



Australian Government
Medical Services Advisory Committee

Public Summary Document

Application No. 1342.2 – Oncotype DX® breast cancer assay to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit

Applicant: Specialised Therapeutics Australia

Date of MSAC consideration: MSAC 65th Meeting, 26 November 2015

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at www.msac.gov.au

1. Purpose of application and links to other applications

MSAC Application 1342.2 was a second resubmission to request Medicare Benefits Schedule (MBS) listing of a 21-gene gene expression profiling (GEP) test (marketed as Oncotype DX) for use in patients with newly diagnosed stage I or II invasive breast cancer who are oestrogen receptor positive (ER+) or progesterone receptor positive (PR+), human epidermal growth factor receptor 2 negative (HER2-) and either lymph node negative (LN-) or lymph node positive (LN+) in post-menopausal women with up to three positive nodes. The original submission and first resubmission were received from Genomic Health Inc. (GHI) and assessed by MSAC in November 2013 and April 2014 respectively. The evidence for assessment of this second resubmission was submitted on 22 June 2015 from Specialised Therapeutics Australia (STA).

2. MSAC's advice to the Minister

After considering the available evidence presented in relation to safety, clinical effectiveness and cost-effectiveness of gene expression profiling of 21 genes in breast cancer to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit, MSAC deferred public funding because of concerns that the optimal population and purpose had not yet been identified.

MSAC advised that the applicant should address issues raised regarding the population of patients who would most benefit from the Oncotype DX (ODX) technology, specify how the ODX results should guide the prescribing decision relating to adjuvant chemotherapy, compare ODX with current predictive algorithms such as Adjuvant! Online, and amend the economic analysis based on the optimised approach. MSAC recommended reconsideration of the application via ESC.

MSAC also requested that the applicant explain how the proposed registry would assist in monitoring the implementation of ODX testing.

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

This application requested a third MSAC consideration of public funding of a 21-gene gene expression profiling test for post-menopausal women with newly diagnosed stage I or II invasive breast cancer who are oestrogen receptor positive (ER+), progesterone receptor positive (PR+), human epidermal growth factor receptor 2 negative (HER2-), either lymph node negative (LN-) or lymph node positive (LN+) with up to three positive nodes. MSAC had previously assessed this application at its November 2013 and April 2014 meetings.

The test predicts ten year cancer recurrence in women and likelihood of response to adjuvant chemotherapy who meet the criteria above. The objectives of testing are to confirm both women at low risk of recurrence who should be spared adjuvant chemotherapy, and also women at high risk of recurrence who should receive adjuvant chemotherapy.

The current resubmission further restricted the patient eligibility criteria for use of ODX to address concerns raised by MSAC at its April 2014 meeting. Specifically, three “negative factors” associated with a poorer clinical prognosis were added to the eligibility criteria for testing. These factors were: tumour size >20 mm, grade 3 tumour, PR or ER <10%, and nodal macrometastases (>2 mm). However, MSAC noted that the justification for choosing these risk parameters was not explicitly justified, and that there were currently four prospective studies underway due to report in 2017 which may provide further clarity on this issue. MSAC considered that the patient population that would derive greatest benefit from ODX testing was poorly defined. MSAC noted that ODX gene expression profiling technology may only provide a significant benefit to the patient group who can't be classified as either low or high risk on the basis of their clinicopathological features. MSAC suggested that the applicant perform additional analysis to define the characteristics of the patient group who can't currently be classified. This population should be used in the cost effectiveness modelling.

MSAC noted that the laboratory performing genetic testing is outside Australia and therefore does not meet the requirements of Section 10(1) or clause 16A(2b) of the *Health Insurance Act 1973*. MSAC discussed the implications of this and advised that this represented an implementation and logistics issue and would require a change in legislation. MSAC considered that this was a matter for government.

MSAC noted that the applicant proposed that clinicians refer both to the recurrence score (a continuous variable) and various risk score thresholds from the ODX technology for decision-making in relation to treatment. However, the evidentiary basis for selecting these thresholds has not been provided and they have varied over time, for example as reflected in the 19 November 2015 New England Journal of Medicine article by Sparano et al defining “low risk” as a recurrence score less than 10 instead of less than 12. MSAC noted that this fluidity in definition obscured whether the evidence presented should be interpreted as discovery studies to develop the test characteristics, or as validation studies to confirm the performance of the test according to a set of pre-defined characteristics.

MSAC considered that the population and the purpose of the test should be more narrowly defined to:

- more clearly exclude patients for whom there is currently no uncertainty over the decision to prescribe adjuvant chemotherapy or not, and

- for those patients for whom this prescribing decision is currently uncertain, more clearly specify the optimal, evidence-based approach to this prescribing decision with reference to how the prescribing decision should pivot around the reported recurrence score and/or pre-defined thresholds of the recurrence score.

MSAC considered the comparative predictive performance of the ODX gene expression profiling technology and noted that the definition of ‘standard care’ used as the control has been subject to considerable change and was difficult to define. MSAC noted that current predictive algorithms such as Adjuvant! Online may be sufficient to predict risk and inform treatment decisions in patients who are low and high risk. The ODX technology may not provide any additional benefit beyond these predictive algorithms in the broader proposed populations. In respect of comparators for cost-effectiveness with current decision-making tools, MSAC noted that neither the ADIS or ADIS2 appeared to compare ODX to Adjuvant! Online. MSAC considered that some of the benefit reported in ADIS and ADIS2 data from incorporation of ODX into decision-making could derive from systematic application of available alternative decision aids, such as Adjuvant! Online.

MSAC noted a number of studies consistently reported a projected change in treatment in 18-40% of women with 1 – 3 “negative factors” compared with the use of informal assessments of risk of recurrence. This evidence was considered of reasonable quality. MSAC also considered the new evidence presented in the Pre-MSAC response. The large prospective study, published in 19 November 2015 New England Journal of Medicine article by Sparano et. al., demonstrated that ODX scoring of low risk women was predictive of freedom from recurrence and overall survival with five years follow-up. MSAC accepted that this data supported the clinical validity of ODX in predicting clinical outcomes in low risk women. However, these data were not directly relevant to ascertaining clinical utility in changing clinical management in women who are not clearly at low risk. The four ongoing studies scheduled to report in 2017 were expected to be more relevant to the question of clinical utility in the MSAC proposed patient population.

MSAC accepted that, for some patients, the ODX technology may be predictive of clinical outcomes and the response to chemotherapy. However, MSAC suggested that the applicant present the data in the form of a receiver/operator characteristic (ROC) curve of adding ODX to current staging and predictive methods to inform the incremental sensitivity and specificity of the ODX test. This would help assess both types of discordant results (eg where ODX is “positive” and Adjuvant! Online is “negative” as well as where ODX is “negative” and Adjuvant! Online is “positive”), and thus assess errors in terms of both under- and over-treatment. Specific consideration should be given to those women who should receive adjuvant therapy, but do not based on ODX results. This is the greater safety concern with use of the test than the procedure to obtain the biospecimen for the test.

MSAC considered the cost effectiveness of the ODX technology. MSAC noted that the applicant increased its proposed MBS fee to \$ **redacted**, but provided no justification of the increased cost. However, the applicant also decreased its proposed cost to the MBS to a confidential \$ **redacted**, achieved by paying a \$ **redacted** rebate to the government after each service rendered and the government has paid its rebate to the patient. MSAC noted that patients may be exposed to severe out of pocket expenses with this test, particularly the requirement for patients to pay the full cost themselves before receiving any MBS rebate because it would not be bulk-billed. The difference between the amount paid upfront by the patient and the amount subsequently received from the government rebate is subject to uncertainty affected by the setting in which the bodily specimen tested is obtained. MSAC considered that these expenses may be a significant barrier for some patients.

MSAC considered that there was considerable uncertainty in the economic modelling. MSAC accepted that, contrary to the advice from its Evaluation Sub-Committee, the model had been modified to use anastrozole as the baseline hormonal therapy rather than tamoxifen, which appropriately reflects contemporary management. Outputs from the model changed depending on what data was used as inputs. In one particular example, although the results of the two small Australian studies predicting change in management fell within the range of similar studies conducted internationally, using ADIS compared to the more favourable ADIS2 resulted in important differences in ICER outputs across the subgroups presented. In addition, although ICERs looked favourable for some populations, ODX was dominated by standard care in more obviously low and high risk groups implying that more careful selection of the eligible patient population is needed to optimise the cost effectiveness of the ODX technology in Australian patients. MSAC suggested that this variation across subgroups should help distinguish between those patients for whom the case for MBS funding is weak or strong. For example, removing those patient subgroups for which the economic evaluation suggests that adding the ODX test is dominated or has unfavourable cost-effectiveness (ie patients who are in scope according to the proposed population, but are clearly high risk or clearly low risk without reference to an ODX test result) would tend to improve the clinical and economic arguments in favour of funding the test for the remaining patient subgroups. For example, the more favourable economic results suggest the following patient subgroups might be worth exploring further: for node negative women, one or two negative factors; for node positive women, one additional negative factor.

MSAC noted advice from its ESC that the estimated QALYs associated with testing were very small, 0.04 – 0.12, and this is perhaps below a threshold for clinical effectiveness. MSAC disagreed with this assessment and noted that the social effect of avoiding chemotherapy was not quantified in the analysis.

MSAC noted that there was uncertainty in the financial impacts of the ODX technology and that the estimated budgetary impacts were influenced by assumed reductions in PBS costs of adjuvant chemotherapy. MSAC agreed with advice from its ESC that there may be a high risk of leakage outside the requested item descriptor for patients who want to ascertain their prognosis for reasons other than decision making regarding adjuvant chemotherapy. The risk of leakage would be expected to be greater beyond a population meeting more tightly defined eligibility criteria. MSAC noted that careful monitoring of any MBS-funded use might therefore be required, and also noted that the applicant had stated its willingness to fund a registry for patients. MSAC suggested that future submissions should address this issue of leakage fully with a defined plan to monitor compliance to the intended population and purpose.

In deferring the application, MSAC requested that the following issues be addressed in particular:

- better description of the patient population that would most benefit from being tested with Oncotype DX by removing those patients groups for which the economic evaluation shows that the test is dominated or has unfavourable cost-effectiveness, together with a clear MBS item descriptor to minimise leakage from this optimal patient group;
- demonstration of the incremental gain in risk prediction, health outcomes, healthcare cost offsets, and cost effectiveness in this narrowed population over currently available predictive algorithms such as Adjuvant! Online;
- demonstration that the clinical and economic evaluations fully encompass the consequences for those eligible patients for whom Oncotype DX and Adjuvant! Online yield both types of discordant results;

- clarification of the Oncotype DX risk score thresholds for decision-making relating to treatment, and provision of the evidentiary basis for selecting these thresholds;
- provision of further detail on the proposed patient registry and the expected value of the information to be collected.

4. Background

The original application was previously considered by MSAC in November 2013, and the first resubmission was considered in April 2014. On both previous occasions, MSAC advised the Minister that it did not support public funding.

The applicant’s resubmission noted that the service had been considered on previous occasions, and that “there remains a number of specific issues around which MSAC seeks further information and clarity”. The applicant’s resubmission stated that “these relate primarily to the applicability of the evidence base for Oncotype DX to current Australian standards of care (SOC) and the impact of the test on decision-making in clinical practice”, and that “the purpose of this resubmission is to address these outstanding issues with the inclusion of new real world evidence about the use of Oncotype DX in an Australian setting”.

5. Prerequisites to implementation of any funding advice

This application related to a test that is conducted in a single laboratory located outside Australia. This means the test would not be subject to regulation by the Australian Therapeutic Goods Administration (TGA).

The Specimen Collection Kit for Oncotype DX has been registered by the TGA and listed on the ARTG since August 2014 by its Sponsor, Emergo, and was registered with the TGA and listed on the ARTG by the current Sponsor, Specialised Therapeutics Australia on 28 April 2015.

6. Proposal for public funding

The applicant proposed the following MBS item descriptor:

Table 1: Proposed Item Descriptor

MBS [item number] (proposed MBS item) Pathology Group P7 Genetics	
Gene expression profiling of tumour samples (surgical resection preferably or core biopsy) by reverse-transcriptase polymerase chain reaction (RT-PCR) technique for 21 genes in breast cancer tissue.	
May only be used to test samples from patients with the following characteristics as determined by the referring clinician:	
<ul style="list-style-type: none"> - early invasive breast cancer (stages I-II) - suitable for hormone therapy - suitable for adjuvant chemotherapy - ECOG performance status 0-2 - with <3 "negative factors" ("negative factors" are defined in notes) 	
and	
<ul style="list-style-type: none"> - as determined by an Australian pathology laboratory: - invasive tumour >2mm - node negative or 1-3 positive nodes - oestrogen receptor positive or progesterone receptor positive as determined by immunohistochemistry - HER2 negative as determined by immunohistochemistry and/or in situ hybridisation 	
May only be used once per new primary breast cancer	
Fee: \$ redacted	Benefit (85%): \$ redacted

Notes: Negative factors include any of the following tumour characteristics:

- tumour size >20 mm
- Grade 3 tumour
- PR or ER <10%
- nodal macrometastases (>2mm)

The application proposed an MBS fee of \$ **redacted** to cover the costs of collecting and preparing the sample (performed in Australia). The proposed fee was higher than the previous resubmission, however no justification for the increase was provided.

The application stated that the majority of the MBS fee is the GHI charge for performing the assay and delivering the results whereas the cost of obtaining the Oncotype DX Specimen Kit amounts to a small fraction of the proposed MBS fee. The applicant indicated that it was willing to negotiate the MBS fee to ensure equitable and cost-effective access in Australia.

This re-submission included a proposal to reduce the MBS fee to \$ **redacted** under a confidential pricing arrangement involving:

- listing the service on the MBS at a fee of \$ **redacted**;
- STA would charge patients \$ **redacted** per service;
- patients would be reimbursed through Medicare for the \$ **redacted** fee, at the 85% rebate level, with a maximum permissible gap of \$ **redacted** gap between the MBS fee and rebate (see Section G.10.1(c) of the Medicare Benefits Schedule, November 2015) or the 75% rebate level if the sample is taken during hospitalisation (See section G.10.1 if the Medicare Benefits Schedule, November 2015);
- the Department of Health or Department of Human Services would record total number of MBS services, as is current standard practice, in a given period (e.g. 12 months); and
- the Department of Health would seek a rebate from STA of an amount equivalent to \$ **redacted** (\$ **redacted** less \$ **redacted**) for each service processed.

7. Summary of Public Consultation Feedback/Consumer Issues

Feedback on the original draft protocol broadly supported GEP testing on the basis that knowledge of the susceptibilities of a patient's breast cancer to chemotherapy and/or endocrine therapy would allow more informed treatment decisions with appropriate combinations of therapy.

Feedback from consumers suggested that public access to the intervention would mean better diagnosis, and therefore better patient outcomes, and noted that breast cancer affected 12,670 women per year. However, it was unclear whether consumers understood the test would be prognostic, providing a risk figure to help inform the broader clinical outlook, rather than diagnostic.

Feedback also suggested that, for women with a recurrence score which indicates chemotherapy is not required, there would be advantages in avoiding a toxic treatment and its associated side effects that may ultimately be of no benefit to them.

Many consultation responses considered the cost of the test as out of reach for most women; and it was suggested that listing the test may improve access. Responses indicated that whilst the test was not perfect, it could be an important tool to assist women in making decisions regarding their treatment.

8. Proposed intervention's place in clinical management

This was a new intervention as there was currently no tumour specific chemotherapy subtyping tool available involving genetic testing to determine the likelihood of benefiting from adjuvant chemotherapy.

Currently, Oncotype DX testing would not be eligible for reimbursement under Medicare as the test is provided by a single laboratory outside Australia, and only laboratories accredited by the National Association of Testing Authorities (NATA) can conduct pathology tests listed in the Medicare Benefits Schedule (MBS).

Without amendment, current legislation governing the MBS would prevent reimbursement through the MBS. If listing of this service were to be supported, this would be a matter for government.

The resubmission maintained that molecular classification would be an adjunct to current clinical practice rather than replacing any part of it.

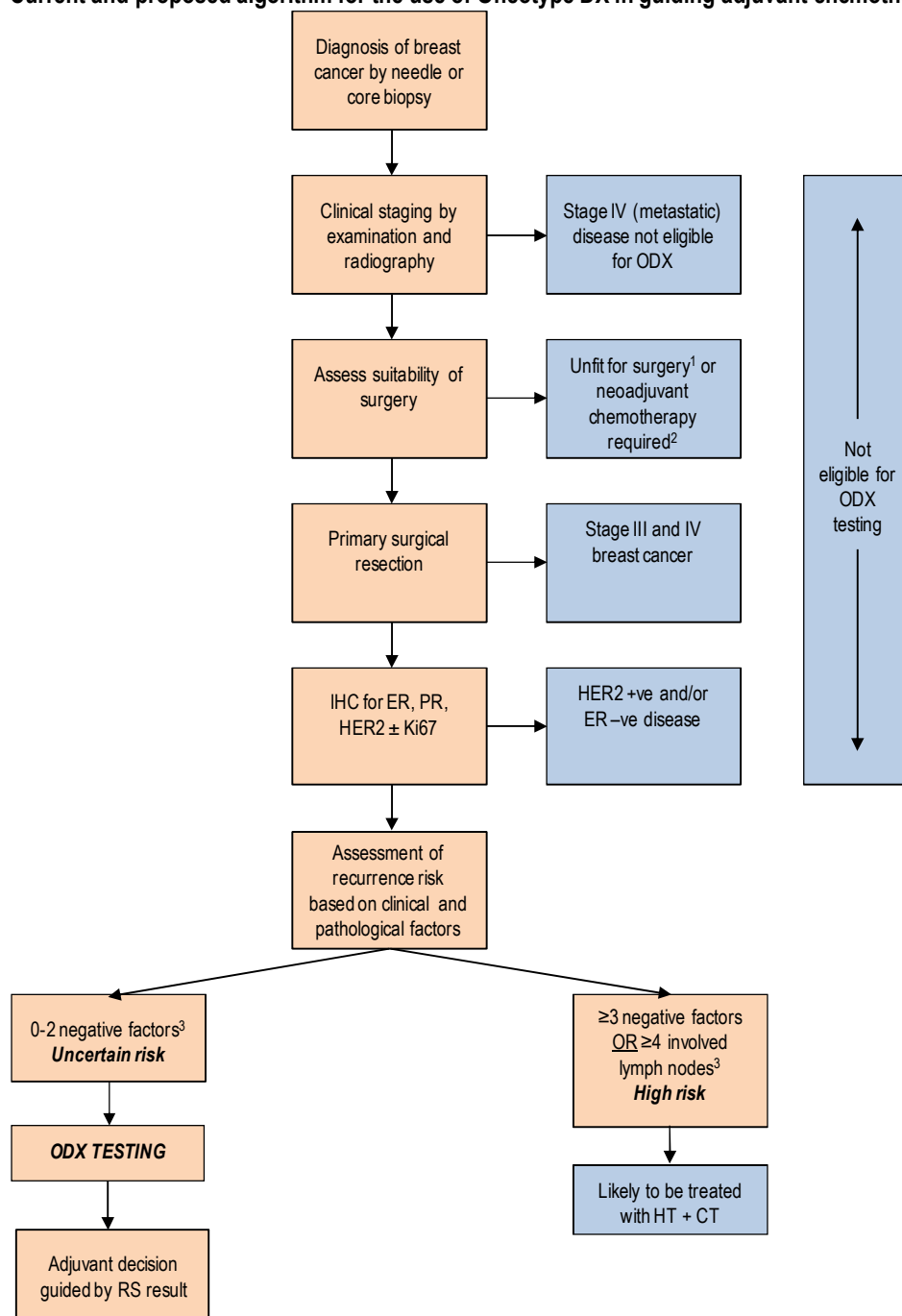
The algorithm provided in the resubmission was updated from the original Protocol and submission. In the algorithm for 1342.2, immunohistochemistry for hormone receptor status, HER2 status and potentially Ki-67 would only be conducted after surgical resection; the assessment of eligibility for the proposed test would also be based on the number of negative factors; and re-testing would not be permitted. Although included in the proposed descriptor, Progesterone receptor status was not explicitly identified in the algorithm.

In current clinical practice (usual care), prognostic factors are considered in combination with clinical judgement to determine a patient's likely risk of recurrence and likely benefit from adjuvant chemotherapy. Factors highlighted in the resubmission included patient characteristics (eg. age, menopausal status), tumour characteristics and the expression of genetic markers.

The resubmission stated that there is a greater level of uncertainty in the decision to recommend adjuvant chemotherapy among patients with less than three of the following four "negative factors": tumour size >20 mm, grade 3 tumour, PR or ER <10%, and nodal macrometastases. These patients would be eligible for the Oncotype DX test. The decisions about adjuvant chemotherapy would be guided by clinical judgement as well as the Recurrence Score, and could result in a lower proportion of patients receiving adjuvant chemotherapy.

The independent critique of the resubmission considered that, overall, the clinical management algorithm appeared reasonable given the proposed MBS item descriptor.

Current and proposed algorithm for the use of Oncotype DX in guiding adjuvant chemotherapy



¹ ODX is only appropriate for post surgical patients

² Patients who have received neo-adjuvant chemotherapy would continue with chemotherapy

³ The following negative factors were considered:

- Tumour size >20 mm
- Grade 3 tumour
- PR or ER <10%
- Nodal macrometastases (>2 mm)

9. Comparator

The resubmission retained the main comparator (usual care) that was previously accepted by MSAC, but changed its definition. Usual care was defined in the resubmission as a subjective assessment of various clinical and pathological factors to estimate the risk of recurrence; which may be combined using formal algorithms or using clinical judgement alone. The independent critique of the resubmission noted that the original consideration defined usual

care as “traditional clinical judgement based on clinical, pathological and molecular parameters to estimate the risk of recurrence by combining them in informal or formal algorithms (PSD for MSAC Application 1342, November 2013).

10. Comparative safety

There was no change to the comparative safety in the re-submission. However, the independent critique noted that, in considering the original submission, MSAC previously considered that, although the test was procedurally safe, because it relied on samples already taken for other purposes, there was a degree of risk in the misallocation of patients to risk categories, which would affect the outcomes of the therapy subsequently selected.

11. Comparative effectiveness

There was no change to the analytic validity or clinical validity analyses presented for resubmission 1342.2 compared the previous considerations. The basis of the clinical utility of the test in the application was retrospective analyses of tumour samples from patients randomised in two randomised comparative trials comparing tamoxifen alone and tamoxifen in combination with chemotherapy (Paik et al (2006; node negative) and Albain et al (2010; node positive).

Table 2: HR for disease free survival of chemotherapy+hormone therapy versus hormone therapy alone by risk subgroup, defined by recurrence score from the proposed 21-gene expression profiling test

Recurrence score subgroup	Node negative (Paik et al., 2006) hormone therapy (95% CI)	Node positive (Albain et al., 2010) hormone therapy (95% CI)
Low recurrence score	1.31 (0.46 - 3.78)	1.02 (0.54 - 1.93)
Intermediate recurrence score	0.61 (0.24 - 1.59)	0.72 (0.39 - 1.31)
High recurrence score	0.26 (0.13 - 0.53)	0.59 (0.35 - 1.01)

Source: Albain 2010, Figure 5; Paik 2006, Figure 3

The resubmission also presented the study design and preliminary results (where available) for four prospective randomised studies including Oncotype DX (OPTIMA, TAILORx, RxPONDER and WSG-PlanB). All were long-term studies with expected completion dates later than December 2017. These studies were expected to provide information on the safety of removing chemotherapy in node positive patients with low RS values (OPTIMA) and the risk of recurrence in specific RS-defined subgroups where the benefit of chemotherapy remains uncertain.

Preliminary prospective data (WSG-PlanB study) “showed that chemotherapy can be safely withdrawn in patients with low RS (<12) by demonstrating a 3-year EFS rate of 98.3% in 348 patients treated with hormone therapy alone.”

12. Economic evaluation

The resubmission provided an updated modelled cost-utility analysis. The structure of the model remained unchanged, but some model inputs were changed from the previous resubmission:

- treatment decisions were based on data from subgroups of the ADIS2 dataset with < 3 negative factors consistent with the proposed MBS population for Oncotype DX (sensitivity analysis conducted on patients with the number of negative factors);
- the risk of disease recurrence beyond 10 years was assumed to be zero for all patients (tested in sensitivity analysis);

- the cost and efficacy of anastrozole hormone therapy were incorporated into the model; and
- all unit costs were updated.

The model generated an ICER/QALY of \$9,277 in the node negative population. This compared with an ICER/QALY of \$18,899 in the models for Application 1342, and resubmission 1342.1. The difference was driven by slight differences in the proportion of patients in the RS categories (from 46.5% to 50.6% in low RS and from 13.9% to 10.9% in high RS), a decrease in the recurrence rates assumed for node negative women in the low and intermediate RS categories (almost halved), the increased assumed relative risk of the effect of the addition of chemotherapy in high RS patients (from 0.26 to 0.22), and the much higher proportion of patients in the low RS category removing chemotherapy from the treatment regimen (-7% in the previous application to -18% according to ADIS2).

As the economic evaluation was based on two trials with relatively small numbers of participants, and a very small QALY gain (0.04 to 0.12, i.e. 16-49 days), ESC questioned whether there should be a minimum threshold before funding is considered. Whilst ESC noted that there could be economic benefits borne through the avoidance of unnecessary chemotherapy, the QALY gain was considered to be very low.

The following table provided by the applicant in its pre-ESC response document showed ICERs by the number of negative factors for the ADIS and ADIS2 studies.

Number of negative factors	ADIS				ADIS2			
	Node negative		Node positive		Node negative		Node positive	
	Treatment changed	ICER	Treatment changed	ICER	Treatment changed	ICER	Treatment changed	ICER
0	10.5% (4/38)	Dominated	23.1% (3/13)	DOMINANT	30.9% (17/55)	\$33,522	55.6% (10/18)	DOMINANT
1	22.2% (10/45)	\$8,598	29.6% (8/27)	DOMINANT	39.5% (32/81)	\$4,454	50.0% (18/36)	DOMINANT
2	42.9% (6/14)	\$1,583	0.0% (0/8)	Dominated	38.9% (7/18)	DOMINANT	50.0% (11/22)	DOMINANT
3	0.0% (0/4)	Dominated	0.0% (0/2)	Dominated	50.0% (2/4)	DOMINANT	16.7% (1/6)	\$78,412

There were uncertainties with the economic model, which when tested by ESC, resulted in significant variances in the ICER. The applicant used input parameters that could lead to model predictions considerably in favour of the proposed intervention. This included the use of ADIS2 instead of ADIS, and a lower hazard ratio for high risk groups than the previous submission (i.e. 0.22 versus 0.26 in node negative patients based on the hazard ratio in intermediate subgroup).

ESC noted that, if the model used ADIS2 instead of ADIS, the proportion of patients who receive chemotherapy in the low and intermediate risk groups would increase considerably in the usual care arm. This meant lower incremental costs and a lower ICER in favour of the proposed intervention. If the model used ADIS instead of ADIS2, the ICER doubled (\$19,168 per QALY) for node negative and moved from dominant to \$10,392 per QALY for node positive. ESC suggested that the negative factor list from the eligible population could include “node positive” and an eligibility criteria of 1-3 negative factors, as this would then exclude all dominated scenarios.

With regard to the two patient populations, ESC suggested that favouring the ADIS population over the ADIS2 population may be more representative of the patient-pay scenario proposed in the submission. ESC noted that the requirement for the ADIS2 population to pay for the test may have significant behavioural impacts on treatment adherence, which would be more favourable for the intervention compared with the low/no cost scenario of either the original ADIS study or public funding through the MBS.

ESC found that there were some other minor issues with model inputs (e.g hazard ratios for chemotherapy), which may have only minimal effects on model, but still generated uncertainty.

ESC noted that the likelihood of recurrence is lower with anastrozole than with tamoxifen. The revised economic model factored in the proportion of anastrozole use in Australia, but did not adjust for the lower recurrence risk with anastrozole. ESC agreed that, given the very small QALY gain indicated by the model, even small changes in favour of anastrozole might negate the gain.

13. Financial/budgetary impacts

The applicant proposed a confidential pricing arrangement.

The following table shows the estimated number of services per year in the assessment report.

Estimated number of services per year

Description	Year 1 (2016/7)	Year 2	Year 3	Year 4	Year 5
Patients eligible for testing	redacted	redacted	redacted	redacted	redacted
Node negative	redacted	redacted	redacted	redacted	redacted
Node positive	redacted	redacted	redacted	redacted	redacted
Node negative	redacted %	redacted %	redacted %	redacted %	redacted %
Node positive	redacted %	redacted %	redacted %	redacted %	redacted %
Patient population initiating Oncotype DX in each year of MBS listing	redacted	redacted	redacted	redacted	redacted
Node negative	redacted	redacted	redacted	redacted	redacted
Node positive	redacted	redacted	redacted	redacted	redacted

Source: Table 101, p195 of Assessment Report

ESC considered that uptake of the service appeared to be underestimated in the model and financial impacts were therefore likely to be higher than those estimated. ESC agreed that the proposed patient reimbursement arrangement in the resubmission was unlikely to occur, as the service is expected to be used primarily for inpatients (75% rebate), and the gap would not be capped. This would result in either uncapped out-of-pocket costs to patients or cost shifting to private health insurers.

ESC noted estimated financial impacts provided in the critique, which showed that the cost to the government would be heavily influenced by the assumed reduction in PBS costs. The impacts are shown in the table below

Sensitivity analysis of the estimated net cost to the Commonwealth

EXAMPLE	Estimate	2014	Year 2	Year 3	Year 4	Year 5
Overall net cost	Base case	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted
Increased patient uptake	Assuming 10% additional uptake each year in node- and node+ patients	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted
Assuming 100% patient uptake	Assuming 100% patient uptake	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted
Reduce PBS savings	Reduce PBS savings by 25%	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted
	Reduce PBS savings by 50%	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted
	Reduce PBS savings by 75%	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted

14. Key issues from ESC for MSAC

ESC considered the full range of documents available for this application, and advised that the key issues below would be most relevant to MSAC decision making:

- There is currently no mechanism to control patients' out of pocket costs under the applicant's proposal to establish a hidden pricing arrangement, and the approach would effectively lock in a monopoly price which is inconsistent with usual practice for the MBS.
- Although the ICER presented in the economic evaluation falls within the cost effective range, it may not represent good value, as it was based on a very small QALY gain (0.04 to 0.12 of a QALY) derived from a small number of non-randomised studies with small populations; and a high potential for use outside of the population where testing is effective.
- ESC also noted that the applicant used input parameters that could lead to model predictions considerably in favour of the proposed intervention (including a failure to adjust for the lower recurrence risk of anastrozole compared with tamoxifen).
- ESC advised that, given the very small QALY gain indicated by the model, even small changes, particularly in favour of anastrozole vs tamoxifen, could negate the gain.
- The economic model did not appear to have been calibrated to ensure internal validity.
- ESC advised that MSAC's concerns regarding the capacity of continuous scores to change therapy decisions remained unaddressed. ESC noted the applicant's advice that, while the analysis was based on the use of cut-scores to determine clinical pathways, they recommended clinicians use the continuous score.
- ESC noted that the use of ADIS2 data in the analysis strongly favoured the intervention as the proportion of patients who received chemotherapy in low risk and intermediate risk groups were higher in the usual care arm, meaning lower incremental costs and hence a lower ICER. Using ADIS data, some proposed scenarios are dominated.

15. Other significant factors

Nil.

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

STA would like to thank MSAC for its consideration of this submission, and appreciates its decision to defer public funding pending the provision of further information. The issues outlined in this Public Summary Document have been addressed in the form of a resubmission that was lodged in February 2016. The applicant is confident that any remaining data gaps have now been satisfactorily addressed and looks forward to receiving a positive recommendation for this innovative and cost-effective technology.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at: www.msac.gov.au.