



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1408 – EndoPredict – A RT-qPCR gene expression profiling test run locally for patients with ER+ve /HER2-ve breast cancer

Applicant: HTAnalysts on behalf of Myriad Genetics

Date of MSAC consideration: MSAC 77th Meeting, 28-29 November 2019

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 Medicare Benefit Schedule (MBS) listing of a quantitative reverse transcription polymerase chain (RT-qPCR) test [EndoPredict[®]], run locally, for oestrogen receptor positive (ER)+ve /human epidermal growth factor receptor two negative (HER2-ve) breast cancer that is claimed to determine the risk of early and late metastasis in node negative and node positive cancer under hormone (endocrine) treatment was received from Myriad Genetics by the Department of Health.

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 for Endopredict, a gene expression profiling test for patients with breast cancer, because its ability to identify those who could safely be spared the addition of chemotherapy to hormone therapy, or those who would benefit from the addition of chemotherapy to hormone therapy, was not adequately demonstrated by the evidence presented.

Consumer summary

Myriad Genetics applied for public funding through the Medicare Benefits Schedule (MBS) for a type of genetic testing. The test, called EndoPredict, is claimed to help determine the risk of a patient getting breast cancer again after they have had surgery. Currently, combining information from clinical assessments and pathology test results helps doctors calculate whether a patient has a low, intermediate or high risk of breast cancer returning after surgery. This helps the patient decide, with their treating clinicians, whether to have chemotherapy in addition to their hormone therapy. Myriad Genetics claims that this decision is most difficult for patients whose existing information shows they have an intermediate risk of the cancer returning and that the EndoPredict genetic test can then provide valuable extra information to help this group of patients.

MSAC's advice to the Commonwealth Minister for Health

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

MSAC advised the Minister for Health that the evidence presented did not give the Committee confidence that the test would identify those patients who could safely avoid chemotherapy or those patients who would benefit from adding chemotherapy.

Most importantly, there was no direct evidence comparing the cancer outcomes for women who had an EndoPredict test result with those who did not. This means there is no way of knowing whether adding an EndoPredict test score to the information patients already get after their surgery will give them an additional, reliable basis to make treatment decisions that lead to better long-term outcomes.

In place of direct evidence that is obtained from a single source, the applicant used a lower quality linked evidence approach – where evidence is collected from a number of different sources and linked together to build a case.

The linked evidence that was used by the applicant had a number of problems, for example, some women whose clinical information and pathology results indicated they were at high risk of the cancer returning decided not to add chemotherapy after getting an EndoPredict result.

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

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

This application was for reverse-transcription PCR (EndoPredict) run locally for breast cancer patients who are being treated with hormonal therapy, and who are ER-positive, HER2-negative and node-negative or node positive (up to three nodes). EndoPredict is proposed as a means to predict the risk of early and late metastasis in women who, before an EndoPredict test is performed, are classified as having an intermediate risk of metastases.

The MSAC noted the applicant's clinical claim for EndoPredict is that it has non-inferior safety and superior effectiveness to current standard of care.

The MSAC noted there was no direct evidence from a comparative randomised trial to show that adding the results of the EndoPredict test to the other results (clinical and pathology) available changes the clinical management of women with an intermediate risk of early or late metastatic breast cancer. This means there is no direct evidence that EndoPredict improves health outcomes for these women (either by avoiding unnecessary chemotherapy or by identifying that chemotherapy would be beneficial).

The MSAC noted the applicant therefore relied on a linked evidence approach to attempt to establish the benefits of using EndoPredict. The linked evidence approach has four steps:

(1) diagnostic performance, (2) clinical validity, (3) therapeutic efficacy (clinical validity; change in management) and (4) therapeutic effectiveness (informed by direct evidence supporting the effectiveness of treatments that are selected as a consequences of performing the investigative medical service. MSAC Investigative Technical Guidelines, December 2016, Version-3.0).

MSAC considered the evidence presented in the submission was inadequate to satisfy the first three steps of the linked evidence approach.

Amongst other things, MSAC considered:

- In terms of step (1), the application did not provide a clear definition of current Australian clinical practice against which the diagnostic performance of EndoPredict could be assessed. Although the diagnostic performance of EndoPredict is satisfactory in absolute terms, it is not possible for MSAC to form a view on the relative performance of the test compared to current practice.
- In terms of step (2), the retrospective analysis of three cohorts derived from four randomised clinical trials (ABCBSG-6, ASCBSG-8, TransATAC, and GEICAM/9906). could not be relied upon for decision making because:
 - o A reduced number of patients were included in the analysis than in the parent trials introducing the risk of selection bias; and
 - o The analysis included the combined results for patients considered low, intermediate and high risk based on their clinical and pathology results, whereas funding is proposed for the intermediate group only. The prognostic performance of EndoPredict may be different in these different patient subgroups.
- In terms of step (3) **redacted** the applicant commissioned local study, PROSPER study which examined whether having the results from an EndoPredict test available led to changes in the clinical management of patients, **redacted**.

MSAC noted the **redacted** PROSPER trial **redacted**, presented in the pre-MSAC response. MSAC noted that the **redacted**.

Overall therefore, MSAC considered that there is low certainty that EndoPredict would provide additional information leading to improvements in care for patients whose existing information shows they have an intermediate risk of metastatic disease. In addition, MSAC could not exclude the possibility that using an EndoPredict result to decide whether or not to add chemotherapy to endocrine therapy would result in worse cancer outcomes overall.

The uncertainties in the clinical data flow on to uncertainties in the economic evaluation. Further, MSAC agreed with its ESC that the economic evaluation presented was overly optimistic and favoured the intervention.

Finally, MSAC noted the applicant's estimate of the eligible patient population was inadequately supported, noting no justification was provided for many of the input variables. Thus, MSAC considered it did not have an adequate basis to advise the Minister on the potential cost to the MBS of funding EndoPredict.

MSAC acknowledged that the choice of whether to receive chemotherapy or not in the context of this application for EndoPredict is a high stakes decision, and patients and clinicians need as much reliable information as possible to be confident in the decision they make. MSAC also acknowledged that avoiding unnecessary chemotherapy is highly desirable and valuable.

MSAC recalled that in previous considerations of other gene expression profiling tests that have been proposed for use in women with early stage breast cancer, it has been unwilling to support funding solely on a linked evidence approach, especially given the weaknesses identified in the linked evidence used in each case. Instead, MSAC has consistently sought confirmative evidence of benefit from direct randomised clinical trials.

MSAC further recalled that, on the two occasions to date where evidence from direct randomised trials has been available: MINDACT for MammaPrint and TAILORx for Oncotype DX, the evidence from those trials has not resulted in a change in MSAC's previous conclusions in respect of those tests.

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

4. Background

MSAC has not previously considered EndoPredict testing.

However, MSAC has considered and not supported other prognostic tests such as OncotypeDX (Applications 1342.1, 1342.2, 1342.3, 1342.4), Prosigna (Application 1473) and Mammprint (Applications 1376 and 1376.1).

Application 1342.4: In brief, MSAC considered that the incremental benefit of the Oncotype DX breast cancer assay over optimal care remains uncertain.

A further application for OncotypeDX (1342.5) was considered by MSAC at the August 2019 meeting (www.msac.gov.au/internet/msac/publishing.nsf/Content/1342.5-public).

Application 1473: In brief, MSAC did not support public funding of Prosigna 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.

Application 1376.1: In brief, MSAC did not support public funding for a diagnostic microassay to measure the expression of 70 genes in breast cancer tissue (MammaPrint; hereafter the 70 gene signature test). MSAC considered the results of the key supporting trial (MINDACT) and noted that, on average, there was a consistent pattern of poorer breast cancer outcomes when chemotherapy was withheld in high clinical risk patients on the basis of a finding of low genomic risk using the 70 gene signature test. As a result, MSAC had little confidence that the 70 gene signature test could be used to justify withholding chemotherapy in such patients without negatively impacting upon important outcomes, including overall survival.

MSAC was concerned that, overall, use of the 70 gene signature test to inform treatment decisions about whether to not add adjuvant chemotherapy to hormone therapy would lead to inferior breast cancer outcomes compared with current clinical care.

5. Prerequisites to implementation of any funding advice

The test is listed on the Australian Register of Therapeutic Goods (ARTG number 285557). The National Pathology Accreditation Advisory Council (NPAAC) advised MSAC that the test is provided exclusively by one laboratory provider in the private sector, and that there is no external quality assurance program (EQA) available. Quality assurance would require the establishment of a sample exchange program with overseas laboratories.

6. Proposal for public funding

The proposed MBS item descriptor is summarised in Table 1. The service would be expected to be delivered once per primary cancer diagnosis per patient at the point of primary tumour analysis. The service could be offered in a public or private hospital setting following surgery or biopsy, or when the patient attends a hospital outpatient service or consulting room.

Table 1 Proposed MBS item descriptor

Category 6 – PATHOLOGY SERVICES Group P7 – GENETICS
MBS XXX RT-qPCR gene expression profiling of FFPE, core needle biopsy or surgical tumour sample in primary breast cancer tissue. The test may be used when all of the following criteria are met: New primary breast cancer, suitable for adjuvant therapy, and not requiring neoadjuvant chemotherapy Oestrogen receptor positive and HER2 negative as determined by IHC and ISH respectively on surgically removed tumour Node negative or positive (up to three nodes) and tumour size determined by histopathology on surgically removed tumour Pre-test <i>intermediate clinical</i> risk of distant metastases defined by at least one of the following characteristics: tumour size ≥ 2 cm; or grade 2/3; or one to three lymph nodes involved (nodes include micrometastases but not isolated tumour cells) The test may be used once per new primary breast cancer diagnosis.
Fee: \$redacted Benefit: 75% = \$redacted ; 85% = \$redacted

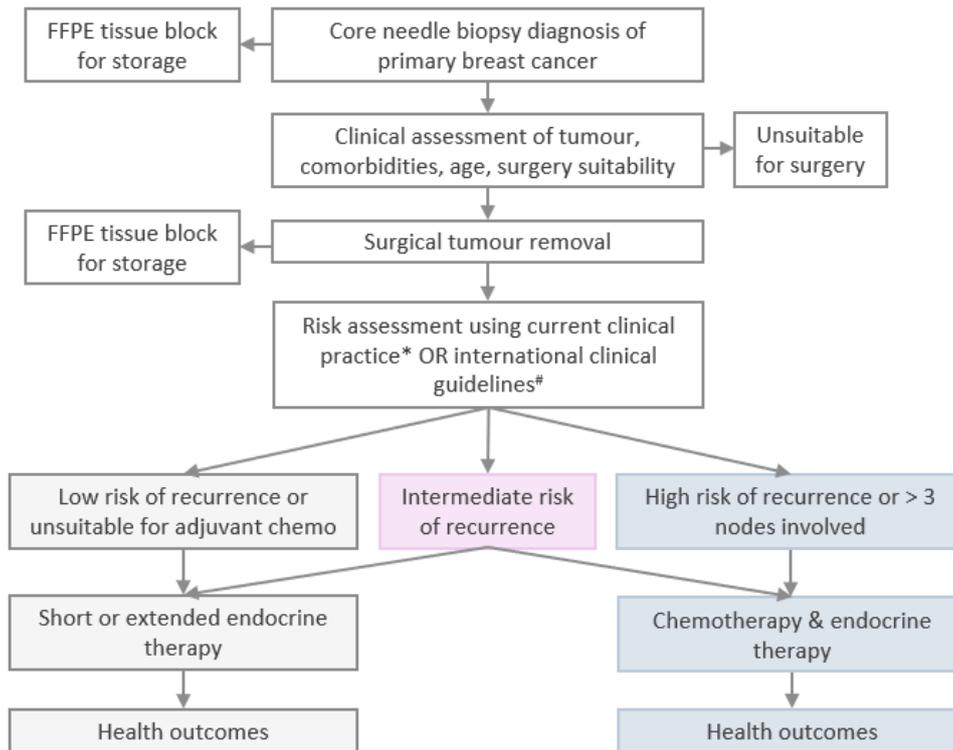
7. Summary of Public Consultation Feedback/Consumer Issues

Key points received during the public consultation period of the PICO Confirmation were related to questions of eligibility of the proposed patient population (pre- or post-menopause women, patients with tumour grade 3), whether prognostic information can infer chemotherapy benefit, and if the intervention is cost-effective.

8. Proposed intervention's place in clinical management

The current clinical management algorithm based on current clinical practice (or international guidelines) for patients who have ER+/HER2– primary breast cancer is shown in Figure 1.

Figure 1 Clinical management algorithm (current clinical practice OR international guidelines) for patients who have ER+/HER2- primary breast cancer



ER+, oestrogen receptor positive; FFPE, formalin-fixed paraffin-embedded; HER2-, human epidermal growth receptor negative;
 * Risk assessment based on age, 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, EMSO, and German S3

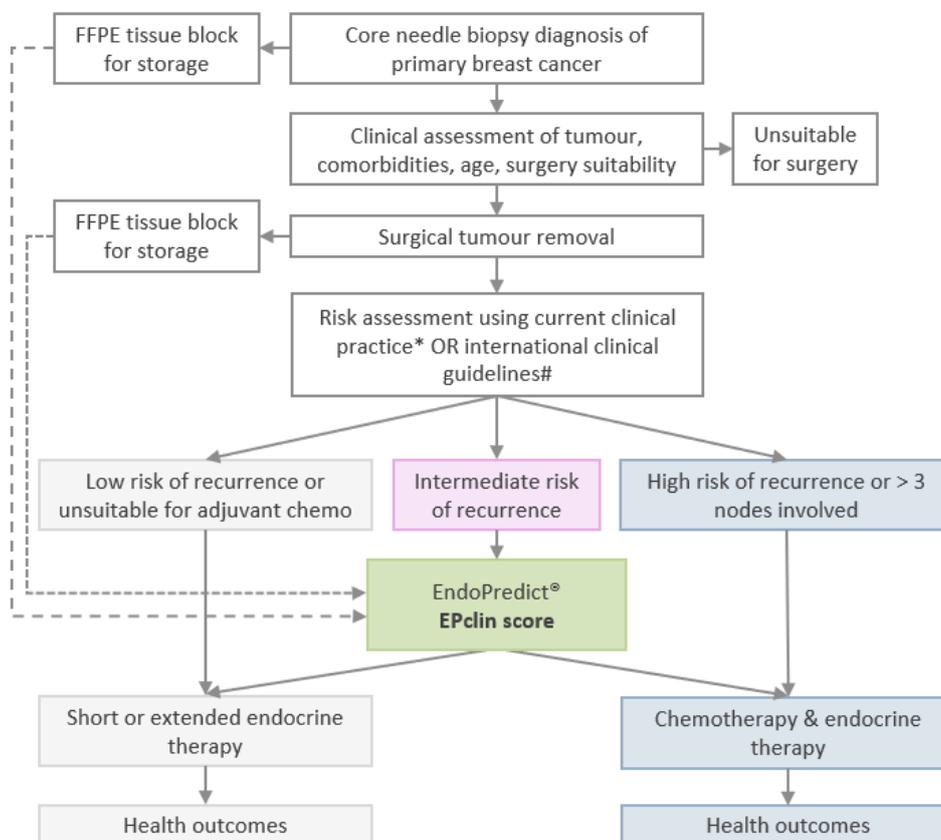
Proposed clinical management algorithm

In the proposed clinical pathway shown in Figure 2, patients with primary breast cancer diagnosed by core needle biopsy are assessed for surgical removal of the tumour in the same manner as performed in current clinical practice. After surgery, a pathologist will determine ER and HER2 status, assess tumour size and nodal status, and report the histological results to the treating oncologist. The oncologist (sometimes in consultation with a multi-disciplinary team [MDT]), will decide whether the tumour is considered at low, intermediate, or high clinical risk of distant recurrence, and, after consultation with the patient, make a treatment decision. As with current practice, patients at low risk of distant metastases would be offered ET, and those considered at high risk of distant metastases would be offered adjuvant chemotherapy in addition to ET.

Patients with ER+/HER2- cancer who are assessed to be at intermediate risk of distant metastases would follow the proposed clinical pathway provided the patient is considered suitable for adjuvant chemotherapy, with the patient offered the EndoPredict test. Here, a 10 µm section of the routine FFPE is used to prepare RNA for RT-qPCR using the EndoPredict Kit reagents. The prepared tissue sample along with quality control samples are run on the RT-qPCR instrumentation to produce data which are exported into the reporter software. Combined with additional clinical information, the reporter software uses an algorithm to generate the EPclin risk assessment score, which predicts the risk of distant recurrence within 10 years (on a continuous scale). Using the EPclin score, the patient is categorised as being at high or low risk of distant recurrence, which may be used by the oncologist and patient to guide treatment decisions.

Patients who fall into the low risk category according to the EndoPredict tool would be offered ET alone (short or extended term), whereas those in the high risk category would be offered ET combined with chemotherapy.

Figure 2 Clinical management algorithm with the proposed medical service for patients who have ER+/HER2– primary breast cancer



ER+, oestrogen receptor positive; FFPE, formalin-fixed paraffin-embedded; HER2–, human epidermal growth receptor negative.

* 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, ESMO, and German S3

9. Comparator

Three comparators are described in the ratified PICO Confirmation:

- Main comparator (base case): *Current standard of care (SOC) clinical practice* based on IHC/ISH analysis of tumour tissue (ER+, HER2– status) and including Ki67 status and tumour grade.
- Secondary comparator: *International breast cancer clinical guidelines* such as St Gallen, NCCN, ESMO, and the German S3 guidelines.
- Secondary comparator: *Other prognostic tests* such as OncotypeDX®, Prosigna® and MammaPrint®.

However, the Critique notes there is no clear definition of current clinical practice in Australia.

The lack of a clear definition of current clinical practice in Australia was considered to be a key issue in previous MSAC considerations of similar GEP tests, Oncotype DX, ([Oncotype DX MSAC Application 1342.4 July 2017](#)) and Prosigna (Prosigna MSAC Application 1473;

November 2019). In its consideration of Prosigna, 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.

10. Comparative safety

No comparative safety data were identified that could directly inform on the safety of EndoPredict and subsequent treatment in patients with HR+, HER2– primary breast cancer who are at intermediate clinical risk of distant recurrence.

Test adverse events

EndoPredict, and other gene expression tools assessed in this report, are considered procedurally safe because they rely on samples already taken for other purposes (i.e. the tissue removed during surgery for breast cancer).

Adverse events from change in management

Harms associated with chemotherapy in early breast cancer patients are well documented, with the majority related to fatigue, nausea, anaemia, change in appetite, and damage to organ function leading to poor quality of life. As such, the decision to recommend chemotherapy in women with ER+, HER2– primary breast cancer is based on clinical judgement relating to the estimated survival probability and the estimated absolute benefit of adjuvant chemotherapy. Thus, for patients at low risk of distant recurrence the side effects of chemotherapy are considered too large to warrant treatment, whereas for those at high risk of distant recurrence, the absolute benefit of chemotherapy is considered appropriate to outweigh the harms.

Any change in management as a result of the EPclin score, carries a risk of misallocation to the wrong treatment risk category, that is, a patient allocated to low risk of distant recurrence does not receive appropriate adjuvant chemotherapy, and a patient allocated to high risk of distant recurrence would receive adjuvant chemotherapy unnecessarily.

11. Comparative effectiveness

The Critique considered that overall, there is adequate evidence to suggest that EndoPredict is prognostic of late distant recurrence, inconsistent evidence that it changes clinical management, and limited evidence that it could be utilised to determine which patients would benefit from chemotherapy in addition to endocrine therapy.

No comparative effectiveness data were identified that could directly inform on the effectiveness of EndoPredict and subsequent treatment on overall survival, disease-free survival, metastases free survival, and quality of life in patients with HR+, HER2– primary breast cancer who are at intermediate clinical risk of distant recurrence.

Instead, the submission used a linked evidence approach by reporting on the following:

- The analytical performance of EndoPredict i.e. the reliability of testing within and between laboratories, protocols, operators and instruments.
- Prognostic accuracy of EndoPredict in comparison with the nominated comparators
- Therapeutic efficacy of EndoPredict in terms of the proportion of patients who receive ET with chemotherapy or ET alone compared to the nominated comparators.
- Therapeutic effectiveness of using EndoPredict in terms of the proportion of patients who are either undertreated without chemotherapy or overtreated with chemotherapy when compared to current clinical practice.

Analytical performance

Four studies relating to the analytical performance demonstrated EndoPredict has good precision and negligible laboratory-to-laboratory variation, indicating the test is suitable for decentralised testing in specialised molecular pathological laboratories instead of a reference laboratory.

Prognostic accuracy

The main evidence for clinical validity was provided by retrospective analysis of three cohorts derived from four phase III Randomised Clinical Trials (RCTs): ABCSG-6, ASCBCSG-8, TransATAC, and GEICAM/9906.

In ABCSG-6&8, post-menopausal women with primary breast cancer were treated with tamoxifen only for five years or tamoxifen for two years followed by anastrozole for three years. (Dubsky, Brase, et al., 2013; Dubsky, Filipits, et al., 2013; Filipits et al., 2019; Filipits et al., 2011).

The GEICAM 9906 trial compared two adjuvant chemotherapy regimens (FEC: 5-fluorouracil, epirubicin and cyclophosphamide; or FEC-P: FEC followed by paclitaxel) in women with lymph node positive disease. Hormone receptor positive patients received ET for 5 years following chemotherapy (Martin et al. (2014) and Martin et al. (2016) included patients from GEICAM 9906 trial if their tumours were ER+/ HER2-).

TransATAC evaluated efficacy and safety of anastrozole vs tamoxifen for five years in postmenopausal women with early stage breast cancer (Buus et al. (2016) and I. Sestak et al. (2018)).

In each of these studies, EPclin scores were generated from archived FFPE samples.

The proportions of pre-test low and high-risk patients in the studies included in the analysis are unknown. The Critique noted EndoPredict may have different prognostic performance in these groups and prognostic performance estimates may be different if only patients with pre-test intermediate risk were included.

Prognostic performance of EndoPredict was evaluated with reference to late distant recurrence as an evidentiary standard (Table 1).

Table 1 Summary of prognostic accuracy: EndoPredict against distant recurrence at 10 years

Study ID Risk of bias	Study Cohort	Clinical markers / Prognostic tool	DRR % ^a		HR (95% CI)	<i>p</i> -value (Log Rank)
			Low risk	High risk ^b		
Dubsky 2013a ^c <i>Moderate</i>	ABCSG-6&8	Luminal A d (Ki67 <14%)	4.6	20.5	4.08 (2.60, 6.41)	< 0.001
		Luminal B (Ki67 >14%)	6.8	29.0	5.54 (2.21, 13.93)	< 0.001
		Grade 1	4.4	17.5	3.11 (1.23, 7.89)	0.012
		Grade 2	5.0	24.2	5.07 (3.23, 7.94)	< 0.001
		Grade 3	0	29.0	Infinitive ^d	0.041
Dubsky 2013a ^c <i>Moderate</i>	ABCSG-6&8	EPclin	4.7	23.4	5.11 (3.48, 7.51)	< 0.001
		S3	5.3	13.2	2.2 (1.16, 4.19)	0.014
		NCCN	5.5	12.5	2.16 (0.80, 5.85)	0.119
		St Gallen	3.1	13.3	2.78 (1.50, 5.14)	< 0.001
Buus 2016 <i>Moderate</i>	TransATAC	EPclin	5.8	28.8	5.99 (3.94, 9.11)	< 0.001
		RS	10.1	23.5	2.73 (1.91, 3.89)	0.008
Martin 2016 <i>Moderate</i>	GEICAM 9906 ^f	EPclin	0	NR	Infinitive ^e	< 0.0001
		ROR-T	12	NR	2.3 (L vs IM) 3.7 (L vs H)	< 0.0001 < 0.0001
		ROR-PT	8	NR	4.5 (L vs IM) 5.8 (L vs H)	< 0.0001 < 0.0001

Abbreviations: CI, confidence interval; DRR, distant recurrence risk; EPclin, EndoPredict score, N, lymph node; RS, OncoTypeDX risk score, ROR, Prosigna risk of recurrence score

a. percentages indicate the Kaplan-Meier survival estimate within 10 years

b. Includes non-low risk patients, i.e those classified as both *intermediate* and *high* risk using RS in Buus 2016 (TransATAC)

c. this patient cohort includes patients who received extended endocrine therapy (N=1702) with median follow-up of 5.25 years.

d. Ki67 cut-off value as recommended by the St Gallen 2011 panel.

e. no events in the low risk group.

f. this patient cohort includes only those with 1–3 positive lymph nodes and is confounded by patients having received chemotherapy.

Overall, the Critique considered there is evidence that EndoPredict® test is reliable, reproducible and prognostic of 10 year distant recurrence in women with ER+, HER2– primary breast cancer who have undergone surgical tumour removal who are at intermediate risk of distant recurrence based on clinical markers of disease. The submission presented evidence showing that EndoPredict can also be used for predicting the likelihood of distant recurrence at 5-15 years in patients who were distant recurrence free after five years of endocrine therapy.

However, when interpreting the evidence presented in the submission, the Critique noted that all studies re-evaluated data from previously published RCTs. While this is generally considered to be good quality of evidence in validation of prognostic models and tests, exclusion of some patients from the re-analyses that were previously included in the RCTs due to insufficient tissue samples, could influence study findings. In the ABCSG-6 and ABCSG-8 trials, there were 1864 blocks with sufficient tissue available out of 4710 that received endocrine therapy. For GEICAM 9906 trial tumour blocks were available from 800 out of the 1246 patients that participated in the trial while the tumour block availability for the TransATAC trial was unclear.

The Critique also considered the risk of bias assessment used in the SBA to assess studies evaluating prognostic performance of EndoPredict was unlikely to identify all areas where bias could have occurred.

Pre-MSAC response

In response to ESC, The Applicant provided additional supplementary data from Dubsky et al 2013a (Table 2, Table 3 below) to further support the applicability of the EndoPredict prognostic evidence to patients with intermediate risk of distant recurrence.

Table 2: Proportion of low vs intermediate/high risk patients (source: Dubsky et al., 2013a; Suppl. Tables S2)

Risk Classification	German S3	NCCN 2007 (n=1702)	StGallen 2011 (n=1681)	EPclin (n=1702)
Low	248 (15%)	99 (6%)	323 (19%)	1066 (63%)
Intermediate/High	1454 (85%)	1603 (94%)	1358 (81%)	636 (37%)

Source: Reproduced from Supplementary Table S2, of Dubsky 2013a

Table 3: 10 year distant recurrence rate in low vs intermediate/high risk patients (source: Dubsky et al., 2013a; Suppl. Tables S3)

German S3		S3 Low 10 (5.3%)	S3 Intermediate/high 127 (13.2%)
EPclin low	35 (4.7%)	9 (5.3%)	26 (4.5%)
EPclin high	102 (23.4%)	1 (4.3%)	101 (24.0%)
NCCN 2007		NCCN Low 4 (5.5%)	NCCN High 133 (12.5%)
EPclin low	35 (4.7%)	3 (3.7%)	32 (4.8%)
EPclin high	102 (23.4%)	1 (25.0%)	101 (23.3%)
St. Gallen 2011		St. Gallen Low 11 (3.1%)	St. Gallen Intermediate/High 126 (14.3%)
EPclin low	35 (4.7%)	8 (3.0%)	27 (5.4%)
EPclin high	102 (23.5%)	3 (3.7%)	99 (25.2%)

Source: Reproduced from Supplementary Table S3, of Dubsky 2013a

Therapeutic efficacy (change in management)

The main evidence for change in management was informed by the interim results from an Australian study (PROSPER) that evaluated the potential decision impact of the EndoPredict test on the clinical management of patients.

Redacted.

Table 4: Redacted

Five additional before-and-after studies found that the use of EndoPredict (EPclin score) changes management in the range of a net 0.7% increase in use of chemotherapy to a 44% reduction. The results of these five studies are summarised and compared with the PROSPER study results in Table 5.

Table 5: Redacted

The Critique considers these differences between studies in the magnitude of a change in management may indicate how influential the experience of the MDT/clinicians recommending the course of treatment is.

Redacted.

Pre-MSAC response

The Applicant provided the **redacted**.

Table 6: Redacted

Therapeutic effectiveness (health benefit from change in management)

A single study (Sestak et al. 2019) of moderate-high risk of bias that reanalysed data from 5 RCTs found that the absolute risk difference of 10-year distant recurrence with ET alone versus ET plus chemotherapy increases with increasing EPclin score.

Sestak et al. used data from the four trials described above as well as one additional trial, GEICAM 2002/03. Participants in GEICAM 2002/03 trial were pre- and post-menopausal women with node-negative disease and received FAC: fluorouracil, doxorubicin and cyclophosphamide or FAC followed by paclitaxel.

The study used data from 3746 patients from the five studies (ABCSG-6 and -8, GEICAM/9906 and 2003/02, and the TransATAC trial). It is not clear whether all eligible patients from these trials were included. The Critique considered this study as being at moderate risk of bias as the two treatment groups had different patient characteristics, which suggests the possibility of selection bias.

Sestak et al found that the absolute risk difference between patients who receive ET alone and patients who receive chemotherapy plus ET jumps considerably from 1.9% to 7.4% between the EPclin scores of 3 and 4, noting that the risk of distant recurrence at 10-year was significantly different between the two treatment groups.

To investigate the risk associated with over- and under-treatment against current practice, Filipits (2011) examined distant recurrence in patients with tumours classified discordantly between Adjuvant!Online and EPclin in the pooled ABCSG-6 & 8 cohort. Within the cohort of patients with discordant results (27.4%), 74% were classified as EPclin low risk, where only 26% were classified as low risk with Adjuvant!Online. In the subgroup of discordant results, the risk of distant recurrence at 10-years followed the EPclin classification rather than the Adjuvant!Online classification ($p = 0.0496$). This suggests a substantial proportion of patients with early stage breast cancer would receive adjuvant chemotherapy unnecessarily.

These data are further supported by the analysis of patients with tumours classified discordantly between EPclin and clinical guidelines in the pooled ABCSG-6 & 8 cohort (Dubsky 2013a). Among the 6–19% of patients classified as low risk by clinical guidelines, the vast majority were also classified as low risk by EndoPredict (82% to 94%). Given the low event rate for distant recurrence, EPclin was not significantly associated with better prognostic accuracy for 10-yr distant recurrence in the low risk group. Among the 81–94% of patients classified as intermediate and/or high risk according to guidelines, patients reclassified as low risk by EndoPredict (range 58% to 61%) were significantly more likely to be free from distant recurrence at 10 years compared with those who remained at high risk (5% vs 23% to 25%; ARR 18 to 20; HR 5.09 to 5.6; $p < 0.001$). Again, these data suggest a substantial proportion of patients with early stage breast cancer would receive adjuvant chemotherapy unnecessarily.

The Critique considered the absolute benefit of reclassification, for both high risk and low risk patients, with EndoPredict is uncertain due to the wide range of change of management results.

Clinical Claim

Overall, and relative to the main comparator - current clinical practice/SOC - the submission claims the EndoPredict test and validated EPclin score has non-inferior safety and superior effectiveness.

However, the Critique considered this may not be supported by the evidence, and in fact, more patients may be receiving chemotherapy in the EndoPredict arm, resulting in higher costs, and less value, once a change in patient management is considered.

12. Economic evaluation

The main economic analysis in the submission compares EndoPredict vs SOC alone with SOC defined as the MDT. This comparison is the most relevant given that the MDT is the current SOC in determining breast cancer treatment in the Australian clinical setting.

A supplementary economic analysis is presented comparing EndoPredict with the S3, NCCN and St Gallen guidelines.

A supplementary economic analysis is presented comparing EndoPredict with other gene expression tests under consideration by MSAC (Oncotype DX, and Prosigna). MammaPrint is not included as a comparator in the economic analysis as there was no direct evidence comparing EndoPredict vs MammaPrint which met the evidentiary standard. However, Oncotype and Prosigna are considered reasonable proxies for the suite of alternative gene expression tests.

The structure of the economic evaluation is a hybrid decision tree-Markov model (Table 7) based on the structure presented in Harnan (2017) for NICE.

Table 7 Summary of the economic evaluation

Perspective	Australian Government
Comparator	Main: SOC (MDT) Supplementary: SOC (guidelines), other prognostic tests
Type of economic evaluation	Cost-utility
Sources of evidence	PROSPER, Filipitis 2011, Dubsky 2013a, Sestak 2018
Time horizon	Lifetime
Outcomes	QALYs, costs
Methods used to generate results	Hybrid decision tree-Markov model
Health states	No distant recurrence, distant recurrence, breast cancer death, natural death
Cycle length	1 year
Discount rate	5% for both benefits and costs
Software packages used	TreeAge 2018.20.0 and Excel

Abbreviations: MDT, multidisciplinary team; QALY, quality-adjusted life year; SOC, standard of care

Key structural assumptions of the model are:

- the EPclin scores of patients in PROSPER are used to calculate transition probabilities for distant recurrence and chemotherapy benefit.
- for the EndoPredict arm, the base case analysis assumes that all patients in the EndoPredict arm receive treatment according to the EndoPredict classification (e.g. 100% of patients classified as high risk by EndoPredict receive chemotherapy) as this analysis best represents the cost-effectiveness of the EndoPredict test. A sensitivity

analysis is included which incorporates when the MDT decides against the treatment decision recommended by EndoPredict (i.e. a patient classified as high risk by EndoPredict is still recommended ET only therapy). However, the Critique stated that this favourable assumption does not take into consideration the actual change in management, dictated by either the MDT (after knowledge of the EndoPredict® result) or the patient (after being informed of the risk by the Clinician).

The submission’s base case ICER (Step 3) for EndoPredict add-on to SOC (MDT) is **\$redacted/quality-adjusted life year [QALY] gained** (Table 8).

However, the Critique stated that once a change in patient management is accounted for in the model (with recalculated data from the **redacted**), this ICER over the lifetime of the patient, **redacted**to **\$redacted/QALY**.

Table 8 Main analysis: Incremental costs and effectiveness

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
<i>Step 1 Trial-based analysis</i>			<i>(treatment decision)</i>		
EndoPredict	\$redacted	\$redacted	-	redacted% change ^a	\$redacted
SOC (MDT)	\$redacted				
<i>Step 2 10 year time horizon</i>			<i>(QALYs)</i>		
EndoPredict	\$redacted	\$redacted	redacted	redacted	\$redacted
SOC (MDT)	\$redacted		redacted		
<i>Step 3 Lifetime horizon</i>			<i>(QALYs)</i>		
EndoPredict	\$redacted	\$redacted	redacted	redacted	\$redacted
SOC (MDT)	\$redacted		redacted		
<i>Critique’s results- including change in patient management^b</i>					
EndoPredict®	\$redacted	\$redacted	redacted	redacted	\$redacted
MDT	\$redacted		redacted		

Abbreviations: ICER, Incremental Cost-Effectiveness Ratio; MDT, multidisciplinary team; QALY, quality-adjusted life year; SOC standard of care

^a Critique stated it was unclear how the applicant determined the redacted% change in effectiveness

^b The Critique presented an analysis where the clinical benefit of EndoPredict was redacted% of patients (redacted%-redacted%) who switch from the high risk group to the low risk group and avoid chemotherapy.

The modelled results were sensitive to discount rate, assumption of constant risk of reduction of chemotherapy, and inclusion of MDT decisions which deviate from that suggested by EndoPredict.

However, the Critique stated that the model results were most sensitive to transition probability for distant recurrence (variable with the most uncertainty), the probability of being categorised to low risk and the time horizon.

The results of the Supplementary economic analyses are shown in Table 9.

Table 9 Supplementary analyses: Incremental costs and effectiveness

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
<i>EndoPredict vs S3</i>					
EndoPredict	\$redacted	\$redacted	redacted	redacted	redacted
S3	\$redacted		redacted		
<i>EndoPredict vs NCCN</i>					
EndoPredict	\$redacted	\$redacted	redacted	redacted	redacted
NCCN	\$redacted		redacted		
<i>EndoPredict vs St Gallen</i>					
EndoPredict	\$redacted	\$redacted	redacted	redacted	redacted
St Gallen	\$redacted		redacted		
<i>EndoPredict vs Oncotype DX</i>					
EndoPredict	\$redacted	\$redacted	redacted	redacted	redacted
Oncotype DX	\$redacted		redacted		
<i>EndoPredict vs Prosigna</i>					
EndoPredict	\$redacted	\$redacted	redacted	redacted	redacted
Prosigna	\$redacted		redacted		

Abbreviations: ICER, Incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year; SOC standard of care

Pre-MSAC response

The Applicant provided updated cost-effectiveness results from the **redacted** (Table 10).

Table 10: Incremental costs and effectiveness: redacted

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
<i>Step 1 (cost per change in decision)</i>					
EndoPredict	\$redacted	\$redacted		redacted% change	\$redacted
SOC (MDT)	\$redacted				
<i>Step 2 (cost per QALY – 10 years)</i>					
EndoPredict	\$redacted	\$redacted	redacted	redacted	\$redacted
SOC (MDT)	\$redacted		redacted		
<i>Step 3 (cost per QALY – 50 years)</i>					
EndoPredict	\$redacted	\$redacted	redacted	redacted	\$redacted
SOC (MDT)	\$redacted		redacted		

Source: Table 2, p5 of pre-MSAC response

Abbreviations: MDT = multidisciplinary team; QALY, quality-adjusted life year; SOC standard of care

The Applicant provided updated sensitivity analyses in Table 11.

Table 11: Key drivers of the economic model: redacted

Description	Incremental cost	Incremental QALY	ICER
Base case	\$redacted	redacted	\$redacted
Discount rate 0%	\$redacted	redacted	\$redacted
Discount rate 3.5%	\$redacted	redacted	\$redacted
Include MDT decisions which deviate from EndoPredict	\$redacted	redacted	\$redacted
Assume constant relative risk reduction from adjuvant chemotherapy used in the NICE model of 0.76	\$redacted	redacted	\$redacted
Reduction of adjuvant chemotherapy costs by 10%	\$redacted	redacted	\$redacted
Utility values for recurrence-free and distant recurrence reported by Lidgren 2007	\$redacted	redacted	\$redacted
Breast cancer mortality rate of used in the NICE model (0.1836)	\$redacted	redacted	\$redacted

13. Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of the introduction of EndoPredict (Tables 12 and 13).

The financial impact analysis assumes that patients will receive only one EndoPredict test, and those assessed to be at high risk will receive chemotherapy consisting of AC (doxorubicin and cyclophosphamide), with 64% also receiving paclitaxel. All patients are assumed to visit a specialist twice for the treatment of adverse events.

Table 12: Projected eligible population for EndoPredict®

	Description	Source	2019	2020	2021	2022	2023	2024
A	Projected incidence in 2019	AIHW	19371					
B	Projected incidence of breast cancer	A x (1+3.23%)		19997	20643	21309	21998	22708
C	early breast cancer	B x 80%		15,997	16,514	17,048	17,598	18,167
D	eBC HR+	C x 67%		10,718	11,064	11,422	11,791	12,172
E	eBC HR+ HER2-	D x 80%		8,575	8,852	9,137	9,433	9,737
F	Suitable for adjuvant therapy	E x 75%		6,431	6,639	6,853	7,074	7,303
G	Intermediate clinical risk of metastases (eligible population)	F x 80%		5,145	5,311	5,482	5,660	5,842

Source: MSAC 1408 CA, Table E-2, p140

Table 13: Total costs to the MBS associated with EndoPredict and subsequent chemotherapy use

	Year 1	Year 2	Year 3	Year 4	Year 5
	2020	2021	2022	2023	2024
Estimated number of patients receiving EndoPredict test ^a	redacted	redacted	redacted	redacted	redacted
EndoPredict					
Number of services	redacted	redacted	redacted	redacted	redacted
MBS costs	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
MBS rebate (75%)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Patient contribution	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Cost savings to other MBS services					
MBS costs	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
MBS rebate (75%)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Patient contribution	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total cost to MBS					
MBS costs	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
MBS rebate (75%)	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Patient contribution	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

Abbreviations: MBS, Medical Benefits Schedule

^a Uptake rate assumed of redacted% for Year 1, increasing to redacted% for Year 2 and stable at redacted% for Years 3-5

The Critique considered the net financial implications for the MBS are uncertain because of uncertainties in the estimation of the eligible patient population and in the uptake rate of the test. Particular areas of uncertainty include:

- the proportion of patients with localised cancer was assumed to be 80 percent of the new cases of breast cancer. It is unclear as to how this proportion was derived.
- the proportion of patients with localised cancer suitable for adjuvant therapy was assumed to be 75 percent. It is unclear how this proportion is derived.
- The update rates for the test were assumed to be 60 percent in Year 1, growing to 80 percent in Year 3. The basis for these assumptions is unclear.
- The assumptions regarding the change in number of patients receiving chemotherapy may not be observed in practice.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Clinical	
Definition of standard of care	No clear definition of current clinical practice in Australia is available (see also MSAC recommendations for Oncotype DX 1342.4 July 2017; and Prosigna (1473, November 2017).)
Evidence to support clinical claim (prognostic accuracy)	No comparative evidence is provided to directly inform the claim that EndoPredict has non-inferior safety and superior effectiveness to current clinical practice/standard of care. The main evidence for clinical validity (prognostic accuracy) is provided by retrospective analysis of three cohorts derived from four RCTs, with reduced number of patients analysed compared to parent trials introducing the risk of selection bias. Proportions of pre-test low and high-risk patients in the studies included in the analysis are unknown. EndoPredict may have different prognostic performance in these groups and prognostic performance estimates may be different if only patients with pre-test intermediate risk were included.
Therapeutic Efficacy (Change in management)	Uncertain whether the PROSPER trial reflects Australian clinical practice, as it is based on a small sample (165 patients) from four specialist centres. Evidence from additional studies very inconsistent.
Therapeutic Effectiveness (Health benefit from change in management)	The absolute health benefit of reclassification is uncertain due to the wide range of change of management results.
Economic	
Overall	The uncertainties in the clinical evidence lead to the outputs of the economic being highly uncertain. The economic evaluation may be too simple to capture all costs and benefits of using EndoPredict.
Assumptions regarding clinical management	Model assumes that all low-risk patients will not have chemotherapy and all high-risk patients will have chemotherapy. This may not be supported by the evidence.
Transition probabilities derived from the EPclin score	The model inappropriately assumes a perfect relationship between the EPclin score and the 10-year rate of recurrence, without any loss of information during the transformation process. The model thus overestimates the transition probabilities in favour of the intervention.
Utility values in model	May not accurately reflect their corresponding health state and are unrealistically high, favouring the intervention.
Financial	
Uncertain financial impact	No justification or rationale for some of the input variables used to estimate the eligible population. Thus, the impact on cost to the MBS is uncertain.
Timing of the test	Consider when the test is requested – for example, before or after surgical discharge, and whether there would be an inpatient/outpatient split (104/110; 75%/85%).

The ESC noted this is the fourth Gene Expression Profiling (GEP) test for breast cancer to request MSAC support for public subsidy in Australia. The three alternative tests considered by MSAC to date are MammaPrint®, Oncotype® DX and Prosigna®. No GEP test is publicly subsidised in Australia at October 2019.

The ESC considered the generic GEP item descriptor proposed by the applicant may not be appropriate as these tests are not necessarily equivalent or interchangeable.

The ESC noted the submission for EndoPredict is based on a linked evidence approach, similar to that taken for Prosigna. There is no direct comparative evidence available to inform the safety and effectiveness of EndoPredict.

The ESC advised MSAC consider whether the linked evidence approach is sufficient to support the applicant's claims. Although the analytical performance and prognostic accuracy of EndoPredict appear adequate, there is inconsistent evidence that use of the test changes clinical management, and limited evidence that it could be utilised to determine which patients would benefit from chemotherapy in addition to endocrine therapy.

The ESC noted the submission included **redacted** from an Australian study conducted to examine the impact of using EndoPredict on clinical management (PROSPER). The ESC considered this study may have **redacted**.

ESC considered that the economic evaluation may be too simple to capture all costs and benefits of using EndoPredict.

ESC also noted some problems with the key assumptions in the model, namely whether:

- the management practices and decisions reported in the PROSPER trial reflect Australian clinical practice
- all patients categorised as high risk would have chemotherapy and all patients categorised as low risk would not
- treatment practices have changed since the publication of the source for costs used in the model and still reflect current practice
- the EPclin score can be directly translated to a 10-year recurrence rate
- the utility values used by Verry et al. (2012) reflect the requested MBS patient population.

These problematic assumptions mean that the outcomes of the economic evaluation are uncertain.

ESC considered the 50-year timeline in the model may not be inappropriate, and agreed with the Critique that any gains of QALYs in the base case and the recalculated case are the incremental benefits over 50 years, and that any change in accumulation of benefit over the course of the model significantly affects the ICER (i.e. the intervention looks better as the time horizon is pushed out). ESC also considered using the 10-year recurrence rate extrapolated directly out to 50 years to be inappropriate.

ESC noted that, in addition to the uncertainties in the Financial Estimates that were raised in the Critique, it is unclear whether EndoPredict would be ordered in the outpatient or inpatient setting. As this affects the MBS rebate, it creates another area of uncertainty in the budget impact.

15. Other significant factors

Nil.

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

We are disappointed in the decision and new standards set by MSAC for gene expression testing in Australia. The requirement of a 'Randomised Control Trial' for MSAC to have confidence in EndoPredict® is counter to its acceptance and recommendation for use by Australian clinical specialists, global breast cancer clinical guidelines, the UK NHS, US Medicare, US private insurers and numerous other insurers and public healthcare systems throughout the world. Running this suggested trial would not be appropriate, ethical or within a suitable timeline for one country considering its evidentiary acceptance around the world. We will continue to work with MSAC and pursue all avenues, ensuring Australian patients

have equitable access to the most accurate innovative tools that improve treatment allocation in a safe and appropriate manner, benefiting both the patient's wellbeing and this healthcare system.

17. Further information on MSAC

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