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Response to: Seguí MA, Crespo C, Cortés J, et al. Genomic profile of breast cancer: cost-effectiveness analysis from the Spanish National Healthcare System perspective. Expert Rev Pharmacoecon Outcomes Res 2014;14(6):889-99.

We read the recent article by Seguí *et al.* on the cost–effectiveness of MammaPrint®, Oncotype DX® and Adjuvant Online! in early-stage breast cancer in Spain with interest [1]. Recent developments in the field of gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in breast cancer, including the publication of NICE guidelines on multi-gene assays, mean that well-conducted cost–effectiveness evaluations will be valuable for reimbursement decision makers in a number of countries. However, there are a number of limitations in the analysis of Seguí *et al.* that are not discussed in the paper that limit its usefulness in this regard.

The key limitation of the modeling analysis is that it foregoes the use of published clinical data to rely on expert opinion regarding the effectiveness profiles of MammaPrint and Oncotype DX in clinical practice. The authors incorrectly assume that the two assays provide the same information despite evidence from three studies revealing that the tests risk classify patients in a different way [2–4]. All three studies reveal that a substantial proportion of patients (33–45%) classified as high risk by Mammaprint have low Recurrence Score results with the Oncotype DX test. The differences in risk classification between the two tests are explained by how the assays were developed. Oncotype DX was developed to predict the risk of recurrence in a homogenous patient population treated with 5 years of endocrine therapy and Mammaprint was developed as a prognosticator in a development study of modest sample size containing triple negative, HER2 positive and ER positive, and HER2 negative patients treated heterogeneously (most without treatment). The prognostic value of Mammaprint in the indication discussed in the manuscript (ER positive, HER2 negative patient population treated with the standard endocrine therapy) has in fact not yet been demonstrated. Seguí *et al.* also failed to consider the evidence supporting the predictive ability of the Oncotype DX test in the modeling analysis, which could be considered a key differentiator between the two tests [5,6]. We would contend that this evidence should have been captured in the base case analysis, as it directly influences the cost–effectiveness profile of Oncotype DX. The publication fails to address the issue of prediction throughout despite the clinical relevance of knowing the likelihood for chemotherapy benefit when making treatment decisions (either in the analysis or the discussion section), thus ignoring the published evidence [5,6] and undermining the reliability of the projected outcomes from the modeling analysis. Given the substantial differences in risk classification between the two assays, it cannot be assumed that Mammaprint would be predictive of chemotherapy benefit simply because published evidence indicates that is the case with Oncotype DX. Mammaprint has not been assessed for prediction of chemotherapy benefit in a randomized trial. The available evidence from pooled analysis of seven studies does not support chemotherapy benefit and no trend for interaction was demonstrated with Mammaprint ($p = 0.45$) [7]. We contend that it is inappropriate to assume that Mammaprint is predictive in a modeling analysis until evidence becomes available to support this assertion.

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Another example where the authors neglect to use clinically relevant data is in the published decision impact results from the Madrid registry of MammaPrint and Oncotype DX in the Spanish setting. Instead Seguí *et al.* rely on data from an expert panel (with no methodological detail provided). Decision impact was assumed to be the same with MammaPrint and Oncotype DX for both low- and high-risk profiles; an assumption that is clearly at odds with published data, including that from the Madrid registry, which indicates that the decision impact is greater with Oncotype DX than with MammaPrint [8]. Moreover, the researchers assumed that the high-risk MammaPrint category was equivalent to a weighted average of the intermediate and high-risk Recurrence Score from Oncotype DX, but failed to provide any evidence to support this contention. This was despite the assumption clearly being contrary to the available published evidence [8].

Statistical uncertainty is not adequately captured or reported in the study as recommended in good modeling practice guidelines [9]. The base case offers no measures of variance or uncertainty in outcomes (despite the inherent uncertainty around model inputs based on expert opinion). It appears that second order Monte Carlo simulation has been added as a sensitivity analysis but is inadequately described, with no numerical estimates of variance in either inputs or outputs recorded. Moreover, Figure 4 appears to suggest that sampling from distributions may have only been used in Markov portion of the model (not the decision tree component where the most uncertainty exists, cf. Tables 1 and 2) as the spread of points would likely be greater if this were the case (although this is speculative as the methodology is not described in the paper). The clinical and cost outcomes reported in the results section do not appear to be discounted as stated in the methods section. Again, this is not in line with good modeling practice (and potentially misleading in terms of the magnitude of benefits reported).

As multi-gene assays become increasingly available, healthcare providers are paying more attention to their routine use in clinical practice. Therefore the number of economic evaluations and health technology assessments of multi-gene assays is growing. Clinicians face difficult decisions when prescribing adjuvant therapy, particularly with regard to chemotherapy, balancing the benefit in terms of reduced risk of recurrence and improved survival with the adverse effects of treatment, both in the short and long term. Multi-gene assays may represent an opportunity to identify patients who will benefit from chemotherapy and those who will not, and thus healthcare providers can adapt prescription of adjuvant chemotherapy accordingly, and improve the standard of care for a large number of patients. It is crucial, therefore, that reimbursement decisions are made based on robust evidence. The analysis by Seguí *et al.* is based on a number of spurious assumptions that are contrary to available evidence, as outlined above, making the analysis and its findings of limited scientific, medical and health-economic value.

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References

1. Seguí MA, Crespo C, Cortés J, et al. Genomic profile of breast cancer: cost-effectiveness analysis from the Spanish National Healthcare System perspective. Expert Rev Pharmacoecon Outcomes Res 2014;14(6):889-99
2. 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
3. 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
4. Shivers SC, Clark L, Esposito N, et al. Direct comparison of risk classification between MammaPrint®, Oncotype DX® and MammoStrat® assays in patients with early stage breast cancer. 2013 San Antonio Breast Cancer Symposium; Abstract #P6-07-03
5. 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;24:3726-34
6. Albain KS, Barlow WE, Shak S, et al. Prognostic and Predictive Value of the 21-Gene Recurrence Score Assay in a Randomized Trial of Chemotherapy for Postmenopausal, Node-Positive, Estrogen Receptor-Positive Breast Cancer. Lancet Oncol 2010;11(1):55-65
7. Knauer M, Mook S, Rutgers EJ, et al. The predictive value of the 70-gene signature for adjuvant chemotherapy in early breast cancer. Breast Cancer Res Treat 2010; 120(3):655-61
8. 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
9. Caro JJ, Briggs AH, Siebert U, Kuntz KM. ISPOR-SMDM Modeling Good Research Practices Task Force. Modeling good research practices-overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. Value Health 2012; 15(6):796-803