Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1473 - 50 gene signature assay for predicting breast cancer recurrence

Applicant: **Nanostring Technologies, Inc.**

Date of MSAC consideration: **MSAC 71st Meeting, 23 November 2017**

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

1. Purpose of application

An application requesting a new Medicare Benefits Schedule (MBS) listing of an *in-vitro* diagnostic signature gene assay (Prosigna®) that measures the expression of 50 genes in order to provide an intrinsic subtype classification and a risk of recurrence (ROR) score for patients with breast cancer was received from Nanostring Technologies, Inc.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support public funding of Prosigna (PAM50) for predicting breast cancer recurrence for postmenopausal, estrogen receptor (*ER*) and/or progesterone receptor (*PR*) -positive, *HER2*-negative females with breast cancer. MSAC considered that the incremental benefit of Prosigna over optimal care in the proposed population had not been sufficiently established and remains uncertain.

MSAC advised that any resubmission should provide further high-quality trial data and a high quality market survey of medical oncologists to determine current standard of optimal care.

Any resubmission would need to be considered by ESC.

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

MSAC noted that the assay would apply to postmenopausal patients with *ER*-and/or *PR*-positive, *HER2*-negative breast cancer, who are determined to be at an intermediate risk of recurrence based on clinico-pathological features. The applicant's claim was that Prosigna provides incremental prognostic and predictive information over current markers and clinical characteristics, so that adjuvant chemotherapy may be targeted to those patients at sufficient risk of breast cancer recurrence, and most likely to benefit from this treatment.

MSAC noted the definition of standard care used as a comparator in the submission (clinical assessment, based on patient and tumour factors). MSAC noted that the definition of a standardised comparator was considered in previous guidance to be the key residual issue regarding the value of Oncotype DX, a similar gene expression profiling (GEP) test, over and above alternative tools and algorithms (Oncotype DX MSAC Application 1342.4 July 2017). MSAC noted that consequently, the most recent submission for Oncotype DX had been rejected on the grounds that incremental benefit over 'usual care' had not been demonstrated (Oncotype DX MSAC Application 1342.4 July 2017). MSAC previously specified that the most appropriate comparator for Oncotype DX testing is usual care, best defined as optimal care when the decision to treat with adjuvant chemotherapy is particularly unclear – and so where all available sources of information are considered for informing treatment decisions (Oncotype DX MSAC Application 1342.3 July 2016).

MSAC considered that the lack of comparison with optimal care was a major weakness in the Prosigna submission as it precluded the determination of the prognostic and clinical utility of Prosigna over and above standard care for the proposed population. MSAC noted the applicant's pre-MSAC response that the lack of a standardised comparator could not be resolved by the applicant because there is no extant standardised comparator in current Australian clinical practice. MSAC noted that a well-designed survey of medical oncologists may help to establish what constitutes standard care in Australia for the proposed population of patients at intermediate risk when the decision to treat with adjuvant chemotherapy is particularly unclear.

MSAC noted that no high level evidence had been provided to support the application. Levels of evidence ranged across the prognostic studies from III-1 (all or none prognostic study) to IV (case series). For the effect of Prosigna on change in patient management, the submission used Level III-2 (comparative studies with concurrent controls) evidence.

MSAC noted that, due to limited evidence for Prosigna, the applicant had taken a linked approach to establishing evidence, largely from Oncotype DX trials. MSAC noted that claims of improved disease-free survival were derived from data from randomised controlled trials of Oncotype DX (NSABP B-20, Paik S 2006; SWOG8814, Albain KS et al 2010) which had been previously evaluated as "moderate evidence of weak prognostic and predictive value" (p6, MSAC 1342.1 PSD, April 2014). MSAC also noted that:

- regimens used in the Oncotype DX trials are not contemporary in the Australian setting;
- assessment of chemotherapy benefit by ROR was also based on the Oncotype DX recurrence score due to lack of data for Prosigna, and may be overestimated in the model;
- degree of overlap in patient risk category allocation by Prosigna and Oncotype DX was markedly lower for intermediate risk compared to high and low risk groups (Dowsett M et al 2013). MSAC considered that this cast doubt on the applicant's claim that data on chemotherapy benefit for those at intermediate risk, as stratified by Oncotype DX testing, are likely to be relevant to Prosigna; and
- comparative correlation of risk categorisation scores between Prosigna and Oncotype DX found overall agreement for risk classification of only 53.8% with poor correlation (r = 0.08) (Alvarado MD et al 2015).

MSAC reiterated other important evidentiary shortcomings raised by ESC, notably:

- discordance between Prosigna and immunohistochemistry (IHC), which ranged from 28.3% to 40% in subtype classification (Martin M et al 2015; Wuerstlein R et al 2016);

- the majority of the evidence for clinical validity was provided by retrospective analyses of archived samples (Dowsett M et al 2013; Sestak I et al 2013, 2016a, 2016b; Filipits M et al 2014; Gnant M et al 2014), with reduced numbers of patients analysed compared to parent trials introducing the risk of selection bias;
- differences between studies with respect to the Prosigna ROR algorithms used, and in some instances, the cut-off values defining risk categories, had an unknown impact on prognostic validity in the Australian setting;
- evidence that assay use will lead to changes in treatment recommendations (and actual treatments undertaken) was based on limited evidence from small trials (Martin M et al 2015) of node-negative patients, with no data for node-positive patients, and whether this was a valid proxy for change in treatment; and
- poor or lacking evidence that use of the test led to avoidance of chemotherapy or improved long term outcomes.

MSAC considered that the evidence provided was insufficient to support the applicant's claim that Prosigna is a superior assay compared to Oncotype DX. MSAC noted the Phase III trials currently underway for two specific GEP tests (Oncotype DX and Mammaprint), which may be informative. However, as the trials have different inclusion criteria, and as the assays are not necessarily equivalent or interchangeable and may have low concordance with Prosigna, each assay would have to be considered separately through ESC/MSAC. Hence, although additional trial data may help to resolve the remaining uncertainty regarding the clinical effectiveness and cost-effectiveness of GEPs currently being trialled, MSAC advised that Prosigna would need to demonstrate equivalency to these GEPs once these findings become available.

MSAC noted that the requirement for appropriate randomised clinical trial evidence had been made clear to GEP applicants, and emphasised the importance of clinical utility data.

MSAC noted that the problems identified in the clinical evidence carried over to the model, making estimates of cost-effectiveness highly uncertain. MSAC noted that the model being sensitive to key drivers such as distant recurrence free survival estimates, extrapolation methods and health state utilities.

MSAC noted that the submission assumed an uptake rate of 100% in women eligible for the test to account for leakage to patients who might undergo the test for other reasons. MSAC noted that potential leakage could be greater than the adjustment of the uptake estimates if patients undergo the test for reasons other than treatment recommendations, and that this would impact on the financial estimates. MSAC considered that the restriction of the test ordering to oncologists may help prevent this leakage.

MSAC noted that the proposed item descriptor specifies the brand-name Prosigna and agreed that a generic item descriptor was unsuitable due to the 'black box' nature of this and similar GEP tests. MSAC advised that the descriptor should specify use in post-menopausal women only due to lack of evidence for test clinical validity in pre-menopausal women and that the descriptor should be female-specific in line with the data pertaining to the assay.

MSAC determined that the test should not be pathologist determinable, but ordering should be limited to oncologists, who are best placed to assess which patients are at intermediate risk and therefore would potentially benefit from use of the assay. MSAC noted that there is no evidence for the use of the test in groups other than those at intermediate risk.

4. Background

MSAC has not previously considered this 50 gene signature assay for predicting breast cancer recurrence.

MSAC has previously considered several applications for the Oncotype DX® breast cancer assay to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit (MSAC Application 1342).

5. Prerequisites to implementation of any funding advice

Prosigna is registered by the Therapeutic Goods Administration (TGA) on the Australian Register of Therapeutic Goods (ARTG), ARTG 226487.

6. Proposal for public funding

The proposed MBS item descriptor is shown in Table 1.

Table 1 Proposed MBS item descriptor for the proposed test

	Category – PATHOLOGY SERVICES
XXXXX	Group P7 – GENETICS
Determination of Risk of Recurrence and Luminal subtype by Prosigna assay in an FFPE sample from the primary breast cancer tissue.	
The test may be used when all of the following criteria are met:	
- New primary breast cancer, suitable for adjuvant chemotherapy but not requiring neoadjuvant chemotherapy	
- Oestrogen and/or progesterone receptor positive and HER2 receptor negative as determined by immunohistochemistry (IHC) and in situ hybridisation (ISH) respectively on a surgically removed tumour or core biopsy sample	
- Node negative or positive (up to 3 nodes) and tumour size determined by histopathology on surgically removed tumour or core biopsy sample	
- Pre-test intermediate risk of distant metastases defined by at least one of the following characteristics: tumour size ≥ 2cm; or Grade 2[a] or 3a; or one to three lymph nodes involved in metastatic disease (nodes include micrometastases but not isolated tumour cells)	
The test may be used once per new primary breast cancer diagnosis.	
Fee[b]: $2,900	Benefit: 75% = $2,175; 85% = $2,819.80[c]

HER2 = human epidermal growth factor receptor 2; FFPE = formalin-fixed paraffin-embedded; IHC = immunohistochemistry; ISH = in situ hybridisation.
[a] The AJCC recommend that all invasive cancer is graded using the Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system)(AJCC 2012).
[b] The fee includes any retesting required provided that an new and adequate tissue sample for RNA isolation can be obtained from a satisfactory core biopsy or FFPE sample. RNA isolates are required to meet quality specifications prior to testing.
[c] It is anticipated that the vast majority of biopsies would be obtained through surgery in a private setting and therefore the 75% benefit has been used in the economic analysis.

7. Summary of Public Consultation Feedback/Consumer Issues

The department received three responses from public consultation from Professional Bodies and one clinical College. All responses were positive, and stated significant benefits to the affected individual, their family and the community. There were no additional issues raised as a result of the consultation survey.

The application stated that Breast Cancer Network Australia (BCNA), the peak consumer organisation for Australians personally affected by breast cancer, support MSAC assessing the Prosigna test. Their opinion is that having more information on the risk of recurrence enables women and their clinician to make better informed decisions about treatment,

particularly the potential benefits or otherwise of chemotherapy. BCNA believe that all women should have equal access to tests if they are likely to benefit from them.

8. Proposed intervention's place in clinical management

Prosigna is a 50-gene test that is designed to identify intrinsic breast cancer subtypes and to generate a ROR score. This is then used to tailor the most appropriate therapy for that type of primary breast cancer. It will be used for women with HER2 negative, ER and/or PR positive breast cancer in whom treatment recommendations based on clinical assessments alone are uncertain. The unique genetic profile is produced using a diagnostic kit which quantifies mRNA expression and can be performed in local laboratories provided they have the NanoString nCounter® Dx technology (Prosigna enabled).

Prosigna is intended to be used in addition to standard care. It provides additional information which will improve clinician choices regarding treatment of the target population of interest. Information provided by the test includes a Risk of Recurrence score (ROR), risk category (low, intermediate or high) and allocation of an intrinsic subtype (Luminal A, Luminal B, HER2-enriched, basal-like).

The algorithm in Figure 1 describes the clinical pathway should Prosigna be publicly funded.

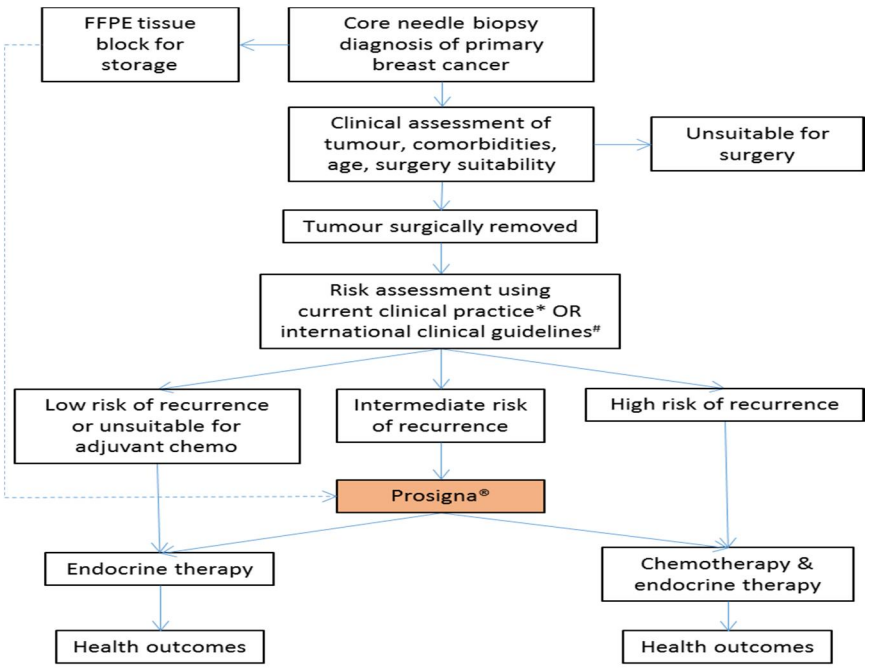

Figure 1 Clinical management algorithm for the proposed new test Prosigna

FFPE = formalin-fixed paraffin-embedded.

*Risk assessment based on ER/HER2 status, tumour size, nodal status, Ki67, tumour grade and other markers most likely to be used in the Australian setting (base case scenario)

#Risk assessment based on ER/HER2 status and international clinical guidelines such as St Gallen, NCCN and German S3

9. Comparator

The primary comparator used for this assessment is standard care.

The application defined standard care as a clinical assessment which includes a number of investigations and tests: physical investigation; imaging; assessment of hormone receptor gene expression through immunohistochemistry (IHC), and in situ hybridisation (ISH) analysis of HER2 receptor expression status (requirement for PBS-subsidised treatment with

trastuzumab); tumour size, grade, stage; number and extent of lymph node involvement; staining according to the TNM system; and menopausal status, age, and co-morbidities.

Other gene expression profiling (GEP) tests such as Oncotype DX®, Mammaprint® and EndoPredict® were secondary comparators.

10. Comparative safety

Chemotherapy has harms as well as benefits in breast cancer. Harms associated with chemotherapy for breast cancer are frequently related to organ function and quality of life.

The application stated that for patients classified as having a low risk of recurrence, the absolute benefit of chemotherapy is considered too small to warrant the side effects of the treatment. Patients who are classed as low risk of recurrence by Prosigna and consequently avoid chemotherapy, should have improved quality of life due to avoiding the side-effects from chemotherapy, without any reduction in distant-recurrence free survival.

For those at high risk of recurrence, the application stated that the absolute benefit of chemotherapy is considered large enough to outweigh the harms of chemotherapy for most patients. The accurate prognostic classifications made by Prosigna can therefore be used to directly inform whether the benefits are likely to outweigh the harms of chemotherapy for the individual.

11. Comparative effectiveness

A summary of the key features of the evidence presented is shown in Table 2.

Table 2 Key features of the included linked evidence

Type of evidence	Description	Number of included studies (k) Number of patients (n)
Analytic performance	Analytic studies testing FFPE samples across and within testing sites, pooled FFPE samples for multiple testing, and FFPE samples for performance associated with tissue interferents	k=4 (4 Prosigna) n (reproducibility)=551 n (precision)=various n (robustness)=23
Clinical validity (prognostic accuracy)	Retrospective analyses of single treatment arms of RCTs comparing different regimens of endocrine therapy and chemotherapy	k=14 (10 Prosigna, 4 PAM50) n=9900
Impact on clinical management	Retrospective and prospective cohort studies of change in treatment recommendations. A qualitative interview assessing clinician and patient views	k=4 (3 Prosigna, 1 GEPs more broadly) n=376
Therapeutic effectiveness (including predictive validity)	RCTs comparing chemotherapy plus tamoxifen with tamoxifen alone for breast cancer RCT evidence of chemotherapy benefit stratified by Luminal subtype Retrospective case series assessing predictive benefit of neoadjuvant systemic therapy Patient QoL compared for chemotherapy plus endocrine therapy relative to endocrine alone	k=9 n(RCTs)=3307 n(case series)=180 n (QoL)=1715

FFPE = formalin-fixed paraffin-embedded; GEPs = gene expression panels; k = study number; n = patients number; QoL = quality of life; RCT = randomised controlled trial.

Analytical performance

The application provided data regarding the reproducibility of the test in terms of subtype allocation and ROR scores across laboratories; operators and lots and gene expression comparing Prosigna and the PAM50 qRNA-PCR platform.

For subtype, concordances of between 94% and 98% were reported and lower concordance for risk category allocation (between 88% and 93%) was reported across up to three laboratories. Appropriate macrodissection of the tumour sample was also demonstrated to be imperative to determining a reliable ROR score.

Reproducibility of gene expression was found to have high concordance between tissue samples, with a Pearson correlation of 0.98 in a pairwise comparison between test sites in one study and variation between 1.1 and 6.7%, and also reported a concordance of 98% for intrinsic subtype allocation in another study.

The breast cancer cohorts used in the studies to test the reproducibility of the test were broader populations than the target HER2-negative, ER/PR -positive patient population who are determined to be at an intermediate risk of recurrence, determined by clinico-pathological features.

Clinical validity (prognostic validity)

The bulk of the evidence for clinical validity was provided by retrospective analyses of two cohorts of postmenopausal ER/PR -positive primary breast cancer patients from the ATAC and ABCSG-8 trials (patients randomised to the endocrine therapy only arms in the RCTs). Prosigna was performed on archived FFPE samples from eligible patients using the NanoString nCounter.

The critique noted that less than two thirds of the parent population of the two trials (ATAC and ABCSG-8) were included in the retrospective analyses, thus representativeness of the study population to the parent population and power to detect differences is not clear. Additionally, the included studies did not consistently report results by the ROR-PT algorithm stated to be used by the SBA, and in some cases the cut-offs applied for categorising patients into low, intermediate or high risk groups also differed.

The prognostic value of Prosigna ROR was compared with that of surrogate measures of clinical assessment (clinical treatment score, CTS and clinical linear predictor, CLP) and found to consistently contribute a significant amount of incremental information for prediction of distant recurrence free survival (DRFS). A similar effect was seen across different sub analyses of nodal status and HER2-negative status and with different comparison statistics. The incremental information provided by Prosigna tended to be greater in node-negative than node-positive patients for distant recurrence-free survival. The Prosigna ROR also provided a significant amount of incremental information for predicting late distant recurrence. Modelling in Kaplan-Meier survival analyses demonstrated the ability of Prosigna ROR to identify separate prognostic risk categories of low, intermediate and high and similarly for intrinsic subtypes (Luminal A, Luminal B, HER2-enriched, Basal-like) and nodal status (positive or negative).

Change in management

Three studies assessed the changes in treatment recommendation before- and after- the results of the Prosigna test (two prospective and one retrospective). Two studies (one via personal communication with the authors) provided changes in treatment recommendations specifically among ER-positive, HER2-negative, patients who were determined to be at an intermediate risk of recurrence by clinico-pathological features. The number of patients enrolled in each study was limited – 67 and 64.

Data reported indicated that treatment recommendations changed with the availability of the Prosigna test results. One study further reported the treatments actually received by patients, which was limited to those who were node-negative, thus no data for node-positive patients is

available. Data reported indicated that recommendations and actual treatments received were consistent, however this was based on very few (n=67) patients.

Health benefit from change in management
The assessment of chemotherapy benefit by luminal subtype was based on a study enrolling premenopausal patients (the requested listing was for postmenopausal patients).

The assessment of chemotherapy benefit by risk of recurrence was based on the Oncotype DX recurrence score, as no data for Prosigna ROR are available.

The critique noted that the Kaplan-Meier curves for patients categorised as high risk appear to be comparable between Prosigna and Oncotype DX, the same cannot be said for those categorised as intermediate risk, or to a lesser extent, low risk. Additionally, the SBA has not provided a comparison of the correlation of risk categorisation scores between Prosigna and Oncotype DX. A study comparing the two GEPs retrospectively analysed 52 tissue samples from postmenopausal, ER-positive and HER2-negative patients. The overall agreement for risk classification between the two GEPs was 53.8% and the correlation between the two was poor (r=0.08, 95% CI: -0.2, 0.35). The authors concluded that "The consistency of the results from this comparison of the Recurrence Score and Prosigna assays and prior studies showing that different assays vary substantially in risk assignation, indicates that genomic assays cannot be used interchangeably." Thus, the use of chemotherapy benefit based on Oncotype DX recurrence scores to inform those for Prosigna, particularly in the economic evaluation, may not be supported.

Clinical claim

The application clinical claim is that Prosigna provides incremental prognostic and predictive information over current markers and clinical characteristics, so that chemotherapy may be used in those breast cancer patients who are at the greatest risk of recurrence, and most likely to benefit from this treatment. The use of the Prosigna assay to tailor treatment options according to risk of recurrence will mean that patients will be more likely to appropriately receive adjuvant chemotherapy.

For patients who are managed by standard care, Prosigna is expected to improve health outcomes in one of two ways:

- by accurately identifying patients at high risk of recurrence who are likely to benefit from chemotherapy that would not have been identified through standard clinical practice. This will result in improved disease-free survival and reduction in breast cancer recurrence by the addition of chemotherapy to the treatment regimen of a patient who would have otherwise been treated with hormone therapy alone; and/or
- by accurately identifying patients at low risk of recurrence that will not benefit from chemotherapy, thus sparing them adverse effects and other risks associated with chemotherapy, with no impact on disease-free survival, but associated improvements in quality of life.

12. Economic evaluation

The application presented a cost-utility analysis as the Prosigna test is anticipated to result in increased health outcomes and superior safety. The analysis is summarised in Table 3.

Table 3 Summary of the economic evaluation

Perspective	Australian healthcare system (direct health care costs only)
Comparator	Risk assessment based on clinico-pathological factors ± prognostic tools
Type of economic evaluation	Cost-utility analysis
Sources of evidence	Systematic review
Time horizon	30 years
Outcomes	QALYs (and LYs)
Methods used to generate results	Decision analytic and Markov processes
Health states	Distant recurrence-free, distant recurrence and dead
Cycle length	1 year
Discount rate	5% p.a.
Software packages used	Microsoft Excel 2013

LY = life year; QALY = quality-adjusted life year.

The overall costs and outcomes, and incremental costs and outcomes as calculated for the testing strategy and comparative testing strategy in the model, and using the base case assumptions, are shown in the Table 4.

Table 4 Incremental cost-effectiveness for the addition of Prosigna to current risk assessment, in node negative and node positive patient groups (base case estimates)

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER $/QALY
Node negative patients					
Prosigna + clinical risk assessment guided endocrine and/or chemotherapy treatment	$13,873	$2,088	10.6228	0.0485	**$43,031**
Clinical risk assessment only guided endocrine and/or chemotherapy treatment	$11,785		10.5743		
Node positive patients					
Prosigna + clinical risk assessment guided endocrine and/or chemotherapy treatment	$21,640	$2,430	10.1043	0.0620	**$39,166**
Clinical risk assessment only guided endocrine and/or chemotherapy treatment	$19,211		10.0423		

QALY = quality adjusted life year, ICER = incremental cost-effectiveness ratio.

In the base case analysis, a predictive relationship is modelled between Prosigna and response to chemotherapy. Due to the paucity of data, this is based on the lesser association between Prosigna ROR and chemotherapy response, rather than the stronger association between intrinsic subtype and chemotherapy response. As Prosigna additionally provides information about intrinsic subtype, the base case estimates are conservative.

The modelled results are sensitive to the treatment effect and the disutility of chemotherapy, and the time horizon and discount rate of the analysis. While the model estimates greater cost-effectiveness in node positive patients, this is less certain, given the modelled change-in-management is from data in node negative patients only. The model is also sensitive to whether or not the assumption of a predictive effect (for chemotherapy treatment benefit by risk level) is incorporated.

13. Financial/budgetary impacts

An epidemiological approach has been used to estimate the financial implications of the introduction of the Prosigna test.

The financial implications to the MBS resulting from the proposed listing of the Prosigna test are summarised in Table 5.

Table 5 Estimated total costs to the MBS directly associated with Prosigna

	2018	2019	2020	2021	2022
Total services	5,001	5,098	5,194	5,294	5,392
Total cost	$10,877,209	$11,087,270	$11,297,331	$11,514,225	$11,727,706

The cost of Prosigna to the MBS is expected to increase from approximately $11 million in Year 1 to $12 million in Year 5, for a total cost of $56.5 million over the first 5 years of listing.

It is assumed that testing will occur on samples taken during hospitalisation (for tumour resection). The test is assumed to primarily attract the 75% level of benefits, consistent with Note G.10.1 of the MBS and with previous MSAC advice (MSAC Application 1342 PSDs)[1].

Potential downstream financial implications, associated with changed patterns of adjuvant chemotherapy administration, are difficult to predict. It is likely there will be some cost offsets from reduced rates of chemotherapy but the magnitude and impact of this change, particularly with regard to women with node positive tumours, is uncertain.

14. Key issues from ESC for MSAC

This submission requested a new MBS item for the *in vitro* diagnostic signature gene assay (Prosigna) that measures the expression of 50 genes from a sample of formalin-fixed paraffin-embedded (FFPE) tissue in order to provide an intrinsic subtype classification (Luminal A, Luminal B, *HER2*-enriched, Basal-like) and a risk of recurrence (ROR) score for patients with breast cancer.

The proposed population is postmenopausal patients with estrogen receptor (ER) and/or progesterone receptor (PR) -positive, *HER2*-negative breast cancer, who are determined to be at an intermediate risk of recurrence based on clinico-pathological features. The claim is that Prosigna provides incremental prognostic and predictive information over current markers and clinical characteristics, so that adjuvant chemotherapy may be targeted to those patients at greatest risk of breast cancer recurrence in addition to endocrine therapy, and most likely to benefit from this treatment.

ESC noted that a number of similar tests aiming to categorise patients by risk of recurrence have been considered; one application has been considered by MSAC (Oncotype DX, MSAC Applications 1342-1342.4) and another two have been considered by PASC (MammaPrint, MSAC Application 1376; EndoPredict, MSAC Application 1408). ESC noted that the proposed population for Prosigna is essentially consistent with the proposed patient population for Oncotype DX.

ESC noted that studies included for the assessment of analytic performance, clinical validity and clinical utility enrolled a broader patient group than the proposed population. The impact of this difference in populations on the reproducibility of the test (in terms of categorising patients into risk categories and intrinsic subtypes) is unknown.

ESC queried the definition of standard of care used as the comparator in the submission (clinical assessment, based on patient and tumour factors).

ESC noted that this issue had been raised previously by MSAC in the response to the Oncotype DX application where a strict definition that includes tumour measures and the use

[1] MSAC Applications 1342.1, 1342.2, 1342.3, Public Summary Documents, April 2014, November 2015 and July 2016

of other available online tools (Adjuvant! and Predict) had been requested in the consideration of the value of Oncotype DX over and above alternative tools and algorithms (p2, MSAC Application 1342.4 PSD, July 2017). This is still unresolved.

ESC noted that the lack of an agreed definition of standard of care precluded the determination of the incremental gain for the proposed service over and above usual treatment.

ESC noted that no high level evidence had been provided to support the proposed listing of Prosigna on the MBS.

ESC noted that the majority of the evidence for clinical validity was provided by retrospective analyses of archived samples of two cohorts of postmenopausal ER/PR-positive primary breast cancer patients from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) (Dowsett M et al 2013; Sestak I et al 2013, 2016a, 2016b) and Austrian Breast and Colorectal Cancer Study Group (ABCSG)-8 (Filipits M et al 2014; Gnant M et al 2014) trials.

ESC noted the uncertainty about the representativeness of the patients considered in the retrospective analyses compared with the parent trials given less than two thirds of the parent population were included (introducing risk of selection bias). Moreover, there were differences between studies with respect to the Prosigna ROR algorithms used, and in some instances, the cut-off values defining low, intermediate and high risk categories. ESC noted that outcomes of these studies were not consistent in magnitude. ESC noted that there is no data on the impact of long term prognostic outcomes of Prosigna testing.

ESC noted that discordance between Prosigna and clinic-pathological factors ranged from 28.3% to 40% in subtype classification (Martin M et al 2015; Wuerstlein R et al 2016).

Regarding therapeutic efficacy, evidence that assay use will lead to changes in treatment recommendations (and actual treatments undertaken) is based on a single prospective study (Martin M et al 2015; n = 200) of 67 node-negative patients who had been assessed as having an initial intermediate risk of distant recurrence which reported both changes in treatment recommendations and actual treatments received (with no outcome data yet available).

ESC noted that results of this study indicated that treatment recommendations changed with the availability of the Prosigna test results in approximately 20% of cases. However, ESC queried the claim that changes in treatment recommendation can be used as a proxy for actual treatments undertaken on the basis of the consistency of findings in this limited sample, and noted that no similar data for node-positive patients are available.

ESC noted that no evidence was provided showing benefit for patients in avoiding chemotherapy and agreed that the evidence for down-grading of treatment is poor. ESC noted that avoiding chemotherapy is an important outcome in considering the potential benefit of the proposed test.

ESC noted that randomised trials have showed benefit in disease free survival but no significant differences in overall survival with the addition of chemotherapy. ESC noted that the assessment of therapeutic effectiveness of Prosigna was based on Oncotype DX studies as there were no Prosigna studies. These studies showed Oncotype DX score correlated with changes in overall survival or disease free survival as a result of the addition of chemotherapy compared to endocrine therapy alone.

ESC noted that the hormone and chemotherapy regimens used in the Oncotype DX trials were not contemporary in the Australian setting and incremental effectiveness of the benefit of chemotherapy may be overestimated. ESC noted that MSAC has previously considered the

Oncotype DX trials and considered that the data represented "moderate evidence of weak prognostic and predictive value" (p7, MSAC Application 1342 PSD, November 2013).

ESC noted that, while there is a high degree of overlap in patient risk category allocation by Prosigna and Oncotype DX for the low- and high-risk categories, this was less so for intermediate risk. ESC noted that, based on the data provided, there is no way to assess which results are "correct" in the intermediate risk group and to support the claim that Prosigna is a superior assay compared to Oncotype DX. ESC also queried whether data on chemotherapy benefit as stratified by Oncotype DX are likely to be relevant to Prosigna.

ESC noted the results of a study excluded from the submission but identified in the critique (Alvarado MD et al 2015) which provided a comparison of the risk categorisation of Prosigna compared with Oncotype DX.

This study showed an overall agreement for risk classification of 53.8% and poor correlation ($r = 0.08$). As such, ESC queried whether the data presented on risk categorisation based on the Oncotype DX recurrence score is applicable to risk categorisation based on Prosigna.

ESC noted that there are no published studies in postmenopausal women assessing the ability of Prosigna to predict who is likely to respond to adjuvant chemotherapy. The submission cited a study which used Prosigna in predicting response to neoadjuvant chemotherapy (Prat A et al 2015), claiming that this as a valid extension of findings, and suggesting additionally that response to neoadjuvant chemotherapy is an appropriate surrogate outcome for long term health outcomes, such as recurrence free survival.

ESC noted that the assessment of chemotherapy benefit by luminal subtype (not Prosigna graded) was based on a study enrolling premenopausal patients who did not undergo endocrine treatment (Nielsen TO et al 2017). ESC queried the claim that on the basis of these findings, Prosigna can identify patients who will not benefit from chemotherapy, and whether these data are applicable to a post-menopausal population.

ESC considered that overall the logic of the model is sound, but that the parameters and the sources of information for them introduce a high level of uncertainty. ESC considered that the problems identified in the clinical evidence carried over to the model, affecting the applicability of this evidence (small sample sizes in cited studies, lack of applicability of European findings to Australian settings, use of pooled data for all risk types, lack of prospective evidence for node positive patients, lack of evidence for change of management for node positive patients, and differences in patient management which may be country-dependent).

ESC noted that the model was sensitive to utility values and noted limitations of the utility weights selected (which potentially did not translate to an Australian population, did not use Australian preference values, were not trial-based, dated from 2007, and were based on small numbers) favouring Prosigna.

ESC noted that the key drivers of the economic model include the distant recurrence free survival estimates, and the relative risk of chemotherapy plus tamoxifen versus tamoxifen and the time horizon, all of which favour Prosigna in the base case.

ESC questioned whether the alternative scenario presented provided any meaningful information.

ESC noted that the rate of repeat testing and its impact on cost and patient outcomes is included in the economic model, but repeat testing is not included in the item descriptor.

The submission assumed the uptake of Prosigna would be 100%, and acknowledged that this may be an overestimate, but argued that there will also likely be a high risk of leakage beyond the proposed item descriptor. ESC considered that the expected leakage under the proposed restriction may still not be adequately accounted for in the base case estimates of the financial implications.

ESC noted that the proposed positioning of Prosigna is as a test available after the initial assessment. It is also not clear whether all testing would be conducted in settings applicable to the 75% Medicare rebate (i.e. private hospitals) as assumed in the financial estimates. ESC also noted the relatively high cost to patients ($725 at 75% rebate), potentially affecting the uptake rate, and the lack of public sector access for the test.

ESC considered that the item descriptor would need to specify:

- that treatment should be limited to females as all the data pertaining to the assay are from females and not males;
- that treatment should be limited to post-menopausal women;
- whether re-testing is allowed; and
- who can order the test.

ESC noted that a pathologist would be required to assess tissue samples for test suitability, but considered that the test should not be pathologist-determinable. ESC noted the PASC recommendation that test ordering be limited to oncologists and surgeons. ESC considered that patient views on treatment of breast cancer with chemotherapy were an important consideration prior to ordering the test, as some patients may not wish to be treated with chemotherapy (rendering the assay unnecessary), and may be more likely to discuss this with an oncologist than a surgeon.

ESC noted that the critique and the Pre-ESC Response were in agreement regarding the necessity for proper training of pathology staff: processing is a critical part of performing the assay and can affect the reliability of the test scores generated.

ESC noted that there are other trials currently in progress (e.g. TailorX, MINDACT for Oncotype DX and Mammaprint, respectively), the results of which may also be informative.

ESC discussed whether a ‘me too’ application would apply here, given that the Phase III trials currently underway relate to these two specific tests (Oncotype DX and Mammaprint) and that the concordance between the tests is low. ESC noted that the assays differ in the numbers of genes analysed and the use of different algorithms, and agreed that each of the assays would need to be considered separately through MSAC/ESC.

ESC noted that given the differences in outcomes of the various tests, with no gold standard and insufficient information on equivalence, using these tests had the potential to create further uncertainty unless additional evidence becomes available to make the treatment recommendations conclusive.

15. Other significant factors

Nil.

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

NanoString wishes to thank the Medicare Services Advisory Committee (MSAC) for their thorough review and consideration of our application #1473 – 50 gene signature assay for

predicting breast cancer recurrence. While we are disappointed with the outcome, we respectfully accept the results. We understand a clear concern arose around sufficient volume of data with a valid comparator. We strongly believe our Optimal Personalized Treatment of early breast cancer usIng Multi-parameter Analysis (OPTIMA) trial currently underway in the United Kingdom will address these concerns in a comprehensive way. We look forward to the opportunity to dialogue with MSAC again and to re-submit an application once these data are available.

17. Further information on MSAC

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