Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1342.4 – 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 70th Meeting, 27 July 2017**

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

1. Purpose of application

A resubmission requesting a new Medicare Benefit Schedule (MBS) listing of Oncotype DX (ODX) testing for patients with early invasive breast cancer (stages I-II) meeting the pre-defined criteria was received by the Department of Health from Specialised Therapeutics Australia.

This public summary document (PSD) should be reviewed in conjunction with the PSDs for Applications 1342, 1342.1, 1342.2 and 1342.3.

2. MSAC's advice to the Minister

After considering the available evidence presented in relation to the comparative safety, clinical effectiveness and cost effectiveness of gene expression profiling of 21 genes in breast cancer to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit, MSAC did not support public funding of the Oncotype DX breast cancer assay to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit. MSAC considered that the incremental benefit of the Oncotype DX breast cancer assay over optimal care remains uncertain.

MSAC noted that there are other trials currently in progress (e.g. TAILORx), the results of which may be informative. Any resubmission would need to be considered via ESC.

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

MSAC noted that this was the fourth resubmission for Oncotype DX (ODX) breast cancer assay to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit. MSAC noted that the complex implementation issues associated with the test being conducted in an overseas laboratory have been previously discussed as documented in public summary documents (PSDs) for Applications 1342, 1342.1, 1342.2 and 1342.3.

MSAC noted that there was no change in the proposed population as defined in the item descriptor, which was previously accepted by MSAC as appropriate.

In the PSD for MSAC application 1342.3, MSAC requested that the applicant demonstrate "the incremental gain of ODX testing over 'usual care', where 'usual care' incorporates currently available prognostic approaches and algorithms for the purpose of deciding whether to use adjuvant chemotherapy". MSAC agreed that the definition of the comparator is the key residual issue in considering the value of ODX over and above alternative tools and algorithms. MSAC confirmed that the most appropriate comparator for ODX testing is usual care and clarified that usual care is best defined as optimal care — where all available sources of information are considered for informing treatment decisions. MSAC acknowledged that the use of online prognostic tools may not be valuable for all breast cancer patients. However, MSAC noted that in the specific population of interest for this resubmission (patients with apparently equivocal risk) the use of these online prognostic tools, along with multidisciplinary team discussions and consideration of tumour and patient factors, is considered good practice. MSAC considered that the use of online prognostic tools would almost certainly add value in this population. As such, MSAC reiterated the need to determine the magnitude of the incremental prognostic utility and incremental clinical utility of ODX testing over and above the currently available prognostic approaches and algorithms. MSAC noted that the resubmission did not provide any additional data to address this question.

MSAC considered the results of the clinician survey provided in the resubmission, noting the shortcomings of the survey design. MSAC noted that it was unclear from the survey what proportion of oncologists who use prognostic tools in intermediate risk patients would use ODX instead of or in addition to these tools. MSAC agreed that the survey did not describe current practice accurately or effectively and therefore could not address the issue of the incremental gain of ODX as previously requested by MSAC. MSAC also noted that the extent of use of online prognostic tools in the Australian Decision Impact Study (ADIS) is unknown and unlikely to be representative of current practice and therefore data from ADIS cannot address the question of incremental gain of ODX over and above currently available prognostic approaches and algorithms.

MSAC noted that no additional cost effectiveness analysis was presented in the resubmission and the uncertainty regarding the cost-effectiveness of ODX remains unresolved.

MSAC noted that additional trial data may help to address the remaining uncertainty regarding the clinical effectiveness and cost-effectiveness of ODX. MSAC noted that the ongoing TAILORx trial may provide additional data, though further consideration would need to be given to whether the trial population and comparator are appropriate and relevant to address this uncertainty.

MSAC acknowledged the applicant's comments that ODX is has been recommended by the National Institute for Health and Care Excellence (NICE) and is used in other countries. MSAC noted that the NICE assessment of ODX identified the same gaps in the evidence base as have been raised by MSAC. MSAC commented that the manufacturer provides ODX to UK National Health Service (NHS) organisations according to the confidential arrangement agreed with NICE, which makes it difficult for MSAC to ascertain the cost-effectiveness of ODX in this context.

MSAC noted the availability of other gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in breast cancer patients (Mammaprint, Endopredict, etc.) which have not been considered as part of any of the resubmissions.

After considering the evidence presented in relation to the safety, clinical effectiveness and cost-effectiveness MSAC did not support public funding of the ODX breast cancer assay to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit. MSAC considered that the incremental clinical utility of the proposed service remain uncertain. MSAC noted that data from ongoing trials, if suitable, may be useful in addressing this uncertainty once it is available.

4. Background

This is the fifth iteration of this application. The original application was considered by MSAC at its July 2013 meeting, subsequent resubmissions were then considered in April 2014, November 2015 and July 2016. The PSDs for these applications can be viewed on the MSAC website.

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 TGA. A November 2015 report by the US 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 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 proposed population and item descriptor have not changed since the previous Application 1342.3.

7. Summary of Public Consultation Feedback/Consumer Issues

See Application 1342.3 PSD on the MSAC website.

8. Proposed intervention's place in clinical management

No change was made to the proposed intervention. See Application 1342.3 PSD on the MSAC website for the proposed clinical algorithm.

9. Comparator

The comparator has not changed from the previous submission. MSAC has accepted the comparator: usual care, defined as subjective assessment of various clinical and pathological factors to estimate the risk of recurrence; which are likely combined using formal algorithms.

The resubmission presented a survey to better define usual care and clarify the influence of online prognostic tools on treatment decisions, particularly chemotherapy recommendations.

10. Comparative safety

The impact of discordant results between Adjuvant! Online (AO) or other online tools and ODX regarding treatment decisions remains unresolved.

11. Comparative effectiveness

No new data on clinical effectiveness were presented in this resubmission.

To address both of MSAC's outstanding concerns regarding the incremental gain of ODX over usual care incorporating available prognostic tools the applicant undertook a survey of Australian medical oncologists and breast surgeons to provide information on the current use of online prognostic tools in the management of these patients.

Overall, the survey showed that online prognostic tools are frequently used, however these tools do not influence treatment decisions as much as discussions within a multidisciplinary team meeting or consideration of tumour and patient factors. The consideration of tumour and patient factors is almost always used in the management of these breast cancer patients, particularly when determining whether or not to recommend chemotherapy. Online prognostic tools such as AO and Predict take into consideration only some of these tumour and patient factors. Multidisciplinary team meetings are not always available to clinicians and mostly exist within public hospitals and larger private hospitals. However, the same patient factors and tumour factors are discussed and considered at such meetings. The principles and individual components of the prognostic tools are incorporated into the consideration of patient and tumour factors as well as the multidisciplinary team decision process.

The critique identified serious issues of bias with the survey, and considered that the survey sample may not be representative.

12. Economic evaluation

The economic evaluation is unchanged from submission 1342.3.

The SBA cost-effectiveness results for the populations accepted in the previous resubmission, 1342.3, based on the ADIS-1 decision impact study, are presented in Table 1. These results are unchanged from the previous resubmission.

Table 1 Decision and economic impact of Oncotype DX by node status and number of negative factors, based on data from the ADIS1 study

Number of negative factors	Node negative		Node positive	
	Treatment changed	ICER	Treatment changed	ICER
MSAC Application 1342.3(ODX eligible in patients with 1 to 2 negative factors where node positivity is considered a negative factor)				
0	10.5% (4/38)	Dominated	Not applicable [a]	
1	22.2% (10/45)	$8,598	23.1% (3/13)	DOMINANT
2	42.9% (6/14)	$1,583	29.6% (8/27)	DOMINANT
3	0.0% (0/4)	Dominated	0.0% (0/8)	Dominated
4	Not applicable [b]		0.0% (0/2)	Dominated

ADIS = Australian Decision Impact study, ICER = Incremental Cost Effectiveness Ratio, ODX = Oncotype DX

Green and red shaded cells respectively represent eligible and ineligible patient groups in submission 1342.3. a. Results of the model are presented separately for node negative and node positive patients because of the different randomised controlled evidence base underlying the economic model (Paik et al. 2006 and Albain et al. 2010, respectively). In this presentation of the results, it is impossible for node positive patients to have zero negative factors because node positivity is itself a negative factor. Likewise, it is impossible for node negative patients to have all four negative factors because they do not have the node positive negative factor.

The previous critique noted several elements of uncertainty with the modelled evaluation. As no new economic model was provided with this resubmission the results could not be verified and it is assumed the same elements of uncertainty remain.

13. Financial/budgetary impacts

The financial implications to the MBS resulting from the proposed listing of ODX were not submitted in this resubmission.

14. Key issues from ESC for MSAC

ESC considered the fourth resubmission requesting MBS listing of Oncotype DX (ODX) testing for patients with early invasive breast cancer (stages I-II) meeting predefined criteria. ESC noted that there are several outstanding implementation issues associated with ODX testing that have been raised previously: the absence of TGA registration or NATA accreditation, delivery of the service outside Australia and the proposed hidden pricing arrangement. These remain matters for Government to consider.

ESC noted the item descriptor now encompasses the changes proposed at the June 2016 ESC meeting and commented that the descriptor now adequately defines the patient population and targets ODX testing to the patient population with apparently equivocal risk, where testing may have the greatest clinical utility.

In the Public Summary Document (PSD) for MSAC application 1342.3, MSAC requested that the applicant demonstrate the incremental gain of ODX testing over 'usual care', where usual care' incorporates currently available prognostic approaches and algorithms for the purpose of deciding whether to use adjuvant chemotherapy, in terms of more accurately estimating the risk of recurrence – i.e., prognostic effect.

ESC noted that the definition of the comparator is the key residual issue in considering the value of ODX testing over and above alternative tools and algorithms (many of which are freely available online). ESC noted that this issue was first raised by ESC during consideration of the initial MSAC application 1342 in 2013.

ESC noted that in this resubmission the applicant sought to define 'usual care' as including the use of the online prognostic tools. To support this claim, the applicant provided a survey of medical oncologists and breast surgeons on the use of prognostic tools in practice, and a statement from the Australian Decision Impact Study (ADIS) investigators confirming that online prognostic tools were employed by each participating physician to the extent that they are employed in practice outside of the study. No information was available regarding how often prognostic tools were used in ADIS or which ones were most common.

ESC agreed with the critique's assessment of the survey as having been poorly conducted and reported, with a small proportion of respondents (11%) and a high risk of bias. ESC noted that the survey did not provide useful detail about the use of online tools in clinical practice and was not sufficiently focused on the specific population in question. The committee also noted that although breast surgeons were included in the survey, they would be unlikely to use prognostic tools.

ESC also noted temporal differences between the description of practice in the survey (2016–2017) and ADIS (conducted in 2010–2011), noting that it is very likely that uptake of online tools has increased over the last five years.

ESC noted that the resubmission referred to advice from the Department to support its approach, and advised that, irrespective of whether or not such advice were given, it could not prejudice MSAC's deliberations. ESC therefore focussed on the request of MSAC as made explicit in the PSD.

ESC noted that the comparison requested by MSAC was 'usual care' *and* online tools *and* ODX testing compared with 'usual care' *and* online tools alone. This comparison was requested with a view to quantifying the clinical utility gain for ODX. In contrast, the comparison actually provided in the resubmission (based on data from ADIS) was 'usual care' *with or without* online tools *and* ODX testing compared with 'usual care' *with or without* online tools. ESC advised that this was important because, if the online tools have any incremental prognostic value over 'usual care' alone, then the incremental gain claimed for ODX may be overstated. ESC noted that although the extent of use of online tools in ADS is not known, it is likely to have been the same across the arms because ADIS was a before and after study. Thus, although it is possible that the clinical utility gain observed in ADIS may be partially attributed to ODX, there is residual uncertainty over the full magnitude of this gain being attributable to ODX. Because it was conducted some years later, the survey does not help in identifying the extent of use of online tools in ADIS. Indeed, ESC noted that the survey highlights the currently high use of prognostic tools other than ODX.
ESC considered that there is still significant uncertainty regarding the magnitude of clinical utility gain for ODX over and above other prognostic tools; particularly given that what is available is linked evidence, rather than direct evidence of clinical outcomes.

ESC noted that head to head comparisons of ODX versus other prognostic approaches may be better placed to address this uncertainty and that MSAC may wish to investigate additional details of head-to-head studies mentioned in previous PSDs and when the results of these studies might become available.

ESC noted that:

- the applicant argued that the comparator is unchanged from the previous resubmission and therefore revised cost-effectiveness estimates are not provided.
- the remaining uncertainty regarding the magnitude of the incremental gain in more accurately estimating the risk of recurrence with ODX testing means that this omission was not justified.

Consumer concerns focused around access and cost, noting that there are perceived benefits in assisting women with difficult decisions about whether or not to undergo chemotherapy but also concerns around patient recourse if the prognosis provided is not accurate.

MSAC ISSUES	WHO WILL/HAS ADDRESSED THIS	ANSWER	ESC ADVICE
Applicant to provide data demonstrating the incremental gain of ODX over and above currently available prognostic approaches and algorithms	**Applicant has attempted to address this in its resubmission by conducting a survey of medical oncologists and breast surgeons.**	**Survey is poorly conducted and reported and does not reliably address the issue. Also, rather than testing the survey findings in the modelled estimates, the current resubmission attempts to use the findings to defend the applicability of ADIS (as previously presented to MSAC)**	**Data from ADIS cannot address this issue as the extent of use of other prognostic approaches was (a) not recorded, and (b) is likely to have changed since ADIS was conducted Earlier PSDs note that head-to-head comparisons of ODX vs other prognostic approaches would address the remaining uncertainty**
If the incremental gain is less than previously estimated then a revised CEA should be prepared	**Not addressed by applicant – asserts incremental gain the same as previously submitted, so no revised CEA included**	**N/A**	**The uncertainty regarding the magnitude of the incremental gain with ODX means that this approach by the applicant is not justified.**

15. Other significant factors

Nil

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

STA is extremely disappointed by the Committee's decision, after it had previously accepted our analysis and economic evaluation, comparing usual care to usual care plus Oncotype DX (ODX). In all submissions for ODX, usual care has included clinical judgment to estimate risk of recurrence using informal or formal algorithms, including online prognostic tools. However, the Committee requested an analysis in which online prognostic tools must be used in the assessment of all patients. This does not reflect usual care or the benefit and impact of ODX over usual care.

This has been the fifth MSAC submission for ODX. Further attempts are not planned given the significant investment of resources expended to date on multiple local studies and surveys supporting past submissions. We note that in our modelling, more than 250 Australian women every year who cannot afford to self fund ODX will endure unnecessary chemotherapy without access to the test.

Following this outcome, ODX remains unaffordable for most Australians. In the rest of the developed world, ODX is reimbursed and recommended in all breast cancer treatment guidelines. In the UK, ODX received a positive NICE assessment. STA submitted the lowest price available in the world. We sincerely thank the many patients, physicians and organisations who have supported our attempts to gain funding of ODX for Australian women with early stage breast cancer.

17. Further information on MSAC

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