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In response: Genomic profile of breast cancer

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Response to: Plun-Favreau J, Svedman C, Valentine W, Rouzier R. Genomic profile of breast cancer. Expert Rev Pharmacoecon Outcomes Res 2015;15(3):393–94

We would like to express our gratitude for the opportunity to respond to the Letter regarding the manuscript 'Genomic profile of breast cancer: cost–effectiveness analysis from the Spanish National Healthcare System perspective' [1]. We also appreciate the comments highlighted by Plun-Favreau-*et al*. related to the study, and the chance to clarify and discuss a number of points from our work.

The usefulness of economic evaluations is that they allow decisions to be rationalized according to the best available information. Models allow an estimate of the clinical and economic consequences of the use or not of a health technology, taking data from different sources. Ultimately, the goal of the model is to obtain information about a clinical problem for which all information required for decision-making is not available; however, this implies that no research is without limitations [2].

The use of publications to nourish a model of economic evaluation is common [3–8]. During the study development, no peer-reviewed research was found that would have provided an objective criterion to compare all alternatives analyzed, therefore, the best level of evidence available was included in the model.

MammaPrint® (70-gene signature) has been validated in multiple peer-reviewed retrospective, prospective, adjuvant and neoadjuvant studies [9–19], to add significant independent prognostic and treatment-predictive information. This information allows physicians to more accurately and consistently provide guidance to their early stage breast cancer patients. Its validation across a much larger breadth of patients of all age groups, independent of endocrine receptor (ER) and HER2 status, and valid in up to three positive nodes, provides clinicians with a relevant tool in the clinical setting than earlier versions of other gene-expression profiles that are limited only to the ER-positive/HER2-negative patients [20].

Differences in the classification of patients by diagnostic tests were considered in the study [5]. The 70-gene signature allows a precise binary clinical classification of either low or high risk and eliminates the ambiguity of a large intermediate group. In a recent meta-analysis, the distribution of recurrence score (RS) categories for Oncotype Dx® (21-gene assay) was 48.8% low, 39.0% intermediate and 12.2% high [21]. This proportion of intermediate RS results is nearly twofold higher than the intermediate RS reported in the original studies by Paik *et al.* [20,22], which may have implications in its clinical utility and cost. That is, the treatment decision suggested by the 21-gene assay test and its clinical and economic impact is clearer for the high and low RS patients, but less precise for intermediate RS patients. This distributional shift may induce high- or low-risk patients classified by traditional clinical-pathological approaches opting against 21-gene assay because they believe it will not change their adjuvant chemotherapy treatment decision [21].

The binary clinical classification of 70-gene signature potentially reduces undesirable clinical variation in the use of adjuvant or neoadjuvant chemotherapy.

Keywords: breast cancer • economic evaluation • genomic profile • MammaPrint® • Oncotype Dx®

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Several studies [15,18,23] have consistently demonstrated that a low-risk 70-gene signature result is associated with no statistically significant benefit from chemotherapy and patients in this low-risk group, who choose to forego chemotherapy, may do so without compromising their outcome. Furthermore, every study that has been conducted using 70-gene signature has consistently demonstrated that a high-risk result is associated with a statistically significant benefit from chemotherapy.

As stated by the European Society for Medical Oncology 2013 guidelines, 'gene expression profiles such as 70-gene signature and 21-gene assay may be used to gain additional prognostic and/or predictive information to complement pathology assessment and to predict response to adjuvant chemotherapy. This is particularly true in patients with ER-positive early breast cancer' [24].

The first pan-European study [25] analyzed the impact of 70-gene signature on clinical decision on patients with ER-positive and HER2-negative breast cancer, the patient group with the highest 70-gene signature clinical utility. The adjuvant chemotherapy treatment advice provided after disclosure of the 70-gene signature results was changed for 24–37% of patients leading to an increased inter-institutional agreement from 51 to 75%. In conclusion, 70-gene signature can decrease the inter-institutional and inter-country variability in the adjuvant treatment advice provided to female patients with early breast cancer.

Regarding the abstracts mentioned by Plun-Favreau *et al.* [26–28], we would like to highlight that as they are congress abstracts, they provided little information for the assessment of the methodological quality and therefore the results should be viewed with caution until the appearance of peer-reviewed article that allows internal validation. Moreover, due to the sample size of these studies, it is difficult to evaluate their external validity or their extrapolation to all types of patients eligible for testing. Besides, what is important is not whether 70-gene signature or 21-gene assay classify differently, but how well they classify patients who really have a worse prognosis. The result of the classification, by construction, is not the same, but the real risk of the cohort should be the same.We would have been delighted to use 'Madrid registry of MammaPrint and Oncotype DX' data to enrich our analysis [29], although during the review process we could not access public data or peer-reviewed publications that would have allowed us to identify the differential configuration in Spain. For this reason, after the literature review, the results were collated with the expert panel to verify a wider range of inputs in the sensitivity analysis, covering the specificity of the Spanish environment.

Any published economic evaluation must explain the study clearly and transparently in order that the work can be reproduced, as in all scientific literature. The results of the probability analysis must be shown and they should be discussed with the methodological aspects. Parameters analyzed in the deterministic sensitivity analysis and their numerical estimates of their variance are already described in the manuscript. The effect of the uncertainty of any of the parameters during the patients' lifetime was evaluated using multivariate sensitivity analysis with a second-order Monte-Carlo simulation. Gamma distributions were applied for the costs and for the utilities, a beta distribution was applied for probabilities and a triangular distribution was applied for the classification and for the parameters provided by the panel of experts; however, due to the synthesis effort and considering the potential dissemination of the manuscript, parameters composing these distributions were excluded from the manuscript.

When analyzing the effect of discount rate variation from 0 to 5%, it showed neither qualitative nor any significant quantitative changes on the cost–effectiveness results in any of the comparisons carried out in the analysis.

To sum up, the study developed makes unavoidable assumptions, based on expert opinion, only for variables or aspects where current evidence is scarce or non-existent, and these assumptions were tested through deterministic and probabilistic sensitivity analysis.

Financial & competing interests disclosure

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References

1. Plun-Favreau J, Svedman C, Valentine W, Rouzier R. Letter to the Editor: genomic profile of breast cancer. Expert Rev Pharmacoecon Outcomes Res 2015;15(3): 393-94
2. Box GEP, Draper NR. 1987. Empirical Model Building and Response Surfaces. John Wiley & Sons; New York, NY
3. Hillner BE, Smith TJ. Efficacy and cost effectiveness of adjuvant chemotherapy in women with node-negative breast cancer. A decision-analysis model. N Engl J Med 1991;324:160-8
4. Chen E, Tong KB, Malin JL. Cost-effectiveness of 70-gene MammaPrint. signature in node-negative breast cancer. Am J Manag Care 2010;16(12):e333-42
5. Yang M, Rajan S, Issa AM. Cost effectiveness of gene expression profiling for early stage breast cancer: a decision-analytic model. Cancer 2012;118(20):5163-70
6. Retel VP, Joore MA, Knauer M, et al. Cost-effectiveness of the 70-gene signature versus St. Gallen guidelines and adjuvant! online for early breast cancer. Eur J Cancer 2010;46:1382-91
7. Retel VP, Joore MA, van Harten WH. Head-to-head comparison of the 70-gene signature versus the 21-gene assay: cost-effectiveness and the effect of compliance. Breast Cancer Res Treat 2012; 131(2):627-36
8. Retel VP, Joore MA, Drukker CA, et al. Prospective cost-effectiveness analysis of genomic profiling in breast cancer. Eur J Cancer 2013;49(18):3773-9

9. Van de Vijver MJ, He YD, van't Veer LJ, et al. A Gene-expression Signature as a Predictor of Survival in Breast Cancer. N Engl J Med 2002;347(25):1999-2009
10. Buyse M, Loi S, van't Veer L, et al. Validation and Clinical Utility of a 70-Gene Prognostic Signature for Women With Node-Negative Breast Cancer. J Natl Cancer Inst 2006;98(17):1183-92
11. Mook S, Schmidt MK, Viale G, et al. The 70-gene prognosis-signature predicts disease outcome in breast cancer patients with 1–3 positive lymph nodes in an independent validation study. Breast Cancer Res Treat 2009;116(2):295-302
12. Wittner BS, Sgroi DC, Ryan PD, et al. Analysis of the MammaPrint Breast Cancer Assay in a Predominantly Postmenopausal Cohort. Clin Cancer Res 2008;14(10): 2988-93
13. Mook S, Schmidt MK, Weigelt B, et al. The 70-gene prognosis signature predicts early metastasis in breast cancer patients between 55 and 70 years of age. Ann Oncol 2010;21(4):717-22
14. Bueno-de-Mesquita JM, Linn SC, Keijzer R, et al. Validation of 70-gene prognosis signature in node-negative breast cancer. Breast Cancer Res Treat 2009;117(3):483-95
15. Drukker C, Bueno-de-Mesquita JM, Retèl VP, et al. A prospective evaluation of a breast cancer prognosis signature in the observational RASTER study. Int J Cancer 2013;133(4):929-36
16. Drukker CK, van Tinteren H, Schmidt MK, et al. Long Term Impact of the 70-gene Signature on Breast Cancer Outcome. Breast Cancer Res Treat 2014;143(3): 587-92
17. Kunz G. Use of a genomic test (MammaPrint™) in daily clinical practice to assist in risk stratification of young breast cancer patients. Arch Gynecol Obstet 2011;283:597-602
18. Straver E. The 70-gene signature as a response predictor for neoadjuvant chemotherapy in breast cancer. Breast Cancer Res Treat 2010;119(3):551-8
19. Whitworth P, Stork-Sloots L, de Snoo FA, et al. Chemosensitivity Predicted by BluePrint 80-Gene Functional Subtype and MammaPrint in the Prospective Neoadjuvant Breast Registry Symphony Trial (NBRST). Annals Surgical Oncology 2014;21(10):3261-7
20. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351(27): 2817-26
21. Carlson JJ, Roth JA. The impact of the Oncotype Dx Breast Cancer Assay in Clinical practice: systematic review and meta-analysis. Breast Cancer Res Treat 2013;141:13-22
22. Paik S, Tang G, Shak S, 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
23. Knauer M, Mook S, Rutgers EJ, et al. The predictive value of the 70-gene MammaPrint signature for adjuvant chemotherapy in early breast cancer. Breast Cancer Res Treat 2010;120(3):655-61
24. Senkus E. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24(6):1-17
25. Cusumano PG, Generali D, Ciruelos E, et al. European inter-institutional impact study of Mammaprint. Breast 2014;23(4): 423-8
26. Denduluri N, Rugo HS, Davis SE, et al. Concordance between the 21-gene recurrence score (RS) and the 70-gene profile (MP) in breast cancer (BC) patients (pts). J Clin Oncol 2011; 29(suppl 27; Abstract 13
27. Poulet B, Jamshidian F, Butler S, et al. Risk classification of early stage breast cancer as assessed by MammaPrint and Oncotype DX genomic Assays. 2012 San Antonio Breast Cancer Symposium. Abstract # P6-07-03
28. Shivers SC, Clark L, Esposito N, et al. Direct comparison of risk classification between MammaPrint®, Oncotype DX® and MammoStrat® assays With patients in early stage breast cancer. 2013 San Antonio Breast Cancer Symposium; Abstract # P6-07-03
29. Estevez LG, Calvo I, Abad MF, et al. A retrospective study in the Spanish population with Oncotype DX recurrence score (RS) in breast cancer patients with positive and negative-lymph nodes. 2013 ASCO Annual Meeting. Abstract No. e11531