s 22

From: s 47F
Sent: Friday, 1 November 2019 9:09 AM
To: s 22
Cc: s 22
Subject: Re: August 2019 MSAC meeting - Draft PSDs for your clearance/comments - by Wednesday 2 October 2019 [SEC=OFFICIAL]

Responses below

s 47F

Apologies for typos ipad message

From: s 22
Sent: Thursday, October 31, 2019 6:30 pm
To: s 47F
Cc: s 22
Subject: RE: August 2019 MSAC meeting - Draft PSDs for your clearance/comments - by Wednesday 2 October 2019 [SEC=OFFICIAL]

s 47F

s 47C

s 47C

s 47E

Thanks

s 22
Office of HTA/Technology Assessment and Access Division
Department of Health
s 22
GPO Box 9848, Canberra ACT 2601
s 22

From: s 47F
Sent: Saturday, 26 October 2019 6:38 PM
To: s 22
Cc: MSAC SECRETARIAT <MSAC.SECRETARIAT@health.gov.au>; s 22

Subject: RE: August 2019 MSAC meeting - Draft PSDs for your clearance/comments - by Wednesday 2 October 2019 [SEC=OFFICIAL]

Hi s 22
Thanks for your comprehensive work, first responses below.
s 47E
s 47F

From: s 22
Sent: Friday, 25 October 2019 8:27 PM
To: s 47F
Cc: MSAC SECRETARIAT <MSAC.SECRETARIAT@health.gov.au>; s 22

Subject: RE: August 2019 MSAC meeting - Draft PSDs for your clearance/comments - by Wednesday 2 October 2019 [SEC=OFFICIAL]

s 47F

Apologies for the delay in replying.

Please find your version marked up by me, with responses to each of your comment boxes identified as s 47C (my third look at this PSD).

s 47C

s 47C

Next steps

- Do you think this attached version should go back to the discussants at this stage (with or without any

s 47E

s 22
Office of HTA/Technology Assessment and Access Division
Department of Health
s 22
GPO Box 9848, Canberra ACT 2601
s 22

From: s 47F
Sent: Sunday, 20 October 2019 6:48 PM
To: MSAC SECRETARIAT <MSAC.SECRETARIAT@health.gov.au>; s 22

Subject: RE: August 2019 MSAC meeting - Draft PSDs for your clearance/comments - by Wednesday 2 October 2019 [SEC=OFFICIAL]

Typo at bottom now highlighted in yellow

From: s 47F
Sent: Sunday, 20 October 2019 6:06 PM
To: MSAC SECRETARIAT <MSAC.SECRETARIAT@health.gov.au>; s 22

Cc: s 47F
Subject: RE: August 2019 MSAC meeting - Draft PSDs for your clearance/comments - by Wednesday 2 October 2019 [SEC=OFFICIAL]

Hi s 22
Firstly apologies I have been so slow in responding. s 22
My changes to the PSD are attached as are queries – for some I cant find the numbers which marry up to the PSD.
s 47C, s 47E

s 47C, s 47E

s 47E

Happy to discuss by telecon – I will prioritise this now.

KR
s 47F

From: MSAC SECRETARIAT <MSAC.SECRETARIAT@health.gov.au>
Sent: Monday, 30 September 2019 8:28 AM
To: s 47F
Cc: s 47F MSAC SECRETARIAT <MSAC.SECRETARIAT@health.gov.au>
Subject: August 2019 MSAC meeting - Draft PSDs for your clearance/comments - by Wednesday 2 October 2019 [SEC=OFFICIAL]

Hi s 47F

The attached PSDs are the last batch from the August 2019 meeting for your clearance.

s 22

Kind regards,
s 22

Assistant Director - Medical Services & Technology Section
Technology Assessment and Access Division | Office of HTA
Australian Government Department of Health
s 22

PO Box 9848, Canberra ACT 2601, Australia

The Department of Health acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders both past and present.

From: MSAC SECRETARIAT <MSAC.SECRETARIAT@health.gov.au>
Sent: Thursday, 19 September 2019 3:43 PM
To: s 47F
Cc: s 47F MSAC SECRETARIAT <MSAC.SECRETARIAT@health.gov.au>
Subject: August 2019 MSAC meeting - Draft PSDs for your clearance/comments - by Monday 23 September 2019 [SEC=OFFICIAL]

Hi s 47F

Attached is the last batch of PSDs from the August 2019 MSAC meeting for your comments. s 47E

If you are able to, your comments would be appreciated **by Monday 23 September 2019.**

Kind Regards,

s 22

Assistant Director - Medical Services & Technology Section

Technology Assessment and Access Division | Office of HTA
Australian Government Department of Health

s 22

The Department of Health acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders both past and present.

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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® or ODX) in women 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 hormone 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 hormone therapy.

s 47C, s 47E

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

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

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.

7

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 ODX 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 ODX.

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 has changed since the previous resubmission (1342.4), and is presented in Table 2~~1~~ (applicant highlighted changes with previous submission in red). The applicant has requested a fee of $5,085 per service, and the resubmission did not request any confidential pricing or fee arrangement.

Table 21 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 endocrine~~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.

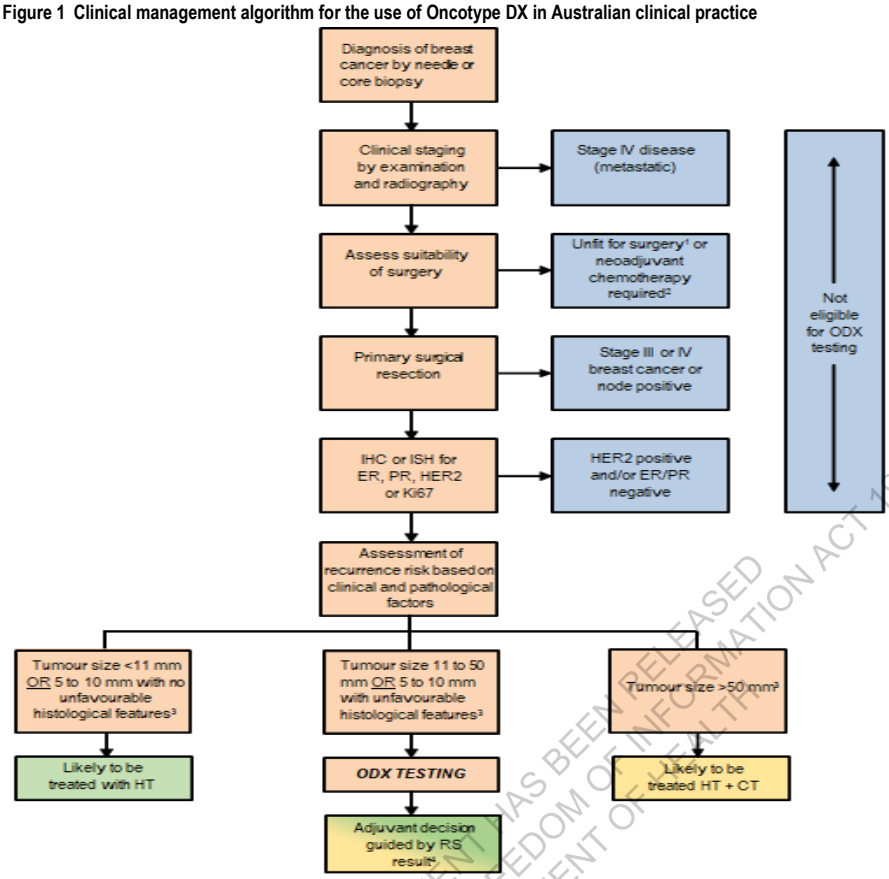
7. Summary of Public Consultation Feedback/Consumer Issues

See Application 1342.4 PSD on the MSAC website.

8. Proposed intervention's place in clinical management

The resubmission proposed clinical management algorithm (Figure 1) differs from that presented in earlier MSAC applications for Oncotype DX in that it excludes node positive patients, and the process used to exclude patients with very high or low clinical risk is based on the approach applied in TAILORx. In addition, the algorithm includes 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 current resubmission remains 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 is based on one prospective randomised trial and one re-analysis of a retrospective cohort study:

- The TAILORx trial was a prospective trial (N=10,2739,719; registered ~~intention- ,to-treat~~ population), that used a patient's recurrence score only to guide treatment. Women with intermediate RS (11-25) were randomised to endocrine~~hormone~~ therapy (EHT) alone or EHT+ chemotherapy (CT) (n=6,9076,711; Arms B and C); and those with low (0-10; n=1,6291,619; Arm A) or high (≥26; n=1,7371,389; Arm D) RS were treated with EHT alone or EHT+CT, respectively (Sparano et al. NEJM, 2018). Results were ~~also~~ 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 per protocol population (~~N= 6,711;~~ 'as treated population'), which the Critique stated was an important comparison for demonstrating non-inferiority of EHT alone vs. EHT+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 trial (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).

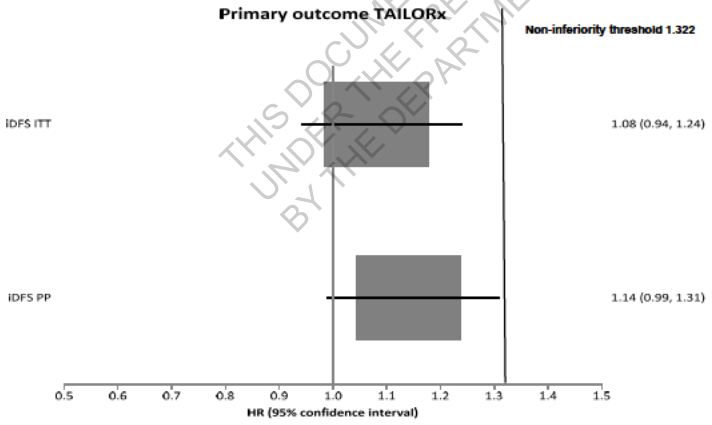


Figure 2 Forest plot of the hazard ratios (HR) of the intention-to-treat (ITT) and 'as-treated' (PP) populations, with the non-inferiority threshold for invasive disease-free survival (iDFS)

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

- For the ITT population, the pre-specified non-inferiority margin of 32.2% decrease in invasive disease-free survival for endocrine~~hormone~~ therapy alone compared to endocrine~~hormone~~ 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 E~~H~~T alone and 'higher' risk women were randomised to E~~H~~T+CT).
- The non-adherence to assigned therapy in the E~~H~~T alone arm was 185/3458 = 5~~.6~~% but 608/3449 = 18~~.4~~% in the E~~H~~T+CT arm, compared to only 89/1737 = 5~~6.4~~% 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 ~~hormone~~ regimens and nine chemotherapy regimens, which may introduce confounding to the extent that they are not equi-effective.

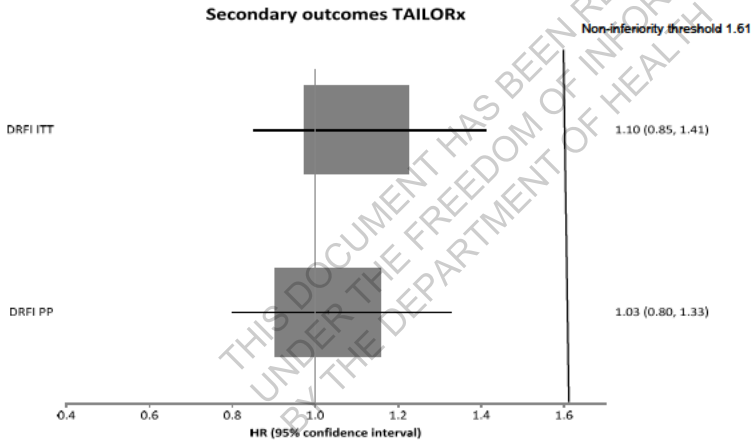


Figure 3 Forest plot of the hazard ratios (HR) of the intention-to-treat (ITT) and 'as treated' (PP) populations with non-inferiority threshold for distant recurrence-free interval (DRFI)

The secondary analysis to support the claim of no difference between the treatment arms - endocrine~~hormone~~ therapy alone compared to endocrine~~hormone~~ therapy plus chemotherapy - also met the pre-specified 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~~hormone~~ therapy alone compared to

endocrine~~hormone~~ 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 pre-specified 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 pre-specified non-inferiority threshold of 1.46 was not provided in the SBA 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~~HT~~ therapy alone	94.0±0.6	84.0±1.3
Score of 11-25, endocrine~~HT~~ therapy alone	92.8 ±0.5	83.3±0.9
Score of 11-25, chemotherapy + endocrine ~~CT+HT~~ therapy	93.1±0.5	84.3±0.8
Score of ≥26, chemotherapy + endocrine ~~CT+HT~~ therapy	87.6±1.0	75.7±2.2
Freedom from recurrence of breast cancer at a distant site		
Score of ≤10, endocrine~~HT~~ therapy alone	99 3±0.2	96.8±0.7
Score of 11-25, endocrine~~HT~~ therapy alone	98.0±0.3	94.5±0.5
Score of 11-25, chemotherapy + endocrine ~~CT+HT~~ therapy	98 2±0.2	95.0±0.5
Score of ≥26, chemotherapy + endocrine ~~CT+HT~~ 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~~HT~~ therapy alone	98.8±0.3	95.0±0.8
Score of 11-25, endocrine~~HT~~ therapy alone	96 9±0.3	92.2±0.6
Score of 11-25, chemotherapy + endocrine ~~CT+HT~~ therapy	97.0±0.3	92.9±0.6
Score of ≥26, chemotherapy + endocrine ~~CT+HT~~ therapy	91.0±0.8	84.8±1.7
Overall survival		
Score of ≤10, endocrine~~HT~~ therapy alone	98.0±0.4	93.7±0.8
Score of 11-25, endocrine~~HT~~ therapy alone	98.0±0.2	93.9±0.5
Score of 11-25, chemotherapy + endocrine ~~CT+HT~~ therapy	98.1±0.2	93.8±0.5
Score of ≥26, chemotherapy + endocrine ~~CT+HT~~ 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 trial 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 from 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

	N	Effect hazard ratio (95% CI)	P value
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 re-submission. Cox proportional Hazards Regression Model adjusted for patient age (>50 years vs ≤50 years), clinical tumour size (> 2.0 vs ≤2.0cm), 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 resubmission clinical claims:

- *A non-inferiority claim, for patients who the Oncotype DX test categorises into the intermediate recurrence group score, that endocrine~~hormone~~ therapy alone is no worse for the risk of distant recurrence free survival compared to endocrine~~hormone~~ 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~~hormone~~ 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 is based on the results from TAILORx and the superiority claim is 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 M NDACT 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	TA LORx 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 economic model 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
EndocrineHormone 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 during the critique.
Source: 72 p155 of the SBA, ODX_EconModel xlsm.
[a] That is, moving any patients with RS ≤25 treated with EHT+CT in the usual care arm to EHT aloneonly 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
EndocrineHormone 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 during the critique.
Source: 72 p155 of the SBA, ODX_EconModel xlsm.

[a] That is, moving any patients with RS ≥26 treated with EHT aloneonly in the usual care arm to EHT+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
EndocrineHormone 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 during critique.
Source: Table 69, p153, Table 70 and 71 p154 of the SBA, 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 has been 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 TA LORx and other supporting studies.
Population (as per the eligibility criteria into the TA LORx trial)	The eligible population should be specified as patients with newly diagnosed breast carcinomas; who are *ER*-positive, *HER2*-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	TA LORx trial protocol specified that women with an RS score of ≥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 economic model 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 TA LORx) 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~~hormone~~ therapy.

ESC noted the resubmission includes 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 a score of ≥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 is higher than the confidential fee in previous submissions ($3,375). The applicant has 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-women 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~~hormone~~ 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*+, *HER2*–, 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~~hormone~~ therapy alone results in significantly worse breast cancer outcomes compared treating these women with both adjuvant chemotherapy and adjuvant endocrine~~hormone~~ 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 the England's National Health Service (NHS), for use in early-stage *ER*+, *HER2*–, 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 yet covered by the 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. estimates 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) is 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 is relied on to demonstrate that also receiving adjuvant chemotherapy is superior to endocrine~~hormone~~ therapy alone in patients with RS ≥26.

ESC noted that the TAILORx trial provides 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 are used in the resubmission to characterise current patterns of care. These data are 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 using the Critique's assumption of four cycles rather than six. However, ESC noted the applicant's comment in 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 applicant agreed to base 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~~hormone~~ therapy in patients with an RS ≥26. The applicant 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 applicant 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 uses revised utility values, which are now more in line with TAILORx.

ESC noted that the base case ICER/QALY from the revised combined model is sensitive to several assumptions, which vary 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 economic evaluation model is correct, it is basic. It includes only univariate sensitivity analyses, but no probability sensitivity analysis or cost-effectiveness acceptability curve. The model includes direct costs only; it does not include 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 results based on the source of clinical utility evidence: evidence for the non-inferiority claim is from the TAILORx randomised trial, but the economic analysis 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 applicant's revised financial analyses resulted in a modest increase in the net budgetary impact to $44.7 million over the first 5 years. The applicant 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

The MSAC Executive 3 February 2012 teleconference agreed for MSAC applicants to be given the opportunity to have a comment inserted in the final outcomes document – to be limited to one paragraph and/or a link to reference material

17. Further information on MSAC

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

s 22

From: s 47F
Sent: Friday, 25 October 2019 7:49 AM
To: s 22
Cc:
Subject: Re: August 2019 MSAC meeting - Draft PSDs for your clearance/comments - by Wednesday 2 October 2019 [SEC=OFFICIAL]

Hi,

s 47C

s 47C, s 47E

s 47C, s 47E

From: s 22
Date: Tuesday, 22 October 2019 at 05:02
To: s 47F
Cc: s 22
Subject: FW: August 2019 MSAC meeting - Draft PSDs for your clearance/comments - by Wednesday 2 October 2019 [SEC=OFFICIAL]

As discussed.

I need to send a second email from s 47F too in which she corrects a typo in the first.

s 22

Sent with BlackBerry Work (www.blackberry.com)

From: s 47F
Sent: 20 Oct. 2019 6:08 pm
To: MSAC SECRETARIAT <MSAC.SECRETARIAT@health.gov.au>; s 22

s 22

Cc: s 47F

Subject: RE: August 2019 MSAC meeting - Draft PSDs for your clearance/comments - by Wednesday 2 October 2019 [SEC=OFFICIAL]

Hi s 22

Firstly apologies I have been so slow in responding. s 22

My changes to the PSD are attached as are queries – for some I cant find the numbers which marry up to the PSD.

s 47C, s 47E

s 47E

KR

s 47F

From: MSAC SECRETARIAT <MSAC.SECRETARIAT@health.gov.au>
Sent: Monday, 30 September 2019 8:28 AM
To: s 47F
Cc: s 47F MSAC SECRETARIAT <MSAC.SECRETARIAT@health.gov.au>
Subject: August 2019 MSAC meeting - Draft PSDs for your clearance/comments - by Wednesday 2 October 2019 [SEC=OFFICIAL]

Hi s 47F

The attached PSDs are the last batch from the August 2019 meeting for your clearance.

s 22

Kind regards,

s 22

Assistant Director - Medical Services & Technology Section

Technology Assessment and Access Division | Office of HTA
Australian Government Department of Health

s 22

PO Box 9848, Canberra ACT 2601, Australia

The Department of Health acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders both past and present.

From: MSAC SECRETARIAT <MSAC.SECRETARIAT@health.gov.au>
Sent: Thursday, 19 September 2019 3:43 PM
To: s 47F
Cc: s 47F MSAC SECRETARIAT <MSAC.SECRETARIAT@health.gov.au>
Subject: August 2019 MSAC meeting - Draft PSDs for your clearance/comments - by Monday 23 September 2019 [SEC=OFFICIAL]

Hi s 47F

Attached is the last batch of PSDs from the August 2019 MSAC meeting for your comments. s 47E

If you are able to, your comments would be appreciated **by Monday 23 September 2019.**

Kind Regards,

s 22

Assistant Director - Medical Services & Technology Section

Technology Assessment and Access Division | Office of HTA
Australian Government Department of Health

s 22

PO Box 9848, Canberra ACT 2601, Australia

The Department of Health acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders both past and present.

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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® or ODX) in women 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 hormone 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 hormone therapy.

s 47C, s 47E

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

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

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 ODX 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 ODX.

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 has changed since the previous resubmission (1342.4), and is presented in Table 1 (applicant highlighted changes with previous submission in red). The

applicant has requested a fee of $5,085 per service, and the resubmission did not request any confidential pricing or fee arrangement.

Table 1 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

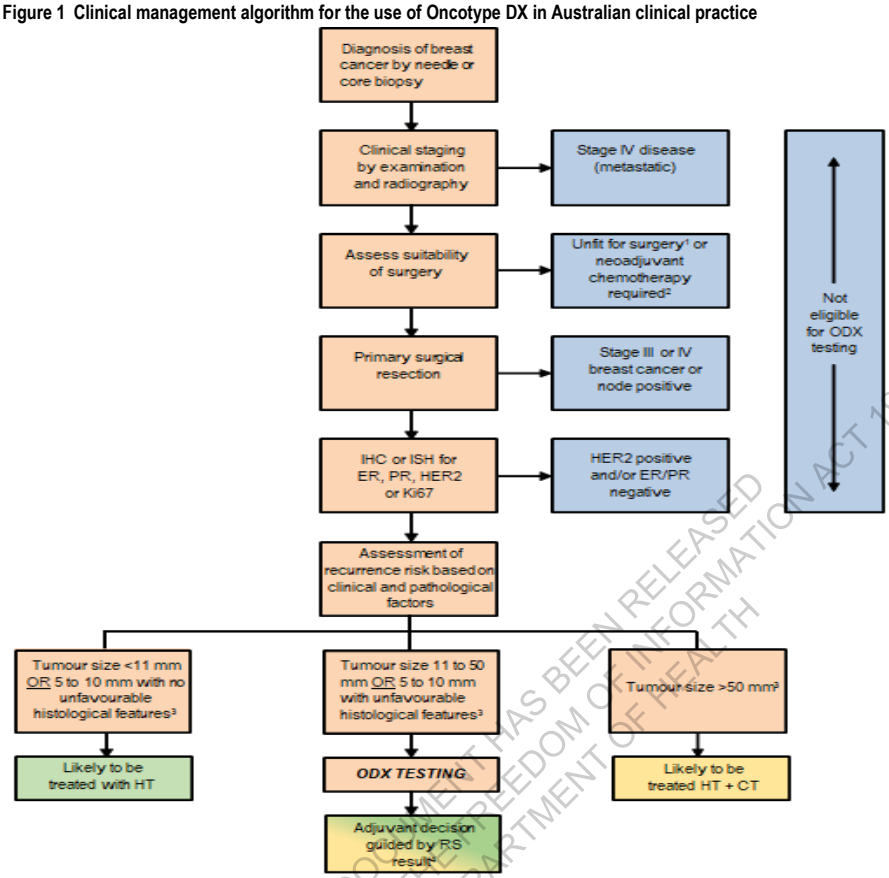
See Application 1342.4 PSD on the MSAC website.

8. Proposed intervention's place in clinical management

The resubmission proposed clinical management algorithm (Figure 1) differs from that presented in earlier MSAC applications for Oncotype DX in that it excludes node positive patients, and the process used to exclude patients with very high or low clinical risk is based on the approach applied in TAILORx. In addition, the algorithm includes 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 current resubmission remains 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 is based on one prospective randomised trial and one re-analysis of a retrospective cohort study:

- The TAILORx trial was a prospective trial (N=9,719; intention-to-treat population), that used a patient's recurrence score only to guide treatment. Women with intermediate RS (11-25) were randomised to hormone therapy (HT) alone or HT+ chemotherapy (CT) (n=6,711; Arms B and C); and those with low (0-10; n=1,619; Arm A) or high (≥26; n=1,389; Arm D) RS were treated with HT alone or HT+CT, respectively (Sparano et al. 2018). Results were also provided for the per protocol population (N= 6,711; 'as treated population'), which the Critique stated was an important comparison for demonstrating non-inferiority of HT vs. HT+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 trial (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).

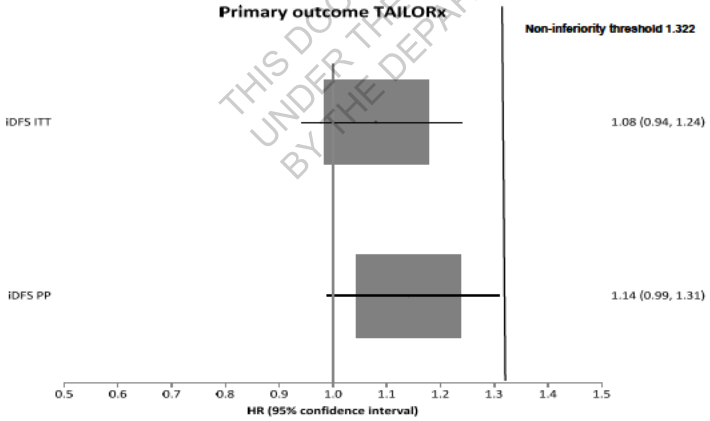


Figure 2 Forest plot of the hazard ratios (HR) of the intention-to-treat (ITT) and 'as-treated' (PP) populations, with the non-inferiority threshold for invasive disease-free survival (iDFS)

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

- For the ITT population, the pre-specified non-inferiority margin of 32.2% decrease in invasive disease-free survival for hormone therapy alone compared to hormone 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 HT alone and 'higher' risk women were randomised to HT+CT).
- The non-adherence in the HT arm was 5.6% but 18.4% in the HT+CT arm compared to only 6.4% 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 hormone regimens and nine chemotherapy regimens, which may introduce confounding to the extent that they are not equi-effective.

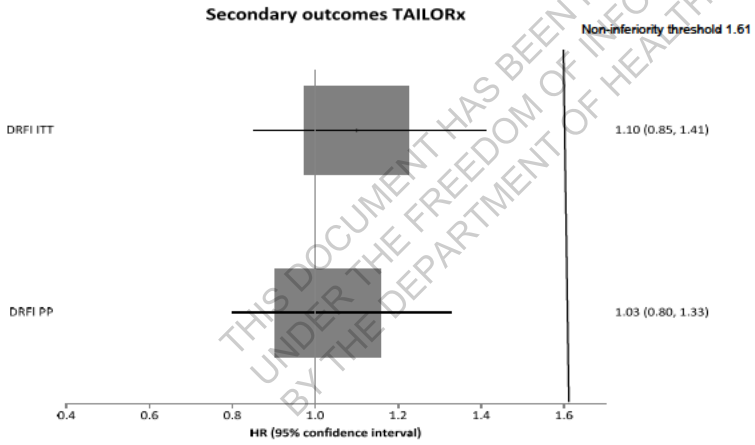


Figure 3 Forest plot of the hazard ratios (HR) of the intention-to-treat (ITT) and 'as treated' (PP) populations with non-inferiority threshold for distant recurrence-free interval (DRFI)

The secondary analysis to support the claim of no difference between the treatment arms - hormone therapy alone compared to hormone therapy plus chemotherapy - also met the pre-specified 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 hormone therapy alone compared to hormone 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 pre-specified 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 pre-specified non-inferiority threshold of 1.46 was not provided in the SBA 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, HT therapy	94.0±0.6	84.0±1.3
Score of 11-25, HT therapy	92.8 ±0.5	83.3±0.9
Score of 11-25, CT+HT therapy	93.1±0.5	84.3±0.8
Score of ≥26, CT+HT therapy	87.6±1.0	75.7±2.2
Freedom from recurrence of breast cancer at a distant site		
Score of ≤10, HT therapy	99 3±0.2	96.8±0.7
Score of 11-25, HT therapy	98.0±0.3	94.5±0.5
Score of 11-25, CT+HT therapy	98 2±0.2	95.0±0.5
Score of ≥26, CT+HT 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, HT therapy	98.8±0.3	95.0±0.8
Score of 11-25, HT therapy	96 9±0.3	92.2±0.6
Score of 11-25, CT+HT therapy	97.0±0.3	92.9±0.6
Score of ≥26, CT+HT therapy	91.0±0.8	84.8±1.7
Overall survival		
Score of ≤10, HT therapy	98.0±0.4	93.7±0.8
Score of 11-25, HT therapy	98.0±0.2	93.9±0.5
Score of 11-25, CT+HT therapy	98.1±0.2	93.8±0.5
Score of ≥26, CT+HT 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 trial 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 from 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		

	N	Effect hazard ratio (95% CI)	P value
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 re-submission. Cox proportional Hazards Regression Model adjusted for patient age (>50 years vs ≤50 years), clinical tumour size (> 2.0 vs ≤2.0cm), 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 resubmission clinical claims:

- *A non-inferiority claim, for patients who the Oncotype DX test categorises into the intermediate recurrence group score, that hormone therapy alone is no worse for the risk of distant recurrence free survival compared to hormone 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 hormone 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 is based on the results from TAILORx and the superiority claim is 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 M NDACT 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	TA LORx 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 economic model 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
Hormone 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 during the critique Source: 72 p155 of the SBA, ODX_EconModel xlsm
[a] That is, moving any patients with RS ≤25 treated with HT + CT in the usual care arm to HT only 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
Hormone 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 during the critique Source: 72 p155 of the SBA, ODX_EconModel xlsm
[a] That is, moving any patients with RS ≥26 treated with HT only in the usual care arm to HT + 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
Hormone 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 during critique
Source: Table 69, p153, Table 70 and 71 p154 of the SBA, 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 has been 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 TA LORx and other supporting studies.
Population (as per the eligibility criteria into the TA LORx trial)	The eligible population should be specified as patients with newly diagnosed breast carcinomas; who are *ER*-positive, *HER2*-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	TA LORx trial protocol specified that women with an RS score of ≥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 economic model 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 TA LORx) 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 hormone therapy.

ESC noted the resubmission includes 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 a score of ≥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 is higher than the confidential fee in previous submissions ($3,375). The applicant has 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-women 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 hormone 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+*, *HER2–*, 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 hormone therapy alone results in significantly worse breast cancer outcomes compared treating these women with both adjuvant chemotherapy and adjuvant hormone 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 the England's National Health Service (NHS), for use in early-stage *ER+*, *HER2–*, 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 yet covered by the 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. estimates 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) is 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 is relied on to demonstrate that also receiving adjuvant chemotherapy is superior to hormone therapy alone in patients with RS ≥26.

ESC noted that the TAILORx trial provides 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 are used in the resubmission to characterise current patterns of care. These data are 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 using the Critique's assumption of four cycles rather than six. However, ESC noted the applicant's comment in 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 applicant agreed to base 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 hormone therapy in patients with an RS ≥26. The applicant 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 applicant 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 uses revised utility values, which are now more in line with TAILORx.

ESC noted that the base case ICER/QALY from the revised combined model is sensitive to several assumptions, which vary 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 economic evaluation model is correct, it is basic. It includes only univariate sensitivity analyses, but no probability sensitivity analysis or cost-effectiveness acceptability curve. The model includes direct costs only; it does not include 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 results based on the source of clinical utility evidence: evidence for the non-inferiority claim is from the TAILORx randomised trial, but the economic analysis 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 applicant's revised financial analyses resulted in a modest increase in the net budgetary impact to $44.7 million over the first 5 years. The applicant 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

Example: Nil

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

The MSAC Executive 3 February 2012 teleconference agreed for MSAC applicants to be given the opportunity to have a comment inserted in the final outcomes document – to be limited to one paragraph and/or a link to reference material

17. Further information on MSAC

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

s 22

From: s 47F
Sent: Sunday, 13 October 2019 10:17 PM
To: MSAC SECRETARIAT
Cc: s 47F s 22
Subject: RE: Oncotype PSD August 2019 MSAC meeting [SEC=OFFICIAL]

Will do this ASAP – sorry for delay

From: MSAC SECRETARIAT <MSAC.SECRETARIAT@health.gov.au>
Sent: Tuesday, 8 October 2019 3:49 PM
To: s 47F
Cc: s 47F s 22 MSAC SECRETARIAT <MSAC.SECRETARIAT@health.gov.au>
Subject: Oncotype PSD August 2019 MSAC meeting [SEC=OFFICIAL]

Hi s 47F

Just checking if you have had a chance to finish the Oncotype PSD?

So you are aware, the applicant is starting to push for the PSD as we are now outside the 6-8 week timeframe in which applicants would normally receive it.

Thanks,

s 22

Assistant Director - Medical Services & Technology Section
Technology Assessment and Access Division | Office of HTA
Australian Government Department of Health
s 22

PO Box 9848, Canberra ACT 2601, Australia

The Department of Health acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders both past and present.

From: s 47F
Sent: Wednesday, 2 October 2019 12:20 AM
To: MSAC SECRETARIAT <MSAC.SECRETARIAT@health.gov.au>
Cc: s 47F
Subject: RE: August 2019 MSAC meeting - Draft PSDs for your clearance/comments - by Wednesday 2 October 2019 [SEC=OFFICIAL]

Hi s 22
The latest batch of PSDs are fine – no changes.
I am still working on oncotype DX.
s 47F

From: MSAC SECRETARIAT <MSAC.SECRETARIAT@health.gov.au>
Sent: Monday, 30 September 2019 8:28 AM

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® or ODX) in women 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 hormone 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 hormone therapy.

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

s 47C, s 47E

s 47C, s 47E

s 47C, s 47E

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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 ODX 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 ODX.

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 has changed since the previous resubmission (1342.4), and is presented in Table 1 (applicant highlighted changes with previous submission in red). The applicant has requested a fee of $5,085 per service, and the resubmission did not request any confidential pricing or fee arrangement.

Table 1 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.

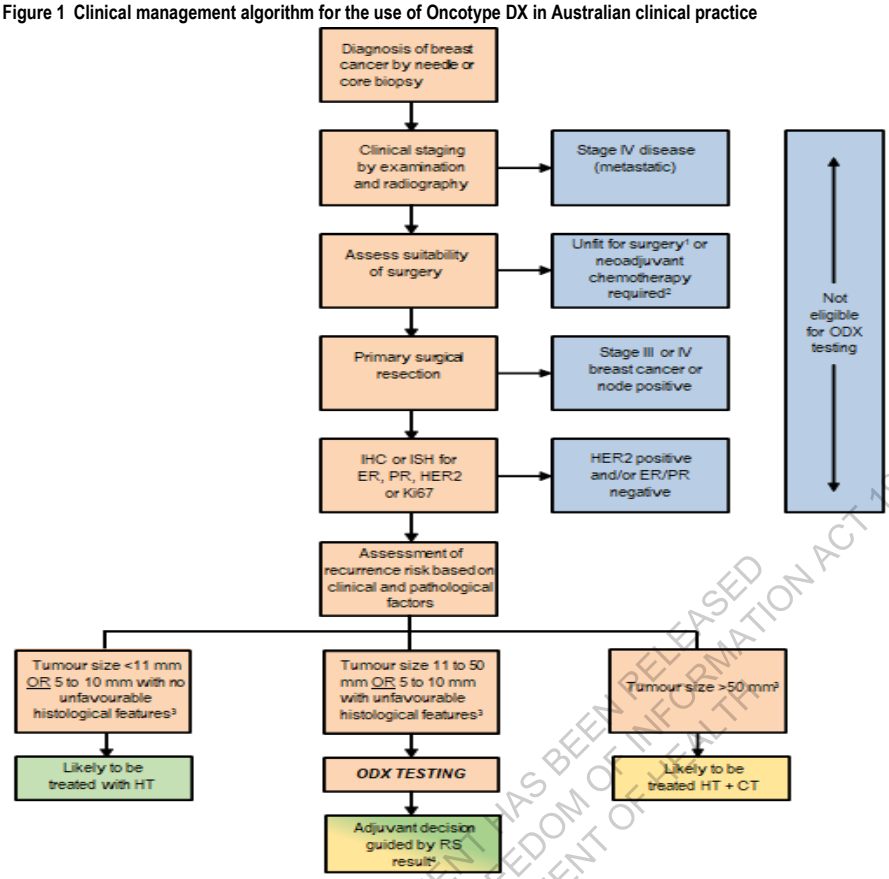
7. Summary of Public Consultation Feedback/Consumer Issues

See Application 1342.4 PSD on the MSAC website.

8. Proposed intervention's place in clinical management

The resubmission proposed clinical management algorithm (Figure 1) differs from that presented in earlier MSAC applications for Oncotype DX in that it excludes node positive patients, and the process used to exclude patients with very high or low clinical risk is based on the approach applied in TAILORx. In addition, the algorithm includes 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 current resubmission remains 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 is based on one prospective randomised trial and one re-analysis of a retrospective cohort study:

- The TAILORx trial was a prospective trial (N=9,719; intention-to-treat population), that used a patient's recurrence score only to guide treatment. Women with intermediate RS (11-25) were randomised to hormone therapy (HT) alone or HT+ chemotherapy (CT) (n=6,711; Arms B and C); and those with low (0-10; n=1,619; Arm A) or high (≥26; n=1,389; Arm D) RS were treated with HT alone or HT+CT, respectively (Sparano et al. 2018). Results were also provided for the per protocol population (N= 6,711; 'as treated population'), which the Critique stated was an important comparison for demonstrating non-inferiority of HT vs. HT+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 trial (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).

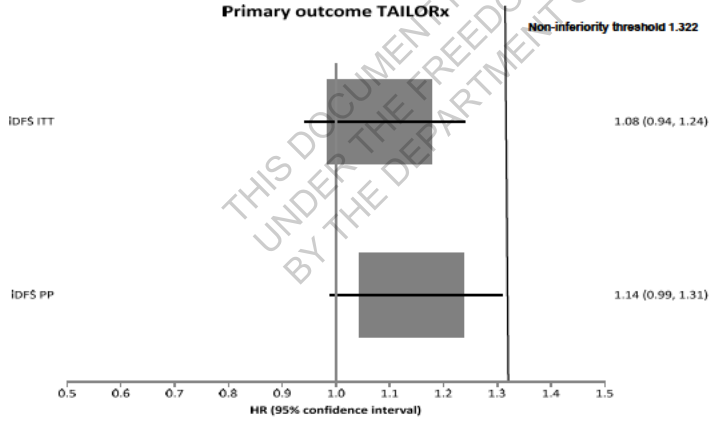


Figure 2 Forest plot of the hazard ratios (HR) of the intention-to-treat (ITT) and 'as-treated' (PP) populations, with the non-inferiority threshold for invasive disease-free survival (iDFS)

The primary analysis to support the claim of no difference between the treatment arms - hormone therapy alone compared to hormone therapy plus chemotherapy - met the pre-

specified non-inferiority threshold. However, the Critique outlined the following issues to consider:

- For the ITT population, the pre-specified non-inferiority margin of 32.2% decrease in invasive disease-free survival for hormone therapy alone compared to hormone 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 HT alone and 'higher' risk women were randomised to HT+CT).
- The non-adherence in the HT arm was 5.6% but 18.4% in the HT+CT arm compared to only 6.4% 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 hormone regimens and nine chemotherapy regimens, which may introduce confounding to the extent that they are not equi-effective.

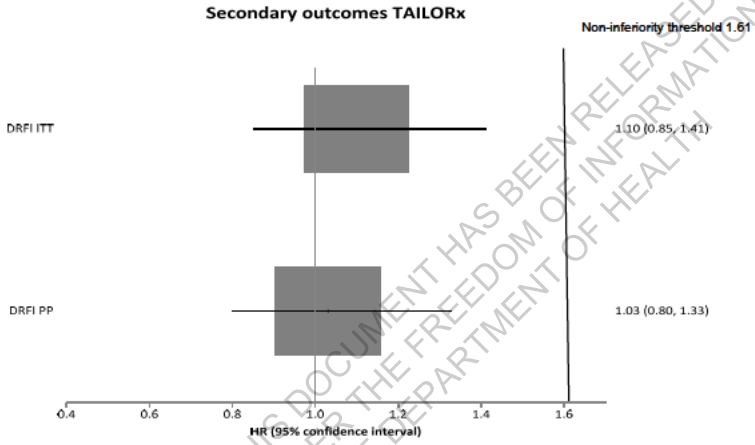


Figure 3 Forest plot of the hazard ratios (HR) of the intention-to-treat (ITT) and 'as treated' (PP) populations with non-inferiority threshold for distant recurrence-free interval (DRFI)

The secondary analysis to support the claim of no difference between the treatment arms - hormone therapy alone compared to hormone therapy plus chemotherapy - also met the pre-specified 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 hormone therapy alone compared to hormone 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 pre-specified 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 pre-specified non-inferiority threshold of 1.46 was not provided in the SBA 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, HT therapy	94.0±0.6	84.0±1.3
Score of 11-25, HT therapy	92.8 ±0.5	83.3±0.9
Score of 11-25, CT+HT therapy	93.1±0.5	84.3±0.8
Score of ≥26, CT+HT therapy	87.6±1.0	75.7±2.2
Freedom from recurrence of breast cancer at a distant site		
Score of ≤10, HT therapy	99 3±0.2	96.8±0.7
Score of 11-25, HT therapy	98.0±0.3	94.5±0.5
Score of 11-25, CT+HT therapy	98 2±0.2	95.0±0.5
Score of ≥26, CT+HT 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, HT therapy	98.8±0.3	95.0±0.8
Score of 11-25, HT therapy	96 9±0.3	92.2±0.6
Score of 11-25, CT+HT therapy	97.0±0.3	92.9±0.6
Score of ≥26, CT+HT therapy	91.0±0.8	84.8±1.7
Overall survival		
Score of ≤10, HT therapy	98.0±0.4	93.7±0.8
Score of 11-25, HT therapy	98.0±0.2	93.9±0.5
Score of 11-25, CT+HT therapy	98.1±0.2	93.8±0.5
Score of ≥26, CT+HT 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 trial 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 from 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 re-submission. Cox proportional Hazards Regression Model adjusted for patient age (>50 years vs ≤50 years), clinical tumour size (> 2.0 vs ≤2.0cm), 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 resubmission clinical claims:

- *A non-inferiority claim, for patients who the Oncotype DX test categorises into the intermediate recurrence group score, that hormone therapy alone is no worse for the risk of distant recurrence free survival compared to hormone 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 hormone 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 is based on the results from TAILORx and the superiority claim is 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 M NDACT 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	TA LORx 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 economic model 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
Hormone 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 during the critique Source: 72 p155 of the SBA, ODX_EconModel xlsm
[a] That is, moving any patients with RS ≤25 treated with HT + CT in the usual care arm to HT only 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
Hormone 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 during the critique Source: 72 p155 of the SBA, ODX_EconModel xlsm
[a] That is, moving any patients with RS ≥26 treated with HT only in the usual care arm to HT + 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			

Parameter	Oncotype DX	Usual care	Incremental
Oncotype DX test costs	$5,085.00	$0.00	$5,085.00
Chemotherapy	$1,809.84	$3,116.03	-$1,306.19
Hormone 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 during critique
Source: Table 69, p153, Table 70 and 71 p154 of the SBA, 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 has been 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-	***$5,301,503***	***$7,200,104***	***$8,247,980***	***$9,328,715***	***$10,442,308***

pay)					

[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 TA LORx and other supporting studies.
Population (as per the eligibility criteria into the TA LORx trial)	The eligible population should be specified as patients with newly diagnosed breast carcinomas; who are *ER*-positive, *HER2*-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	TA LORx trial protocol specified that women with an RS score of ≥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 economic model 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 TA LORx) 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 hormone therapy.

ESC noted the resubmission includes 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 a score of ≥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 is higher than the confidential fee in previous submissions ($3,375). The applicant has 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-women 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 hormone 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*+, *HER2*–, 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 hormone therapy alone results in significantly worse breast cancer outcomes compared treating these women with both adjuvant chemotherapy and adjuvant hormone 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 the England's National Health Service (NHS), for use in early-stage *ER+*, *HER2–*, 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 yet covered by the 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. estimates 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) is 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 is relied on to demonstrate that also receiving adjuvant chemotherapy is superior to hormone therapy alone in patients with RS ≥26.

ESC noted that the TAILORx trial provides 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 are used in the resubmission to characterise current patterns of care. These data are 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 using the Critique's assumption of four cycles rather than six. However, ESC noted the applicant's comment in 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 applicant agreed to base 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 hormone therapy in patients with an RS ≥26. The applicant 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 applicant 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 uses revised utility values, which are now more in line with TAILORx.

ESC noted that the base case ICER/QALY from the revised combined model is sensitive to several assumptions, which vary 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 economic evaluation model is correct, it is basic. It includes only univariate sensitivity analyses, but no probability sensitivity analysis or cost-effectiveness acceptability curve. The model includes direct costs only; it does not include 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 results based on the source of clinical utility evidence: evidence for the non-inferiority claim is from the TAILORx randomised trial, but the economic analysis 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 applicant's revised financial analyses resulted in a modest increase in the net budgetary impact to $44.7 million over the first 5 years. The applicant 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

Example: Nil

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

The MSAC Executive 3 February 2012 teleconference agreed for MSAC applicants to be given the opportunity to have a comment inserted in the final outcomes document – to be limited to one paragraph and/or a link to reference material

17. Further information on MSAC

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

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