitless replicative potential, tissue invasion, and metastasis and sustained angiogenesis) are shared by all most cancer genes and are predictive of metastasis development and tumor progression[22].

The 70-gene signature has been developed on several retrospective clinical trials and validated by few randomized prospective studies that compared the results obtained by using expression arrays to guide therapy to those achieved using contemporary standards for treatment decisions.

MammaPrint can classify early-stage breast cancer patients as being at either a genomic high or low risk of recurrence. A genomic low risk indicates that patients will gain no benefit from adjuvant chemotherapy[23].

MammaPrint was the first gene-expression signatures that had its clinical utility validated prospectively in a randomized phase III clinical trial (*MINDACT-Microarray In Node negative and 1-3 positive lymph node Disease may Avoid Chemotherapy*).

MINDACT was designed to answer the question of whether MammaPrint could identify patients with genomically low-risk early-stage breast cancer who could safely avoid adjuvant overtreatment and the associated toxicity. The particularity of this trial is that it also included early-stage hormone, receptor-negative patients. Another original aspect is that it evaluated the use of the MammaPrint in comparison with Adjuvant Online, an online tool using a universal algorithm for clinical risk assessment.

Between 2007 and 2011, 6.693 newly diagnosed breast cancer patients with 0-3 metastatic lymph nodes from 9 European countries were enrolled. 88.4% of the women were endocrine receptor-positive and 9.5% were HER2-positive.

Of the total number of patients approximately 50% of all patients were classified as clinically low risk, and 50% as clinically high risk, while MammaPrint identified 64% as genomically low risk, and 36% as genomically high risk.

Clinical risk assessment and genomic risk assessment were similar in 68% of all patients, with 41% clinically and genomically low risk and only 27% clinically and genomically high risk. On the other hand, there was an overall discordance rate of 32% between the two risk-assignment methods. When such discordance appeared, patients were randomized between chemotherapy or no chemotherapy.

The trial reached its' primary endpoint: to prove that among the cohort of patients with high-clinical/low-genomic risk, who did not receive chemotherapy, had a 1.5 percent lower survival rate at 5 years compared to those who did. With this insignificant difference, it can be considered safe to omit chemotherapy in low-risk patients.

In conclusion, the addition of MammaPrint to the traditional clinical and pathological factors provided important information for considering which patients might benefit from adjuvant chemotherapy. This proves the superiority of MammaPrint 70-Gene Assay in predicting the benefit of chemotherapy in early-stage breast cancer patients when compared to clinic-pathological risk assessment[18,19,20].

A similar pattern was observed in RASTER (microarray-prognostics-in-breast-cancer), a phase III observational, prospective, clinical trial that investigated the prognostic value of the 70-gene signature for distant recurrence in patients with breast cancer. This trial enrolled 427 breast cancer patients of cT1-3N0M0. Decisions on adjuvant treatment were based on the Dutch CBO 2004 clinical risk assessment or the 70-gene signature. Median follow-up was 61.6 months.

MammaPrint identified 51% of patients with low-genomic risk and 49% of patients with high risk. Using the alternative, 43% of patients in the study were clinically high risk and 57% were low risk. When compared to the Dutch CBO, the clinical risk was discordant with the prognosis signature for 30% of cases.

Adjuvant! Online was also used for the enrolled population and it identified 69% of patients with clinical high risk. Discordance with the MammaPrint occurred in 37% cases.

The five-year distant recurrence-free survival rate for low-genomic risk patients was 96.1% and 89.8% for high genomic risk. This result confirms the conclusion of MINDACT, that for low- genomic risk patient groups, it could be safe to omit chemotherapy[18].

Survival data was updated in 2017 to establish the 10 years distant recurrence-free interval (DRFI) in patients assessed with MammaPrint.

The 10-year DRFI showed an excellent prognostic value for the test: the patients with low genomic risk 93.7% vs. 86.8% for high risk, confirming the results at 5 years.

Clinical criteria assessments identified a 10-years DRFI of 91.7% in clinical low risk and 88.2% in clinical high risk.

Considering the combined genomic and clinical risk groups, the 10-years DRFI was 94.4% in patients with a clinical low/genomic low profile, and only 11.6% of them received chemotherapy. In the clinical low/genomic high group the outcome was 10-years DRFI 88.5%, and over 90% of them received chemotherapy.

The overall conclusion of the 10-years distant recurrence-free interval, confirms that patients who omitted chemotherapy based on MammaPrint low risk has a good prognosis[24].

Multigene assay use in Europe

International treatment guidelines (*St Gallen International Consensus, the European Society for Medical On-*

cology (ESMO), *American Society of Clinical Oncology* (ASCO), and *National Comprehensive Cancer Network* (NCCN)), do admit that many patients do not benefit from chemotherapy. Despite this, adjuvant chemotherapy is highly recommended when using clinico-pathological parameters such as age, tumor size, type and grade, lymph node status and hormone status. Some of these features are prognostic but not predictive of chemotherapy benefit.

Multiple studies have shown the role of multigene assays in narrowing the indication for adjuvant chemotherapy.

The worldwide Multidisciplinary Application of Genomics in Clinical Practice (MAGIC) survey is an international panel of 8 breast cancer experts from Genomic Health (Geneva, Switzerland) and TRM Oncology (The Hague, The Netherlands). The survey provides precious insight into worldwide chemotherapy recommendations for early breast cancer patients and the clinical and pathologic parameters used for these decisions.

Overall, 879 clinicians and 32 pathologists from 52 countries completed the MAGIC survey.

Of the respondents, only 54% of the practicing clinicians used multigene assays, and there was a large variation between countries. The conclusions indicate that there is an important heterogeneity in how patients are treated and a significant insecurity in treatment recommendations. Multigene assays are frequently used in Greece (91%), Germany (89%), and The Netherlands (89%), and the most currently used assays were Oncotype DX Breast Cancer Assay (78%) and MammaPrint (34%).

Despite their efficacy, multigene assays are not yet fully embedded in clinical practice and the main reason for not using them are the price, lack of reimbursement and availability.

There is a need for new pricing and reimbursement models to accelerate the adoption of these tests, and perhaps additional prognostic and predictive markers to support a more-informed treatment decisions[25,26].

CONCLUSIONS

Multigene assays represent an original approach to prognostic and predictive tumor classification.

The use of genomic testing to guide treatment decisions in clinical practice has important benefits in the selection of patients in whom adjuvant chemotherapy can be safely omitted.

Both, Oncotype DX and MammaPrint, have demonstrated efficacy for evaluation of recurrence risk in women with stage I and II breast cancer with up to 3 positive lymph nodes. These assays were created to reduce overtreatment and to guide treatment decisions for or against chemotherapy in endocrine positive patients when conventional clinical-pathological features (tumor size, lymph node status, histologic grading) are not convincing.

Consequently, multigene assays were defined as prognostic tests by measuring the risk of recurrence disease. Patients with a low gene risk have a small advantage from cytotoxic chemotherapy.

However, risk stratification according to clinical-pathological features remains crucial, but molecular assays may help the final decision when there is no clear indication for chemotherapy.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

References

1. Fisher B, Jeong J-H, Bryant J, et al. Treatment of lymph-node-negative, estrogen-receptor-positive breast cancer: long-term findings from National Surgical Adjuvant Breast and Bowel Project randomized clinical trials. Lancet. 2004;364(9437):858–68. doi:10.1016/s0140-6736(04)16 981-x.
2. Fisher B, Costantino J,et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. N Engl J Med. 1989;320(8):479–84
3. Ivana Sestak, Richard Buus, et al. Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor-Positive Breast Cancer. A Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol February 15, 2018.
4. DuffyMJ, Harbeck N, Nap M, et al. Clinical use of biomarkers in breast cancer: updated guidelines from the European Group on Tumor Markers (EGTM). Eur J Cancer. 2017;75:284-298.
5. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med. 2004;351(27):2817–25.
6. Harris LN, Ismaila N, McShane LM, Andre F, Collyar DE, Gonzalez-Angulo AM, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2016;34(10):1134–50.
7. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Prospective validation of a 21-gene expression

assay in breast cancer. N Engl J Med. 2015;373(21):2005–14. doi:10.1056/NEJMoa1510764.
8. Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol.2006;24(23):3726–34. doi:10.1200/JCO.2005.04.7985.
9. Gianni L, Zambetti M, Clark K, Baker J, Cronin M, Wu J, et al. Gene expression profiles in paraffin-embedded core biopsy tissue predict response to chemotherapy in women with locally advanced breast cancer. J Clin Oncol. 2005;23(29):7265–77. doi:10.1200/JCO.2005.02.0818
10. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med. 2015;373(21):2005–14. doi:10.1056/NEJMoa1510764.
11. Dowsett M, Allred C, Knox J, Quinn E, Salter J, Wale C, et al. Relationship between quantitative estrogen and progesterone receptor expression and human epidermal growth factor receptor 2 (HER-2) status with recur-rence in the Arimidex, tamoxifen, alone or in combination trial. J Clin Oncol2008;26:1059–65
12. Jakesz R,Jonat W, Gnant M, et al. ABCSG and the GABG Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial, Lancet, 2005, vol. 366 (pg. 455-462)
13. Dowsett M, Sestak I, Lopez-Knowles E, et al. Comparison of PAM50 risk of recurrence score with Oncotype DX and IHC4 for predicting the risk of distant recurrence after endocrine therapy. J Clin Oncol. 2013;31(22):2783-2790.
14. Dubsky P, et al. EndoPredict improves the prognostic classification derived from common clinical guidelines in ER-positive, HER2-negative early breast cancer. Ann Oncol. 2013;24(3):640-647
15. Filipits M, et al. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent prognostics information to conventional clinical risk factors. Clin Cancer Res. 2011;17(18)6012-20
16. Buus R, et al. Comparison of EndoPredict and EPclin with Oncotype DX recurrence score for prediction of risk of distant recurrence after endocrine therapy. J Natl Cancer Inst. 2016;108(11):djw149.
17. Sestak I, et al. Comparison of the performance of 6 prognostic signatures for estrogen receptor-positive breast cancer: A secondary analysis of a randomized clinical trial. JAMA Oncol. 2018 Feb 15 [Epub ahead of print].
18. William Audeh1, Lisa Blumencranz, et al. Prospective Validation of a Genomic Assay in Breast Cancer: The 70-gene MammaPrint Assay and the MINDACT Trial, Narrative Review Acta Medica Academica 2019;48(1):18-34 DOI: 10.5644/ama2006-124.239
19. Fatima Cardoso, Martine Piccart-Gebhart, et al. The MINDACT trial: The first prospective clinical validation of a genomic tool, Mol Oncol. 2007 Dec; 1(3): 246–251. Published online 2007 Oct 22. doi: 10.1016/j.molonc.2007.10.004
20. Brandão, M., Pondé, N., et al. (2018). Mammaprint: a comprehensive review. Future Oncology. doi:10.2217/fon-2018-0221
21. Ling Xin,a,b Yin-Hua Liu, et al.The Era of Multigene Panels Comes? The Clinical Utility of Oncotype DX and MammaPrintWorld J Oncol. 2017 Apr; 8(2): 34–40. Published online 2017 May 4. doi: 10.14740/wjon1019w.
22. Sun Tian, Paul Roepman, et al. Biological Functions of the Genes in the Mammaprint Breast Cancer Profile Reflect the Hallmarks of Cancer. 2010 Nov 28, Biomark Insights. 2010; 5: 129 138. doi:10.4137/BMI.S6184
23. CA Drukker, JM Bueno-de-Mesquita, el al. A prospective evaluation of a breast cancer prognosis signature in the observational RASTER study, Int J Cancer. 2013 Aug 15; 133(4): 929–936.Published online 2013 Mar 4. doi: 10.1002/ijc.28082
24. Vliek, Sonja & Retèl, Valesca & Drukker,et. al,. (2017). 10-years follow-up of the RASTER study; implementing a genomic signature in daily practice.. 10.13140/RG.2.2.35528.83200
25. Aapro M., De Laurentiis, et al. (2017). The MAGIC survey in hormone receptor positive (HR+), HER2-negative (HER2–) breast cancer: When might multigene assays be of value? The Breast, 33, 191–199. doi:10.1016/j.breast.2017.01.012
26. Matti Aapro, The Role of Multigene Assays in Addressing Treatment Heterogeneity for Breast Cancer, Clinique de Genolier, Breast Center, Genolier, Switzerland, Biomed Hub 2017;2(suppl 1):481247 (DOI: 10.1159/000481247)