Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1342.5 Gene expression profiling of 21 genes in breast cancer to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit

Applicant: **Specialised Therapeutics Australia Pty Ltd**

Date of MSAC consideration: **MSAC 76th Meeting, 1-2 August 2019**

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

1. Purpose of application

A resubmission seeking public funding for the gene expression profiling (GEP) test using the real-time reverse-transcriptase polymerase chain reaction (RT-PCR) technique for 21 genes (Oncotype DX®) in patients with newly diagnosed stage I or II breast cancer, who are oestrogen receptor positive (ER-positive) or progesterone receptor positive (PR-positive), Human Epidermal Growth Factor Receptor 2 negative (*HER2*-negative), and lymph node negative (LN-negative), was received from Specialised Therapeutics by the Department of Health.

2. MSAC's advice to the Minister - August 2019

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support public funding for this gene expression profiling test for patients with breast cancer primarily because its ability to identify those who could safely be spared the addition of chemotherapy to endocrine therapy was not demonstrated by the new trial. The re-analysis of previously provided evidence was also insufficient to change the previous conclusion that the test could not satisfactorily identify those intermediate-risk patients who would benefit from the addition of chemotherapy to endocrine therapy.

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

Note: due to the technical nature of many aspects of MSAC's considerations, this summary is divided into two parts:

- *a standard summary with its usual lay summary*
- *a more technical description of some aspects of MSAC's considerations.*

Standard summary of consideration and rationale for MSAC's advice

MSAC noted that Oncotype DX generates a Recurrence Score® (RS) that the applicant claims can be used to identify patients with early breast cancer following surgery who would:

- be likely to receive no benefit, in terms of cancer outcomes, from receiving adjuvant chemotherapy (in addition to endocrine therapy), and who would not have been identified through usual care (referred to as "chemotherapy sparing")
- be likely to benefit, in terms of cancer outcomes, from receiving adjuvant chemotherapy (in addition to endocrine therapy), and who would not have been identified through usual care (referred to as "chemotherapy indicating").

MSAC noted that the recommended RS thresholds for clinical decision making had changed from 18 and 30 in the previous submissions to recommending adjuvant chemotherapy with endocrine therapy (≥26) versus endocrine therapy alone (<26). MSAC noted that the threshold was adjusted to minimise the potential for under-treatment with chemotherapy in both high-risk and intermediate-risk patients. The resubmission simply used the RS from the recently published randomised trial (TAILORx, Sparano et al., NEJM 2018) and did not provide any other evidence to support the selection of the revised threshold.

MSAC noted that the proposed fee was higher than that in the previous submissions, but no justification for the increase was provided. MSAC considered the proposed fee to be higher than expected for conducting a gene expression assay.

MSAC acknowledged that targeted gene expression assays potentially provide a means to stratify risk in early breast cancer. However, there has been no head-to-head randomised comparison of Oncotype DX with prediction of risk and treatment response against existing usual practice decision algorithms which combine clinical and pathological information (e.g. IHC-4). As yet, it has not been proven that Oncotype DX testing is either non-inferior or superior to usual clinical practice. All patients in the key trial, TAILORx, were risk-stratified via Oncotype DX, thus there is no "non-Oncotype DX" sub-group that could be used to inform the desired direct comparison. Put simply, TAILORx does provide a measure of the relative performance of the Oncotype DX tool, but only relative to itself.

MSAC recalled that Oncotype DX testing is performed by one laboratory based in the United States of America (USA), and has not been subject to regulatory approval by USA's Food and Drug Administration. MSAC noted the differences in regulation, oversight, standards and accreditation between Australia and the USA. The implications of these differences would need further consideration should the test be recommended for funding.

MSAC noted that the eligible population requested for funding had been changed from the previous submissions to match the eligibility criteria of the TAILORx trial, the results of which had been recently published. Notable differences were the removal of node positive patients and the narrower specification of tumour size (1.1-5.0 cm, or 5 mm-1.0 cm with unfavourable histology).

MSAC noted that the comparator was usual care involving clinico-pathological risk prediction. However, "usual care" did not specify which risk prediction models were used. Data to support claims of the clinical utility of Oncotype DX testing with usual care compared with usual care alone were not presented or available from the TAILORx trial (which as noted above reported on the relative performance of Oncotype DX with itself).

MSAC recalled that the major issue in previous submissions was that comparative clinical utility had not been demonstrated in Australia (or elsewhere). MSAC noted that the new

evidence in the resubmission did not directly address this concern. Substantial uncertainty remains about the relative analytic performance, clinical validity and especially clinical utility of Oncotype DX in the Australian context.

Evidence provided to support Oncotype DX testing to identify patients in the "chemotherapy sparing" group was from the TAILORx trial (based on the results reported by Sparano et al. (NEJM, 2018). This trial was a randomised comparison of chemotherapy plus endocrine therapy versus endocrine therapy alone. MSAC noted that the trial was designed to show non-inferiority in terms of cancer outcomes of endocrine therapy alone for invasive disease-free survival in women at intermediate risk of breast cancer (RS threshold of 11-25). As such, it was not a randomised comparison of Oncotype DX against any other risk prediction method to assess non-inferiority or superiority in terms of cancer outcomes. MSAC therefore considered that the trial did not provide direct evidence of the comparative effectiveness of Oncotype DX. In this regard, the randomised comparison for MammaPrint® in MINDACT (Cardoso et al, 2016) was more clinically relevant because it compared the outcomes following chemotherapy plus endocrine therapy or endocrine therapy alone in patients who had discordant clinical and genomic risk predictions. In other words, MINDACT quantified the differential outcomes of patients according to the use of a gene expression profile or not. The trial design of TAILORx does not allow such a comparison, but rather reports the relative performance of Oncotype DX with itself.

MSAC further identified a number of methodological issues with the design, conduct and reporting of the TAILORx trial that substantially increase uncertainty and the risk of bias towards concluding non-inferiority and thus in favour of Oncotype DX (further details are provided in the technical description below):

- randomisation was not used to inform a comparison of Oncotype DX with current best supported clinical judgement (that is, RS in the range of 11-25 was used as a stratifying variable to identify all trial participants who were then randomised)
- substantial and differential changes in the flow of the numbers of patients randomised to each group were reported in the trial all tend to diminish any true differences between the randomised groups, and thus bias the trial results towards concluding non-inferiority
- use of an intention-to-treat (ITT) analysis was inappropriate for a non-inferiority trial design and also biased the results towards concluding non-inferiority.

MSAC also noted new evidence from a subsequent analysis of the TAILORx trial by Sparano et al. (NEJM, 2019) investigating whether combining a further assessment of "clinical risk" with RS has further prognostic value beyond RS alone. "Clinical risk" of breast cancer recurrence was classified as "low" or "high" based on tumour size and histologic grade. "Clinical risk" was generally prognostic of distant recurrence in women with an intermediate RS of 11-25. In women under 50 years of age receiving endocrine therapy alone, the risk of distant recurrence at 9 years was less than 2% for women with a low RS of 0-10 (irrespective of "clinical risk") and around 5% for women with an intermediate RS of 11-25 and "low clinical risk". However, for women under 50 years of age with an intermediate RS of 11-25 and "high clinical risk", the risk of distant recurrence at 9 years was 12.3±2.4% for women with who received endocrine therapy alone, and 6.1±1.8% for women who received chemotherapy plus endocrine therapy. MSAC therefore concluded that for some women under 50 years of age and an intermediate RS of 11-25, withholding chemotherapy is more likely to result in an important worsening of cancer outcomes.

Overall, MSAC concluded that non-inferiority and clinical utility of Oncotype DX testing were not demonstrated for the "chemotherapy sparing" group. MSAC accepted that, for most patients, relying on the results of Oncotype DX testing to spare the addition of chemotherapy does not appear to cause harm, but for an important minority, this could result in poorer cancer outcomes. Further, the modelled economic evaluation relied on the assumption that Oncotype DX testing would lead to a marked reduction in use of chemotherapy in those patients whose RS is less than 26. The validity of this assumption was not supported by the TAILORx trial which showed a high and differential loss to follow up and a high rate of non-adherence to recommendations based on the test results.

MSAC then noted that re-analyses of data reported by Geyer et al. (NPJ Breast Cancer, 2018) from the NSABP B-20 study were presented as evidence to support Oncotype DX testing using the revised RS threshold to identify cancer outcome improvements for patients in the "chemotherapy indicating" group, including a re-analysis that also excluded those women who were *HER*-positive. Although more closely aligning with the revised RS threshold and the eligible population, MSAC concluded that these retrospective re-analyses did not strengthen the evidence previously available to support the claim for Oncotype DX resulting in superior cancer outcomes in the "chemotherapy indicating" group.

MSAC considered the modelled economic evaluation to be unreliable and highly favourable to Oncotype DX. MSAC concluded that cost-effectiveness is uncertain.

MSAC noted that the drivers of the modelled economic evaluation were:

- *the proportions of patients in the "chemotherapy indicating" component who get each treatment*

  MSAC noted that the major driver of the model was the health benefits that accrue to the "chemotherapy indicating" component of the model arising in the high-risk group (a greater proportion of whom receive chemotherapy in the Oncotype DX arm); however, the clinical claims for this component of the model were based on the Geyer et al. 2018 retrospective re-analysis of the NSABP B-20 study.

- *adherence to Oncotype DX recommendations in decision-making*

  MSAC noted that the model assumed very high rates of adherence (93.6% to 99.5%) to Oncotype DX-based recommendations for therapy management, but this was inconsistent with substantially lower rates of adherence observed in the TAILORx trial.

- *the comparator*

  MSAC noted that inputs used in the model indicated that relying on Oncotype DX testing would change clinical practice substantially from existing management, which assumes low analytic performance and adherence to current prognostic algorithms, but the source of these data for existing management was not clear.

MSAC also noted that the clinical claim of non-inferiority in the "chemotherapy sparing" component of the model was based on the group recording an intermediate-risk RS in the TAILORx trial, but changes in care were also modelled for those who would have recorded either a low- or high-risk RS in the TAILORx trial.

MSAC noted that, in the base case, "chemotherapy sparing" and "chemotherapy indicating" groups had differential effects on the incremental cost-effectiveness ratio (ICER). The base case ICER was more favourable when the two subpopulations were combined, but this was driven by benefits in the "chemotherapy indicating" group for which data are weaker.

MSAC noted that the ICER increased in the revised model, which included four cycles of chemotherapy rather than six. MSAC considered that this counter-intuitive result also raised doubts about the reliability of the model.

MSAC considered that the revised estimated budget impact is uncertain due to the uncertain uptake rate.

MSAC acknowledged that the choice of whether to receive chemotherapy or not in the context of this application for Oncotype DX is a high stakes decision, and patients and clinicians need as much reliable information as possible to be confident in the decision they make. MSAC also acknowledged that avoiding unnecessary chemotherapy is highly desirable and valuable. However, MSAC concluded that the TAILORx evidence presented for Oncotype DX testing does not provide high enough certainty about the extent to which Oncotype DX provides additional assurance over usual care regarding which patients can avoid chemotherapy safely. MSAC further acknowledged that adding necessary chemotherapy is also highly desirable and valuable. However, MSAC concluded that the Geyer et al. 2018 re-analyses provided no more certainty than the previous retrospective analyses about the extent to which Oncotype DX provides additional assurance over usual care regarding which patients need to add chemotherapy.

Lay summary
Specialised Therapeutics Australia Pty Ltd has applied for public funding of Oncotype DX testing, a type of genetic testing that is claimed to help determine the risk of a patient getting breast cancer again after they have had surgery.

The Oncotype DX test is performed in a single laboratory in the United States of America (USA). It has not been approved for use by the USA's Food and Drug Administration nor by the Australian Therapeutic Goods Administration: agencies who assess the safety of medical tests and products.

Currently, combining information from clinical assessments and pathology test results helps doctors calculate whether a patient has a low, intermediate or high risk of breast cancer returning after surgery. This helps the patient decide, with their treating clinicians, whether to have chemotherapy in addition to their hormone therapy. Specialised Therapeutics claims that this decision is most difficult for patients whose existing information shows they have an intermediate risk of the cancer returning and that the Oncotype DX genetic test can then provide valuable extra information to help this group of patients. Specialised Therapeutics presented the results from a new trial, the TAILORx trial, to MSAC to help support its claims that an Oncotype DX score of 25 or less means chemotherapy is not necessary, whereas a score of 26 or higher means chemotherapy would be beneficial.

MSAC acknowledges that patients and clinicians need as much reliable information as possible to make decisions about whether or not to have chemotherapy following surgery for breast cancer.

MSAC advised the Minister for Health that the evidence presented for Oncotype DX did not give the Committee confidence that the test would identify those patients who could safely avoid chemotherapy or those patients who would benefit from adding chemotherapy. In particular, the TAILORx trial did not compare outcomes for women who were given the Oncotype DX test with those who were not. This means there is no way of knowing whether adding an Oncotype DX test score to the information patients already get after their surgery will give them an additional, reliable basis to make treatment decisions that lead to better long-term outcomes. MSAC also advised that there were problems with how the TAILORx

trial ran, including that many of the women who started the trial dropped out before it was finished, so MSAC could not be sure that an Oncotype DX test score between 11 and 25 means it is in fact safe to avoid chemotherapy.

MSAC acknowledges that funding advice differs across the world, particularly when tests have been assessed on the basis of preliminary information. MSAC has based its advice on the most up to date information – which in this case includes the full analysis of the TAILORx results. MSAC considered that, based on all the evidence, Australian patients would likely have better cancer outcomes overall if they and their doctors continue to use existing information to decide on follow-up treatment after surgery for breast cancer.

Technical aspects of consideration and rationale for MSAC's advice

1. *Oncotype DX may be inferior than current approaches when guiding patients towards the "chemotherapy sparing" option (in terms of the likelihood of clinically meaningful worsening of cancer outcomes)*

    a. *Incorrect comparison in the submitted randomised trial (TAILORx)*
    MSAC considered that the preferred randomised comparison (like MINDACT for MammaPrint) would be between using Oncotype DX or using current approaches. The actual comparison relied on an Oncotype DX result for both arms; patients with a particular range of results were randomised to adjuvant chemotherapy with endocrine therapy or to versus endocrine therapy alone. This makes it difficult to apply the results of this trial to address the question of how the uptake of this test in Australia would affect the health of patients proposed as being suitable candidates for the test.

    b. Flawed conduct of the submitted randomised trial
    - MSAC considered that the extensive and differential losses of randomised participants after entering the trial suggested that important biases contributing to at least partially informative censoring were not adequately minimised in the trial. Such biases would be expected to extend the upper limits of the 95% confidence intervals towards and possibly beyond the prespecified minimal clinically important differences (MCIDs).

      Specifically, in the context of a trial recording low events overall (836 events of invasive disease recurrence in a total of 6907 patients with an RS of 11-25 randomised, such that 12% experienced such an event), substantial and differential changes in the flow of the numbers of patients randomised to each group were reported in Figure 1 of Sparano et al. (NEJM, 2018), see Table 1 below. Of the 3449 assigned to the chemotherapy plus endocrine therapy arm, 1101 (32%) would not contribute to a per protocol analysis, yet only 584 (17%) of the 3458 assigned to the endocrine therapy alone arm did not contribute to this analysis. The mostly differential changes between these two randomised arms listed below tend to diminish any true differences in the trial results between them, and thus bias them towards concluding non-inferiority:

        - patients who were excluded from the intention to treat analysis after randomisation (more in the chemotherapy plus endocrine therapy arm [137, 4%] than in the endocrine therapy alone arm [59, 2%])
        - crossover of treatments given between groups (i.e. there were more patients in the chemotherapy plus endocrine therapy arm who did not receive

chemotherapy [608, 18%], than patients in the endocrine therapy alone arm who did receive adjuvant chemotherapy [185, 5%])

- patients who withdrew consent (more in the chemotherapy plus endocrine therapy arm [148, 4%] than in the endocrine therapy alone arm [116, 3%])
- patients who were lost to follow-up (similar in the chemotherapy plus endocrine therapy arm [208, 6%] and in the endocrine therapy alone arm [224, 6%]).

Table 1 Flow of randomised patients in Sparano et al (NEJM, 2018)

Registered trial participants with RS = 11-25	Chemotherapy + endocrine therapy arm	Endocrine therapy alone arm
Randomised	3449 (100%)	3458 (100%)
Excluded from intention-to-treat analysis	137 (4%)	59 (2%)
Received endocrine therapy alone	608 (18%)	(not excluded)
Received chemotherapy + endocrine therapy	(not excluded)	185 (5%)
Withdrew consent	148 (4%)	116 (3%)
Lost to follow-up	208 (6%)	224 (6%)
Total not contributing to a per protocol analysis	1101 (32%)	584 (17%)
Available for a per protocol analysis	2348 (68%)	2874 (83%)

MSAC noted other signals from the reporting of the TAILORx which further substantiated its concerns about introducing bias towards concluding non-inferiority:

- different 9-year cumulative incidences of lost to follow-up events were reported in the Supplementary Appendix of Sparano et al. (NEJM, 2018) for the chemotherapy plus endocrine therapy arm (14.7%) and for the endocrine therapy alone arm (12.2%)

- for the chemotherapy plus endocrine therapy arm (but not the endocrine therapy alone arm), there was a "significant association of lost to follow-up with RS, with 9-year cumulative drop out of 16.6% for RS of 11-25, 14.3% for RS of 16-20, and 12.5% for RS of 21-25" reported in the Supplementary Appendix of Sparano et al. (NEJM, 2018).

- MSAC considered that not presenting a per protocol analysis was unusual for the analysis of a non-inferiority designed trial. The upper limit of the 95% confidence interval in the "as-treated" analysis for the primary outcome is closer to the MCID than the main analysis presented, which supported MSAC's view that a per protocol analysis would help inform the robustness of the main analysis.

  Further, MSAC noted that the "as-treated" analyses were incompletely reported. For example, survival rates across the various groups and outcome types were reported only on an ITT basis, and absolute risk differences together with their 95% confidence intervals at 5 and 9 years were not reported at all.

c. *Non-inferiority conclusion of the submitted trial subject to doubt*
Taking the two aspects of the previous point b. together, if the upper limit of the 95% confidence interval in an adjusted per protocol analysis extended beyond the prespecified MCID, MSAC considered that it could change the conclusion that, across the trial participants, endocrine therapy only is non-inferior to adjuvant chemotherapy with endocrine therapy.

Specifically, MSAC considered that the more appropriate per protocol analysis of

the primary outcome of interest (invasive disease-free survival = freedom from invasive disease recurrence, second primary cancer or death) would favour combined therapy, given that – even with the biases towards concluding non-inferiority remaining due to the trial design and conduct – the upper limit of the 95% confidence interval of the "as-treated" analysis was very close to showing clinically important worse cancer outcomes in the group receiving endocrine therapy alone (hazard ratio of 1.14 [95% CI: 0.99 to 1.31] against the prespecified minimal clinically important threshold of 1.322). MSAC recalled that this threshold was derived from an absolute difference in event rates of 3% at 5 years, which would be a greater absolute difference at 9 or 10 years. MSAC considered that these differences in risk were high, and would have an impact on whether patients with an RS of 11-25 would choose to add chemotherapy or not.

d. Other matters of concern

MSAC noted other matters of concern in seeking to interpret the results of the TAILORx trial:

- the need for a large increase in sample size during the conduct of the trial. Specifically, based on a Lachin-Foulkes correction, Sparano et al. (NEJM, 2018) reported that a 73% increase in sample size was required to account for non-adherence to assigned treatment (which is also relevant for applicability and cost-effectiveness given that non-adherence will lead to increased costs but not change outcomes), which improved precision by narrowing the resulting confidence intervals, but did not address the primary concern about bias towards concluding non-inferiority.
- the justification for the prespecified minimal clinically important differences (MCIDs). Specifically, no apparent justification was given for the prespecified non-inferiority margins, and the absolute differences at 5 years on which the wider non-inferiority margins for the secondary outcomes were based (a hazard ratio of 1.46 for overall survival and of 1.61 for distant recurrence-free interval compared with 1.322 for the primary outcome) were also not specified.
- the reporting of standard errors when 95% CIs would be appropriate. Specifically, many results of the TAILORx trial were reported with standard errors instead of confidence intervals, which convey an apparently smaller spread of uncertainty.

2. If the first issue can be satisfactorily resolved, then other aspects of the submission would need to be addressed satisfactorily in order to give advice on the circumstances in which Oncotype DX is acceptably cost-effective

a. Weaker evidence supporting the "chemotherapy indicating" option

MSAC noted that the evidentiary basis for this claim did not change since the previous MSAC decision not to support. The re-analysis primarily sought to adjust for the re-definition of the RS thresholds to those used in TAILORx.

b. *Relatively large reliance on health outcome gains from this option*

MSAC noted that, despite being based on arguably weaker evidence, this option contributed 0.1177/0.1222 = 96% to the modelled estimate of health outcomes gained (the QALYs gained for this ratio were extracted from Tables 7 and 8, below).

c. *Reservations about key adherence assumptions in the modelled economic evaluation*
MSAC expressed the following reservations regarding the key adherence assumptions:
   - The assumed estimates of adherence to Oncotype DX-based guidance on whether to add chemotherapy or not to endocrine therapy were greater than observed in the TAILORx results.
   - The assumed increments in adherence suggested comparatively low confidence in existing decision-support options, but the basis for this was unclear.

d. *Other matters of concern*
MSAC noted other matters of concern in seeking to interpret the information provided in the resubmission:
   - assumptions in the model about changes in care for RS categories outside the RS of 11-25 for participants randomised in the TAILORx trial
   - counter-intuitive consequences for the model result when changing model inputs
   - no clear rationale for the change in RS threshold
   - additional doubts relating to inferior cancer outcomes for women less than 50 years of age with an RS of 11-25 who withheld chemotherapy.

Other discussion
MSAC advised that any future submission should include:

- a more detailed rationale for the changes in the recommended RS threshold
- more detailed justifications for the prespecified minimal clinically important differences (MCIDs) with reference to the associated absolute differences at 5 years and 9 years
- use of more appropriate measures of spread of uncertainty such as 95% confidence intervals rather than standard errors
- re-assessment of whether the recommended threshold is suitable for all eligible patients under 50 years of age
- TAILORx RS data stratified by clinical risk (i.e. an analysis of the effect of RS on low and high clinical risk groups separately, for composite and distant recurrence-free outcomes)
- disaggregated modelled economic evaluation according to the clinical claims of "chemotherapy sparing" and "chemotherapy indicated" prior to aggregating into an overall modelled economic evaluation, with more convincing estimates of adherence rates and extent of change from usual care.

MSAC also discussed the possibility of requesting individual patient data from Sparano et al. to undertake a wider set of per protocol analyses, and to assess the consequences of bias.

4. Background

The original application (Application 1345) was considered by MSAC at its July 2013 meeting, subsequent resubmissions were then considered in April 2014, November 2015, July 2016 and July 2017. The PSDs for these applications can be viewed on the MSAC website.

At its July 2017 meeting, MSAC did not support Oncotype DX breast cancer assay due to the uncertainty of the incremental benefit of the Oncotype DX breast cancer assay over optimal care (Application 1342.4 Public Summary Document (PSD) 2017, p2). MSAC noted that

data from ongoing trials like the TAILORx trial, if suitable, may be useful in addressing this uncertainty (PSD, p3).

5. Prerequisites to implementation of any funding advice

The Oncotype DX Breast Cancer Assay test is performed in a single laboratory in the United States by Genomic Health Inc. Therefore, the test would not be subject to approval or regulation by the Therapeutic Goods Administration (TGA). A November 2015 report by the US Food and Drug Administration (FDA) raised concerns about the current lack of regulation within the US for assays that are 'Laboratory Developed Tests' (LDTs), such as Oncotype DX.

MSAC previously raised concerns about the reliance on a single laboratory performing the test located in the US outside Australian standards maintained through the TGA or the National Association of Testing Authorities (NATA). MSAC also previously noted that a number of complex implementation issues would need to be considered by Government if this test was supported for listing in Australia.

6. Proposal for public funding

The proposal for public funding was changed since the previous resubmission (1342.4), and is presented in Table 2 (applicant-highlighted changes with the previous submission are in red text). The resubmission requested a fee of $5,085 per service, and did not request any confidential pricing or fee arrangement.

Table 2 Proposal for public funding; changes from previous submission annotated (in red)

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.

See Note for information on how results should be interpreted.

Previous submissions did not include a note on how results should be interpreted.

May only be used to test samples from patients with all of the following characteristics as determined by the referring clinician:

- early invasive breast cancer (stages I-II)

No substantial change.

- oestrogen receptor positive or progesterone receptor positive as determined by immunohistochemistry at an approved Australian pathology laboratory

No substantial change.

- HER2 negative as determined by immunohistochemistry and/or in situ hybridisation at an approved Australian pathology laboratory

No substantial change.

- node negative

Previous submissions allowed for node positivity. Public funding no longer requested for node positive patients.

- tumour size >= 10 mm and < 50 mm, or tumour size >= 5 mm and < 10 mm with unfavourable histological features (intermediate or poor nuclear and/or histologic grade, or lymphovascular invasion)

The minimum tumour size of 2 mm has increased to 10 mm (or 5 mm with unfavourable histology).

There was previously no maximum tumour size.

Eligibility was also previously determined by the presence of 1 or 2 negative prognostic risk factors.

- suitable for hormone therapy
- suitable for adjuvant chemotherapy (ECOG performance status 0-2)
- may only be used once per new primary breast cancer

No substantial change.

Fee: $5,085

Note:

Chemotherapy decisions are guided by a patient's Recurrence Score (RS). Patients with RS <26 are recommended endocrine therapy and patients with RS ≥26 are recommended adjuvant chemotherapy according to Oncotype DX. There is some evidence that there may be a chemotherapy benefit in patients aged ≤ 50 years, with RS 16-25.

Previous submissions did not include a note on how results should be interpreted.

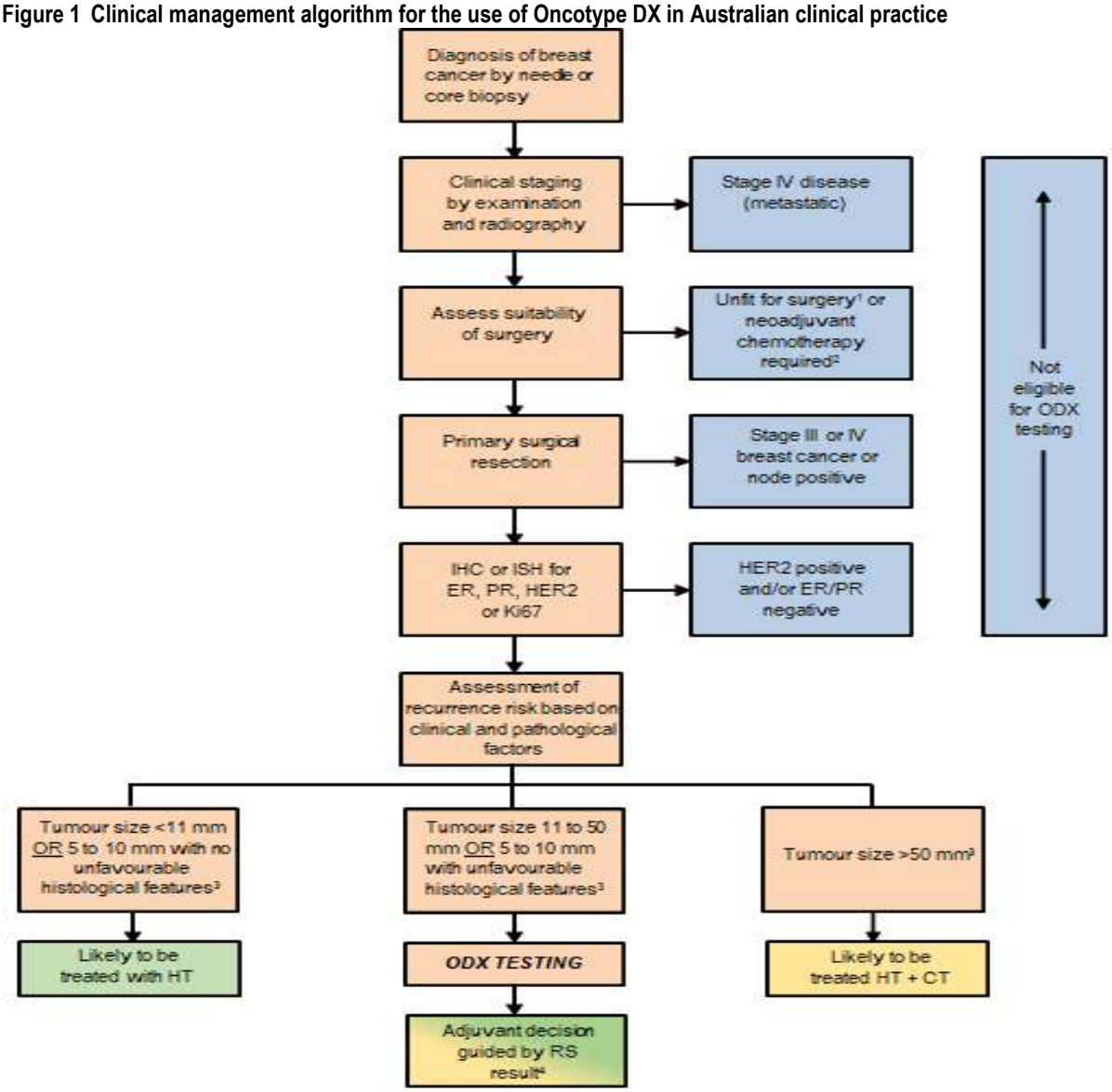
7. Summary of public consultation feedback/consumer issues

See Application 1342.4 PSD on the MSAC website.

8. Proposed intervention's place in clinical management

The resubmission's proposed clinical management algorithm (Figure 1) differed from that presented in earlier MSAC applications for Oncotype DX in that it excluded node positive patients, and the process used to exclude patients with very high or low clinical risk was based on the approach applied in TAILORx. In addition, the algorithm included a footnote to clarify how recurrence score (RS) results should be interpreted and used to guide chemotherapy decisions.

Figure 1 Clinical management algorithm for the use of Oncotype DX in Australian clinical practice



[1] ODX is only appropriate for post-surgical patients
[2] Patients who have received neo-adjuvant chemotherapy would continue with chemotherapy and Oncotype DX has not been validated for patients who have undergone neoadjuvant therapy
[3] Tumour size and grade parameters are based on eligibility for the TAILORx trial (Sparano, 2018)
[4] Chemotherapy decisions are guided by a patient's Recurrence Score (RS). Patients with RS<26 are recommended endocrine therapy and patients with RS≥26 are recommended adjuvant chemotherapy according to Oncotype DX; there is some evidence that there may be a chemotherapy benefit in patients aged ≤ 50 years, with RS 16-25.
Abbreviations: CT, chemotherapy; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; HT, hormone therapy; IHC, immunohistochemistry; ISH, in situ hybridization; PR, progesterone receptor; ODX, Oncotype DX, RS, Recurrence Score

9. Comparator

The comparator for the resubmission remained the same as that for the previous submissions - usual care. MSAC has previously accepted the comparator as usual care, defined as optimised subjective assessment of various clinical and pathological factors to estimate the risk of recurrence; which are likely combined using formal algorithms.

10. Comparative safety

The resubmission did not present a specific assessment of comparative safety. The Critique stated that the safety concerns remain as those outlined by MSAC previously and quoted in the resubmission. "MSAC previously noted that although the test is procedurally safe because

it relies on samples already taken for other purposes, there is a degree of risk in the misallocation of patients to risk categories, which would affect the outcomes of the therapy subsequently selected" (PSD for MSAC Application 1342, November 2013).

11. Comparative effectiveness

The resubmission was based on one prospective randomised trial and one re-analysis of a retrospective cohort study:

- The TAILORx trial was a prospective trial (N=10,273; registered population), that used a patient's recurrence score only to guide treatment. Women with intermediate RS (11-25) were randomised to endocrine therapy (ET) alone or ET+ chemotherapy (CT) (n=6,907; Arms B and C); and those with low (0-10; n=1,629; Arm A) or high (≥26; n=1,737; Arm D) RS were treated with ET alone or ET+CT, respectively (Sparano et al. NEJM, 2018). Results were provided for the 'main analysis set' or 'intention-to-treat (ITT) population' (n=9,719 across all four arms), and some results were also provided for the "as-treated" population, which the Critique stated was an important comparison for demonstrating non-inferiority of ET alone vs. ET+CT. In addition, Sparano et al. stated comparisons of ITT population, stratified by randomisation, could still be biased because of differences in the group refusing chemotherapy (Arm C) and the group receiving chemotherapy (Arm B).
- Geyer et al. (2018) was a retrospective re-analysis of the NSABP B-20 study (Fisher et al. 1997; Paik et al. 2006, previously considered by MSAC); a re-analysis of this study based on the recurrence scores used in the TAILORx trial and removing patients who were *HER2*-positive (Geyer et al. 2018).

TAILORx
The Critique presented forest plots for the primary outcome- invasive disease-free survival (iDFS) (Figure 2) and secondary outcome- freedom from recurrence at a distant site or distant recurrence-free interval (DRFI) (Figure 3).

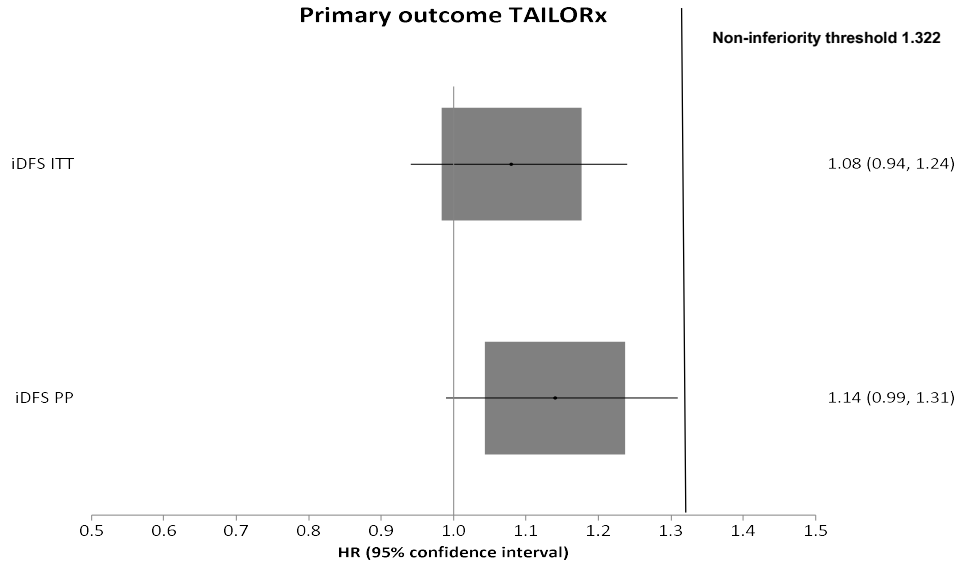


Figure 2 Forest plot of the hazard ratios (HR) of the intention-to-treat (ITT) and "as-treated" (labelled PP) populations, with the non-inferiority threshold for invasive disease-free survival (iDFS)

The primary analysis to support the claim of no difference between the treatment arms - endocrine therapy alone compared to endocrine therapy plus chemotherapy - met the prespecified non-inferiority threshold. However, the Critique outlined the following issues to consider:

- For the ITT population, the prespecified non-inferiority margin of 32.2% decrease in invasive disease-free survival for endocrine therapy alone compared to endocrine therapy plus chemotherapy appears to be quite large and not supported by the references cited in the trial report.
- Results for the "as-treated" population are close to rejecting the null hypothesis of no difference between the treatment arms.
- The "as-treated" population baseline characteristics were statistically significantly different for important baseline prognostic variables such as age, menopausal status, tumour size and tumour grade (such that, on average, 'lower risk' women were randomised to ET alone and 'higher' risk women were randomised to ET+CT).
- The non-adherence to assigned therapy in the ET alone arm was 185/3458 = 5% but 608/3449 = 18% in the ET+CT arm, compared to only 89/1737 = 5% in the non-randomised high RS score chemotherapy arm.
- There was a high risk of bias in the trial design.
- There was significant loss to follow up which was deemed not important due to the lower than expected iDFS rate.
- There are four endocrine therapy regimens and nine chemotherapy regimens, which may introduce confounding to the extent that they are not equi-effective.

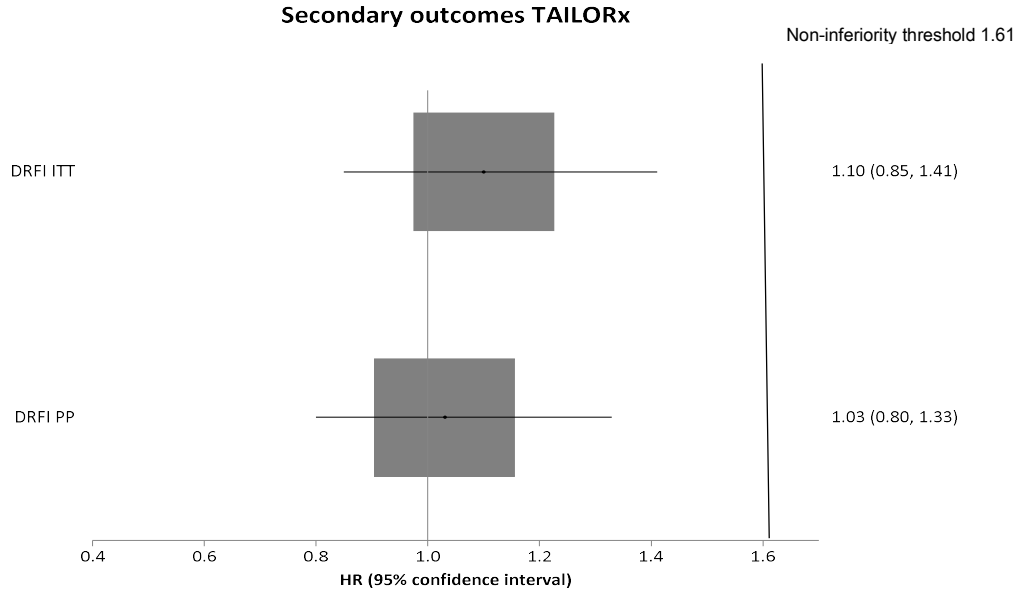


Figure 3 Forest plot of the hazard ratios (HR) of the intention-to-treat (ITT) and "as-treated" (labelled PP) populations with non-inferiority threshold for distant recurrence-free interval (DRFI)

The secondary analysis to support the claim of no difference between the treatment arms - endocrine therapy alone compared to endocrine therapy plus chemotherapy - also met the prespecified non-inferiority threshold. However, the Critique outlined issues to consider:

- For the ITT population, the non-inferiority margin of a 61% decrease in freedom from recurrence at a distant site for endocrine therapy alone compared to endocrine therapy

plus chemotherapy appears to be quite large and not supported by the references cited in the trial report.

- Full statistical power to do this comparison was not achieved: the prespecified number of events of 284 was not reached, but only 199 events were recorded.

Table 3 presents the estimated survival rates according to recurrence scores and assigned treatment in the ITT population. The Critique stated that similar issues as identified above for the primary and secondary analyses also occurred; the number of events required for full statistical power was not achieved and the evidence to support the assumptions for the prespecified non-inferiority threshold of 1.46 was not provided in the resubmission or the trial report.

Table 3 Estimated survival rates according to RS and assigned treatment in the ITT population

End point and treatment group	Rate at 5 years (%)±SE	Rate at 9 years (%)±SE
Invasive disease-free survival		
Score of ≤10, endocrine therapy alone	94.0±0.6	84.0±1.3
Score of 11-25, endocrine therapy alone	92.8 ±0.5	83.3±0.9
Score of 11-25, chemotherapy + endocrine therapy	93.1±0.5	84.3±0.8
Score of ≥26, chemotherapy + endocrine therapy	87.6±1.0	75.7±2.2
Freedom from recurrence of breast cancer at a distant site		
Score of ≤10, endocrine therapy alone	99.3±0.2	96.8±0.7
Score of 11-25, endocrine therapy alone	98.0±0.3	94.5±0.5
Score of 11-25, chemotherapy + endocrine therapy	98.2±0.2	95.0±0.5
Score of ≥26, chemotherapy + endocrine therapy	93.0±0.8	86.8±1.7
Freedom from recurrence of breast cancer at a distant or local-regional site		
Score of ≤10, endocrine therapy alone	98.8±0.3	95.0±0.8
Score of 11-25, endocrine therapy alone	96.9±0.3	92.2±0.6
Score of 11-25, chemotherapy + endocrine therapy	97.0±0.3	92.9±0.6
Score of ≥26, chemotherapy + endocrine therapy	91.0±0.8	84.8±1.7
Overall survival		
Score of ≤10, endocrine therapy alone	98.0±0.4	93.7±0.8
Score of 11-25, endocrine therapy alone	98.0±0.2	93.9±0.5
Score of 11-25, chemotherapy + endocrine therapy	98.1±0.2	93.8±0.5
Score of ≥26, chemotherapy + endocrine therapy	95.9±0.6	89.3±1.4

Source: Table 7 of the Critique.

Geyer et al. (2018)

The re-analysis of the Paik et al. (2006) study by Geyer et al. (2018), considering only *HER2*-negative women and applying the 'old' and 'new' RS thresholds applicable for the definition of low, intermediate and high risk of recurrence is presented in Table 4. The Critique stated that the issues previously identified by MSAC about the 2006 Paik 2006 study design remain.

Table 4 HR of adjuvant chemotherapy by RS subgroup, distant recurrence free survival (Geyer et al. 2018)

	N	Effect hazard ratio (95% CI)	P-value
Overall (without *HER2*+ patients)	569	0.59 (0.31, 1.04)	Log rank P=0.06
Original RS subgroup n=569*	569		
Chemotherapy in RS <18	347	1.19 (0.40, 3.49)	
Chemotherapy in RS 18-30	125	0.64 (0.23, 1.75)	
Chemotherapy in RS ≥31	97	0.18 (0.07*, 0.46);*	
Likelihood ratio test on interaction			0.023
TAILORx RS groupings	569		
Chemotherapy in RS ≤10	176	1.19 (0.41, 3.51)	
Chemotherapy in RS 11-25	271	0.61 (0.26, 1.35)	
Chemotherapy in RS >25	122	0.27 (0.12, 0.62)	
Likelihood ratio test on interaction			0.014

Source: Tables 2 & 3 Geyer et al. 2018, Table 42 of the resubmission. Cox proportional Hazards Regression Model adjusted for patient age (>50 years vs ≤50 years), clinical tumour size (>2.0 vs ≤2.0 cm), ER by ligand blinding assay (≥100 vs <100 fmol/mg), PR by ligand blinding assay (≥100 vs <100 fmol/mg), and tumour grade (well differentiated, moderately differentiated and poorly differentiated.

Clinical claim

The Critique summarised the clinical claims in the resubmission:

- A non-inferiority claim, for patients who the Oncotype DX test categorises into the intermediate recurrence group score, that endocrine therapy alone is no worse for the risk of distant recurrence free survival compared to endocrine therapy plus chemotherapy.
- A superiority claim, for patients who the Oncotype DX test categorises into the high recurrence group score, but usual care had determined treatment with endocrine therapy as sufficient, that the addition of chemotherapy would improve their disease free survival, risk of distant recurrence and overall survival.

The non-inferiority claim was based on the results from TAILORx, and the superiority claim was based on retrospective predictive data from the NSABP B-20 study (Paik et al. 2006; Geyer et al. 2018).

12. Economic evaluation

Table 5 summarises the economic evaluation.

Table 5 Summary of the economic evaluation

Perspective	Australian health care system
Comparator	Usual care, as defined by the MINDACT protocol used in TAILORx. Specifically, patients with low clinical risk do not receive adjuvant CT, patients with high clinical risk do receive adjuvant CT
Type of economic evaluation	Cost-utility analysis
Sources of evidence	TAILORx trial to determine allocation of CT in the usual care and Oncotype DX arms of the model NSABP B-20 Geyer et al. (2018) re-analysis to determine benefit of CT in patients who otherwise would not have received it
Time horizon	Lifetime
Outcomes	Life years gained, QALYs
Methods used to generate results	Markov cohort analysis
Health states	Free of disease recurrence • stratified by underlying Oncotype DX RS category and allocation to CT Disease recurrence Breast cancer death Other death
Cycle length	Annual
Discount rate	5% per annum
Software packages used	Microsoft Excel

The Critique stated that the model structure and modelling assumptions overwhelmingly favours Oncotype DX as all instances where Oncotype DX/RS score does not lead to optimal treatment were not considered, therefore the modelled economic evaluation presented is likely the most optimistic (and possibly implausible) scenario. The Critique presented the disaggregated incremental cost and effectiveness for "chemotherapy sparing" (Table 6) and "chemotherapy indicating" (Table 7) components of the model.

Table 6 Summary of disaggregated incremental cost and effectiveness in "chemotherapy sparing" only[a]

Parameter	Oncotype DX	Usual care	Incremental
Disaggregated costs			
Oncotype DX test costs	$5,085.00	$0.00	$5,085.00
Chemotherapy	$1,253.65	$3,116.03	-$1,862.38
Endocrine therapy	$3,160.85	$3,160.85	$0.00
Recurrent disease	$5,791.22	$5,791.22	$0.00
Total	**$15,290.72**	**$12,068.10**	**$3,222.62**
Disaggregated outcomes (discounted with half cycle correction)			
Life years	**13.6530**	**13.6530**	**0**
Disease-free	*13.4577*	*13.4577*	*0*
Post recurrence	*0.1953*	*0.1953*	*0*
QALY	**13.4621**	**13.4575**	**0.0045**
Disease-free	*13.3066*	*13.3021*	*0.0045*
Post recurrence	*0.1554*	*0.1554*	*0*
		$ per life year gained	**$NA**
		$ per QALY gained	**$711,529**

Text in italics indicate values calculated for the Critique.
Source: 72 p155 of the resubmission; ODX_EconModel.xlsm.
[a] That is, moving any patients with RS ≤25 treated with ET+CT in the usual care arm to ET alone in the Oncotype DX arm.

Table 7 Summary of disaggregated incremental cost and effectiveness in "chemotherapy indicating" only[a]

Parameter	Oncotype DX	Usual care	Incremental
Disaggregated costs			
Oncotype DX test costs	$5,085.00	$0.00	$5,085.00
Chemotherapy	$3,672.22	$3,116.03	$556.19
Endocrine therapy	$3,175.34	$3,160.85	$14.50
Recurrent disease	$4,750.80	$5,791.22	-$1,040.43
Total	**$16,683.36**	**$12,068.10**	**$4,615.26**
Disaggregated outcomes (discounted with half cycle correction)			
Life years	**13.7665**	**13.6530**	**0.1135**
Disease-free	*13.6063*	*13.4577*	*0.1486*
Post recurrence	*0.1602*	*0.1953*	*-0.0351*
QALY	**13.5752**	**13.4575**	**0.1177**
Disease-free	*13.4466*	*13.3021*	*0.1445*
Post recurrence	*0.1275*	*0.1554*	*-0.0279*
		$ per life year gained	**$40,660**
		$ per QALY gained	**$39,217**

Text in italics indicate values calculated for the Critique.
Source: 72 p155 of the resubmission; ODX_EconModel.xlsm.
[a] That is, moving any patients with RS ≥26 treated with ET alone in the usual care arm to ET+CT in the Oncotype DX arm.

The overall base case ICER is presented in Table 8 (combining the "chemotherapy sparing" and "chemotherapy indicating" components).

Table 8 Summary of disaggregated incremental cost and effectiveness from base case

Parameter	Oncotype DX	Usual care	Incremental
Disaggregated costs			
Oncotype DX test costs	$5,085.00	$0.00	$5,085.00
Chemotherapy	$1,809.84	$3,116.03	-$1,306.19
Endocrine therapy	$3,175.34	$3,160.85	$14.50
Recurrent disease	$4,750.80	$5,791.22	-$1,040.43
Total	**$14,820.98**	**$12,068.10**	**$2,752.88**
Disaggregated outcomes (discounted with half cycle correction)			
Life years	**13.7665**	**13.6530**	**0.1135**
Disease-free	*13.6063*	*13.4577*	*0.1486*
Post recurrence	*0.1602*	*0.1953*	*-0.0351*
QALY	**13.5798**	**13.4575**	**0.1222**
Disease-free	*13.4522*	*13.3021*	*0.1501*
Post recurrence	*0.1275*	*0.1554*	*-0.0279*
		$ per life year gained	**$24,253**
		$ per QALY gained	**$22,525**

Text in italics indicate values calculated for the Critique.
Source: Table 69, p153, Tables 70 and 71 p154 of the resubmission; ODX_EconModel.xlsm.

The Critique highlighted that the base case ICER/QALY ($22,525) was driven by the "chemotherapy indicating" component (based on Geyer et al. 2018), contributing more benefit than the "chemotherapy sparing" component (incremental QALYs: 0.1177 *vs*. 0.0045, respectively); considered the "chemotherapy indicating" component was based on weaker evidence base, which MSAC had considered before when previously deciding not to support Oncotype DX.

The Critique's sensitivity analyses showed the modelled results were most sensitive to the effect of chemotherapy on absolute risk of recurrence in RS ≥26 patients and the model duration.

13. Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of the introduction of the Oncotype DX test (Table 9).

Table 9 Net financial impact of Oncotype DX over five years by Commonwealth health budget and patient population

Summary	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)
Patients diagnosed with breast cancer [A]	17,210	17,530	17,850	18,170	18,490
Number of patients eligible for Oncotype DX [B]	4,652	4,739	4,825	4,912	4,998
Number of patients using Oncotype DX testing [C]	1,396	1,896	2,171	2,456	2,749
Total expenditure on Oncotype DX [D]	$6,980,873	$9,480,899	$10,860,713	$12,283,795	$13,750,143
Critique values (removed $83.40 co-pay)	*$6,942,488*	*$9,428,768*	*$10,800,995*	*$12,216,251*	*$13,674,537*
Change in expenditure due to Oncotype DX [E]	-$1,795,774	-$2,438,885	-$2,793,832	-$3,159,908	-$3,537,114
Critique values (removed $83.40 co-pay)	*-$1,640,985*	*-$2,228,663*	*-$2,553,015*	*-$2,887,537*	*-$3,232,229*
Net impact of Oncotype DX on expenditure	**$5,185,099**	**$7,042,014**	**$8,066,882**	**$9,123,887**	**$10,213,029**
Critique values (removed $83.40 co-pay)	***$5,301,503***	***$7,200,104***	***$8,247,980***	***$9,328,715***	***$10,442,308***

[A] AIHW Cancer incidence projections; [B] 27% of [A]; [C] After applying expected uptake rates of 30 to 55%; [D] $5085 per test less patient contribution of $83.40 per test; [E] Savings of $1287 per patient tested due to reduction in chemotherapy.

The Critique stated that sensitivity analysis indicated that the estimates of net cost to the Commonwealth health budget is heavily reliant on the assumed uptake of the Oncotype DX test and also, but to a lesser extent, assumptions around cost offsets to the PBS.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Recurrence Score® (RS) thresholds for categorising low, intermediate and high risk of distant recurrence appear to be arbitrary and subject to change	The RS thresholds were modified in the context of the TAILORx trial. It is not unreasonable to adjust parameters based on additional data, and the new threshold level of 26 appears safe based on the TAILORx and other supporting studies.
Population (as per the eligibility criteria into the TAILORx trial)	The eligible population should be specified as patients with newly diagnosed breast carcinomas; who are ER-positive, *HER*2-negative, lymph node-negative and post-surgical; and who have not received neoadjuvant therapy.
Proposed note defining eligibility for funding should be modified, as it suggests that patients with an RS ≥26 should receive chemotherapy only	TAILORx trial protocol specified that women with an RS ≥26 were assigned to receive chemotherapy plus endocrine therapy. Therefore, this should be reflected in the note.
Clinical need	There is a view among clinicians that knowledge of the genomic features of breast cancers is required to provide a higher level of evidence on which to base systemic treatment decisions. Multigene assays are being employed routinely by clinicians in the US.
Context	Oncotype DX represents one of the more rigorously developed gene assays with good quality control; NCCN preferred and 'strong' recommendation by ASCO.
Uncertain chemotherapy benefit – 26% or 15% or 20.5%?	20.5% may be an acceptable estimate.
Costs of adding chemotherapy may be underestimated	The cost of chemotherapy needs to be revisited – if it is higher, cost offsets would be higher.
Test is not registered for use in Australia and a single laboratory in the US performs the test and may not be eligible for listing on the MBS. Who will pay for this? What about out-of-pocket costs?	Since testing is done outside Australia, is it possible for MBS to pay the small pathology fee for collecting and preparing the sample to be sent, and then adopt a separate arrangement to reimburse the patient for the rest?
Different results from the modelled economic evaluation depending on accepting different sources of clinical evidence	Given MSAC's published views on the strength of the evidence available previously, it may be useful for MSAC to consider the disaggregated analyses of the non-inferiority (based on TAILORx) and effectiveness (based on re-analysing the previous retrospective predictive evidence) components of the model.

ESC discussion

Application 1342.5 is a resubmission seeking public funding for a gene expression profiling test, Oncotype DX®, for patients with breast cancer. The test generates a Recurrence Score® (RS) that is used to predict the likelihood of breast cancer recurrence and the potential benefit of also receiving adjuvant chemotherapy for surgically treated patients with early-stage invasive breast cancer receiving adjuvant endocrine therapy.

ESC noted the resubmission included two therapeutic claims:

1. Oncotype DX will identify patients who would not benefit from also receiving adjuvant chemotherapy, thus sparing them the adverse effects and other risks associated with chemotherapy (referred to as "chemotherapy sparing"; RS <26)

2. Oncotype DX will identify patients likely to benefit from also receiving adjuvant chemotherapy who would not have been identified through standard clinical practice; appropriate use of chemotherapy will result in improved disease-free survival (referred to as "chemotherapy indicating"; RS ≥26).

ESC noted MSAC's previous concerns about reliance on a single United States (US) laboratory performing the test. However, ESC considered that centralisation of testing could be seen as a significant strength of Oncotype DX in terms of reproducibility. It does not suffer from the same problems as other assays based on technologies that are difficult to standardise across different laboratories. Hence, there is no laboratory-based need for an Australian laboratory to implement new testing strategies.

ESC noted that the US Food and Drug Administration is currently obtaining guidance and feedback on its proposed oversight of laboratory-developed tests such as Oncotype DX, but new guidelines are not yet in place. The laboratory is accredited by the College of American Pathologists under the US Clinical Laboratory Improvement Amendment (CLIA) of 1988, which has parallels with accreditation by the National Association of Testing Authorities (NATA) in Australia.

ESC noted that the resubmission used the structure of an MBS item with descriptor, fee and note to frame its request for public funding. The note is intended to help interpret RS scores for making chemotherapy decisions. It states that patients with RS <26 are recommended endocrine therapy and patients with RS ≥26 are recommended adjuvant chemotherapy. However, ESC noted that the TAILORx trial protocol specified that women with RS ≥26 were assigned to receive adjuvant chemotherapy plus endocrine therapy. This should be reflected in the note.

ESC noted that the proposed fee of $5,085 per test service was higher than the confidential fee in previous submissions ($3,375). The resubmission proposed that $85 of the fee is for the Australian pathology laboratory retrieving and preparing the tissue.

ESC noted that some of the PICO criteria have changed since the previous MSAC considerations of this application, to align with the TAILORx trial:

- population – narrowed to include node-negative patients with larger tumour size (the initial submission and first resubmission allowed for node positivity, while the second and third resubmissions excluded lymph node positivity but allowed smaller tumour sizes)
- intervention – RS threshold for decision-making with respect to recommending adjuvant chemotherapy as well as receiving adjuvant endocrine therapy is now 26 instead of 31
- comparator – usual care is now more clearly defined, and aligned with the MINDACT protocol used in TAILORx.

ESC considered that the eligible population should be specified as patients with newly diagnosed breast carcinomas ER-positive, *HER2*-negative, lymph node-negative who are post-surgical and who have not received neoadjuvant therapy. Restrictions might also include requesting by a specialist medical or surgical oncologist.

Although changing the RS threshold will change the consequences for the eligible population, ESC noted that the TAILORx trial was specifically designed to establish whether treating women with a mid-range RS of 11-25 with adjuvant endocrine therapy alone results in significantly worse breast cancer outcomes compared treating these women with both adjuvant chemotherapy and adjuvant endocrine therapy. This is the patient group for whom the decision around the use of adjuvant chemotherapy is not clear based on clinical-pathological factors such as tumour size and grade.

From the consumer point of view, ESC noted that genomics is becoming a part of better patient-centred care. There is considerable positive benefit for patients of better diagnoses leading to better treatment decisions, including patients being able to avoid chemotherapy if it is not required. ESC noted that equity of access issues arise from this test not being rendered in Australia.

ESC noted that Oncotype DX is a rigorously developed gene assay with good quality control. It is given a 'strong' recommendation in the American Society of Clinical Oncology (ASCO) guidelines, and the National Comprehensive Cancer Network (NCCN) has designated it as the preferred multigene panel assay.

ESC noted that other countries fund Oncotype DX. The National Institute for Health and Care Excellence (NICE) recommended it in 2013 for coverage under England's National Health Service (NHS), for use in early-stage ER-positive, *HER2*-negative, node-negative invasive breast cancer patients with 'intermediate risk'. Coverage was renewed in 2018 and expanded to include patients with micrometastases. Node-positive disease is not covered by England's NHS, but some patients are covered by private insurance.

Oncotype DX is publicly funded for almost all eligible patients in England, with no patient co-payment. Genomic Health Inc. estimated that 95% of the trusts serving breast cancer patients in the UK use the test, and over 22,000 women in the UK had undergone the test as of late 2018.

In Canada, all 10 provinces provide Oncotype DX under their public healthcare systems. Seven of the 10 provinces provide the test for node-negative and micrometastases patients; three provinces also provide, and one is considering providing, the test for node-positive patients.

In the USA, Oncotype DX is covered by Medicare (which covers people over 65 years of age) in all states except two, and by Medicaid (which covers people on low incomes) in all 50 states. The test is also covered by all major private insurers. Medicare and other public systems cover node-negative and node-positive patients; about half the private insurers cover node-positive patients.

ESC noted that there is an increasing view that clinicians should be using a higher level of evidence based on genomic subtyping of individual cancers (in addition to traditional histological features and immunohistochemical markers) to provide more specific and tailored treatments for breast cancer patients. Oncotype DX and other similar multigene assays are being increasingly used worldwide, and there is an increasing clinician-led demand for access to these types of assays. Assays like Oncotype DX are intended for use as an additional tool to guide decision-making, not to dictate treatment. ESC noted that clinicians and researchers are also currently using whole exome sequencing (WES) and whole genome sequencing (WGS) to investigate the genomic profile of breast cancers.

ESC considered that most clinicians would order the Oncotype DX assay selectively, particularly in instances when decision-making is complex. However, ESC considered that there is some risk of leakage. ESC noted that NICE guidance for Oncotype DX has recently been updated, which may inform concerns regarding leakage.

ESC noted the limitations of the current online prediction tools used to estimate the risk of recurrence and to make treatment decisions (Wazir et al. 2017):

- Adjuvant! Online tends to overestimate the number of patients at high risk; overestimate the survival rates of younger women with ER-positive breast cancer; overestimate the added value of chemotherapy for older patients; and *HER2* assessment is not included
- NHS Predict does not provide any estimate of local relapse; and does not consider mortality due to causes other than breast cancer. Some patients, particularly those with small, biologically aggressive cancers, may therefore not receive chemotherapy that would be of benefit.

ESC noted that the previously provided retrospective predictive data from the randomised NSABP B-20 study (Paik et al. 2006) was again relied on to support the clinical claim that Oncotype DX will identify patients likely to benefit from also receiving adjuvant chemotherapy who would not have been identified through standard clinical practice. The re-analysis of these data by Geyer et al. 2018 was relied on to demonstrate that also receiving adjuvant chemotherapy is superior to endocrine therapy alone in patients with RS ≥26.

ESC noted that the TAILORx trial provided NHMRC Level II evidence that adjuvant chemotherapy can be withheld in patients with an RS <26 without affecting the patient's risk of disease recurrence (Sparano et al. 2018). ESC also noted that exploratory analyses indicated that also receiving adjuvant chemotherapy was associated with some benefit for women aged ≤50 years with an RS of 16-25.

ESC noted that two Australian Decision Impact Studies (ADIS) previously presented to MSAC were used in the resubmission to characterise current patterns of care. These data were used to investigate the applicability of usual care in TAILORx to Australian practice. One of these studies (de Boer et al. 2013) found that the Oncotype DX RS changed the treatment recommendation in 24% of patients with node-negative tumours. In the other study (Chin-Lenn et al. 2018), the Oncotype DX RS changed treatment recommendations in 38% of patients, noting that the change in treatment recommendation could be in either direction: to include chemotherapy when it would have otherwise been excluded, or to exclude chemotherapy when it would otherwise have been included. However, ESC considered that the lack of proven clinical utility in the Australian context to be an ongoing issue. There is still no good description of current Australian practice as the ADIS studies are now several years old. It is likely to be different to practice in the US and UK, and it cannot be assumed that incremental clinical utility will be the same in Australia as in other countries.

ESC noted that the cost of adjuvant chemotherapy used in the model revised since the previous submission was recalculated by the applicant for its pre-ESC response using the Critique's assumption of four cycles rather than six. However, ESC noted the comment in the pre-ESC response that the revised cost is likely to be an underestimate of the true burden of this chemotherapy to the health care system. ESC commented that most adjuvant chemotherapy treatments go beyond four cycles so the cost might be underestimated, and noted that if this cost is higher, cost offsets would be higher.

ESC noted that the period of adjuvant chemotherapy treatment was based on six cycles; the pre-ESC response based this cost on four cycles, but did not change the disutility duration to reflect four cycles. ESC queried whether using four cycles would reduce the estimate of quality-adjusted life years gained from avoiding the toxicity of adjuvant chemotherapy.

ESC noted translation issues arising from uncertainty regarding the appropriate extent of benefit (i.e. reduction in absolute risk of disease recurrence) of receiving adjuvant chemotherapy as well as adjuvant endocrine therapy in patients with an RS ≥26. The resubmission originally used a value of 26% (based on Geyer et al.), but the Critique suggested 15% would be more appropriate in the Australian context. Instead, the pre-ESC response reduced the incremental benefit of chemotherapy from 26% in the base case to a mid-point of 20.5%. ESC advised that 20.5% may be acceptable.

ESC noted that the revised model used revised utility values, which were more in line with TAILORx.

ESC noted that the base case ICER/QALY from the revised combined model was sensitive to several assumptions, which varied this estimate within the range of $22,000–$50,000 (using a chemotherapy benefit of 20.5%). However, ESC noted that the ICER/QALY calculated using a chemotherapy benefit of 15% was more than $67,500.

ESC noted that although the modelled economic evaluation was structurally correct, it was basic. It included only univariate sensitivity analyses, but no probability sensitivity analyses or cost-effectiveness acceptability curves. The model included direct costs only; but not out-of-pocket costs. ESC queried whether the PBS cost of new chemotherapy drugs used in the TAILORx trial had been included in the cost offsets.

ESC noted that the analysis also gave two disaggregated results based on the two sources of clinical utility evidence: evidence for the non-inferiority claim is from the TAILORx randomised trial, but the modelled economic evaluation is driven by superiority claim from the retrospective predictive re-analysis from Paik/Geyer. ESC noted that it may be useful for MSAC to consider the disaggregated analyses of the non-inferiority and superiority components of the model (as well as the combined analysis).

ESC noted that the resubmission's revised financial analyses resulted in a modest increase in the net budgetary impact to $44.7 million over the first 5 years. The resubmission also provided a revised estimate incorporating updated (2017) breast cancer incidence data from the Australian Institute of Health Welfare of $50.3 million over the first 5 years. ESC considered these two estimates to be more realistic than the estimate of $51.6 million over 5 years using UK uptake data. However, ESC considered that the financial estimates remained subject to significant uncertainty due to low uptake rate assumptions and the fact that the TAILORx trial did not report important patient baseline characteristics, such as the percentage expression of ER or PR.

15. Other significant factors

Nil.

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

STA is dismayed and frustrated at the MSAC decision to reject the Oncotype DX Breast Recurrence Score® Test for the sixth time. STA was encouraged in pre-submission meetings to proceed with this submission, based on the availability of new data from the landmark TAILORx trial, the largest breast cancer treatment study ever conducted providing an unprecedented level of evidence. These data, along with an extensive dossier of clinical evidence, were submitted for evaluation. MSAC's interpretation of the TAILORx evidence is at odds with how the data are viewed by other key medical, regulatory and reimbursement authorities in the developed world. This body of evidence is recognised and validated

globally by oncology authorities, including the National Comprehensive Cancer Network (NCCN) in the United States and the National Institute for Health and Care Excellence (NICE) in the United Kingdom. Indeed, MSAC's Evaluation Sub-Committee (ESC) noted in June 2019 that it regarded the Oncotype DX test as "one of the more rigorously developed gene assays with good quality control" that was given a "preferred" rating on the NCCN guidelines and "strongly" recommended by the prestigious American Society of Clinical Oncology. ASCO delegates were advised that this test "would transform care immediately, for the better". We further note that the ESC acknowledged the Oncotype DX test is a standard of care and reimbursed in most other developed countries, including the US, UK and Canada. The ESC further conceded that clinicians should be using a higher level of evidence based on genomic subtyping of individual cancers (in addition to traditional histological features and immunohistochemical markers) to provide more specific and tailored treatments for breast cancer patients. This decision to reject the Oncotype DX test for reimbursement is therefore contrary to international medical opinion and global breast cancer treatment guidelines. MSAC's rejection means Australia remains an isolated outlier when it comes to the provision of cutting-edge genomic tests to make informed treatment decisions and only those women who can afford to access this personalised genomic technology have the opportunity to benefit. Specialised Therapeutics would welcome the opportunity to engage the government in seeking solutions to make this technology accessible to all eligible Australian women.

17. Further information on MSAC

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