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Tumour profiling tests to guide adjuvant chemotherapy decisions in lymph node positive early breast cancer

Addendum: Additional scenario analyses presented in response to comments on the draft guidance

Produced by	Sheffield Centre for Health and Related Research (SCHARR), School of Medicine and Population Health, University of Sheffield
Authors	Paul Tappenden, Professor of Health Economic Modelling, SCHARR, University of Sheffield, Sheffield, UK
Correspondence author	Paul Tappenden, Professor of Health Economic Modelling, SCHARR, University of Sheffield, Sheffield, UK
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Introduction

This addendum contains a small number of additional analyses which are intended to address comments raised in response to the draft guidance.

Table 1: Additional deterministic scenario analyses

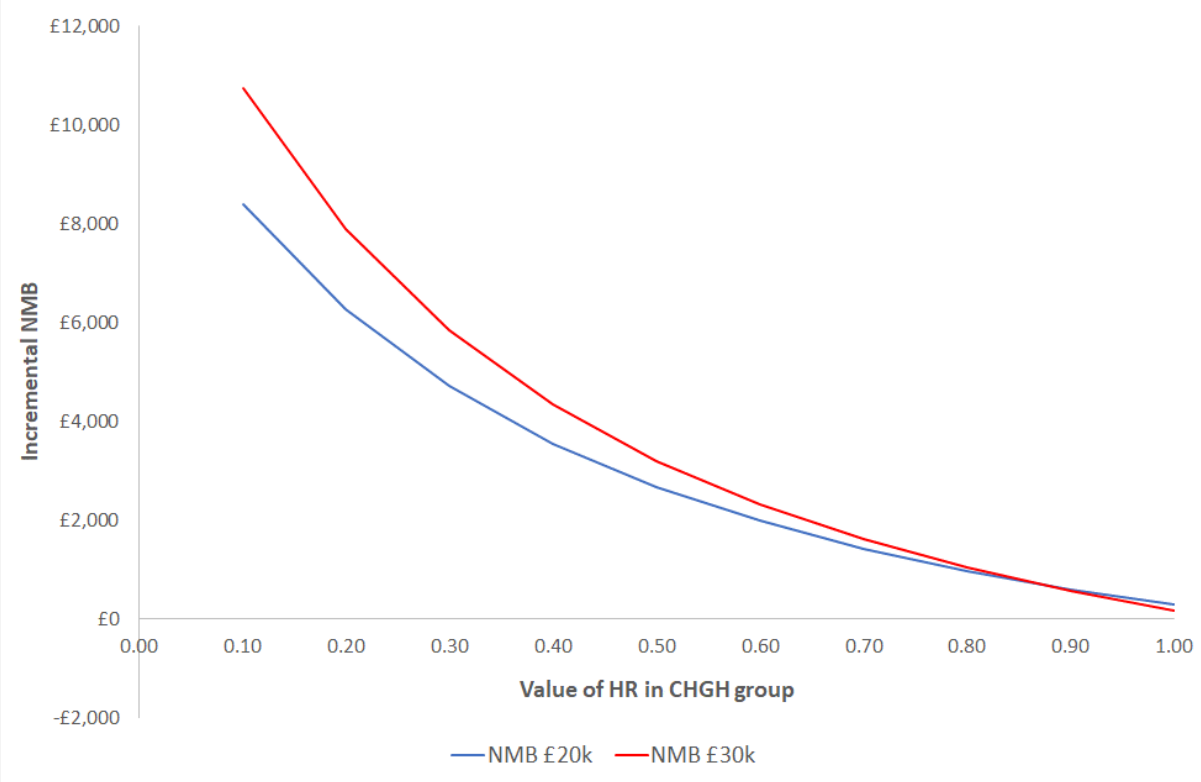
DSA	BC1 – Oncotype DX, RxPONDER pre-menopausal, predictive	BC2 – Oncotype DX, RxPONDER post-menopausal, predictive	BC3 – Oncotype DX, TransATAC post-menopausal, predictive	BC4 – Oncotype DX, TransATAC post-menopausal, non-predictive	BC5 – Prosigna, TransATAC post-menopausal, non-predictive*	BC6 – EPclin, TransATAC post-menopausal, non-predictive	BC7 – MammaPrint, MINDACT, non-predictive
Deterministic base case ICER	Dominated	Dominating	Dominating	Dominated	£25,403	£5,580	Dominated
DSA28: Risk of death reduced by 25%	Dominated	Dominating	Dominating	Dominated	£27,638	£6,199	Dominated
DSA29: HR for BC2 low-risk equal to 1.00	N/a	Dominating	N/a	N/a	N/a	N/a	N/a
DSA30: Chemotherapy effect lost after 5 years	Dominated	Dominating	Dominating	Dominated	£35,700	£3,179	Dominated
DSA31: Chemotherapy effect lost after 10 years	Dominated	Dominating	Dominating	Dominated	£28,288	£4,482	Dominated

** All analyses of Prosigna are based on an updated list price of £1,488*

DSA32: Predictive benefit of MammaPrint

The EAG maintains its view that there is insufficient evidence to demonstrate that MammaPrint is predictive of chemotherapy benefit. However, the Appraisal Committee may wish to know the consequences of considering such an assumption of predictive benefit, despite the lack of evidence. Figure 1 presents a threshold analysis on incremental net monetary benefit (NMB) for MammaPrint versus current decision-making using the EAG's model. The analysis applies the point estimate of the HR for the HR+/HER2-/LN+ age>50 subgroup of MINDACT (HR=0.88) in the clinical high genomic low (CHGL) risk group of the model, and explores the results of applying HRs of 0.1 to 1.0 in the clinical high genomic high (CHGH) risk group of the model. The model settings for this analysis have been adjusted to reflect a post-menopausal population (model start age = 62 years). Post-test probabilities are based on the post-menopausal subgroup of Holt *et al.* Test risk classification probabilities have not been amended as Agendia has not provided these.

Figure 1: Threshold analysis around the HR for the clinical high genomic high group, using an HR of 0.88 for the clinical high genomic low risk group estimated from the HR+/HER2-/LN+ age>50 subgroup of MINDACT



Note: MammaPrint dominates current decision-making if the HR in the CHGH group is 0.85 or lower

Options for decision-making on MammaPrint

With respect to MammaPrint, the EAG believes that the Appraisal Committee has three main options for decision-making, each of which is subject to problems.

Option 1. Use the estimated HR of 0.71 from the EBCTCG meta-analysis in both the CHGL and CHGH groups of the model, thereby assuming no predictive benefit for MammaPrint (EAG's BC7). This approach is consistent with the other non-predictive analyses of the other tumour profiling tests. As noted in Agendia's comments on the draft guidance, this HR is inconsistent with the HR estimated for the HR+/HER2-/LN+ age>50yr CHGL subgroup of MINDACT (HR=0.88). This analysis suggests that MammaPrint is dominated by current decision-making. This scenario is not shown in Figure 1.

Option 2. Apply the HR of 0.88 for the HR+/HER2-/LN+ age>50yr subgroup in both the CHGL and CHGH groups of the model, thereby assuming no predictive benefit. This approach would mean that the HR for the CHGL group of the model is consistent with the MINDACT analyses, but would be inconsistent with the other non-predictive scenarios for the other tumour profiling tests (as these are informed by the EBCTCG meta-analysis). The EAG notes that the MINDACT analysis relies on a much smaller population than the EBCTCG meta-analysis. In addition, because this analysis also involves applying an HR of 0.88 in the CHGH group of the model, it would assume that chemotherapy is not particularly effective overall, regardless of genomic risk. This scenario suggests that MammaPrint results in a positive incremental net benefit at thresholds of £20,000 and £30,000 per QALY gained (Figure 1, value of 0.88 on the x-axis).

Option 3. Apply the HR of 0.88 for the HR+/HER2-/LN+ age>50yr subgroup in the CHGL risk group of the model and apply a different HR in the CHGH group, thereby assuming a predictive benefit. This analysis has been suggested by Agendia. This approach would mean that the HR for the CHGL group of the model is consistent with the MINDACT analyses, but would assume that the reason for lower chemotherapy benefit in this group is specifically due to low MammaPrint genomic risk. The value of the HR in the CHGH subgroup is unknown and cannot be estimated from MINDACT. The EAG did not identify any external studies which report interaction tests on chemotherapy benefit by genomic risk to support this assumption of predictive benefit. This analysis suggests that MammaPrint has a positive incremental net benefit at thresholds of £20,000 and £30,000 per QALY gained (Figure 1, any value <0.88 on the x-axis).