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

Applicant: **Genome Investigation Pty Ltd**

Date of MSAC consideration: **MSAC 72nd Meeting, 28-29 March 2018**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of a 70 gene signature test (MammaPrint) for use in breast cancer to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit was received from Genome Investigation by the Department of Health.

The 70 gene signature test is proposed to inform decisions about the use of adjuvant chemotherapy in women with high clinical risk breast cancer.

2. MSAC's advice to the Minister

After considering safety, clinical effectiveness and cost-effectiveness, MSAC did not support public funding for a diagnostic microassay to measure the expression of 70 genes in breast cancer tissue (MammaPrint; hereafter the 70 gene signature test).

MSAC considered the results of the key supporting trial (MINDACT) and noted that, on average, there was a consistent pattern of poorer breast cancer outcomes when chemotherapy was withheld in high clinical risk patients on the basis of a finding of low genomic risk using the 70 gene signature test. As a result, MSAC had little confidence that the 70 gene signature test could be used to justify withholding chemotherapy in such patients without negatively impacting upon important outcomes, including overall survival.

MSAC was concerned that, overall, use of the 70 gene signature test to inform treatment decisions about whether to not add adjuvant chemotherapy to hormone therapy would lead to inferior breast cancer outcomes compared with current clinical care.

MSAC considered that, despite its concerns, the 70 gene signature test may already be used in clinical practice and paid for by patients. MSAC therefore advised that a communication strategy should be developed to inform relevant health professional and consumer groups of the Committee's concerns.

MSAC advised that any resubmission would need to be considered by ESC.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that the submission requested a new MBS item for an in vitro diagnostic microassay (MammaPrint) that measures the expression of 70 genes from either a core biopsy or a sample of formalin-fixed paraffin-embedded (FFPE) breast cancer tissue in order to quantify the risk of disease recurrence and assist in decision making around the benefits of adjuvant chemotherapy.

MSAC noted that the proposed population is patients diagnosed with breast cancer, classified as being at 'high clinical risk' who meet the following criteria:

- early stage (I-II) breast cancer;
- tumour size up to 50mm diameter;
- node negative or up to three positive nodes; and
- oestrogen receptor (ER) positive and HER2-negative.

MSAC noted that the key evidence to support the use of the 70 gene signature test was the MINDACT trial (Cardoso F et al 2016). MSAC noted that MINDACT was an open-label randomised controlled trial (RCT) in which 6693 women with early-stage breast cancer were assigned a clinical risk status (high or low) and a genomic risk status (high or low). Clinical risk status was assigned on the basis of clinical and pathological criteria and the predictive Adjuvant! Online algorithm. Genomic risk status was assigned on the basis of results from the 70 gene signature test. Women who had concordant clinical and genomic results (i.e. high clinical risk/high genomic risk or low clinical risk/low genomic risk) were not randomised and were treated as usual. However, women who had discordant results (i.e. low clinical risk/high genomic risk or high clinical risk/low genomic risk) were randomised to either receive chemotherapy or to not receive adjuvant chemotherapy in addition to hormone therapy.

MSAC noted results from the MINDACT trial were reported in the per-protocol (PP) population, the intention to treat (ITT) population and in a per protocol sensitivity (PPS) population (which excluded all patients enrolled between May 2009 and January 2010 due to a temporary problem in risk calculation caused by a change in an assay).

MSAC noted that the clinical claim made for the 70 gene signature test was that it will provide incremental prognostic and predictive information over and above that of usual care and will reduce the use of adjuvant chemotherapy, without negatively impacting upon survival, in some patients who would otherwise have been classified as being at high risk of recurrence and undergone chemotherapy (i.e. the high clinical risk/low genomic risk group).

MSAC acknowledged the benefits of avoiding unnecessary chemotherapy in terms of avoiding the toxicity of this therapy, but noted that clinicians and patients would want to be very certain that, in doing so, there are no adverse impacts in terms of surviving breast cancer. MSAC considered that evidence from high quality RCTs are the best way to assess whether this can be ensured. MSAC therefore welcomed the strength of the RCT evidence presented in this application, noting that it provided better quality evidence upon which to make a decision than the weaker linked evidence approaches MSAC had previously seen for other gene expression profiling tests.

MSAC noted that the best way to establish whether the 70 gene signature test results could be used to withhold chemotherapy without having a negative impact upon survival would be via an RCT comparing outcomes in patients with high clinical risk/low genomic risk who did not receive chemotherapy with those who received chemotherapy. MSAC noted that the MINDACT trial was designed to do this and thus could be used to directly compare important breast cancer outcomes, including overall survival. Despite this, MSAC noted that

the primary analysis reported in MINDACT instead relied solely upon data from a single arm of the study (i.e. those who did not receive chemotherapy) against a separately defined external standard, rather than directly comparing the observed results across the randomised groups. MSAC considered that the primary analysis reported by the trial investigators was essentially evidence from a case series.

MSAC noted the reported primary analysis in the MINDACT trial was whether the lower boundary of the 95% confidence interval (95% CI) for distant metastasis free survival (DMFS) at five years was at least 92% in high clinical risk/low genomic risk patients who did not receive chemotherapy. MSAC noted that five year DFMS was reported to be 94.7% in these patients, and the 95% CI was 92.5% to 96.2% (i.e. did not cross the 92% threshold).

However, given the primary analysis relied solely upon data from a single arm of the trial without reference to a comparison with the results from the other arm of the RCT (high clinical risk/low genomic risk patients who did receive chemotherapy), MSAC was not confident that this was adequate evidence that high clinical risk/low genomic risk patients could avoid chemotherapy without worsening clinical outcomes.

MSAC noted that direct comparisons on important breast cancer outcomes among high clinical risk/low genomic risk patients randomised to receive or not to receive chemotherapy were reported as 'secondary' analyses in the MINDACT trial. While MSAC acknowledged MINDACT had not been powered to test for differences in 'secondary' analyses, MSAC considered these to be more reliable for decision-making than the primary analysis because they represent direct comparisons of randomised data.

MSAC noted that in the high clinical risk/low genomic risk patients, the MINDACT trial had reported direct comparative evidence on DFMS (the primary outcome), disease free survival (DFS), and overall survival. MSAC considered that these randomised comparisons consistently indicated that using the 70 gene signature test to justify withholding chemotherapy in these patients would result in inferior outcomes. In reaching this conclusion, MSAC noted that:

- DFS was significantly poorer in patients who did not receive chemotherapy compared with those that did:
    - the PP population hazard ratio (HR) at five years was 0.64 (95% CI 0.43 to 0.95; p=0.03);
    - the PPS population HR at five years was 0.57 (95% CI 0.37 to 0.87; p=0.009);
    - five year DFS in the PP population was 93.3% in the chemotherapy group and 90.3% in the non-chemotherapy group — an absolute risk decrement of 3.0%;
    - five year DFS in the PPS population was 93.3% in the chemotherapy group and 88.8% in the non-chemotherapy group — an absolute risk decrement of 4.5%.
- There were consistent trends in the PP population towards poorer DFMS outcomes (HR 0.65, 95% CI 0.38 to 1.10; p=0.11) and overall survival outcomes (HR 0.63, 95% CI 0.29 to 1.37; p=0.25) in patients who did not receive chemotherapy compared to those that did. These trends were consistent with those reported for the PPS population and ITT populations.
    - The absolute risk decrement in five year DFMS associated with the first of these hazard ratios was 1.9% in the PP population, consistent with those reported for the PPS (2.5%) and ITT (1.5%) populations.
    - The absolute risk decrement in five year overall survival associated with the second of these hazard ratios was 1.5% in the PP population, consistent with those reported for PPS (1.8%) and ITT (1.4%) populations.

MSAC noted that, in its pre-MSAC response, the applicant had indicated that a 2% to 3% absolute difference in distant metastasis free survival benefit afforded by the use of chemotherapy is clinically important. In this context, MSAC considered that the overall set of absolute risk decrements reported above indicated likely clinically important reductions across these breast cancer outcomes as a result of not using chemotherapy in the high clinical risk/low genomic risk patient group. MSAC noted that the trial has a planned 10 year follow-up, but considered that the observed 5-year trends would be unlikely to change with longer follow-up because chemotherapy benefits have emerged relatively early in other trials.

In summary, MSAC considered that, on average, there was a consistent pattern of poorer outcomes (DFMS, DFS and overall survival) when chemotherapy was withheld in high clinical risk patients on the basis of a finding of low genomic risk using the 70 gene signature test. MSAC noted that consistent poorer outcomes were reported even though the study had not been powered to test for statistically significant differences across these outcomes, with event rates being greatest for DFS and smallest for overall survival. As a result, MSAC had little confidence that the 70 gene signature test could be used to justify withholding chemotherapy in such patients without negatively impacting upon important breast cancer outcomes, including overall survival.

MSAC noted that no claim for the 70 gene signature test was made with respect to the clinical utility of adding adjuvant chemotherapy to adjuvant hormone therapy in patients reported as having low clinical risk but high genomic risk, and thus concluded that the test provider did not support its use for this purpose. MSAC noted that MINDACT provided evidence for the use of the 70 gene signature test in this other discordant risk group. MSAC noted that in usual practice, women classified as being at low clinical risk would not receive adjuvant chemotherapy and so the information from the 70 gene signature test may identify patients who could benefit from chemotherapy, but would otherwise miss out. However, MSAC noted that there were no significant differences in DFMS, DFS or overall survival in the group of women with low clinical risk/high genomic risk who received chemotherapy and those who did not, indicating that there would be no benefit in undertaking 70 gene signature testing in this group. MSAC therefore concluded that the results for this population from the MINDACT trial indicated that the 70 gene signature test could not be used to justify adding chemotherapy in such patients because there would be either no or insufficient gains in terms of their important breast cancer outcomes, including overall survival, and likely increased toxicity.

MSAC noted that the MINDACT trial did not report any evidence that demonstrated that using the 70 gene signature test to inform decisions about adjuvant chemotherapy would improve patient quality of life.

MSAC considered that the open label nature of the study, dropout rates and changes in patient eligibility requirements may have introduced some bias into the MINDACT results.

MSAC dismissed the economic modelling presented as being uninformative. MSAC noted the model relied upon the claim that the 70 gene signature test had superior safety and non-inferior effectiveness over usual care, a claim that MSAC did not accept. Instead, MSAC expected that, given the results seen in the randomised comparisons, use of the 70 gene signature test in women at high clinical risk and low genomic risk would be dominated (i.e. more expensive with inferior outcomes) by usual care.

MSAC noted that a breakdown of each component cost would be informative to justify the proposed fee of ~$5400 ($4200 USD).

4. Background

This is a resubmission of MSAC application 1376. MSAC Application 1376 was considered by PASC at its April and August 2014 meetings but did not progress to ESC or MSAC. In November 2016, the MSAC Executive recommended that the application should be submitted as a new application under the MSAC reform process, via the standard pathway.

Application 1376.1 was considered by PASC at its 12 April 2017 meeting.

5. Prerequisites to implementation of any funding advice

MammaPrint® is not registered on the Australian Register of Therapeutic Goods (ARTG). The applicant has identified that it is currently applying to the Therapeutic Goods Administration (TGA) for registration on the ARTG. The test is registered with the USA Food and Drug Administration (FDA).

Currently, only two facilities are accredited to perform the 70 gene signature testing, one in Irving, Los Angeles, and the other in Amsterdam, Holland. Currently, Australian patient specimens are sent to the Los Angeles Agendia laboratory. The contracted assessment report stated that a commercial Australian Laboratory is willing to obtain accreditation for 70 gene signature testing, should an application for listing on the MBS be supported by MSAC.

6. Proposal for public funding

The proposed MBS item descriptor is summarised in Table 1.

Table 1 Proposed MBS item descriptor

Category 6 (Pathology Services) – Group P7 Genetics
Proposed item descriptor: 733XX
Microarray 70 gene signature expression profiling of breast cancer, performed on either core biopsy or surgically resected formalin-fixed paraffin-embedded histological specimen. May only be used to test samples from patients considering chemotherapy treatment, classified as high clinical risk, with the following characteristics as determined by the referring specialist oncologist: • early stage breast cancer (Stages I-II) • invasive tumour size up to 50mm in diameter • node negative or up to three positive nodes • oestrogen receptor positive as determined by immunohistochemistry • HER2 negative as determined by immunohistochemistry May only be used once per new primary breast cancer tumour diagnosis. Fee: $5,588 AUD *(based on estimation of $USD4,200 sought on 9th March 2017)*

7. Summary of public consultation feedback/consumer issues

Public consultation feedback was received from a peak body. This was not supportive for two reasons:

- The application should be generic enough that a number of acceptable tests could be performed by Australian laboratories and reimbursed through Medicare or any one type of cancer. This application is specifically for MammaPrint even in the way the item descriptor has been constructed.
- At this stage, MammaPrint is being performed in an overseas laboratory.

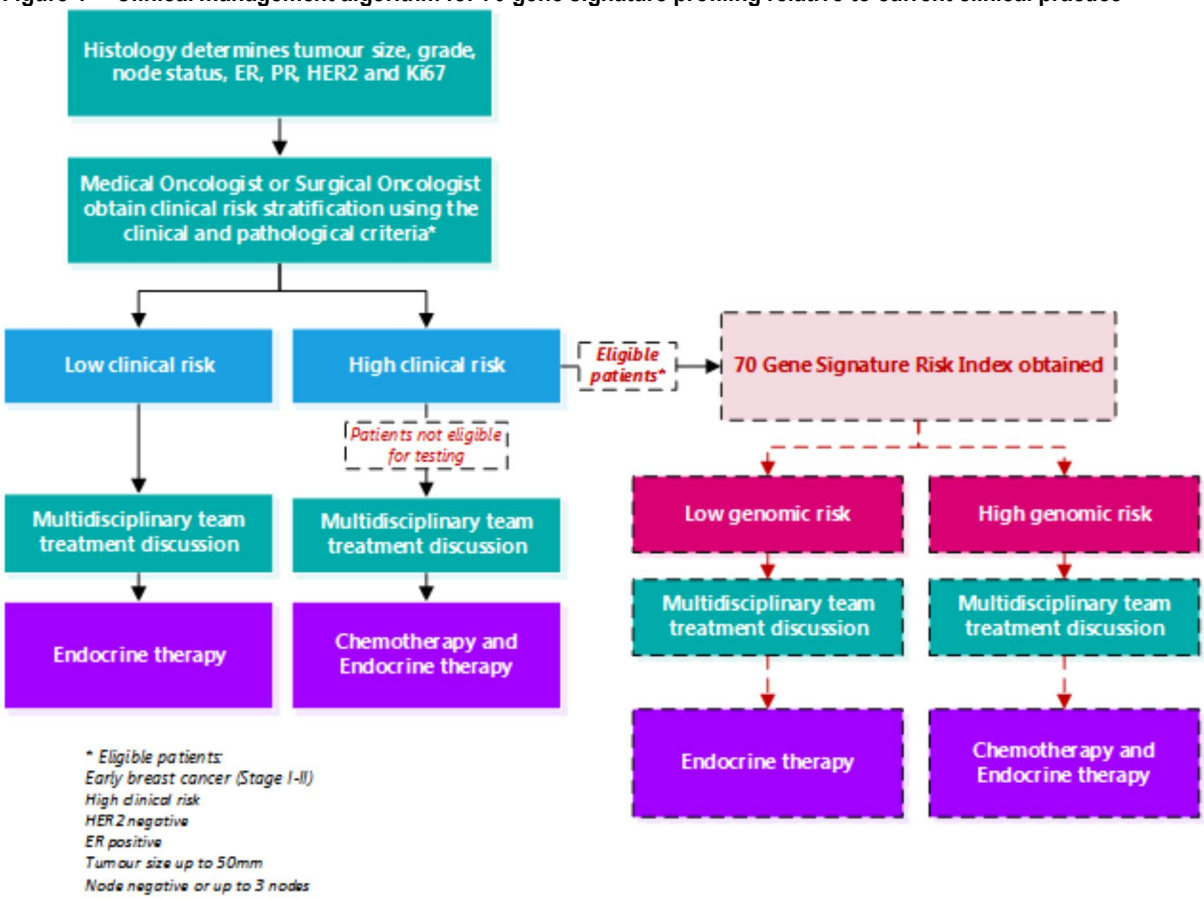
8. Proposed intervention's place in clinical management

The proposed medical service is a 70 gene expression profiling test, using a microarray assay performed on either a core biopsy or surgically resected formalin-fixed paraffin-embedded

(FFPE) histological specimen. The analysis is designed to determine the gene activity of specific genes in a tissue sample compared to a set reference standard.

In current clinical practice, a clinical risk assessment of high clinical risk is used to determine if chemotherapy (together with hormone therapy) is recommended to the patient. The proposed changes are an addition to current practice, and apply to patients categorised as having a high clinical risk. The clinical management algorithm presented below (Figure 1) depicts both current clinical practice, with the addition of the proposed changes in the context of the intended use of the proposed medical service following a listing on the MBS. The proposed changes are indicated with a dashed outline on the right of the algorithm.

Figure 1 Clinical management algorithm for 70 gene signature profiling relative to current clinical practice



9. Comparator

The main comparator for the 70 gene signature test is usual care, which involves no gene signature expression profiling, for women with early breast cancer that meet the defined histological and clinical criteria. Usual care includes the optimal use of existing algorithms that provide an estimate of the risk of these patients subsequently experiencing cancer-related mortality or relapse by incorporating their information about tumour and patient characteristics including patient age, tumour size, histological grade, lymph node status (positive or negative) and oestrogen receptor, progesterone receptor and HER2 status. Clinical risk assessment tools include Adjuvant! Online (Adjuvant! Inc, San Antonio, USA), PREDICT, PREDICT Plus (National Cancer Registration and Analysis Service, Fulbourn, Cambridge, UK), The Nottingham Prognostic Index, and Numeracy (Mayo Foundation for medical education and research, Rochester, USA).

The reference standard for the intervention is the MammaPrint Index designated reference standard.

10. Comparative safety

The pivotal randomised controlled trial (RCT), MINDACT (n=6,693), provided direct evidence for the comparative effectiveness and safety of 70 gene signature testing versus usual care in women with early stage breast cancer. Supportive evidence was also provided for the analytical validity and clinical utility of 70 gene signature testing, noting that there is no reference or evidentiary standard for determining the level of clinical and/or genomic risk.

Test adverse events

Including the 70 gene signature test into usual care is comparatively safe.

Adverse events from change in management

Safety implications of changes in the subsequent treatment recommendation and treatment decisions following the inclusion of the 70 gene signature test in usual care would be related to the adverse events from chemotherapy. Results of the MINDACT trial suggest that the use of the 70 gene signature test to guide chemotherapy treatment decisions could result in up to a 46% reduction in patients using adjuvant chemotherapy. There may be changes in the safety outcomes and adverse events experienced by patients who decide to forgo adjuvant chemotherapy following a low genomic risk result from the 70 gene signature test. However, previous studies noted that short-term events (e.g. nausea, vomiting, mouth soreness, diarrhoea, tiredness, hair loss and temporary lowering of the blood count) and long-term adverse events (e.g. damage to the heart and a small increase in the risk of leukaemia, which are not reversible) will affect a proportion of patients receiving chemotherapy, imposing costs and reducing quality of life.

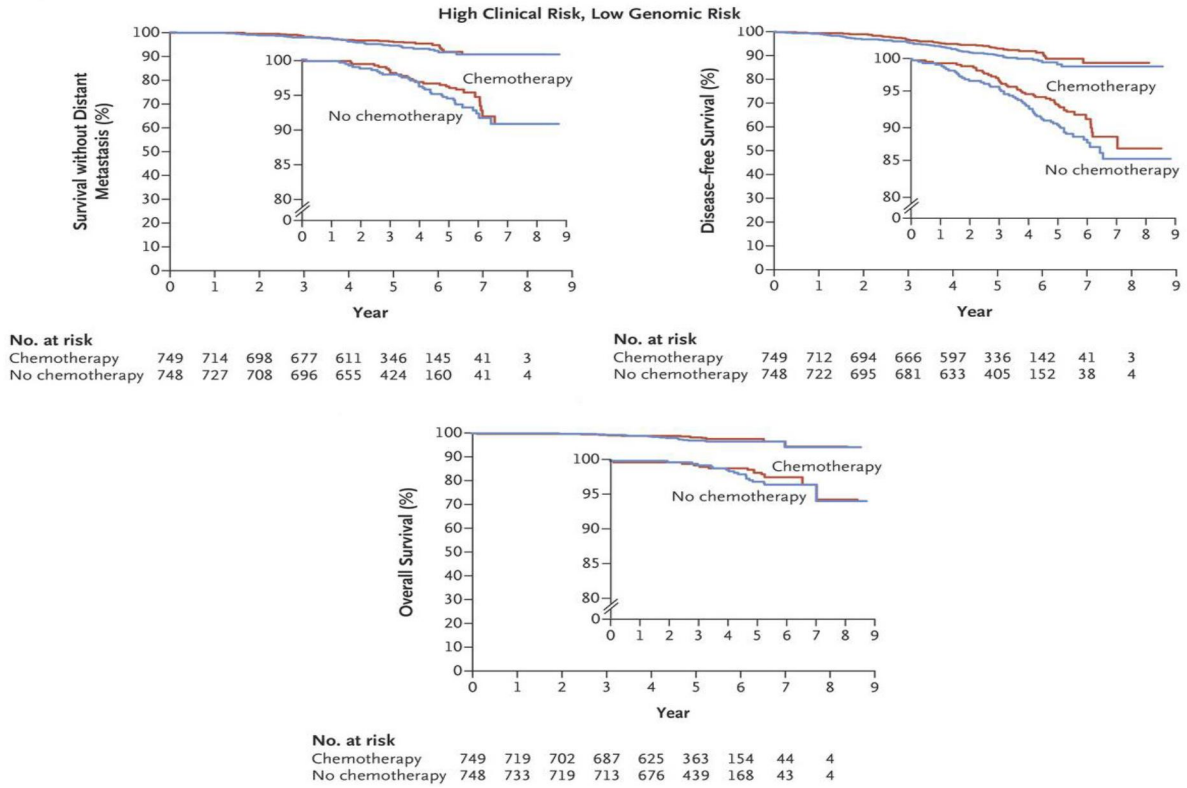
11. Comparative effectiveness

Direct effectiveness

Breast cancer outcomes

In the MINDACT trial, among women with early stage breast cancer who were at high clinical risk and low genomic risk for recurrence, the receipt of no chemotherapy on the basis of the 70 gene signature test led to no difference in 5-year rate of survival without distant metastasis (the 5-year rate of survival without distant metastasis was 1.5 percentage points lower (not statistically different) than the rate with chemotherapy) (see Table 2 and Figure 2).

Figure 2 KM curves for DMFS, DFS and OS from patients at high clinical, low genomic risk in MINDACT trial



Source: Adapted from Cardoso *et al* (2016), Figure 2, p725
DFS = disease free survival; DMFS = distant metastases free survival; KM = Kaplan Meier; OS = overall survival

Table 2 Results of key patient-relevant breast cancer outcomes across the high clinical risk and low genomic risk patients in the MINDACT trial

Effectiveness outcome	Risk of bias	Intervention: Treatment strategy using genomic risk (No chemotherapy) n with event/N (%) and 95% CI	Comparator: Treatment strategy using clinical risk (Chemotherapy) n with event/N (%) and 95% CI	Absolute difference RD (95% CI) NNT(95% CI)	Relative difference HR and 95% CI[a]	P-value
DMFS	low	37/636 (94.8%, 92.6-96.3)	22/592 (96.7%, 94.7-98.0)	0.02 (0, 0.05) 48 (22, -333)	0.65 (0.38-1.10)	0.11
DFS	low	66/636 (90.3%, 87.6-92.4)	39/592 (93.3%, 90.7-95.2)	0.04 (0.01, 0.07) 26 (14, 143)	0.64 (0.43-0.95)	0.03
OS	low	18/636 (97.3%, 95.6-98.4)	10/592 (98.8%, 97.4-99.5)	0.01 (-0.01, 0.03) 88 (36, -200)	0.63 (0.29-1.37)	0.25

Source: Cardoso et al., 2016, Table 2, p726
CI = confidence intervals; DFS = disease free survival; DMFS = distant metastases free survival; HR=hazard ratio; NNT = number needed to treat; OS=overall survival; RD = risk difference
[a]Base case = treatment according to genomic risk

Health-related quality of life

A non-randomised study provided outcomes on patient well-being in a sample of women taken from the MINDACT trial (Retel et al., 2013a). Some key results are presented in Table 3.

Table 3 Results of key patient-relevant outcomes across the high clinical risk and low genomic risk patients

Outcome	Risk of bias	Treatment strategy using genomic risk (70 gene signature: no chemotherapy) Mean (95% CI)	Treatment strategy using clinical risk (Usual care: chemotherapy) Mean (95% CI)
Distress [a]	high	2.11 (1.70-2.52)	1.68 (1.45-1.91)
Cancer-specific worry [b]	high	1.85 (1.61-2.10)	1.49 (1.34-1.6
Quality of life [c]	high	26.9 (24.6-29.1)	26.9 (25.1-28.8)

Source: Retel *et al* (2013), Table 5, p8
CI = confidence interval
[a] Based on 10 items from Lynch's distress scale, note: a higher number indicated improvement in distress
[b] Adapted 7-item version of Lerman's Cancer Worry Scale, note: a higher number indicated improvement in cancer-specific worry
[c] Based on 9 items from the Breast Cancer Subscale of the Functional Assessment of Cancer Therapy (FACT-B), note: a higher number indicated an improvement in health-related quality of life

Overall, there was some improvement in the level of distress and cancer specific worry in the no chemotherapy group, but no difference in the quality of life measure used in the study.

On the basis of the benefits and harms reported in the evidence base (summarised above), it is suggested that, relative to the comparator, the investigative intervention has superior safety and non-inferior effectiveness.

Clinical claim

The clinical claim is that 70 gene expression profiling provided to women with early breast cancer with a defined histological criteria and deemed to be at high clinical risk is superior in terms of safety and non-inferior in terms of clinical effectiveness compared to usual care.

12. Economic evaluation

A stepped economic evaluation was presented with the base case using the trial-based incremental cost-effectiveness ratio (ICER) up to five years, and the lifetime modelled evaluation extrapolated out to 30 years, applying convergence of survival curves (Year 6).

Table 4 Summary of the economic evaluation

Perspective	Australian health system
Comparator	Usual care
Type of economic evaluation	Cost-effectiveness evaluation
Sources of evidence	MINDACT trial (RCT)
Time horizon	• Trial based evaluation: 5 years, base case • Modelled evaluation: lifetime (30 years), convergence of survival curves applied at year 6 (see Section C.3)
Outcomes	LYs and QALYs
Methods used to generate results	Cohort expected value analysis, Markov model
Health states	Three state model: 1. Alive, recurrence free: no distant metastases 2. Alive, recurrence: after recurrent disease (distant metastases) 3. Dead
Cycle length	1 year
Discount rate	5%
Software packages used	TreeAge Pro 2017 R2

LY = life years; QALY = quality-adjusted life year; RCT = randomised controlled trial

The overall costs and outcomes, and incremental costs and outcomes as calculated for the testing strategy and comparative testing strategy in the model, using the base case assumptions, are shown in Table 5.

Table 5 Stepped economic evaluation

Step and component	70 gene signature test	Usual care	Increment
Step 1-2: trial-based economic evaluation (5 years): base case			
Cost	$13,482	$10,132	$3,350
LYs	4.38	4.38	Negligible
QALYs	4.23	4.18	0.05 a
Incremental cost per QALY gained, base case			**$66,640**
Step 3: modelled economic evaluation extrapolated after 5 years to 30 years (convergence applied at 6 years)			
Cost	$31,557	$28,346	$3,211
LYs	13.30	13.33	-0.03
QALYs	12.81	12.79	0.02
Incremental cost per LY gained			**70 gene signature test dominated**
Incremental cost per QALY gained			**$131,663**

Source: Mammaprint.trex

The results suggest that the 70 gene signature test was more cost-effective in the within trial period (5 years) than in the lifetime extrapolated model (ICER: $66,640 versus $131,663). The trial-based estimates were considered more reliable, due to high censoring of survival curves beyond five years in Cardoso *et al* 2016, and treatment with hormone therapy being typically given for five years.

The modelled results were most sensitive to the disutility of chemotherapy, and to a lesser extent the prevalence of low genomic risk (for patients who avoid chemotherapy in the 70 gene signature test arm), the cost of genomic testing with 70 gene signature test, and the cost of chemotherapy (which included costs associated with adverse events).

13. Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of the introduction of the 70 gene signature test.

The financial implications to the MBS resulting from the proposed listing of the 70 gene signature test are summarised in Table 6.

Table 6 Total costs to the MBS associated with the 70 gene signature test

	2018-19	2019-20	2020-21	2021-22	2022-23
Number of services	437	594	757	771	786
Total MBS cost for test (85% benefit)	$2,076,331	$2,822,614	$3,595,983	$3,663,699	$3,731,415
Total MBS offset	-$50,412	-$68,531	-$87,308	-$88,952	-$90,596
Total PBS cost offset	-$1,022,550	-$1,390,079	-$1,770,947	-$1,804,296	-$1,837,644
Net cost to government	$1,003,369	$1,364,004	$1,737,728	$1,770,451	$1,803,174

14. Key issues from ESC for MSAC

This submission requested a new MBS item for an *in vitro* diagnostic microassay (MammaPrint) that measures the expression of 70 genes from either a core biopsy or a sample of formalin-fixed paraffin-embedded (FFPE) breast cancer tissue in order to quantify the risk of disease recurrence and assist in decision making around the benefits of adjuvant chemotherapy.

The proposed population is patients diagnosed with breast cancer, classified as being at 'high clinical risk' who meet the following criteria:

- early stage (I-II) breast cancer;
- tumour size up to 50mm diameter;
- node negative or up to three positive nodes; and
- oestrogen receptor (ER) positive and *HER2*-negative.

The claim is that the 70 gene signature test provides incremental prognostic and predictive information that is over and above that of usual care and will reduce the use of adjuvant chemotherapy in some patients who would otherwise have been classified as being at high risk of recurrence and undergone chemotherapy.

ESC noted that similar genetic expression profiling (GEP) tests aiming to categorise patients with early breast cancer by risk of cancer recurrence have been considered by MSAC — Oncotype DX (MSAC Applications 1342–1342.4) and Prosigna (MSAC Application 1473) — and PASC (EndoPredict; MSAC Application 1408).

ESC recalled that MSAC had previously focussed on intermediate risk patients as being the most likely to benefit in previous considerations of GEP assays. ESC noted that while Oncotype DX and Prosigna classify patients as being at high, low or intermediate risk of recurrence, the proposed use for the 70 gene signature test is as a way to categorise patients already classified as being at high clinical risk of recurrence into 'high genomic risk' and 'low genomic risk' subgroups.

ESC noted the methodology for defining low or high genomic risk. Once patients were classified as low genomic risk they were stated to have on average a 10% chance of recurrence within 10 years without additional adjuvant chemotherapy or additional adjuvant hormone therapy, while high genomic risk patients have a 29% chance of recurrence in these circumstances (http://www.agendia.com/healthcare-professionals/breast-cancer/test-results/; Delahaye LJM et al 2013, Future Medicine 10 9(8), https://doi.org/10.2217/pme.13.88).

ESC recalled that MSAC had previously defined 'usual care' for GEP tests as 'optimal care' — where all available sources of information (clinical risk, pathological results and predictive algorithms) are considered for informing treatment decisions (MSAC Application 1342.4; MSAC Application 1473). ESC noted that the patients recruited into the MINDACT trial had been identified using clinical and pathological criteria and the predictive Adjuvant! Online algorithm.

ESC noted that incorporating the 70 gene signature test results into usual care was comparatively safe. ESC noted that if use of the test results reduced use of chemotherapy as proposed, it would reduce the number of adverse events associated with chemotherapy.

ESC noted that the key evidence to support the use of the 70 gene signature test was the MINDACT trial which enrolled four different groups of patients (n = 6693) (Cardoso F et al 2016). The four patient groups were:

- low clinical risk and low genomic risk (41.0%);
- low clinical risk and high genomic risk (8.8%);
- high clinical risk and low genomic risk (23.2%); and
- high clinical risk and high genomic risk (27.0%).

ESC noted that while four groups were enrolled, the application relied upon the results seen in the group of patients with **high clinical risk** and **low genomic risk** as this is the relevant proposed population (n = 1497) for which it was proposed that the 70 gene signature test would change clinical management — half of whom were randomised to chemotherapy and hormone therapy and half of whom were randomised to hormone therapy alone.

ESC noted that the MINDACT trial was designed to demonstrate the superiority of the 70 gene signature test over usual care when assigning risk categories and making decisions about the need for chemotherapy. ESC noted that the trial was ongoing.

ESC noted that, in the high clinical risk and low genomic risk group, five year DFMS in those who also did not receive adjuvant chemotherapy was 94.7% (95% confidence interval

[CI] 92.5%–96.2%). This was above the 92% non-inferiority boundary set by the investigators, meeting the non-inferiority objective of the trial, and was interpreted as evidence that such patients could avoid chemotherapy without worsening clinical outcomes. No rationale was provided in the protocol or the trial report as the basis for setting this 92% non-inferiority boundary. The pre-MSAC response from the applicant subsequently provided a rationale for this boundary.

However, ESC noted that in a secondary intention to treat (ITT) analysis in the high clinical risk and low genomic risk group, five year DFMS was 95.9% (95% CI 94.0%–97.2%) in the patients randomised to chemotherapy and 94.4% (95% CI 92.3%–95.9%) in those who did not receive chemotherapy. ESC noted that, while not statistically significant (p=0.27), this meant there was a 1.5% absolute benefit in five year DFMS in the group who received chemotherapy (adjusted hazard ratio (HR) for distant metastasis or death with chemotherapy versus no chemotherapy of 0.78 (95% CI 0.50–1.21). ESC queried whether this potential benefit would be attractive to patients despite the side effects of chemotherapy.

ESC also noted that per-protocol analyses indicated there were no significant differences in five-year DFMS (HR 0.65; 95% CI 0.38–1.10) or overall survival (HR 0.63; 95% CI 0.29–1.37) in the high clinical risk and low genomic risk patients regardless of whether they received chemotherapy or not. However, per-protocol five-year disease free survival was significantly lower in those patients who did not have chemotherapy (90.3%) compared with those who had chemotherapy (93.3%; HR 0.64, 95% CI 0.43–0.95).

ESC suggested that, given that there were no significant differences in DFMS or overall survival seen in the high clinical risk and low genomic risk group regardless of whether they received chemotherapy or not, use of chemotherapy still seems to be a safe option in risk averse patients.

ESC also noted that there were no significant differences in the ITT or per-protocol analyses of DFMS, disease free survival or overall survival in the group of patients who were classified as being at **low clinical risk** and **high genomic risk** regardless of whether they received chemotherapy or not. The absolute difference in five year DFMS was smaller at 0.8%, derived from 95.8% (95% CI 92.9%–97.6%) in the patients randomised to chemotherapy and 95.0% (95% CI 91.8%–97.0%) in those who did not receive chemotherapy.

Overall, ESC queried whether the MINDACT trial results indicated that the test was not particularly useful to direct chemotherapy decisions in patients with discordant clinical and genomic risk assessments.

In conclusion, ESC suggested that the evidence from the MINDACT trial was not compelling and suggested that longer term follow-up greater than five years was required.

ESC noted that the economic model relied upon the MINDACT trial. ESC noted that this was a European trial and that information on how this translated to the Australian setting was limited. ESC noted that only the costs included in the model were Australian while the health state utilities were from a 2002 UK study and chemotherapy disutility was from a 2007 Swedish study.

ESC noted that the economic model was driven by the MINDACT finding that the 70 gene signature test would reduce adjuvant chemotherapy use in 46.2% of high risk clinical patients. ESC queried whether such a reduction was likely in the Australian setting, noting that:

- some of the patients in the MINDACT study did not meet the PICO criteria (removing these patients resulted in a revised estimate of 40–42% reduction in chemotherapy use);
- Australian evidence suggesting that reported rates of chemotherapy (29–49%) were lower than the optimal chemotherapy utilisation rate of 56% for early breast cancer (Ng W et al 2010);
- patients may prefer to undergo chemotherapy despite being classified as having low genomic risk — alternatively, some patients classified as having high genomic risk may choose not to have chemotherapy; and
- the 70 gene signature test may identify patients who should be getting chemotherapy but currently are not.

ESC suggested information on current patterns of care data for Australian women with early breast cancer would be helpful for decision making.

ESC noted that, in the base case, use of the test would cost an additional $3,350 for an additional 0.05 QALYs. The incremental cost-effectiveness ratio (ICER) was $66,640 per QALY in the base case. However, ESC noted that the outcomes of the economic model were largely driven by the disutility (-0.12) associated with having chemotherapy; the sensitivity analysis varying this value resulted in ICERs of ~$56,000 per QALY to ~$130,000 per QALY.

ESC did not accept the time horizon of five years for the model, noting that the time horizon for the base case in both the Oncotype DX and Prosigna applications was 30 years. ESC noted that using a 30 year time horizon in the model increased the incremental cost per QALY gained to ~$131,000.

ESC noted that the model indicated that the 70 gene signature test may actually reduce life years by 0.03 over the 30 year time horizon. ESC queried whether patients may prefer to undergo chemotherapy despite its adverse effects if it slightly prolongs life. ESC suggested that providing the cost per life year gained would be used for decision making.

ESC agreed that, while not all of the adverse events of chemotherapy had been included in the economic model, those that had not been included were likely to be irrelevant in this population and/or difficult to quantify.

ESC noted that, if supported, the item descriptor should specify that the test should not be used to inform decisions about neoadjuvant chemotherapy.

ESC suggested that a generic item descriptor may not be feasible for the 70 gene signature test or the other breast cancer GEP tests. ESC noted a paper comparing the different tests in the same population concluded that while the tests were broadly similar at the population level, there are marked differences between tests with respect to risk stratification and molecular subtyping at the individual patient level (Bartlett JMS et al 2016). The paper reported 60.6% of tumours were assigned to different risk categories by different tests.

ESC also noted that a generic GEP item descriptor had the potential to set a floor price that may result in the MBS paying a higher price than is reasonable for later, and potentially cheaper, GEP tests. ESC noted that there was variation in the requested fees for the GEP tests already considered by ESC or MSAC (MammaPrint ~$5,400 [$4,200USD], Prosigna $2,900 and Oncotype DX $4,500).

ESC considered that patient views on treatment of breast cancer with chemotherapy were an important consideration prior to ordering the test, as some patients classified as being at high

clinical risk may already have firm preferences for or against treatment with chemotherapy (rendering the test unnecessary).

ESC noted a draft recommendation by the National Institute for Health and Care Excellence (NICE) in England against routine adoption of the GEP tests (EndoPredict, MammaPrint, Oncotype DX, Prosigna and IHC4+C) citing the need for further evidence to prove that these tests have a positive effect on patient outcomes (https://www.nice.org.uk/guidance/gid-dg10015/documents/diagnostics-consultation-document).

ESC noted that, while discussions to grant a licence to perform the test in an Australian laboratory are ongoing, all testing is currently performed overseas.

ESC KEY ISSUES	ESC ADVICE
Evidence base	Variable interpretation of MINDACT results. Difficulties with the reported non-inferiority analysis. Longer follow-up needed (need more than 5 years).
Testing location	ARTG application in process for Australian lab to perform (could help solve legislative issues for performing the service in an overseas laboratory)
MBS item descriptor	Exclusion of neoadjuvant chemotherapy. Item descriptor can only be specific to GEP in question (in response to RCPA query).
Genetic profiling tests	Future issues with different GEP tests; different questions with different results. NICE (England) draft guidelines in contradiction to USA ASCO guidelines on breast cancer GEP.
Cost effectiveness calculations	Need actual Australian patterns of care data on chemotherapy use in this group to help calculations.
Time horizon	Literature and previous submissions all suggest the model horizon should be longer than 5 years and most likely expected lifetime.
Applicability of evidence	Consider if the MINDACT trial is applicable to the Australian setting, not only in terms of study population and rates of CT treatment, but also in terms of the change in practice.
Model uncertainty	There is some uncertainty in the model associated with the heterogeneity of sources of input parameters.
Approach to economic evaluation	Confirm that the approach to economic evaluation is appropriate in light of clinical evidence of safety and effectiveness and their demonstrated superiority/non-inferiority.
No evidence and ICERs available for sub-groups	Consider if the current level of information is sufficient for making a recommendation decision.

15. Other significant factors

Nil

16. Applicant's comments on MSAC's Public Summary Document

There are many risks to Australian women who receive adjuvant chemotherapy for breast cancer. These risks include hair loss, hyperbilirubinemia, fatigue, asthenia, lethargy, malaise, rash/skin reactions, diarrhoea, nausea, vomiting, abdominal discomfort, other infections, sensory neuropathy, long-term cardiac toxicity, secondary leukaemia, cognitive function, neurotoxicity, fertility issues and sexual dysfunction as well as the 1:325 chemotherapy-induced short term mortality risk. Most of these complications have not been mentioned or calculated within the Griffith Evaluation Group's cost effectiveness analysis section of their independent Assessment Report. Even so, they still concluded that "MammaPrint is superior in terms of safety and non-inferior in terms of clinical effectiveness compared to no testing (usual care)." Further, they concluded that "Overall, there is supportive evidence that 70-gene signature is cost=effective at the selected willingness-to-pay threshold." MINDACT has demonstrated with internationally accepted and peer reviewed Level IA randomised controlled evidence that in clinically high risk breast cancer patients who return a low risk 70-gene signature genomic result, that there is no statistically significant difference in 5 year distant metastasis free survival or 5 year overall survival outcome between patients treated with or without chemotherapy. Therefore, we strongly disagree with any statement by MSAC to the contrary. Furthermore, TAILORx has just published very similar findings to MINDACT, and as such, there are now two international Level IA studies supporting the widespread introduction of genomic testing for eligible women with a new diagnosis of breast cancer. Finally, ASCO, NCCN, ESMO & St Gallen all recommend the use of the 70-gene signature in their published guidelines, such that the 70-gene signature is now the international standard of care. Therefore, Genome Investigation, the Applicant, formally requests that MSAC changes it's recommendation to the Minister of Health - so that Australian women can now benefit from the publicly funded introduction of this new genomic technology. This would prevent the over-treatment of many genomically low risk Australian women suffering from a diagnosis of breast cancer, along with preventing the many unnecessary complications of chemotherapy.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
visit the MSAC website