Addendum to: Harnan S, Tappenden P, Cooper K, Stevens J, Bessey A, Rafia R, Ward S, Wong R, Stein R, Brown J. Tumour profiling tests to guide adjuvant chemotherapy decisions in people with breast cancer (update of DG10). *Technology Assessment Report: Final report to the National Institute for Health and Care Excellence, 2017.*

28th November 2017

In response to the DAR consultation responses collated by NICE and sent to the EAG on 13th November 2017, the EAG provide the following addenda to the report. These are grouped by test, and include addenda on Oncotype DX, MammaPrint and Endopredict.

1. Oncotype DX

1.1 Inclusion of NSABP B-20 endocrine monotherapy arm in the prognostic data set

In response to Agendia's comment (#2), the EAG agree that the NSABP B-20 patients who were used as part of the derivation set (the monotherapy arm of the trail, N=233) should not have been included in the set of studies reporting prognostic performance in patients with LN0 disease and treated with endocrine monotherapy (Paik et al 2006)[1-3]. This reduces the number of studies reporting this subgroup to three for DRFI, but does not alter the conclusions drawn, as the three remaining studies all demonstrated prognostic performance in this group. The inclusion of NSABP B-20[1-3] patients in the set of studies reporting patients with LN0 disease treated with endocrine therapy and chemotherapy was not problematic, as the chemotherapy patients did not form part of the derivation set.

1.2 Inclusion of NSABP B-20 endocrine monotherapy arm in the chemotherapy benefit data set

The EAG also agree with Agendia's comment (#2) on the inclusion of the NSABP B-20 analysis[1-3] in the studies reporting chemotherapy benefit, in that 233 (the endocrine monotherapy patients) of the 651 patients were from the derivation cohort. The remaining patients were from the two endocrine therapy plus chemotherapy arms of the same trial. It is unclear whether inclusion of the derivation set patients would augment or reduce any apparent interaction between chemotherapy and RS, but it does put the study at high risk of bias. However, because there is no other analysis in LN0 patients, the data is still of relevance, as the next level of evidence.

Agendia also note that the interaction test p value relates to a 50 point difference in recurrence score in the Albain et al 2010[4] analysis of SWOG-8814 patients. There is a lack of consistency between the methods section and results section of the journal article, and the EAG had interpreted this as relating to an analysis using the continuous score.[4] However, upon closer inspection, the EAG agree that the analysis stated in the methods section using the continuous score has not been reported, and instead an analysis using the 50-point difference has been reported. This means the study can be considered at high risk of reporting bias, and the analysis has very low clinical relevance.

In the report, the EAG concluded that there is weak evidence for the prediction of chemotherapy benefit by Oncotype DX. Now, with the high risk of bias associated with the B-20 cohort analysis[1-3] and the Albain et al 2010[4] analysis, the evidence base could be judged to be very weak with a very high risk of bias.

1.3 Inclusion of NSABP B-20 endocrine monotherapy arm in the validation set for RSPC

Whilst not mentioned by Agendia, the B-20 cohort was also used to validate the RSPC algorithm.[2] This validation data should therefore be interpreted with caution, as some patients were included in the derivation of Oncotpye DX, which is one component of the RSPC algorithm.

1.4 Use of 50-point difference in analysis of chemotherapy benefit (Albain 2010).[4]

The use of the 50-point difference in the analysis of an interaction between RS and chemotherapy benefit does not indicate the clinical significance of the 18 -30 RS cut points. However, the study does conclude that there is little benefit from chemotherapy at RS<20.

1.5 Use of 50-point difference in adjusted analyses of prognostic performance.

The use of the 50-point difference in the adjusted analyses of prognostic performance indicate that RS is prognostic after adjusting for clinicopathological factors, but does not provide information about the clinical significance of the 18 -30 RS cut points.

2. EndoPredict

2.1 EP score adds information to clinicopathological factors in years 0-10 as well as years 5-10 (section 4.6.2)

The EAG report already notes that the EP score adds significant information to clinicopathological factors or Adjuvant! Online in ABCSG6 and ABCSG8, shown via c-index analyses, in years 5-10. We agree with comment #8 from Myriad that this also applies in years 0-10 (reported in Filipits 2011).[5]

2.2 Time to test results for EndoPredict (section 4.11)

The EAG agrees with the comment (#18) from Myriad that the publication by Müller et al. (2013)[6] reports the time to test result for EndoPredict. In this study the median handling time was three working days (range 0 to 11 days), while 59% of tests were performed within 3 days or less.

3. MammaPrint

3.1 MINDACT trial provides randomised controlled trial evidence of treatment guided by test versus usual practice, in patients who are high-risk via either mAOL or MammaPrint (section 4.4.4)

We agree with Agendia (comment #1a) that MammaPrint is the only one of the five tests to have reported evidence of a RCT (MINDACT) where patients were randomised to treatment guided by the test or by usual clinical practice. These patients were high-risk via either mAOL or MammaPrint. Patients with high-clinical but low-MammaPrint risk showed a non-significant effect of chemotherapy.

3.2 MINDACT data for prognostic performance of MammaPrint (section 4.4.2 and 4.4.4)

Agendia (comment #1e) note that it may be possible to generate prognostic performance data from MINDACT by comparing outcomes for low-MMP vs high-MMP patients using the concordant-risk groups plus the discordant-risk groups in which treatment was determined by mAOL rather than MammaPrint. However, we were not able to locate these data in the time available to respond to these comments. The EAG report does note that, in a multivariable analysis adjusted for chemotherapy use, clinical risk, and patient and tumour characteristics, MammaPrint low/high-risk grouping was statistically significantly associated with 5-year DMFS (HR for high vs low-risk 2.41, 95% CI: 1.79, 3.26, p<0.001). This analysis does not omit the patients treated according to MammaPrint, but the adjustment for other factors may mitigate this. These data could potentially be considered prognostic data. This is consistent with the findings of other MammaPrint prognostic studies which showed that MammaPrint was statistically significantly prognostic in multivariable analyses.

3.3 Difficulties of obtaining trial data/samples to assess chemotherapy benefit

The EAG agrees with Agendia (comment #17) that it is difficult to undertake further assessments of predictive ability for chemotherapy benefit, since there are few trials in which patients were randomised to chemotherapy versus no chemotherapy, and the few trials of this type that are available have insufficient tumour samples left on which to undertake tumour profiling tests.

3.4 Correction for inclusion of derivation patients in Van de Vijver 2002[7] study

Re Agendia comment #54, the Van de Vijver 2002[7] study included a correction for the fact that a small proportion of patients derived from the derivation set were included in the validation study. The small proportion (n=61) were included to avoid selection bias, since the previous study included a disproportionately large number of patients in whom distant metastases developed within five years. The correction in analysis was made using the “leave-one-out” cross-validated classification to predict the outcomes among these patients. This approach minimizes to some extent the possibility of overestimating the value of the prognosis profile while it keeps the consecutive series complete. The study also provides validation results taking only the new samples into account.

3.5 Reference 292

The EAG agree with Agendia that reference 292 is incorrect. However, the authors are correct, and the title and bibliographic information was incorrect, rather than the other way araound. All “Author et al. year” citations relating to 292 should read “van’t Veer *et al.* 2017”, and the reference should read:

292. van‘t Veer, L.J., Yau, C., Nancy, Y.Y., Benz, C.C., Nordenskjöld, B., Fornander, T., Stål, O., Esserman, L.J. and Lindström, L.S. Tamoxifen therapy benefit for patients with 70-gene signature high and low risk. Breast Cancer Research and Treatment (2017): 1-9.

1. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *Journal of Clinical Oncology* 2006;24(23):3726-34.
2. Tang G, Cuzick J, Costantino JP, et al. Risk of recurrence and chemotherapy benefit for patients with node-negative, estrogen receptor-positive breast cancer: recurrence score alone and integrated with pathologic and clinical factors. *Journal of Clinical Oncology* 2011b;29(33):4365-72. doi: https://dx.doi.org/10.1200/JCO.2011.35.3714
3. Tang G, Shak S, Paik S, et al. Comparison of the prognostic and predictive utilities of the 21-gene Recurrence Score assay and Adjuvant! for women with node-negative, ER-positive breast cancer: results from NSABP B-14 and NSABP B-20. *Breast Cancer Research & Treatment* 2011a;127(1):133-42. doi: https://dx.doi.org/10.1007/s10549-010-1331-z
4. Albain K, Barlow W, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncology* 2010;11(1):55-65.
5. Filipits M, Rudas M, Jakesz R, et al. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. *Clinical Cancer Research* 2011;17(18):6012-20. doi: https://dx.doi.org/10.1158/1078-0432.CCR-11-0926
6. Muller BM, Keil E, Lehmann A, et al. The EndoPredict gene expression assay in clinical practice - performance and impact on clinical decisions. *PLoS ONE* 2013;8(6):e68252. doi: https://dx.doi.org/10.1371/journal.pone.0068252
7. van de Vijver MJ, He Y, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. *New England Journal of Medicine* 2002;347(25):1999-2009.