



Australian Government
Medical Services Advisory Committee

Public Summary Document

Application No. 1342.3 – 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 67th Meeting, 28-29 July 2016**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at [MSAC Website](#)

1. Purpose of application and links to other applications

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 pre-defined criteria was received from Specialised Therapeutics Australia by the Department of Health.

Specialised Therapeutics currently provides access to the ODX test in Australia under an agreement with Genomic Health.

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

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 deferred public funding because of concerns that the incremental benefits of the proposed Oncotype DX (ODX) testing over currently available predictive algorithms had not been demonstrated. While the clinical validity data provided by the applicant in the resubmission supports that the ODX test has prognostic utility (in predicting the likelihood of disease recurrence), it does not support that claim that ODX has incremental utility in predicting patients' likely response to chemotherapy.

MSAC requested the following information before it could finalise its advice:

- demonstration of the incremental gain of ODX testing over ‘usual care’ incorporating currently available prognostic approaches and algorithms currently used for the purpose of deciding whether to use adjuvant chemotherapy, in terms of more accurately estimating the risk of recurrence i.e. prognostic effect;
- where this incremental gain is less than what has been estimated in the current resubmission, use of the reduced estimate of gain to revise the modelled estimates of: reduced risk of recurrence and/or reduced harm through better therapeutic management i.e. predictive effect; improved health outcomes; greater healthcare cost offsets; and thus cost effectiveness in the population proposed for testing.

MSAC noted that there are several significant issues arising from the current regulatory status of the test that would be matters for Government to consider.

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

MSAC noted that this was the fourth consideration of an application requesting public funding of a 21-gene gene expression profiling (GEP) test for women with newly diagnosed stage I or II invasive breast cancer who are: oestrogen receptor positive (ER+) or progesterone receptor positive (PR+); human epidermal growth factor receptor 2 negative (HER2-); and either lymph node negative (LN-) or lymph node positive (LN+) with up to three positive nodes. MSAC noted that in its most recent consideration of the application in November 2015, the committee deferred public funding because the optimal population and purpose of the proposed test had not been clearly defined.

MSAC recalled that the proposed ODX GEP test is claimed to predict ten-year cancer recurrence and the likelihood of response to adjuvant chemotherapy in women who meet the criteria outlined above. The objectives of testing are to identify women at low risk of recurrence, who should be spared adjuvant chemotherapy, and also women at high risk of recurrence who should receive adjuvant chemotherapy. MSAC noted that the result of the ODX test is presented as a recurrence score (RS), which is used to triage patients according to their level of risk: low risk (RS <18); intermediate risk (RS 18-30); and high risk (RS ≥31). MSAC noted that the proposed testing procedure requires the extraction of tumour samples from unstained slides by an Australian laboratory prior to being subsequently sent to a specific Genomic Health Inc. (GHI) laboratory in the United States (US), where the GEP test is carried out.

MSAC noted that, in addressing the concerns raised at its November 2015 meeting, the current resubmission proposed narrower patient eligibility criteria for ODX testing. The revised criteria stipulate that patients must also have at least one, but no more than two of the following negative risk factors for disease recurrence: node positivity (1-3 positive nodes); tumour size >20mm; grade 2 tumour; and progesterone receptor (PR) or oestrogen receptor (ER) expression <10%. MSAC clarified that the revised criteria have essentially excluded those with no negative risk factors (likely to have a low risk of recurrence, unlikely to require adjuvant chemotherapy) and those with three or more negative risk factors (likely to have a high risk of recurrence, likely to require adjuvant chemotherapy). MSAC considered that the narrowed patient population was appropriate to improve the clinical utility of using the proposed test.

MSAC reiterated the concerns raised during consideration of the previous resubmission in relation to the fact that the ODX test is performed in the US by GHI. Under section 10(1) of the *Health Insurance Act 1973*, the entitlement to Medicare Benefits is limited to professional services rendered in Australia and, in addition, clause 16A(2b) provides that only laboratories

accredited by the National Association of Testing Authorities (NATA) can conduct pathology test listed on the MBS. MSAC noted that in its resubmission, the applicant indicated that GHI's pathology lab is accredited by the American Association for Laboratory Accreditation (A2LA) to perform the ODX assay under ISO 15189:2012. The applicant stated that, as with NATA, A2LA is a member of the International Laboratory Accreditation Cooperation (ILAC) Mutual Recognition Arrangement (MRA) and in accordance with this, NATA has previously recognised accreditations by A2LA. MSAC also acknowledged that the applicant has stated that it is open to accreditation by NATA. MSAC reiterated that the test is not currently registered with the Therapeutic Goods Administration (TGA) and noted that neither is it approved as an In Vitro Diagnostic by the TGA's equivalent in the US, the Food and Drug Administration (FDA). The FDA has no oversight of the ODX test – instead as a Laboratory Developed Test, the GHI laboratory is compliant to the *Clinical Laboratory Improvement Amendments 1988* (CLIA) legislation, which governs operation of the laboratory but includes no assessment of the clinical or analytical performance of the test itself.

While the applicant has indicated in its resubmission that GHI will be responsible for maintaining records of all complaints and incidents, MSAC remained concerned that the TGA would not have any direct overview of adverse events associated with the proposed ODX testing.

MSAC also considered the findings of a report published by the FDA in November 2015 which discussed a number of tests with the potential to yield negative results when the disease or condition is actually present (i.e. false negatives), including ODX. MSAC noted that while the specific test referred to in this report (ODX HER2 RT-PCR) but concluded that these were not relevant because they would not apply to the proposed population in the current resubmission, who would need to have been previously determined as being HER2- to be eligible. MSAC also noted points raised separately by the FDA regarding the current lack of regulation of Laboratory Developed Tests specifically including ODX. In particular, that FDA considers there is currently a lack of evidence of clinical validity, deficient adverse event reporting as well as other concerns surrounding Laboratory Developed Tests in the US.

In deferring the previous resubmission, MSAC advised the applicant to demonstrate the incremental gain in risk prediction, health outcomes and cost effectiveness of ODX testing over “predictive algorithms such as Adjuvant! Online” (AO). In an attempt to address the incremental gain in risk prediction, MSAC noted that the applicant compared the findings of the Australian Decision Impact Study (ADIS) (de Boer RH et al 2013) with those of another ODX decision impact study by Holt S et al 2013.

MSAC noted that in the study by Holt S et al 2013, clinicians made a recommendation for or against chemotherapy on the basis of “tumour size, grade, type, ER, PR, HER2 and node status and with added information from AO”, prior to and following the ODX assay. The ADIS study also assessed clinicians' recommendations about chemotherapy before and after ODX testing. However, initial decisions were made on clinical judgement alone without an apparent use of additional information from AO. The applicant indicated the decision impact results of Holt S et al 2013 were similar to the ADIS study for the proposed restricted patient group (those with one to two negative factors), with ODX testing resulting in a treatment change for approximately 27% of patients and of these, 70% opting to remove chemotherapy. The applicant consequently suggested that ODX provides clinicians with information over and above that provided by AO or usual care. However, MSAC was concerned that:

- the study by Holt S et al 2013 included women who were human epidermal growth factor receptor 2 positive (HER2+); and
- the decision impact results presented in Holt S et al 2013 included patients with 0, 1 and ≥ 2 negative factors whereas the ADIS results related to the restricted patient group only.

Therefore, MSAC considered that the claimed consistency in the decision impact between AO in the Holt S et al, 2013 study and ODX in ADIS was uncertain.

MSAC also considered the evidence presented in the resubmission from the study by Tang G et al 2011 to address the committee's concerns about the incremental gain in health outcomes associated with ODX testing. The study compared the predictive and prognostic utilities of ODX and AO in node negative breast cancer patients. MSAC noted that this comparison may not be applicable to the proposed target population (node negative and node positive patients).

MSAC noted that Tang G et al 2011 used data from NSABP B-14, a validation study in which ODX was used to establish the prognostic ability of the test (Paik S et al 2004); and NSABP B-20, the same pivotal study presented in the previous two resubmissions (Paik S et al 2006). MSAC noted that the first analysis presented in this study relied on NSABP B-20 data to compare the utility of the ODX recurrence score (ODX-RS) and the AO Risk Index (AO-RI) in predicting chemotherapy benefit for patients with respect to distant recurrence-free interval (DRFI), overall survival (OS) and disease-free survival (DFS). MSAC noted that the findings of the study suggested that based on DFRI and OS, compared with ODX-derived RS values, AO-based RI values were unable to predict chemotherapy benefit.

MSAC considered the findings of another analysis presented by Tang G et al 2011, which used data related to node negative patients from the NSABP B-14 trial to compare the prognostic utility of ODX-RS and AO-RI values, based on distant recurrence at 10 years. MSAC noted that where both tests categorised a patient as low risk, the risk of recurrence at 10 years was indeed low. However, MSAC noted that a substantial proportion of patients rated as high-risk according to the AO-derived RIs actually had low ODX-derived RS values, and a low risk of distant recurrence. In addition, for patients with intermediate risk according to AO-derived RIs, MSAC noted that concordance with RS scores was particularly low (i.e. a number of patients had high or low RS values). As noted in the Critique, the resubmission has only reported on the relative predictive and prognostic utilities of ODX compared to AO based on these findings from Tang et al, 2011. However, a conclusive statement regarding the comparative clinical outcomes associated with ODX plus usual care versus AO plus usual care was not provided by the applicant.

MSAC noted the evidence presented to support the incremental cost effectiveness of ODX compared to AO in the resubmission was derived from the findings of the study by Paulden M et al 2013. The study presented a cost effectiveness analysis of ODX compared to AO and revealed that the incremental cost per QALY ratios for ODX in conjunction with AO compared to AO alone were: \$22,440 for patients with low risk on AO; \$3,626 for patients with intermediate risk on AO; and \$1,111 for patients with high risk on AO.

MSAC noted that in deferring the previous resubmission, the applicant had also been advised to demonstrate that the clinical and economic evaluations presented fully encompassed the consequences for those eligible patients for whom ODX and AO yielded both types of discordant results (i.e. where one is 'positive' and the other is 'negative') and thus, assessed

errors in terms of both under- and over-treatment. At the time, MSAC noted that specific consideration should be given to those women who should receive adjuvant chemotherapy, but do not based on ODX results. MSAC noted that the applicant did not provide this data in the current resubmission as the AO website was offline and could not be accessed by the applicant. MSAC acknowledged the issues that had been encountered with the use of the AO website, but questioned why alternative data sources or analyses had not been explored to address the issue of discordant results, particularly given the applicant's recognition that AO is not the only alternative usual care tool available to clinicians, and that AO was only identified as an example of these tools.

MSAC considered the evidence included in the resubmission to provide clarification on the ODX risk score thresholds for decision-making about treatment and the evidentiary basis for selecting these thresholds. MSAC accepted that, as stated by the applicant, the ODX RS thresholds adhere to the cut-offs used in the original validation studies by Paik S et al 2006 and Albain KS et al 2010. MSAC noted that patients with RS values <18 are considered to be low risk and are recommended treatment with hormone therapy alone compared to high risk patients (RS values ≥ 31) who are also recommended adjuvant chemotherapy. MSAC reiterated that treatment decisions for intermediate risk patients (RS 18-30) should be made in conjunction with other relevant factors. MSAC's concerns regarding the variation in the cut-offs used in studies included as part of the previous resubmission, for example the TAILORx study (Sparano JA et al 2015), were also addressed by the applicant through acknowledging that these thresholds were used to minimise the risk of under-treatment with chemotherapy within the trials, rather than provide a decision point for a change in clinical management. The applicant also presented data which indicated that marginal changes to the thresholds used do not have any substantial impact on clinical outcomes. MSAC considered that this conclusion of small impact of clinical outcomes was plausible. MSAC also considered the new data provided in the resubmission from the Israeli Clalit (Stemmer SM et al 2015) and the Surveillance, Epidemiology and End Results (SEER) registries (Shak S et al 2015) to support how ODX is used to manage intermediate risk patients. MSAC noted that these patients were prescribed chemotherapy at a rate of 25% (Stemmer SM et al 2015) and 34% (Shak S et al 2015) and the 5-year recurrence rates were low at 1.1% and 1.4%, respectively. MSAC also considered these findings to be informative. However, MSAC reiterated that the results of four prospective randomised trials due to report in 2017 (TAILORx, OPTIMA, RxPONDER and WSG-PlanB) are likely to inform this further.

MSAC noted that the final deferral reason for the previous resubmission, regarding the need for further detail about the proposed patient registry for ODX testing, was also addressed in the current resubmission. The applicant expressed willingness to monitor ODX use through the implementation of an Australian registry similar in design to the Israeli Clalit registry. MSAC also noted that the applicant has expressed willingness to have further discussions about the most appropriate design for this clinical registry. Although the applicant expressed interest in exploring ways of linking this registry data with existing State-based registries, MSAC anticipated that there would be a number of issues to overcome before this could be achieved.

MSAC noted that the applicant provided two versions of the revised economic model: a 'main model' (informed by de Boer RH et al 2013) which accounted for the updated restricted population; and a second model comparing ODX alone (informed by Paik S et al 2006) with AO plus usual care (informed by Tang G et al 2011) as an addendum. As noted in the ESC report, the 'main' model revealed that the ICERs for ODX testing were: \$8,598 in node negative, one negative factor patients; \$1,583 in node negative, two negative factor patients; and dominant in both node positive, one and two negative factor patients. The

addendum model indicated that ODX is associated with higher upfront costs compared to AO, but more accurately predicts risk of recurrence and response to chemotherapy. MSAC noted that as reported by ESC, the ICER per QALY in the addendum model was \$4,533 and that this was within the range of ICERs reported for the 'main' model.

MSAC noted that the net MBS expenditure associated with ODX testing was projected to be **\$redacted** in the first year of listing, however when offset with the anticipated PBS savings associated with decreased use of chemotherapy, the net impact of ODX on Commonwealth health expenditure was estimated to be **\$redacted** in year 1, increasing to **\$redacted** in the fifth year of listing. MSAC considered that these projected figures are likely to vary from actual expenses as there remains a potential for the number of eligible patients to be greater than estimated in the current resubmission.

MSAC foreshadowed that any implementation of funding would raise a series of substantial policy issues for Government. In particular, MSAC remained concerned about the potential for significant out of pocket costs for patients as the testing is likely to be undertaken on samples obtained during hospitalisation and will consequently be subject to a 75% rebate i.e. patients would incur an upfront out of pocket payment of **\$redacted** per test. MSAC reiterated that if the applicant's proposal for a 'special pricing arrangement' is accepted by Government, then 25% of the schedule fee will be reimbursed to the Commonwealth (**\$redacted**). However, the schedule fee will appear as **\$redacted** and therefore the rebates and patient upfront out of pocket payment will be dependent on this published figure. MSAC noted that this is a matter for consideration by Government.

MSAC also remained concerned about the potential for the ODX test to be used beyond the intended patient population, by those who wish to ascertain their prognosis for reasons other than decision-making regarding adjuvant chemotherapy. In light of these concerns, MSAC agreed with advice from its ESC that the Government may also wish to consider negotiating a risk share arrangement with the applicant to safeguard against any potential unjustified use of the proposed service outside of the intended population. MSAC highlighted that the applicant has indicated that it would be open to discuss such an arrangement. MSAC noted that this is another matter for consideration by Government. MSAC also considered the possibility that some laboratories may charge additional fees for the preparation of tumour blocks and samples for testing, particularly in instances where multiple attempts are required before an optimal sample is obtained. MSAC emphasised that these additional fees should not be viewed as add-on costs and recommended that provisions are made within the proposed risk-share arrangement to account for these potential extra expenses.

MSAC expressed particular concern about the potential for over-reliance on the proposed test in clinical practice and its use in a reflexive manner, as highlighted by clinicians in a study by Bombard Y et al 2015. MSAC considered that this is likely to be one of the challenges associated with the implementation of the service. In light of this, MSAC foreshadowed that there will be a need for preventative measures to ensure tight compliance with the MBS item descriptor and suggested that the introduction of an authority approval mechanism may be one such measure. MSAC considered that the applicant and the Department may wish to consider additional mechanisms to assist in regulating the usage of the proposed service.

MSAC noted that the proposed item descriptor intentionally states the specific number of genes assessed as part of the proposed ODX test as means of circumventing the need to list specific brand names on the MBS. If public funding was approved for the test, MSAC was concerned that in future, other companies may develop a GEP test with the same number of genes and thus qualify for funding without MSAC assessment, or a GEP test with a greater

number of genes and claim that this newer test is a more attractive option for patients. However, MSAC noted that if the Government was to enter into a formal deed of agreement with the current applicant, it is possible that the specific brand of the test could be stated in the item descriptor, as under these conditions the service will not be open to challenge by other parties. MSAC noted that the Government might also wish to consider incorporating the establishment of the proposed patient registry as a pre-requisite to this legal deed of agreement. MSAC again considered these to be matters for consideration by Government.

MSAC summarised that the applicant addressed all of the deferral reasons raised in relation to the previous resubmission with one exception, the requested comparisons between ODX and other prognostic approaches and algorithms such as AO, with the consequential effects on the clinical and economic evaluations. The committee was not satisfied that the data provided clearly demonstrated the incremental gain in risk prediction of ODX compared to these current alternatives and, although recognising that the AO website has been offline, questioned why comparisons to other prognostic approaches and algorithms had not been made. MSAC emphasised that in the previous guidance provided by the committee, AO was listed only as an example of currently available options. MSAC recommended that, in the event that AO continues to be unavailable, the applicant should explore other available risk-prediction tools. MSAC noted that the PREDICT Tool available on the National Health Service (NHS) website is another such example. MSAC also noted that, while the clinical validity data provided by the applicant in the resubmission supports that the ODX test has prognostic utility (in predicting the likelihood of disease recurrence), it does not directly support that claim that ODX has utility in predicting patients' likely response to chemotherapy. MSAC noted that the latter claim is hinged only upon an assumption that patients with a higher risk of recurrence will have greater benefit from chemotherapy but accepted that, in light of currently available evidence, it is unlikely that a stronger evidentiary basis can be provided regarding this claim.

In deferring the application, MSAC requested that the applicant provides data demonstrating the incremental gain of ODX over and above currently available prognostic approaches and algorithms, in terms of more accurately estimating the risk of recurrence i.e. prognostic effect. MSAC considered that if the incremental gain is the same as what has been estimated in the current resubmission, the applicant does not need to undertake a revised cost effectiveness analysis. However, if the incremental gain is less than what was estimated in the current resubmission, the applicant should use the reduced estimate of gain to revise the modelled estimates of: reduced risk of recurrence and/or reduced harm through better therapeutic management (i.e. predictive effect); improved health outcomes; greater healthcare cost offsets; and thus cost effectiveness in the more targeted population proposed for testing.

4. Background

This is the fourth iteration of this application. The original application was considered by MSAC at its November 2013 meeting, subsequent resubmissions were then considered in April 2014 and November 2015. 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.

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 resubmission proposed narrowing the criteria by further restricting eligibility for ODX testing to patients with 1 to 2 of a possible four negative factors. The differences compared with Application 1342.2 are shown in Table 1.

Table 1 Differences between the current and previous MSAC resubmissions

	Current MSAC Application 1342.3	Previous MSAC Application 1342.2
Threshold of negative risk factors	1-2 negative risk factors	<3 negative risk factors
List of negative risk factors	<ul style="list-style-type: none"> • node positivity (1-3 positive nodes) • tumour size >20 mm • Grade 3 tumour • PR or ER <10% 	<ul style="list-style-type: none"> • nodal macrometastases (>2mm) • tumour size >20 mm • Grade 3 tumour • PR or ER <10%

The wording of the revised item descriptor is presented in Table 2.

Table 2 Proposed MBS item descriptor

MBS [item number] (proposed MBS item) Pathology Group P7 Genetics	
Gene expression profiling of tumour samples (surgical resection preferably or core biopsy) by reverse-transcriptase polymerase chain reaction (RT-PCR) technique for 21 genes in breast cancer tissue.	
May only be used to test samples from patients with all of the following characteristics as determined by the referring clinician:	
<ul style="list-style-type: none">- early invasive breast cancer (stages I-II)- oestrogen receptor positive or progesterone receptor positive as determined by immunohistochemistry at an Australian pathology laboratory:- HER2 negative as determined by immunohistochemistry and/or in situ hybridisation at an Australian pathology laboratory:- node negative or 1-3 positive nodes- invasive tumour >2mm- suitable for hormone therapy- suitable for adjuvant chemotherapy- ECOG performance status 0-2	
and	
Patients must also have at least one, but no more than two, of the following negative risk factors for disease recurrence:	
<ul style="list-style-type: none">- Node positivity (1-3 positive nodes)- tumour size >20 mm- Grade 3 tumour- PR or ER <10%	
May only be used once per new primary breast cancer	
Fee: \$redacted	Benefit (85%): \$redacted

7. Summary of Public Consultation Feedback/Consumer Issues

See Application 1342.2 PSD on the MSAC website.

8. Proposed intervention's place in clinical management

No change was made to the proposed intervention. See Application 1342.2 PSD on the MSAC website for the proposed clinical algorithm.

9. Comparator

No change was made to the comparator from Application 1342.2.

The resubmission presented a comparison to the predictive algorithm Adjuvant! Online (AO) within an updated economic model, citing the Paulden (2013) cost-effectiveness analysis and evidence for predicting chemotherapy response from Tang (2011).

10. Comparative safety

MSAC expressed safety concerns regarding the previous resubmission about the use of ODX in those women who do not receive appropriate adjuvant therapy due to the ODX results and requested data on discordant results from ODX and AO testing to assess both under- and over-treatment.

The resubmission did not provide such results given there was no timely access to the AO website.

11. Comparative effectiveness

The resubmission presented Israeli Clalit registry and US SEER registry data to address the use of risk score thresholds in clinical practice. Allocation of chemotherapy was based on ODX Recurrence Score (RS) from ADIS, ADIS2, the Israeli Clalit registry and the US SEER registry.

Distant recurrence at 5 years and breast cancer specific mortality (BCSM) at 5 years following the RS guided treatment decisions in the Clalit and SEER registries are summarised in Table 3. In the Clalit registry, the rate of distant recurrence in the RS<18 group was 0.8% at 5 years, compared with 3.2% for the RS 18-30 group and 10.6% for the RS≥31 group, respectively. BCSM rates were low at 5 years in both registries, ranged from 0-0.4% in the RS <18 group, 1.1-1.4% in the RS 18-30 group to 4.4-6.8% in the RS≥31 group.

Table 3 Breast cancer outcomes following ODX guided treatment decisions in the Clalit and SEER registries

Recurrence score category	Distant recurrence at 5 years; Risk, % (95% CI)	Breast cancer-specific mortality at 5 years; Risk, % (95% CI)	
	Clalit registry (Stemmer 2015)	Clalit registry (Stemmer 2015)	SEER registry (Shak 2015)
Low RS (RS < 18)	0.8% (0.4-1.6)	0.0% (0.0-0.0)	0.4% (0.3-0.6)
Intermediate RS (RS 18-30)	3.2% (2.2-4.7)	1.1% (0.5-2.1)	1.4% (1.1-1.7)
High RS (RS ≥ 31)	10.6% (7.2-15.5)	6.8% (4.1-11.2)	4.4% (3.4-5.6)

Abbreviations: ADIS, Australian Decision Impact Study; LN +, lymph node positive; LN -, lymph node negative; RS, Recurrence Score

The critique commented that the resubmission claimed that when the recommended RS cutoffs (RS<18, RS 18–30, and RS≥31) were adhered to, long-term patient relevant outcomes were good for patients that use the ODX test. In particular, patients with a low RS had extremely low breast-cancer related mortality despite the low use of chemotherapy. However, it should be noted that the clinical claim is derived from non-comparative observational studies which are not powered to demonstrate the required clinical benefit and are prone to bias.

The resubmission presented the study by Paulden et al (2013) as further justification of the cost effectiveness of “ODX + AO” vs “usual care + AO”.

The applicant expressed willingness to monitor the use of ODX through the implementation of an Australian registry which would be similar to the Israeli Clalit Health Services Registry, and proposed a mock data collection form.

The critique noted that the data in the registry are similar to information currently being collected by the applicant in Australia. The applicant proposed not to include health outcomes, such as distant recurrence and breast cancer death, in the Australian registry due to

the long term follow up required. However, these treatment outcome data are captured in the Israeli registry.

12. Economic evaluation

No change was made to the model structure from Application 1342.2.

The resubmission presented the base case results for the following four scenarios:

1. Node negative patients with 1 negative factor
2. Node negative patients with 2 negative factors
3. Node positive patients with 1 negative factor, where node positivity is considered one negative factor
4. Node positive patients with 2 negative factors, where node positivity is considered one negative factor

The results from these scenarios are shown in Table 4.

Table 4 Base case results included within resubmission 1342.3

Number of negative factors	Node negative		Node positive*	
	Treatment changed	ICER	Treatment changed	ICER
MSAC resubmission 1342.3 (ODX eligible in patients with 1 or 2 negative factors)				
1	22.2% (10/45)	\$8,598	23.1% (3/13)	DOMINANT
2	42.9% (6/14)	\$1,583	29.6% (8/27)	DOMINANT

* where node positivity is considered one negative factor

In Application 1342.2, the base case results of the model estimated a cost per QALY gained of \$9,277 in node negative patients. The difference appears to be driven by changes to the MBS item restriction from 0-2 negative factors to 1-2 negative factors and the reversion to ADIS 1 RS scores.

The resubmission also presented an updated economic model comparing ODX testing alone versus “AO + usual care”. The model used Tang (2011) to inform the AO + usual care arm and Paik (2006) to inform the ODX testing arm, in place of ADIS data. The updated model is largely identical to the ‘main’ economic model. The following main assumptions have been modified:

1. Impact of ODX and AO on treatment decisions.
2. Natural history of breast cancer including risk of disease recurrence (and impact of chemotherapy) and survival post disease recurrence.

The population represents a node negative, no negative factor restriction, assumed allocation to chemotherapy group. The results are shown in Table 5.

Table 5 Results of updated model base case

Variables		ODX	AO	Incremental
Disaggregated costs (all discounted)	ODX	\$redacted	\$0.00	\$redacted
	CT (incl admin & monitoring)	\$5,273.84	\$6,499.45	-\$1,225.61
	HT	\$3,264.49	\$3,247.43	\$17.06
	Recurrence	\$4,602.63	\$6,000.30	-\$1,397.66
	Total	\$redacted	\$15,747.17	\$redacted
Disaggregated outcomes	Disease free years (undiscounted)	23.1678	22.7623	0.4055
	Life years (undiscounted)	23.3855	23.0460	0.3395
	Life years (discounted)	13.6696	13.5145	0.1552
	QALYs (discounted)	13.4630	13.2941	0.1688
Cost Effectiveness Analysis	Discounted Cost	\$redacted	\$15,747.17	\$redacted
	Discounted LYs	13.6696	13.5145	0.1552
	Discounted QALYs	13.4630	13.2941	0.1688
	ICER (Cost per LY)			\$4,955
	ICER (Cost per QALY)			\$4,553

The critique noted that the updated model shows that the ODX test is associated with higher upfront costs compared to AO but more accurately predicts risk of recurrence and response to chemotherapy. As a result, the ODX test is associated with lower use of chemotherapy and lower risk of recurrence, which drives the model result.

The updated model base result estimates an ICER of \$4,553 compared to ICERs of \$1,583 in node negative, one negative factor patients, \$8,598 in node negative, two negative factor patients, and dominant ICERs in both node positive, one and two negative factor patients in the original model. Therefore the ICER for the updated model lies within the range of ICERs for the 'main' model.

The sensitivity analysis results for the updated model show that it is sensitive to the proportion of intermediate patients having a higher uptake of chemotherapy; however the incremental cost per QALY is not high enough to make the comparison not cost-effective. This shows that the assumption made within chemotherapy decision making does affect the results. Sensitivity analyses conducted by the evaluator showed the updated model was most sensitive to the change in time horizon. This is expected as the utility of the test relates to preventing breast cancer recurrence over the long-term.

13. Financial/budgetary impacts

Unlike the economic model, Application 1342.2 did not use ADIS 2 data for the financial implications. For the resubmission, these inputs remain sourced from the ADIS study and have not changed.

The critique noted that the key modifications from Application 1342.2 was the change in MBS item restriction from 0-2 to 1-2 negative factors, and the removal of the patient contribution of \$redacted from the previous cost to the MBS of \$redacted, resulting in an updated cost to the MBS of \$redacted.

The estimated number of eligible patients/year for ODX testing in the resubmission is 4,466 in 2016/7, increasing up to 4,825 in Year 5 of listing. This compares with an estimated number of eligible patients/year for ODX testing in Application 1342.2 of 6,298 in 2014, increasing up to 6,804 in Year 5 of listing. Although the total breast cancer population is increasing over time, the restriction to only those women who have one to two negative factors has reduced the eligible population. However, as with Application 1342.2, there remains potential for the number of eligible patients to be greater than the estimate in the resubmission.

The resubmission provided an estimated number of services/year for ODX testing of 893 in Year 1, increasing up to 1,930 in Year 5 of listing. These estimates compare with an estimated number of services/year for ODX testing in Application 1342.2 of 1,260 in Year 1, increasing up to 2,722 in Year 5 of listing. The reduction in the number of services is due to the changes in the MBS item restriction reducing the eligible population.

The estimated cost to the MBS for ODX testing in the resubmission is \$redacted in Year 5 of listing, with a fee to the MBS of \$redacted per test. The MBS cost for ODX testing in Application 1342.2 was \$redacted in Year 5 of listing, with an effective fee of \$redacted per test. The reduced costs are due to the reduced fee per test (\$redacted to \$redacted) and a reduction in the assumed number of tests due to the changes in the proposed MBS restriction.

As with Application 1342.2, the sensitivity analyses conducted in the critique indicate that the estimates of net cost to Commonwealth Health budgets is heavily reliant on the assumed cost savings to the PBS, as well as a strict adherence to the given MBS indication.

14. Key issues from ESC for MSAC

ESC noted the applicant addressed the intended patient population issue raised in the previous submission(s). The patients intended for Oncotype DX[®] (ODX) testing to now exclude patients that are clearly low risk and those that are clearly high risk, thus removing patients for whom the ICER was dominated/unfavourable in the previous submission (1342.2).

The new population definition was however not reflected in the economic model, which specifically included a group of high risk patients (node positive, two negative risk factors) as one of the four modelled patient groups. ESC noted the applicant should amend the economic analysis to reflect the appropriate population. Also, given the node-positive risk scores (with or without ODX) drive the cost-effectiveness outcomes, the ICERs may be less favourable for ODX once this is taken into account.

The economic model structure is unchanged compared with the previous re-submission, thus the uncertainty attached to the resulting ICERs remains unaddressed.

The re-submission did not fully address the requested information describing how the ODX results should guide treatment decisions with respect to prescribing adjuvant chemotherapy. In particular, no information was provided on how to manage intermediate risk patients (those having a score RS 18-30). ESC suggested that, if the ODX test is recommended, the MSAC should consider adding a note to the item descriptor to provide this information. No new data were provided regarding the risk thresholds, though clinical studies due to report in 2017 are likely to be informative for intermediate risk patients.

The application was previously requested to quantify the incremental gains with ODX, including comparison with tools such as Adjuvant! Online (AO). However the AO tool has been offline since February 2016 and unavailable to both applicant and evaluator. The critique raised concerns that studies cited by the applicant to support incremental gains may not be applicable to the intended population (in particular Paulden, 2013; Tang 2011). However, ESC considered that the newly defined population, having pre-defined clinical-pathological parameters, made the comparison to the AO tool less relevant in this re-submission.

The applicant explained how the proposed registry would assist in monitoring compliance to the intended MBS population. ESC questioned whether the last four parameters proposed for the registry were realistic. These are intended to gauge the consequences of this testing by recording post-test information.

ESC made the following observations about the applicant's hidden price proposal, which is a matter for government. In particular, ESC noted the potential disproportionate consequence for out of pocket patient costs to patients. Without a cap on the actual charge to patients (compared with the item fee), the out-of-pocket costs to patients would be large compared with those of other genetic tests.

Related to this, ESC considered that many elements of the financial estimates calculations were uncertain, and advised that if the government would be prepared to consider a hidden pricing arrangement, it may be worth also considering whether a risk share arrangement should also be negotiated, noting that a single entity would render all tests according to the proposed MBS item. This would share the financial risk of the costs associated with the potential unjustified use outside the intended patient population.

The applicant's plan to conduct ODX testing outside Australia, without approval by the Therapeutic Goods Administration (TGA), remained unchanged and was a continuing source of concern to ESC. Consumers would not have recourse to the usual mechanisms within Australia in the event of the incorrect diagnosis or other problems (such as TGA's adverse event reporting procedures).

ESC noted that the United States' regulator, the Food and Drug Administration (FDA), has no oversight of the ODX test and has published a report in November 2015 detailing its view that the current system of compliance to the *Clinical Laboratory Improvement Amendments 1988* (CLIA) legislation is insufficient to ensure clinical validity, safety and effectiveness of laboratory developed tests, including ODX. In the light of FDA's overall concerns, ESC raised a question for MSAC as to whether compliance with US CLIA represented an adequate substitute for TGA approval of the test and NATA (National Association of Testing Authorities) accreditation of the laboratory.

The financial estimates were updated to account for the change in population but otherwise remains unchanged compared to the 1342.2 submission, with issues as previously identified therein. Minor issues were identified (inclusion of individuals with node positive breast

cancer and two other risk factors; no accounting for the stated 12% of individuals with unknown node status; independence of some of the variables used in calculations was not justified) that should be clarified by the applicant (12. Financial /budgetary impacts).

ESC noted G.10.1 of the Medicare Benefits Schedule which states that pathology tests performed after discharge from hospital on bodily specimens taken during hospitalisation also attract the 75% level of benefits. Given the ready availability of resected tissue in patients with early breast cancer obtained during surgery in a hospital, ESC considered that the majority of patients would incur an out-of-pocket payment of \$redacted unless the service was bulk billed. The applicant is requested to supply data, with evidence, to support a likely split of in-patient to out-patient samples.

15. Other significant factors

Nil

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

STA would like to thank MSAC for their consideration of Resubmission 1342.3, and the many physicians, patients and professional organisations who supported the submission with letters and statements of support, advice and participation in an online survey.

It is evident that only one issue has led to the deferral. The PSD stated that the resubmission *'addressed all of the deferral reasons raised in relation to the previous resubmission with one exception, the requested comparisons between ODX and other prognostic approaches and algorithms such as AO, with the consequential effects on the clinical and economic evaluations.'* In contrast, the ESC report of June 10, 2016 stated that *'ESC considered that the newly defined population, having pre-defined clinical-pathological parameters, made the comparison to the AO tool less relevant in this re-submission.'* STA agreed with the ESC on this issue and as such, it was not addressed further in our response.

In the final paragraph of section 3 in the PSD, referring to a comparison of ODX over and above currently available prognostic approaches and algorithms, MSAC stated that *'if the incremental gain is the same as what has been estimated in the current resubmission, the applicant does not need to undertake a revised cost effectiveness analysis.'* The resubmission has clearly demonstrated the incremental gain of ODX over 'usual care'. 'Usual care' already encompasses the currently available prognostic approaches and algorithms; therefore these tools provide no incremental gain over 'usual care'.

The applicant has requested a meeting to discuss what is specifically required to progress this application.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at: [MSAC Website](#).