MammaPrint® (70 gene signature) test information summary for medical colleges and health professionals: rationale for the Medical Services Advisory Committee decision not to recommend public funding for use in breast cancer to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit

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Gene profile tests

A number of gene profile tests have been developed with the aim of providing a more accurate means of assessing the risk of breast cancer recurrence through genomic analysis. The addition of genomic risk profiling to existing clinical risk assessment has the potential to provide an additional level of detail to inform decision-making about the use of adjuvant chemotherapy.

MammaPrint® (70 gene signature) test

MammaPrint® is a gene profile test that measures the expression of 70 genes from either a core biopsy or sample of formalin-fixed paraffin-embedded breast cancer tissue. Sample testing is currently undertaken in two centres in the USA.

Medical Services Advisory Committee (MSAC) application

In March 2018, MSAC reviewed an application by the manufacturer requesting Medicare Benefits Schedule (MBS) listing of the MammaPrint® for use in breast cancer to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit.

After considering safety, clinical effectiveness and cost-effectiveness, MSAC did not support public funding for MammaPrint®. Findings were presented in a Public Summary Document published on the MSAC website.[1] The Public Summary Document states that: "*MSAC was concerned that, overall, use of the 70 gene signature test to inform treatment decisions about whether or not to add chemotherapy to hormone therapy would lead to inferior breast cancer outcomes compared with current clinical care.*"

This conclusion only applies to the MammaPrint® test. MSAC's conclusion in relation to the MammaPrint® test does not necessarily mean that the Committee would reach the same conclusion for other gene profile tests in the future.

Basis of the MSAC application for MammaPrint®: the MINDACT trial

The MSAC application for funding of MammaPrint® was based on the MINDACT trial.[2] This open label randomised controlled trial explored whether genomic risk information could be used to inform the use of chemotherapy. Clinical criteria and the 70 gene signature test were used to triage 6693 women with oestrogen receptor (ER) positive HER2-negative early breast cancer into one of four risk categories (Table1) and the results used to determine whether women would or would not receive chemotherapy.

Table 1: Risk categories used in the MINDACT trial and randomisation

	1	2	3	4
Clinical risk	**High**	**Low**	**Low**	**High**
Genomic risk	**High**	**Low**	**High**	**Low**
	Women in these groups were not randomised Management plan continued as normal		Women in these groups were randomised to receive chemotherapy or not to receive chemotherapy	

[1] Australian Government. Medical Services Advisory Committee. Public Summary Document. Application No. 1376.1 – 70 gene signature (MammaPrint) for use in breast cancer to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit. Accessed 12 February 2019

[2] Cardoso F et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med 2016;375(8):717–29.

The MSAC application was based on the primary analysis reported for the trial, which focused on the group of women in the high clinical risk, low genomic risk category (column 4) who did not receive chemotherapy. This analysis assessed 5-year distant metastasis-free survival (DMFS) against a survival threshold set in advance of the trial of 92%. The underlying assumption in this analysis was that if DMFS did not go below this pre-determined threshold in the women with high clinical risk, low genomic risk breast cancer who did not have chemotherapy, it would mean that survival had not been adversely affected.

The trial results presented in the application to MSAC showed that at 5 years, DMFS was 94.7% in the women who did not receive chemotherapy. Although this was 1.5% lower than the DMFS in women who received chemotherapy, the rate was above the 92% non-inferiority threshold set in advance of the trial. Based on this finding, the trial publication reported that survival was not adversely affected in women at high clinical risk and low genomic risk breast cancer who did not have chemotherapy.

Rationale for the MSAC conclusion

The priority for the MSAC committee was to ensure that the decision not to have chemotherapy in women at high clinical risk and low genomic risk of breast cancer recurrence would not impact negatively on breast cancer outcomes, including overall survival.

MSAC undertook a review of secondary analysis results available in the trial publication, which directly compared breast cancer outcomes for women with high clinical risk, low genomic risk breast cancer who did and did not receive chemotherapy (Table 2). These randomised comparisons showed:

- significantly poorer disease-free survival (DFS) in women who did not receive chemotherapy compared with those who did (absolute decrease in five-year DFS of 3% in the per protocol population and 4.5% in the per protocol sensitivity population)
- consistent trends in the per protocol population towards poorer DMFS and overall survival (OS) in women who did not receive chemotherapy compared with those who did (absolute decrement in DMFS of 1.9% and in OS of 1.5%); results were consistent with trends reported for the per protocol sensitivity analysis and intention to treat populations.

Table 2: Summary of results of the surrogate overall survival endpoints for women with high clinical risk, low genomic risk breast cancer in the MINDACT trial

Trial population	Patients (n)	Hazard ratio (95% Confidence interval, p value)	Absolute benefit comparing outcomes for women with high clinical risk low genomic risk breast cancer who did and did not receive chemotherapy
Per protocol sensitivity	1045	OS: 0.54 (0.23–1.26, p=0.154) DFS: 0.57 (0.37–0.87, **p=0.009**) DMFS: 0.60 (0.34–1.06, p=0.080)	OS: –1.8% DFS: –4.5% DMFS: –2.5%
Per protocol	1228	OS: 0.63 (0.29–1.37, p=0.25) DFS: 0.64 (0.43–0.95, **p=0.03**) DMFS: 0.65 (0.38–1.10, p=0.11)	OS: –1.5% DFS: –3.0% DMFS: –1.9%
Intention to treat	1497	OS: 0.69 (0.35–1.35, p=0.278) DFS: 0.71 (0.50–1.01, p=0.055) DMFS: 0.78 (0.50–1.21, p=0.267)	OS: –1.5% DFS: –1.9% DMFS: –1.4%

OS: overall survival; DFS: disease-free survival; DMFS: distant metastasis-free survival

The box overleaf provides a modelled summary for the likely impact of use of MammaPrint® on clinical management and breast cancer outcomes for people with early breast cancer in Australia.

Modelled summary of the impact of use of MammaPrint® on breast cancer outcomes[1]

Assume 1000 patients tested per year. Of these patients, over five years:*

- 770 would have no change in clinical management
- 223 more would no longer receive chemotherapy
- 2 more would live with a local recurrence of their cancer
- 1 more would live with a metastatic recurrence of their cancer
- 4 more would die

*Based on MINDACT proportions with high clinical risk / low genomic risk per protocol analysis of the randomised comparison of this group with and without adding chemotherapy and assuming 100% compliance with MammaPrint® genomic risk recommendation

Given that a 2–3% increase in survival is viewed as clinically important in applications for new treatments, MSAC considered that the difference in DMFS in women who did not receive chemotherapy was important, even when balanced against avoiding the side effects of chemotherapy. Moreover, the Committee noted that it would not be possible to assess which patients within the high clinical risk, low genomic risk group would be adversely affected by not having chemotherapy.

On balance, MSAC considered that these results consistently indicated that using MammaPrint® to justify withholding chemotherapy in patients at high clinical risk and low genomic risk would result in inferior breast cancer outcomes. While MSAC also considered the financial implications of public funding for MammaPrint®, these were not a factor in the recommendation not to publicly fund the test.

[1]Cardoso F et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med 2016;375(8):717–29.