



**Australian Government**

**Medical Services Advisory Committee**

## **Public Summary Document**

### ***Application No. 1408.1 – A prognostic RT-qPCR test for prediction of risk of distant recurrence of breast cancer under endocrine treatment***

**Applicant:** Myriad Genetics Australia Pty Ltd

**Date of MSAC consideration:** 28-29 July 2022

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 Benefits Schedule (MBS) listing of a gene expression profiling test, EndoPredict®, for determining the prognosis (risk of distant recurrence), and for the prediction of absolute benefit of chemotherapy (in addition to endocrine therapy) for patients with primary oestrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) early stage breast cancer, was received from Myriad Genetics Australia Pty. Ltd. by the Department of Health and Aged Care.

#### **2. MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the creation of a new Medicare Benefits Schedule (MBS) item for the EndoPredict® brand gene expression profiling (GEP) test. MSAC advised the test had modest incremental prognostic value in establishing the risk of distant recurrence of breast cancer in patients at intermediate risk of recurrence. MSAC did not accept predictive value had been demonstrated, and so could not conclude that using the test would improve health outcomes by affecting treatment decisions. MSAC supported a fee per service of \$1,200 benchmarked against the fees of other genomic tests it has supported on the basis of having incremental prognostic value. MSAC supported the following MBS item (Table 1).

**Table 1 MSAC's supported MBS item**

Category 6 – PATHOLOGY SERVICES Group P7 – GENETICS
<p>MBS XXX</p> <p>EndoPredict®, a gene expression profiling test that algorithmically combines tumour size and lymph node status with gene expression in formalin-fixed, paraffin-embedded primary breast cancer tissue from core needle biopsy or surgical tumour sample to generate a result to estimate the risk of distant recurrence within 10 years.</p> <p>The test may be used when all the following criteria are met:</p> <ul style="list-style-type: none"> <li>(a) New primary breast cancer, suitable for adjuvant chemotherapy.</li> <li>(b) Oestrogen receptor positive and HER2 negative as determined by IHC and ISH respectively on surgically removed tumour.</li> <li>(c) Axillary node negative or positive (up to 3 nodes) and tumour size 1-5 cm determined by histopathology on surgically removed tumour.</li> <li>(d) No evidence of distal metastasis.</li> <li>(e) Pre-test intermediate risk of distant metastases defined by at least one of the following characteristics: Grade 2; or Grade 3; or one to three lymph nodes involved in metastatic disease (nodes include micrometastases but not isolated tumour cells).</li> </ul> <p>For any particular patient, applicable once per new primary breast cancer diagnosis. Not to be used as a predictive test to change treatment decisions.</p>
Fee: \$1,200.00    Benefit: 75% = \$900.00    85% = \$1,112.10

FFPE = formalin-fixed paraffin-embedded; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry test; ISH = *in situ* hybridisation test.

85% benefit reflects the 1 November 2021 Greatest Permissible Gap (GPG) of \$87.90. All out-of-hospital Medicare services that have an MBS fee of \$586.20 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).

**Consumer summary**

Myriad Genetics Australia Pty. Ltd. lodged this application requesting Medicare Benefits Schedule (MBS) listing for a gene expression profiling (GEP) test called EndoPredict®. EndoPredict® is a genetic test that looks at the expression levels of several genes that can be involved in breast cancer. It then combines their results with other clinical information using an algorithm to calculate a score. The score provides a patient's risk of getting breast cancer again, called recurrent breast cancer.

Patients who have certain types of early breast cancer and are at intermediate risk of recurrence can use the score to estimate their likely future risk of cancer recurrence after surgery (prognostic value). Knowing their prognosis is valuable for patients and their clinicians. MSAC accepted that for patients who are at intermediate risk of recurrence, EndoPredict® has some prognostic value beyond the other information that clinicians and patients already use to estimate the risk of cancer recurrence.

Myriad Genetics also claimed that EndoPredict® test results can be used to predict which patients can safely avoid chemotherapy after surgery or would benefit from adding chemotherapy, and that this can result in improved health outcomes (predictive value). However, MSAC found that the evidence provided did not show that using EndoPredict® to change treatment decisions will improve health outcomes.

MSAC accepted that EndoPredict® is comparatively effective and safe when used as a prognostic test only. MSAC considered the test to be good value for money and a reasonable cost to the MBS at the same fee as other prognostic tests. MSAC emphasised that there was not enough evidence to show that it would be effective or safe to use EndoPredict's results to change treatment decisions, such as to decide whether to have chemotherapy or not.

## Consumer summary

### MSAC's advice to the Commonwealth Minister of Health and Aged Care

MSAC supported MBS funding of EndoPredict® because it considered it to be comparatively safe, effective and good value for money when used as a prognostic test.

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

MSAC noted that this was a re-application requesting listing of EndoPredict® on the MBS. EndoPredict® is a GEP test for patients with breast cancer, specifically a reverse transcription quantitative polymerase chain reaction (RT-qPCR) test that measures the expression of 12 genes of interest in breast cancer tissue. The applicant claimed the test can determine the prognosis (of late cancer recurrence) in patients with estrogen receptor positive (ER+) and human epidermal growth factor receptor 2 negative (HER2-) early breast cancer, and additionally predict the benefit of chemotherapy (in addition to endocrine therapy) in this population.

MSAC noted that EndoPredict® includes not only the RT-qPCR test but also an algorithmic tool that outputs a score categorising patients as high or low risk of distant recurrence (DR) based on the expression of the 12 genes of interest. Although not specified in the proposed MBS item descriptor, the application referred to the "EPclin score", rather than the "EP score". The EP score ranges from 0 to 15 and is algorithmically calculated based on the expression levels of eight cancer-related genes and three reference genes, with a low/high threshold score of 5. The EPclin score ranges from 1 to 6 and is calculated by combining the EP score with the clinical factors of nodal status and tumour size, with a low/high threshold score of 3.3.

MSAC recalled that it had previously considered public funding of EndoPredict® at its November 2019 and July 2021 meetings, and that there had been insufficient evidence to support it for public funding in both instances. At its November 2019 meeting, MSAC considered the item descriptor was orientated to predictive use, but concluded that there was insufficient evidence to demonstrate the predictive value of the test – to identify those patients who could safely avoid chemotherapy or those patients who would benefit from adding chemotherapy. At its July 2021 meeting, MSAC recalled it had *"accepted that GEP tests provided some modest prognostic information, however no applicant provided sufficient evidence for additional prognostic value beyond current standard of care"*. MSAC also noted the applicant proposed a reduced fee in its July 2021 application, and that the item descriptor remained orientated to predictive use.

MSAC considered that the 1408.1 re-application differed from both previous applications in that its clinical claim was for incremental prognostic information, and that the proposed item descriptor aligned with use for prognosis rather than for prediction. MSAC also noted that the 1408.1 ADAR presented new evidence supporting claims of incremental prognostic value, from Ettl 2020 and Penault-Llorca 2021 (Table 8).

MSAC agreed with ESC's proposed revisions to the proposed item descriptor to better define patients at intermediate risk of recurrence, including with reference to the populations defined in the supportive studies. MSAC noted the applicant's suggested revisions in its pre-MSAC response, but considered that they would allow leakage to testing in patients at low or high risk of recurrence.

MSAC noted that brand-agnostic MBS item descriptors are generally preferred where possible, however it considered that the evidence base presented was specific to the EndoPredict® brand GEP test. MSAC considered that different brands of GEP tests are not equivalent, so advised it

was appropriate to restrict public funding as supported under this re-application to EndoPredict®. MSAC advised the item descriptor should specify the brand EndoPredict® to avoid leakage to other brands of GEP test not supported by MSAC for public funding in Australia. MSAC noted that EndoPredict® is currently offered by only one private provider in Australia, and acknowledged that only supporting public funding for EndoPredict® may risk geographically restricting equitable patient access to testing if this remains the case in the future.

MSAC considered that the decision to use EndoPredict® would typically be undertaken by a requester operating as part of a multidisciplinary team (MDT), so advised it was not appropriate to make the test pathologist-determinable.

MSAC noted and accepted the clinical management algorithm.

MSAC noted that the re-application included no new evidence on the safety of EndoPredict®.

MSAC considered that incremental prognostic value was demonstrated through the independent prognostic value of EP score in multivariate and bivariate Cox analyses, beyond that of standard clinical markers (tumour size, nodal status, tumour grade, quantitative ER, quantitative progesterone receptor (PR), Ki67 and age). MSAC noted the prognostic value of nodal status was an order of magnitude greater than the prognostic value of EndoPredict®. MSAC considered that incremental prognostic value was also evidenced by the c-statistic showing a modest 0.03-0.04 gain in discrimination for predicting distant recurrence at 0 to 5 or 10 years with the addition of the EPclin score. However MSAC also considered that the way these two sources of data had been analysed and presented did not inform a judgement of the extent of the incremental prognostic value. MSAC concluded overall that they provided evidence of modest incremental prognostic value, and again noted the 1408.1 ADAR also presented new evidence supporting incremental prognostic value (see Table 8).

MSAC noted the re-application relied on a linked evidence assessment framework to connect the test population to health outcomes. MSAC noted the applicant's claims regarding changes in management and health outcomes (i.e. predictive value) were largely based on evidence it had considered previously and found insufficient. MSAC noted this re-application presented a re-analysis of the PROSPER study data considered in November 2019 (n=220, with n=197 in the MBS-eligible subgroup) based on an enlarged population (Dinh 2022; n=233, with n=215 MBS-eligible). MSAC considered that the revised estimates of requesters and patients who might change their clinical management decisions in this component of the linked evidence assessment framework were not sufficient to change its previous conclusions that incremental predictive value had not been sufficiently demonstrated across the overall evidence base for EndoPredict®.

MSAC noted that, beyond this, the re-application presented no new evidence to show a predictive benefit of EndoPredict®, and that no results from prospective studies (e.g. effect modification in a randomised controlled trial) were provided to support the claim for a predictive effect. MSAC recalled that the 1408 ADAR had included Sestak 2019, a retrospective analysis of five trials with indirect comparisons across studies, and that its conclusion in 2019 had been that "*the retrospective analysis of three cohorts derived from four randomised clinical trials ... could not be relied upon for decision making*". MSAC considered that the fundamental problems with the study design and applicability that it had previously identified remained, and that the evidence provided in the 1408.1 ADAR did not sufficiently demonstrate predictive value. MSAC therefore advised there was insufficient evidence to conclude that using EndoPredict® to change treatment decisions would improve health outcomes.

Overall, MSAC accepted that EndoPredict® has incremental prognostic value, but the magnitude is uncertain due to the study designs and population (applicability) differences. MSAC did not

accept that the evidence sufficiently demonstrated predictive value, so it could not conclude that using the test would likely improve health outcomes by affecting treatment decisions, and considered that any predictive value of EndoPredict® remains uncertain.

MSAC noted the applicant's proposed item descriptor included "to predict greater than or equal to 10-year prognosis". MSAC considered that as the studies finished within 10 years of follow-up, the test result cannot provide an estimate of prognosis beyond 10 years, so advised the wording in the item descriptor wording should be revised to instead reflect the risk of distant recurrence within 10 years.

MSAC noted clinician and consumer support for public funding of GEP tests for patients with early breast cancer, however that comments from clinicians and patients indicated they would use the result of a GEP test to inform treatment decisions (predictive use). MSAC noted that some patients have already used EndoPredict® at their own cost. MSAC noted that one Australian pathology website claims that EndoPredict® can supply information about whether the patient can safely avoid chemotherapy, how beneficial chemotherapy would be and whether the patient can avoid extended endocrine therapy. MSAC reiterated that there was insufficient evidence to conclude that using EndoPredict® would change health outcomes (predictive value), so to reduce the potential for inappropriate use on the MBS, advised that the supported item descriptor should state that the test is not to be used for predictive purposes. MSAC recognised that the difference between prognostic and predictive use is a nuance that could be complex for test requesters to explain and for consumers to understand, and advised that the government should arrange for additional education and consumer engagement be undertaken independently of the applicant.

MSAC noted that the 1408.1 ADAR presented an updated cost-utility analysis using the updated PROSPER data and other minor updates to costs and life tables. MSAC considered that the 1408.1 ADAR did not address MSAC's previous concerns about model structure and inputs, and that the ADAR and pre-MSAC response continued to infer predictive value of the test because they both estimated a net increment in QALYs (i.e. improved health outcomes). MSAC considered that patients placed value in knowing their prognosis, though that "value of knowing" is considered by MSAC qualitatively and separate to the value of health outcomes in an economic evaluation.

MSAC noted the applicant proposed a volume-based fee structure, however considered that the proposed approach was impractical and understood that it could not be implemented via the MBS. In order to provide a basis to support the MBS listing in the context of all the relevant information considered, MSAC recalled that it had previously supported a fee of \$1,200 for other similar gene panel tests with similar incremental prognostic value and incremental costs per measure of diagnostic yield, estimating roughly comparable cost-effectiveness on the basis that the additional genetic diagnoses have prognostic value overall (Table 2). MSAC therefore applied these benchmarks to advise the same fee of \$1,200 be applied to its supported MBS listing for EndoPredict®. In doing so, MSAC considered that the differences between testing blood and testing tissue were not sufficiently material to justify a variation in its nominated fee for EndoPredict®. MSAC also considered that although there is variation in the previously supported incremental costs per measure of diagnostic yield, these were also not sufficiently material to justify a variation in its nominated fee for EndoPredict®. Overall, MSAC advised that a key rationale for its support for the nominated fee reflects its qualitative judgement that the incremental prognostic value of EndoPredict® is sufficiently similar to previously supported incremental prognostic value in Table 2 to support a similar fee. MSAC further noted the estimated net financial implications to the MBS of listing EndoPredict® at a flat fee of \$1,200 and an 85% benefit would be \$3.5 million in the first year, which MSAC also considered to be broadly consistent with the annual net financial implications of these previously supported

genomic tests (Table 2). For all these reasons, MSAC rejected the volume-based fee structure and advised the appropriate fee is a flat fee of \$1,200.

**Table 2 Recent MSAC-supported gene panel tests: cost per measure of diagnostic yield, fee for gene panel test, and financial cost of testing**

MSAC application number: disease	Diagnostic yield (measure) – population	Cost per measure of diagnostic yield	MSAC advice	MSAC supported fee for gene panel test	Annual net financial cost
1585: Neuromuscular disorders	20% (proband detected)	\$1,444	✓	\$1200 gene panel (318 or 375 genes, NGS methods)	\$2,290,317 (first year)
1599: Cardiomyopathies	67% (P/LP variant identified) – AIs + FDRs	\$2,446	✓	\$1200 gene panel (≥24 genes, virtual panel using NGS methods)	\$1,292,654 (average of years 1-5)
1598: Cardiac arrhythmias	26% (positive genotyping) – AIs only	\$4,721	✓	\$1200 gene panel (≥20 genes, virtual panel using NGS methods)	\$1,173,845 (average of years 1-5)
	26% AI, 50% FDR (positive genotyping) – AIs + FDRs	Dominant			

Annual net financial cost of application describes the net cost (i.e. taking into account both costs and cost-offsets) to the MBS, of the application as a whole (i.e. including all proposed items). For 1598 this also includes the cost of testing second-degree relatives, in line with MSAC advice.

AI = affected individual (i.e. an individual eligible for genetic testing based on symptoms/signs); FDRs = first-degree relatives; NGS = next generation sequencing; P/LP = pathogenic or likely pathogenic.

Source: MSAC

MSAC noted that, as is required for the MBS, the fee is for the provision of the entire service accounting for the cost of all components of the service that are required to report the result to the requester of the service: in this case the professional service encompasses the pathologist and the laboratory pathology components as well as the cost of the EndoPredict® assay (inclusive of its algorithm). MSAC therefore advised that, to clarify this, the item descriptor should specify that the service includes the generation of a risk result. MSAC noted that the MBS is only a part payer in a complex system, and that although the MBS could list the supported item and the MSAC-supported fee, the MBS could not restrict the amount that would be ultimately charged to the patient. MSAC considered that there was a reasonable risk of substantial out-of-pocket costs to the patient, and advised the government not to implement the listing without first obtaining appropriate reassurances from the applicant on the price it would charge pathology laboratories for the test in order to be confident that there would be minimal grounds to expect substantial out-of-pocket costs to the patient.

MSAC anticipated that other brands of GEP tests may be able to demonstrate similar incremental prognostic value over current usual care in optimising the available clinical and pathology information in patients of intermediate risk of recurrence, and, if so, would consider revisiting this item descriptor if any applicant for another brand could provide this information and similar reassurances of pricing its test against a fee of \$1,200 to reduce the risk of substantial out-of-pocket costs to the patient. In such a circumstance, MSAC foreshadowed its advice for an amended item would likely be to one GEP test per new primary breast cancer diagnosis.

MSAC noted that the ADAR proposed the test would receive a 75% benefit on the basis that it would be typically provided on an inpatient basis, however MSAC considered that the test would typically be provided on an outpatient basis, therefore the 85% benefit was more appropriate. MSAC noted that its advice on the fee and the outpatient use alters the estimated financial cost of supporting this testing (see additions to Table 19), with cost to the MBS now estimated to be

\$3,549,480 in year 1 increasing to \$5,400,049 in year 5. MSAC considered that the eligible population was likely underestimated, and also that the claimed cost offsets (mostly due to reduced utilisation of adjuvant chemotherapy) were uncertain – so the cost to the MBS and to the government’s health budget may be higher than estimated.

MSAC noted advice from the National Pathology Accreditation Advisory Council (NPAAC) that external quality assurance (EQA) would need to be addressed using sample exchange with other laboratories. MSAC recommended that the service be reviewed in detail after two years, including the out-of-pocket costs for consumers, co-claiming, determining whether the test is being used in the appropriate patient group, and equity of access including review of the geographical distribution of testing to ensure that the test was widely available. MSAC considered that it would also be important to understand impacts for patients as part of the two-year review, and requested stakeholder input be sought at that time, potentially including Cancer Australia.

## 4. Background

Myriad Genetics has made two prior applications to MSAC for public funding for EndoPredict®, in 2019 and 2021.

In 2019 Myriad Genetics provided a submission-based assessment (1408 ADAR) to MSAC requesting support for its 12-gene expression profile RT-qPCR test (GEP test) in patients with ER+, HER2- early breast cancer. The applicant’s claim was that EndoPredict® could improve treatment decisions and health outcomes for patients of intermediate risk based on clinicopathological features by predicting the risk of late recurrence.

Following the 77th MSAC meeting in November 2019 MSAC advised:

*“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.”*

In June 2021, the Department invited focussed applications from applicants that had applied for funding support in Australia for GEP tests for patients with ER+, HER2- early breast cancer, including EndoPredict®, MammaPrint®, OncotypeDX®, and Prosigna®. The applications were invited following a stakeholder meeting held on 21 June 2021 by the Royal College of Pathologists of Australasia (RCPA), Cancer Australia and the Australian Government Department of Health. The Department requested that the applications address some specific issues common to previous applications, similar to those listed in Table 3.

In July 2021, after consideration of focussed applications, MSAC did not support funding for any of the applications. In its consideration of EndoPredict®, MSAC’s advice was:

*“MSAC considered that the incremental prognostic value was uncertain for EndoPredict® and that there were missing data, resulting in an uncertain effect. MSAC did not accept the claimed predictive value of EndoPredict®, and noted that the applicant claimed the TGA has approved EndoPredict® for predictive use. MSAC recalled its previous consideration of EndoPredict® in 2019, and the uncertainties around whether*

*incremental prognostic value had been established, and its concerns regarding selection biases and missing data in the studies presented.*

*MSAC noted that the applicant proposed a reduced fee and requested it be kept confidential”.*

Pages 4 and 5 of the July 2021 Public Summary Document (PSD) listed key matters of concern that MSAC advised must be addressed to enable MSAC to consider whether to support MBS funding for a GEP test in early breast cancer, in the absence of robust evidence supporting predictive value.

Following further consultation with the Department in October – November 2021, Myriad proposed writing a new application specifically addressing the issues raised by MSAC. In December 2021, the MSAC Executive advised that a re-application could bypass PASC. In addition, it was requested by the MSAC Executive that data from clinical studies published late in 2021 and early 2022 should be included as relevant. As a result, Myriad Genetics submitted the current assessment report (1408.1 ADAR) in February 2022.

Table 3 provides a summary of key matters raised by MSAC in the July 2021 PSD and the MSAC Executive in communication with the applicant by email on 9 December 2021, and how the re-application from Myriad Genetics addressed them.

**Table 3 Summary of key matters of concern**

Component	Matter of concern	How the re-application addresses it
<b>Key clinical matters of concern</b>		
TGA IVD approval, NATA and NPAAC accreditations	MSAC advised that the GEP must be TGA approved; NATA and NPAAC accreditation must be met for the GEP by laboratories to be performing the test in Australia (PSD July 2021, p.4)	Evidence for TGA registration was provided. The requirement for NATA and NPAAC accreditations were acknowledged but no evidence was provided. The applicant indicated that if funded, there would be appropriate measures in place for the test.
QAP program in place	MSAC advised an appropriate QAP must be in place. (PSD July 2021, p.4)	QAPs were not provided. The applicant indicated that if funded, there would be appropriate measures in place for the test.
Appropriate clinical place for the GEP test: 1. evidence for prognostic value and incremental prognostic value	MSAC advised that there must be an appropriate clinical place for the GEP test, acceptable prognostic value and acceptable incremental prognostic value above what is currently used in clinical practice and compared with other GEP test options in Australia (PSD July 2021, p.4)	No additional evidence was presented by the applicant. The commentary re-presented evidence on incremental prognostic value and predictive treatment benefit.



Component	Matter of concern	How the re-application addresses it
<p>Appropriate clinical place for the GEP test: 2. Evidence of clinical utility in Australia</p>	<p>MSAC advised that there must be an acceptable clinical utility that leads to improved patient care, which should lead to less patient harm and better cancer-related outcomes. (PSD July 2021, p.4)</p>	<p>A recent publication was included that provided updated data on clinical utility in Australia. The data showed that EPclin influenced a change in treatment recommendation for a significant number of both low-risk and high-risk patients, when compared to treatment recommendations in the absence of EPclin. The final treatment choice was impacted by personal patient preference and this ameliorated the impact of EPclin to some extent. Patient preference can also change treatment decisions in the absence of EndoPredict®. There was evidence from two non-Australian studies of similar change in management outcomes that supported the Australian data, although the populations varied to some degree.</p>
<p>Clinical evidence must align with the GEP test's proposed clinical place, noting the current MSAC guidelines for assessment reports</p>	<p>MSAC advised the importance of presenting development and validation datasets, the concepts of incremental (prognostic) clinical validity and preferably (predictive) clinical utility, and considering results of relevant randomised controlled trials (RCTs) to date. MSAC considered that additional evidence would need to be provided to demonstrate at least incremental prognostic value, and noted the PROGRESS framework as relevant for assessing such evidence. (PSD July 2021, p.4)</p>	<p>The applicant did not address these concerns.</p>
<p>Restricted access to funded GEP</p>	<p>MSAC advised an MBS-listing mechanism would be needed to limit use to such patients to those most likely to benefit, such as a capped number of funded services per early breast cancer diagnosis.</p>	<p>Not addressed</p>
<p>Clearer definition of "intermediate risk"</p>	<p>MSAC recommended using a more concrete definition of "intermediate risk", and noted the NICE guidelines restriction for GEP use based on PREDICT or NPI tools. (PSD July 2021, p.5)</p>	<p>No changes were made to the definition of "intermediate risk".</p>

Component	Matter of concern	How the re-application addresses it
Item descriptor changes	<p>MSAC advised that while a generic item may be the best option for administrative purposes, the item descriptor needs to reflect the evidence provided: "MSAC noted a key difficulty with a generic MBS item would be that the three considered GEP tests have different prognostic values and thus will have different incremental prognostic values. MSAC also noted difficulties for clinicians in choosing which GEP test would be appropriate for each patient, as the three considered GEP tests assess different genes (with some overlap). (PSD July 2021, p.5)</p> <p>If the GEP tests are not interchangeable with respect to prognostic value then a separate item for each approved GEP test could be considered more advantageous than a generic item (1408 pre-MSAC response).</p> <p>The MSAC Executive advised that the proposed label "statistically significant incremental prognostic value" in the item descriptor was problematic and will need to be reworded, as this does not readily define which GEP test(s) are in scope for the proposed item (email to the applicant dated 9 December 2021).</p>	The applicant made changes to the wording, but did not address all issues.
Test distribution plan	The MSAC Executive requested further information on how Myriad would plan to distribute the test if publicly funded (email to the applicant dated 9 December 2021)	The applicant noted that technical competency exists in most Australian molecular pathology laboratories, and that one laboratory per state would meet testing demand.
Inclusion of latest published clinical data	The MSAC Executive requested inclusion of results of additional clinical studies published in late 2021 and early 2022 (email to the applicant dated 9 December 2021).	Study updates and additional data for the PROSPER study were provided.
<b>Key economic matters of concern</b>		
Acceptable fee	MSAC advised that the GEP test must have an acceptable fee based on acceptable incremental cost-effectiveness and net budget impact (PSD July 2021, p4)	A fee structure was proposed based on the volume of use of the test in the year prior. This included four tiers. The highest fee (\$████) would apply if use was $\leq 1,555$ services, and the lowest (\$████) where use was $\geq 4,666$ services.
Acceptable incremental cost-effectiveness	No economic analysis was considered by MSAC in July 2021. However a number of issues were raised on the economic analysis presented in the 1408 application (considered by MSAC in November 2019), and the results were considered overly optimistic (PSD November 2019, p3).	The economic evaluation was updated to reflect the proposed fee arrangement, updated change in management data and other minor updates to costs and life tables. However, these changes did not address the issues noted in the November 2019 PSD.
Matters of economic concern outstanding from the November 2019 consideration		
Overall	The uncertainties in the clinical evidence lead to the outputs of the economic evaluation being highly uncertain (PSD November 2019, p18).	While updated data were presented to support a change in management following EndoPredict®, no new data were presented to support the effect of this change in management.
	The economic evaluation may be too simple to capture all costs and benefits of using EndoPredict® (PSD November 2019, p18).	The model structure is unchanged from the 1408 application.

Component	Matter of concern	How the re-application addresses it
Assumptions regarding clinical management	The model assumes all low-risk patients will not have chemotherapy and all high-risk patients will have chemotherapy. This may not be supported by the evidence (PSD November 2019, p18).	This assumption was unchanged from the 1408 application in the base case analysis. No justification was presented to support this approach. A sensitivity analysis was presented that modelled treatment decisions that deviated from EndoPredict®.
Applicability of the PROSPER trial	Management practices and decisions reported in PROSPER were assumed to reflect Australian clinical practice. However, as PROSPER was conducted in a limited number of Australian sites that have a reputation for cancer care, the decisions made may not reflect treatment decisions more broadly (PSD November 2019, p19).	This assumption was unchanged from the 1408 application.
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 (PSD November 2019, p18). The transition probabilities applied also assume that the EPclin score is predictive of chemotherapy response. MSAC recently confirmed (PSD July 2021, p1) that it did not accept predictive value had been adequately demonstrated for any GEP test.	This assumption was unchanged from the 1408 application. No justification was presented to support this approach. A sensitivity analysis was presented assuming the same relative treatment effect of chemotherapy by EPclin score (i.e. no predictive effect).
Extrapolation of 10-year recurrence rate	Extrapolation of the 10-year recurrence rate directly out to 50 years was inappropriate (PSD November 2019, p19).	This assumption was unchanged from the 1408 application and was not explored in sensitivity analyses. No justification was presented to support this approach.
Utility values in model	Utility values may not accurately reflect their corresponding health state and are unrealistically high, favouring the intervention (PSD November 2019, p19).	The utility values used were unchanged from the 1408 application. No justification was presented to support this. A sensitivity analysis was presented using alternate values.
Applicability of costs reported in Verry et al. (2012)	Some costs used in the model were sourced from the literature and inflated to current prices using the CPI. This approach assumed that treatment practices had not changed since publication and were reflective of current practice (PSD November 2019, p19).	This assumption was unchanged from the 1408 application. No justification was presented to support this approach.
Time horizon	While ESC considered that the 50-year time horizon may not be inappropriate, it was noted that longer time horizons appear to favour the intervention (PSD November 2019, p19).	The time horizon was unchanged from the 1408 application. This was longer than the 30-year time horizons applied in other applications for GEP tests presented to MSAC. <sup>a</sup>
<b>Key financial matters of concern</b>		
Acceptable net budget impact	MSAC advised that the GEP test must have an acceptable budget impact, based on robust estimates of the expected utilisation rates of testing for the proposed eligible population (PSD July 2021, p4). During the November 2019 consideration, MSAC considered that the estimated size of the eligible population was uncertain as no justification or rationale had been provided for some of the input variables (PSD November 2019, p3).	The financial impact analysis was updated to reflect the proposed fee arrangement, updated PROSPER data for the net change in chemotherapy use, and minor updates to costs and incidence estimates. However, these changes do not address the concerns regarding the input variables used to estimate the size of the eligible population noted in the November 2019 PSD.

Component	Matter of concern	How the re-application addresses it
Matters of financial concern outstanding from the November 2019 consideration		
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 assumption that all services would incur the 75% benefit was unchanged from the 1408 application. No justification was provided to support this approach.

<sup>a</sup> MSAC Application 1376.1, March 2018 MSAC Meeting PSD; MSAC Application 1473, November 2017 MSAC Meeting PSD; and MSAC Application 1342, November 2013 MSAC Meeting PSD.

GEP = gene expression profile; IVD = *in vitro* diagnostic; MSAC = Medical Services Advisory Committee; NATA = National Association of Testing Authorities; NICE = National Institute for Health and Care Excellence; NPAAC = National Pathology Accreditation Advisory Council; NPI = Nottingham Prognostic Index; PSD = Public Summary Document; TGA = Therapeutic Goods Administration.

Source: commentary, Table COM.1

## 5. Prerequisites to implementation of any funding advice

The proposed technology is an IVD Class 3, and was included in the Australian Register of Therapeutic Goods (ARTG) on 13 February 2017 (ARTG identifier 285557).

The ARTG listing provides for the intended purposes of EndoPredict® as being:

*“An in vitro diagnostic kit for patients with estrogen-receptor-positive, HER-2 negative primary breast cancer to determine the risk of distant recurrence and to estimate the adjuvant chemotherapy benefit.”*

As part of its pre-ESC response, the applicant provided the TGA-approved Instructions for Use document accompanying this ARTG listing in order to confirm the intended purposes of EndoPredict® in this document.

In addition to TGA approval, MSAC advised that NATA and NPAAC accreditation requirements must be met for the GEP test by laboratories that are to be performing the test in Australia (PSD July 2021, p.4). While the applicant acknowledged this, the commentary noted the re-application did not provide any documentation to say where the GEP test would be performed or of the laboratory accreditation status.

MSAC further advised that an appropriate quality assurance program (QAP) would need to be in place to perform the tests. QAPs would be specific to each GEP test, as each has a unique set of genes and individual algorithm. The applicant did not provide documentation of a QAP, but indicated that laboratories performing the test would have an appropriate QAP if it were publicly funded.

## 6. Proposal for public funding

The applicant proposed that a new MBS item be publicly funded for a GEP test for patients with early ER+, HER- breast cancer. The test would be in addition to other diagnostic tests currently funded by the MBS, including items 73332 – *in situ* hybridisation (ISH) for human epidermal growth factor receptor 2 (HER2) amplification eligibility for trastuzumab, and item 66662 – quantitation of hormone receptors in breast or ovarian carcinoma.

MSAC advised that although a “generic” MBS item may mitigate risk and simplify administrative arrangements, allowing future GEP test options to be added, this may not be possible if the tests assess different genes, have different incremental prognostic values, and require different QAPs.

MSAC also noted that it was unlikely to support funding that would allow multiple tests in diagnosed patients (1408 PSD July 2021, p.5).

The applicant’s revised MBS item descriptor is in Table 4. Previous wording (1408 application) is shown in strikethrough text. The **bolded** wording indicates the applicant’s additions in the 1408.1 re-application compared to the 1408 application. It is suggested that MSAC consider whether the GEP test should be pathologist determinable.

**Table 4 Proposed MBS item**

Category 6 – PATHOLOGY SERVICES Group P7 - GENETICS
MBS XXX <b>Clinically validated gene expression profiling test that algorithmically combines tumour size, lymph node status with tumour gene expression</b> of FFPE from core needle biopsy or surgical tumour sample in primary breast cancer tissue to predict ≥10 year prognosis. <del>RT-qPCR gene expression profiling of FFPE, core needle biopsy or surgical tumour sample in primary breast cancer tissue.</del> The test may be used when all the following criteria are met: (a) New primary breast cancer, suitable for adjuvant chemotherapy, and not requiring neoadjuvant chemotherapy. (b) Oestrogen receptor positive and HER2 negative as determined by IHC and ISH respectively on surgically removed tumour. (c) Node negative or positive (up to 3 nodes) and tumour size determined by histopathology on surgically removed tumour. (d) Pre-test intermediate clinical risk of distant metastases defined by at least one of the following characteristics: tumour size ≥2 cm; or Grade 2; or Grade 3; or one to three lymph nodes involved in metastatic disease (nodes include micrometastases but not isolated tumour cells). <b>Laboratory pathologist can determine if required as a reflex test when criteria are met.</b> The test may be used once per new primary breast cancer diagnosis.
Fee: See proposed volume-based fee structure Fee: \$█ Benefit: 75%=\$█, 85%=\$█

Notes: strikethrough and bolded text indicate the applicant’s deletions and additions (respectively) proposed in the 1408.1 re-application compared to the 1408 application.

The proposed volume-based fee structure is presented in Table 5. The applicant proposed a four-tier structure. The fee would be set annually based on utilisation in the previous year. The proposed starting fee is \$█ (Tier 3), based on the expected utilisation in Year 1 (see below). If the utilisation is higher than expected (i.e. above 4,665 services), then the fee would reduce to the Tier 4 fee (\$█) the following year. Conversely, if the anticipated uptake is not achieved in the first year (i.e. below 3,112 services), it would revert to the Tier 2 (\$█) fee the following year.

**Table 5 Proposed volume-based fee structure**

Tier	Volume (MBS services)	MBS fee
1	≤1555	\$█
2	1556-3111	\$█
3	3112-4665	\$█
4	≥4666	\$█

MBS = Medicare Benefits Schedule

The commentary considered that there is considerable uncertainty in the extent of use estimated over the first five years of listing. Given that the fee in the first year of listing is based on expected use estimated in the 1408.1 re-application (not based on actual utilisation), if use is higher or lower than predicted in the first year, the fee charged may not reflect the proposed volume-based fee structure. While this risk is shared between the applicant and the MBS, given that the alternate estimates identified during the evaluation suggest that the size of the eligible population may be an underestimate, the MBS may be more likely to bear this risk.

The commentary noted the expectation is that the cost of the other components would remain constant with the change in MBS fee across the proposed structure. In its pre-ESC response, the applicant provided a breakdown of the cost of providing the test, including the price of the test and the other cost components of delivering the service. This showed the proposed fee is comprised of cost of the EndoPredict® test (fixed per test) and standard consumables, as well as pathologist time (fixed per test) and technician time (dependent on the batch size).

The commentary noted that EndoPredict® is recommended in a number of recently updated international clinical Guidelines for early breast cancer management. Guidelines including ASCO (2016), ESMO (2019), EGTM (2017) and NICE (2019)<sup>1</sup> recommend using EndoPredict® for guiding adjuvant chemotherapy decisions. The recommended early ER+, HER2- eligible populations vary across the guidelines. EndoPredict® is available for private patients within Australia, where its use is not limited to the “intermediate risk” population.

In addition, at least one Australian pathology website (Australian Clinical Labs website<sup>2</sup>) claims that EndoPredict® can supply information for the following questions for ER+, HER2- early breast cancer about treatment effect:

- whether the patient can safely avoid chemotherapy
- how beneficial chemotherapy would be
- whether the patient can avoid extended endocrine therapy (source: [Australian Clinical Labs](#)).

## 7. Population

The new GEP test is intended for patients with early primary breast cancer who meet the specific requirements of ER+, HER-, no positive lymph nodes or 1 to 3 positive lymph nodes, and tumour size determined following surgical removal. Eligible individuals will have an intermediate risk of distant recurrence based on the clinical features of tumour size  $\geq 2$  cm, or tumour grade 2 or grade 3, or 1-3 lymph nodes involved shown to have metastatic disease (nodes include micrometastases but not isolated tumour cells).

Patients with low risk of distant recurrence based on the clinical features are treated with hormone therapy alone, and those with high risk of recurrence are treated with hormone therapy plus adjuvant chemotherapy, according to standard clinical practice. The proposed test is intended to assist in treatment decision making for those who fall into the intermediate risk group, and for whom the treatment pathway is not clear.

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<sup>1</sup> ASCO = American Society of Clinical Oncology; ESMO = European Society of Medical Oncology; EGTM = European Group on Tumor Markers; NICE = National Institute for Health and Care Excellence

<sup>2</sup> Australian Clinical Labs <https://www.clinicallabs.com.au/endopredict/>

In its November 2019 PSD, MSAC requested that those of intermediate risk be more clearly defined and separated from low-risk and high-risk patients by the eligibility criteria. According to the 1408 application, risk classification may be based on international clinical guidelines, or clinical practice in Australia, across which there is considerable variation. There were no changes made to the eligibility criteria in the 1408.1 re-application. Criteria for the PROSPER trial are given in Table 6. A smaller tumour size was accepted into the study (>10 mm) than is in the item descriptor criteria (≥20 mm). Proposed MBS criteria and inclusion criteria for the intermediate population in the change in management study by Penault-Llorca et al (2020)<sup>3</sup> are included for comparison.

**Table 6 Inclusion criteria for early ER+, HER- breast cancer for the PROSPER study, Penault-Llorca et al 2020 study and proposed MBS criteria**

Criteria	PROSPER	Penault-Llorca et al 2020	Proposed MBS criteria
ER status	>1% ER positive nuclei by IHC	>10% expression by IHC	Positive by IHC
HER2 status	Negative by IHC or ISH	Negative by IHC (0/1 + or non-amplified)	Negative by ISH
TNM (Tumour, Node, Metastasis) stage	T1c (tumour >1cm, ≤2 cm) to T2/N0-N1/M0 (tumour >2 cm, ≤5 cm / zero to one node involved / no metastasis)	pN0 (pathological assessment of zero nodes involved) or pN1mi (pathological assessment of ≥1 node with micrometastases)	Not stated
Tumour grade	Not stated	Grade 2 or Grade 3 and pT <2 cm (pathological assessment of tumour size <2 cm) or Lobular histology	Grade 2 or Grade 3 or 1 to 3 positive nodes <sup>a</sup>
Tumour size	10 to 50 mm	Not stated	≥2 cm <sup>a</sup>
Lymph nodes	0 to 3 positive nodes	Not stated	0 to 3 positive nodes <sup>b</sup>
Age	18 to 80 years	Not stated	Not stated
ECOG status scale	0-1	Not stated	Not stated

<sup>a</sup> Tumour should be ≥2 cm or Grade 2 or Grade 3, or 1 to 3 nodes involved

<sup>b</sup> When there are no nodes involved, tumour should be ≥2 cm or Grade 2, or Grade 3 to classify as intermediate risk

ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry test; ISH = *in situ* hybridisation test; MBS = Medicare Benefits Scheme; TNM = Tumour, node and metastases status: TNM

## 8. Comparator

Three sets of comparators are considered in the 1408.1 re-application.

- 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, and two recognised clinical nomograms – Adjuvant!Online and Clinical Treatment Score (CTS).
- Secondary comparator: international breast cancer clinical guidelines St Gallen, NCCN, and the German S3 guidelines.
- Secondary comparator: other prognostic tests Oncotype DX®, Prosigna® and MammaPrint®.

<sup>3</sup> Penault-Llorca F, et al. (2020). Decision of adjuvant chemotherapy in intermediate risk luminal breast cancer patients: A prospective multicenter trial assessing the clinical and psychological impact of EndoPredict® (EpClin) use (UCBG 2-14). *Breast*, **49**:132-40.

## 9. Summary of public consultation input

Consultation input for application 1408.1 was received from one organisation, the Breast Cancer Network Australia (BCNA), which supported the re-application.

The consultation input noted that GEP tests such as EndoPredict® are already being used in Australia, and providing access through the MBS will improve equity of access. GEP tests can provide consumers and their treatment team with additional information, and international guidelines include EndoPredict® in their clinical guidelines.

In communications with the Department on 15 November 2021, the applicant reported on stakeholder support for the proposed GEP test.

*On 3rd June 2021, a 'Transform cancer care in Australia to Fund Gene Expression Profiling for Breast Cancer' petition was signed by over 17,000 Australian signatories and presented to the Australian Minister of Health. Additionally, in early June Breast Surgeons of Australia and New Zealand and Australian Society for Breast Disease (ASBD) submitted separate statements of support letters.*

## 10. Characteristics of the evidence base

A summary of the evidence presented is given in Table 7. The italicised studies in italics are the main evidentiary basis of the re-application, all updates of studies presented in the 1408 application considered by MSAC in November 2019. The articles by Ettl (2020)<sup>4</sup> and Penault-Llorca (2020)<sup>5</sup> are updates of the authors' earlier publications (Ettl (2017) and Penault-Llorca (2017) respectively) and Dinh (2022)<sup>6</sup> provides an updated analysis of the PROSPER study.

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<sup>4</sup> Ettl J, et al. (2020). First prospective outcome data for the second-generation multigene test EndoPredict in ER-positive/HER2-negative breast cancer. *Arch Gynecol Obstet*, **302**(6):1461-1467.

<sup>5</sup> Penault-Llorca F, et al. (2020). Decision of adjuvant chemotherapy in intermediate risk luminal breast cancer patients: A prospective multicenter trial assessing the clinical and psychological impact of EndoPredict® (EpClin) use (UCBG 2-14). *Breast*, **49**:132-40.

<sup>6</sup> Dinh P, et al. (2022). Impact of the EndoPredict genomic assay on treatment decisions for oestrogen receptor-positive early breast cancer patients: benefits of physician selective testing. *Breast Cancer Res Treat*, **191**: 501-511.



**Table 7 Key features of the included evidence for EndoPredict®**

Trial/s Study design	N	Reference Duration	Patient population	Outcome(s)	Used in modelled evaluation
<b>EndoPredict® vs standard clinical practice, Adjuvant!Online and CTS</b>					
ABCSG 6 & trials R single arm analyses	1702	Filipits 2011 10y fu	Postmenopausal ER+, HER2- breast cancer patients	EP & EPclin validation	-
	1702	Dubsky 2013b 10y fu	Postmenopausal ER+, HER2- breast cancer patients	EP & EPclin prognosis	-
	1702	Filipits 2019 15y fu	Postmenopausal ER+, HER2- breast cancer patients	EPclin prognosis vs CTS5; DRFR	-
TransATAC trial R single arm analyses	928	Buus 2016 10y fu	Postmenopausal ER+, HER2- breast cancer patients	EP & EPclin prognosis vs CTS	-
	774	Sestak 2018 10y fu	Postmenopausal ER+, HER2- breast cancer patients	EPclin prognosis vs CTS & BCI	-
ABCSG 6/8, TransATAC, GEICAM 2003-02/9906 trials joint R analyses	3746	Sestak 2019 10y fu	Pre & postmenopausal ER+, HER2- breast cancer patients	Predictive treatment effect; DRFI for ET alone & ET+C	Yes
<i>Prospective comparative cohort</i>	373	<i>Ettl 2020 41.6m fu</i>	<i>ER+, HER- breast cancer</i>	<i>DR following EPclin directed treatment; predictive treatment effect</i>	-
<i>MC, prospective single arm study</i>	200	<i>Penault-Llorca 2021 1y fu</i>	<i>ER+, HER2- early breast cancer</i>	<i>Change in management; psychological impact of decision making</i>	-
<i>PROSPER study 2 cohort single arm analyses</i>	233	<i>Dinh 2022 fu not reported</i>	<i>Pre &amp; postmenopausal ER+, HER2- early breast cancer</i>	<i>Change in management</i>	Yes
<b>EndoPredict® vs guidelines</b>					
ABCSG 6, 8 trials R single-arm analyses	1702	Dubsky 2013a 10y fu	Postmenopausal ER+, HER2- breast cancer patients	DR	-
<b>EndoPredict® vs other GEP tests</b>					
TransATAC trials R single arm analyses	928	Buus 2016 10y fu	Postmenopausal ER+, HER2- breast cancer patients	EP & EPclin prognosis vs RS	-
	774	Sestak 2018 10y fu	Postmenopausal ER+, HER2- breast cancer patients	EPclin prognosis vs RS & ROR	-

C = chemotherapy; CTS = clinical treatment score; DR = distant recurrence; DRFI = distant recurrence free interval; DRFR = distant recurrence free rate; EP = EndoPredict® algorithm score; EPclin = EndoPredict® + clinical algorithm score; ER+ = estrogen receptor positive; ET = endocrine therapy; fu = follow-up; HER- = human epidemiological growth factor receptor negative; m = months; MC = multicentre; R = retrospective; RS = recurrence score (Oncotype DX®); ROR = risk of recurrence score (Prosigna®); y = years

The evidence for EndoPredict® fits into the linked evidence pathway for investigative technologies illustrated in the MSAC Guidelines and shown in Figure 1. Evidence identified for EndoPredict®

falls into the framework steps circled in green: test results information (incremental prognostic value and predicted treatment benefit prediction), change in clinical decisions (change in treatment given), and health outcomes (distant recurrence following treatment).

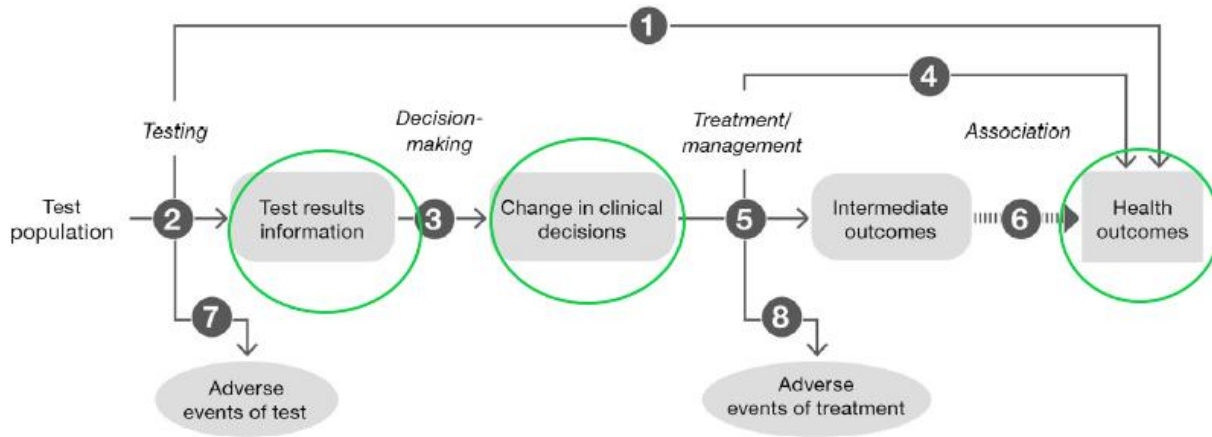


Figure 1 Linked evidence assessment framework showing links from test population to health outcomes

## 11. Comparative safety

No additional evidence was presented on the safety of EndoPredict® in the 1408.1 re-application.

As with all investigative tests, it would be expected that there would be safety issues related to patients who either have false positive or false negative results from EndoPredict®. The outcomes for patients with false negative and false positive results are implicit in the EndoPredict® Kaplan-Meier analyses.

Patients who are over treated for their level of risk of recurrence may suffer the adverse effects of chemotherapy unnecessarily.

Patients who do not receive chemotherapy but who have high risk of distant recurrence may experience disease relapse unnecessarily.

## 12. Comparative effectiveness

### Clinical claim

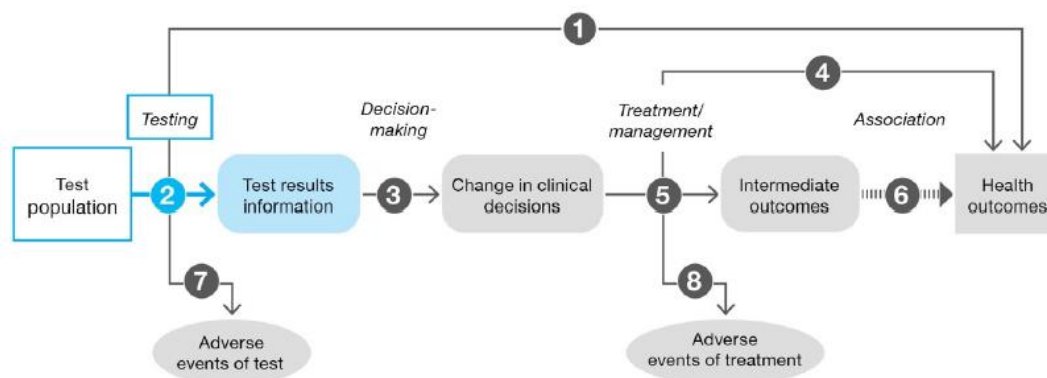
There was no clinical claim submitted with the 1408.1 re-application.

In its 1408 application, the applicant claimed that EndoPredict® has superior effectiveness and non-inferior safety for targeting the use of systemic therapy for patients with ER+, HER2- early breast cancer who have been assessed as intermediate risk of distant recurrence.

There was some evidence that EndoPredict® has incremental prognostic value over clinical characteristics (including nodal status, tumour grade, and tumour size) and standard assessment tools (Adjuvant!Online, IHC4, CTS5, Ki67), that it impacts patient management, and that it has treatment benefit predictive value, however the evidence is uncertain due to low level study design and population differences.

## Incremental prognostic value

Evidence for incremental prognostic value was provided in *Step 2 Test results information* in the linked evidence framework shown in blue in Figure 2.



**Figure 2** Linked evidence assessment framework

### *EndoPredict® compared with other GEP tests for early ER+, HER- breast cancer*

MSAC requested a comparison with of EndoPredict® with other relevant GEP tests. A comparison with other GEP tests was performed in an earlier application. There was no additional evidence of incremental prognostic value compared to other GEP tests provided in the 1408.1 re-application.

### *Comparative incremental prognostic value over current clinical practice*

In 2021, MSAC advised that incremental prognostic value for EndoPredict® above what is currently used in clinical practice must be shown. Incremental prognostic value was presented in the 1408 application. The 1408.1 ADAR provided some new evidence of incremental prognostic value (Table 8).

**Table 8** New evidence in the 1408.1 ADAR for incremental prognostic value: EndoPredict® against distant recurrence at 10 years

Study ID	Study cohort	Clinical markers / Prognostic tool	DRR % <sup>a</sup>		HR (95% CI)	p-value (log rank)
			Low risk	High risk		
Ettl 2020 <sup>f</sup>	ABCSG-6&8	EPclin	0.4 <sup>b, c</sup>	2.4 <sup>b, c</sup>	5.18 (1.04, 25.74)	0.044
Penault-Llorca <sup>f</sup> 2021 <sup>7</sup>	UNIRAD	EPclin	0 <sup>d</sup>	5.4 <sup>d</sup>	N/A <sup>e</sup>	0.0189

<sup>a</sup> Percentages indicate the Kaplan-Meier survival estimate within 10 years

<sup>b</sup> Reported 3-year DMFS

<sup>c</sup> Recurrence risk calculated through subtraction of %DMFS from 100%

<sup>d</sup> Reported rate of events at 60 months for MFS

<sup>e</sup> HR could not be calculated due to no events in the low-risk group

<sup>f</sup> This patient cohort includes patients who were treated with adjuvant/neoadjuvant chemotherapy

CI = confidence interval; DMFS = disease metastasis-free survival; DRR = distant recurrence risk; EPclin = EndoPredict + clinical algorithm score, HR = hazard ratio; MFS = metastasis free survival; N/A = not applicable.

Source: 1408.1 ADAR, Table 3.

<sup>7</sup> Penault-Llorca F, et al (2021). Prognostic value of EndoPredict test in patients screened for UNIRAD, a UCBG randomized, double blind, phase III international trial evaluating the addition of everolimus (EVE) to adjuvant hormone therapy (HT) in women with high risk HR+, HER2-early breast cancer (eBC). San Antonio Breast Cancer Symposium. 2021 Dec 7-10.

Results based on the data presented in the 1408 application are summarised below.

Data are presented from the studies by Filipits et al (2011)<sup>8</sup> and Dubsky et al (2013a)<sup>9</sup> as a summary of incremental prognostic value for EP and EPclin of distant recurrence (DR) in the ABCSG 6 and 8 populations.

In a multivariate Cox analysis EPclin was shown to have independent prognostic value, showing statistical significance in independence from standard clinical markers tumour size, nodal status, tumour grade, quantitative ER, quantitative progesterone receptor (PR), Ki67 and age. In the multivariate analysis, only nodal status and EPclin showed statistically significant prognostic value (both  $p < 0.001$ ). In a bivariate analysis, both Adjuvant!Online and EPclin showed statistically significant independent prognostic value (both  $p < 0.001$ ). Results are shown in Figure 3.

Cox model	Variable	ABCSG-6		ABCSG-8	
		Unit HR (95% CI)	P	Unit HR (95% CI)	P
Multivariate Cox model	Age	1.00 (0.96–1.04)	0.864	1.02 (0.99–1.04)	0.194
	Tumor size	1.09 (0.70–1.71)	0.704	1.57 (1.15–2.16)	0.005
	Nodal status	2.47 (1.75–3.48)	<0.001	2.32 (1.69–3.20)	<0.001
	Grade	0.81 (0.48–1.37)	0.435	1.09 (0.60–1.99)	0.770
	ER (IHC)	0.90 (0.58–1.40)	0.650	0.97 (0.70–1.34)	0.868
	PR (IHC)	0.83 (0.63–1.10)	0.199	0.94 (0.77–1.15)	0.559
	Ki67	1.03 (1.00–1.06)	0.086	1.00 (0.98–1.02)	0.974
	Treatment arm	–	–	0.78 (0.51–1.19)	0.243
	EP score	1.19 (1.04–1.36)	0.010	1.26 (1.15–1.38)	<0.001
Bivariate Cox model	Adjuvant! score	1.03 (1.02–1.04)	<0.001	1.05 (1.04–1.07)	<0.001
	EP score	1.19 (1.06–1.32)	0.002	1.27 (1.18–1.37)	<0.001

NOTE: The table shows 4 different Cox regression models with different sets of variables in both validation cohorts. Each model is shown in 2 columns: column "Unit HR" contains the 95% CIs for the unit HR of the respective variable whereas column "P" contains the P value for the probability of the regression coefficient to be 0. Variables/units were coded according to Supplementary Table S6 in the Supplementary Appendix.

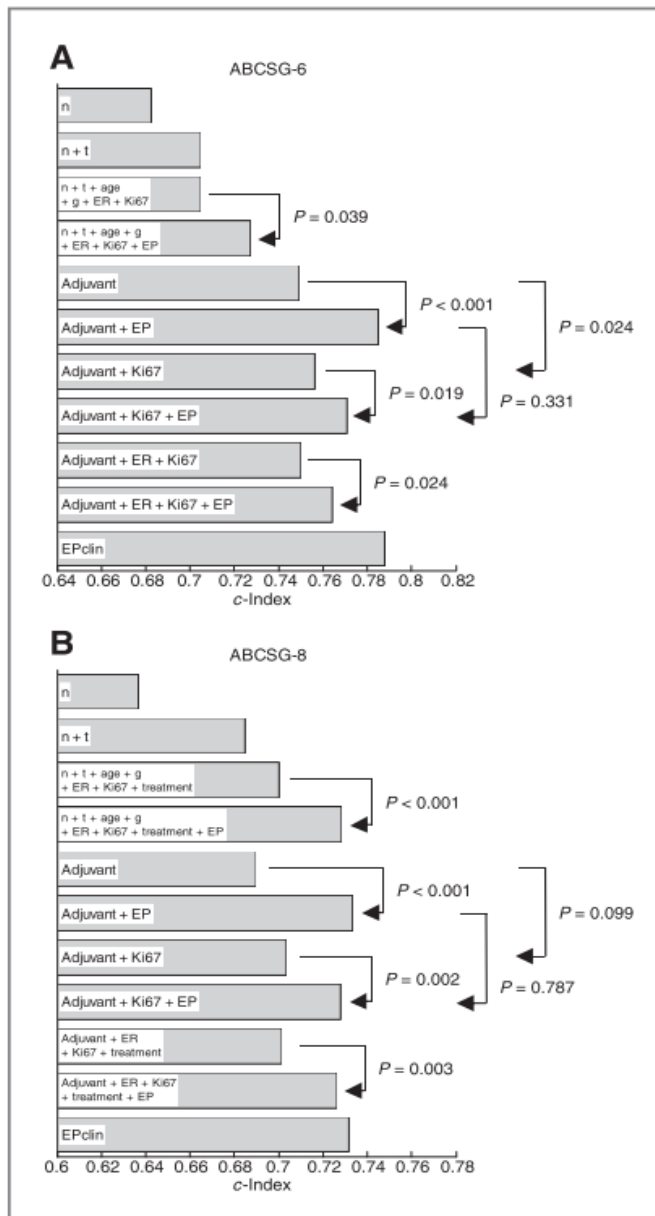
**Figure 3 Multivariate Cox proportional hazard models for estimating the contribution of variables to predict distant recurrence**

#### *Distant recurrence at 0 to 10 years*

In Figure 4 data from a c-index analysis shows the incremental prognostic value of EndoPredict<sup>®</sup> over conventional prognostic markers tumour size, nodal status, tumour grade, quantitative ER or PR, Ki67 and age for prediction of distant recurrence for up to 10 years. The EPclin score had higher c-indices than all combinations of clinicopathological variables tested (0.788 in ABCSG 6 and 0.732 in ABCSG 8). Multivariate HRs for DR are shown in Figure 4 (Filipits et al, 2011).

<sup>8</sup> Filipits M, et al. (2011). A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. *Clin Cancer Res*,17(18):6012-20. PMID: 21807638.

<sup>9</sup> Dubsky P, et al (2013a). EndoPredict improves the prognostic classification derived from common clinical guidelines in ER-positive, HER2-negative early breast cancer. *Ann Oncol*, 24(3):640-7. PMID: 23035151.



**Figure 4 C-index indicating the performance of combinations of different prognostic factors in the ABCSG-6 (A) and -8 (B) studies**

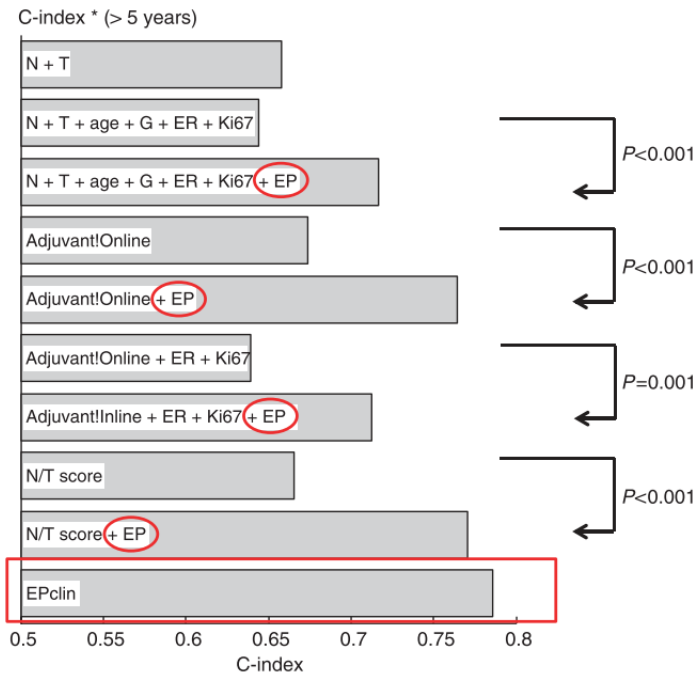
The values on the x-axis are unbiased estimates of the c-index of the linear combination of one or more variables by Cox regression. Statistical tests indicate whether the c-index increases significantly by addition of EP to a fixed set of clinicopathologic variables.

n = nodal status; t= tumour size; g = grade; ER = estrogen receptor; EP = EndoPredict® score (EP score).

Source: Filipits et al (2011)

#### *Distant recurrence at >5 years*

Dubsky et al (2013a) confirmed incremental prognostic value with reanalysis to show late >5 year recurrence. C-index analysis showed that EPclin provided statistically significant independent data over the conventional prognostic markers and Adjuvant!Online for >5 year recurrence (Figure 5).



**Figure 5 C-indices demonstrating the prognostic performance of different clinical and molecular parameters in 1702 ER+, HER- breast cancer patients (ABCSG 6 & 8) after 5 years follow up**

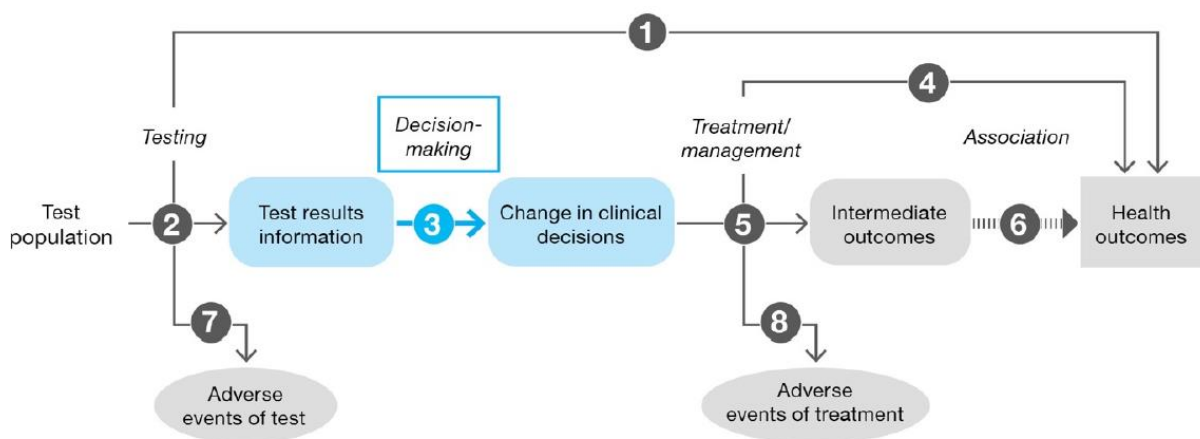
The values on the x axis are unbiased estimates of the c-index of the linear combination of one or more variables by Cox regression. Statistical tests indicate whether the c-index increases significantly by addition of EP to a fixed set of clinico-pathological variables.

EP = EndoPredict® score (continuous); ER = oestrogen receptor (categorical); G = grade (categorical); N = nodal status (categorical); T = tumour size (categorical).

Source: Dubsy et al (2013a)

## Clinical utility

Evidence for clinical utility, showing the impact of EndoPredict® test results on clinical treatment decisions, was provided in *Step 3 Decision making* in the linked evidence assessment framework (Figure 6).



**Figure 6 Linked evidence assessment framework**

## ***Change in management in Australia***

Data from the PROSPER study were provided in the 1408 pre-MSAC response and considered by MSAC in November 2019 (n=220, with n=197 in the MBS-eligible subgroup). The 1408.1 re-application included a reanalysis of these data based on the enlarged population in the publication by Dinh et al (2022) (n=233, with n=215 in the MBS-eligible subgroup). In the PROSPER study two cohorts of patients were recruited in a multicentre Australian based trial. The first cohort (n = 123) was recruited from consecutive patients attending site 1, and cohort 2 (n = 110) was a group of selected patients attending sites 2 to 5. In cohort 2, patients were selected because it was more difficult to decide on their treatment pathway based on clinical and pathological features alone, and was similar to the intermediate risk proposed population for the proposed GEP. The first cohort ranged from low to high risk based on clinical and pathological characteristics alone. In Cohort 2 patients were more likely to be premenopausal, have larger tumour size, and have higher tumour grade when compared to cohort 1. All patients underwent EPclin risk assessment, and treatment recommendations by a multidisciplinary team (MDT) were recorded before and after EPclin.

In cohort 2, chemotherapy was added to the treatment regimen for 15 of 110 patients (13.6%) and chemotherapy was removed from the regimen for 28 of 110 patients (25.5%) based on the results of EPclin. There were recommendation changes in 39.1% of all patients in Cohort 2, a similar rate to intermediate risk cohort in a French study by Penault-Llorca et al (2020) (34.5%) following EndoPredict® (Table 9). In the PROSPER cohort 1, there were treatment recommendation changes in 8.9% of the total group, with 6 of 123 (6.5%) patients adding chemotherapy and 3 of 123 (2.4%) withdrawing chemotherapy.

The commentary presented additional analysis of change in management of the group meeting the proposed MBS eligibility criteria using the data from the PROSPER data spreadsheet provided with the re-application. There was an overall reduction in the uptake of chemotherapy. In the group of 215 patients, 29 (13.5%) did not undergo adjuvant chemotherapy that was initially recommended, and 15 (7.0%) added chemotherapy to their treatment that was not initially recommended, following EndoPredict®.

The analysis in Table 9 estimates the number of final treatment decisions for the whole that were not likely to be impacted by EPclin. Out of 103 initially high-risk patients recommended for chemotherapy following EPclin, 15 decided against the recommendation. These patient decisions were unlikely to be influenced by EPclin as MDT recommendations did not change following EndoPredict®. Out of the 56 initially low-risk patients recommended for hormone therapy alone following EPclin, four opted for chemotherapy. Similarly, these four patients were unlikely to be influenced by EPclin. The resultant estimates for rates of change in management are 21.5% in the high-risk group, and 18.8% in the low-risk group. This analysis reduces the overall change in management proportion from 29.2% (63/215 patients) to 20.5% (44/215 patients). The net reduction in chemotherapy is estimated to be -6.5%<sup>10</sup>.

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<sup>10</sup> 15 patients upgraded from no CTX to CTX and 29 patients downgraded from CTX to no CTX. There is therefore a net reduction in chemotherapy use in 14 patients (14/215, 6.5%).

**Table 9 Change in management decisions following EndoPredict®**

Study Patients	Initial MDT recommendation	MDT recommendation after EndoPredict	Treatment given	Change in management
PROSPER data spreadsheet MBS eligible group n=215	CTX [n=135]	CTX [n=103] 47.9%	CTX [n=88] 40.9%	No
			No CTX [n=15] 7.0%	Yes, not likely due to EndoPredict®
		No CTX [n=32] 14.9%	CTX [n=3] 1.4%	No
			No CTX [n=29] 13.5%	Yes
	No CTX [n=80]	CTX [n=24] 11.2%	CTX [n=15] 7.0%	Yes
			No CTX [n=9] 4.2%	No
		No CTX [n=56] 26.0%	CTX [n=4] 1.9%	Yes, not likely due to EndoPredict®
			No CTX [n=52] 24.2%	No
Penault-Llorca et al 2020 <sup>a</sup> – intermediate risk population n=200	CTX [n=95]	CTX [n=40] 20.0%	CTX [n=37] 18.5%	No
			No CTX [n=3] 1.5%	Yes, not likely due to EndoPredict®
		No CTX [n=55] 27.5%	CTX [n=1] 0.5%	No
			No CTX [n=54] 27.0%	Yes
	No CTX [n=105]	CTX [n=20] 10%	CTX [n=15] 7.5%	Yes
			No CTX [n=5] 2.5%	No
		No CTX [n=85] 42.5%	CTX [n=0] 0%	No
			No CTX [n=85] 42.5%	No
Ettl et al 2021 – combined low, intermediate and high risk population n=373	CTX [n=NR]	CTX [n=128] 34.3%	CTX [n=92] 24.7%	No
			No CTX [n=36] 9.7%	Yes, unknown impact of EndoPredict®
		No CTX [NA]	NA	NA
			NA	NA
	No CTX [n=NR]	CTX [NA]	NA	NA
			NA	NA
		No CTX [n=245] 65.7%	CTX [n=3] 0.8%	Yes, unknown impact of EndoPredict®
			No CTX [n=242] 64.9%	No

<sup>a</sup> This data was presented in the 1408 application, but in a different format.

CTX = chemotherapy; MDT = multidisciplinary team; NA = not available.

Source: Constructed during the evaluation using the 'Attachment 3\_PROSPER final analysis.xlsx' workbook included in the 1408.1 re-application.

### ***Change in management within Australia compared to other countries***

The applicant provided evidence of the impact of EndoPredict® on the change in management of breast cancer patients from two prospective studies, one performed in Germany, Ettl et al (2020), and one in France, Penault-Llorca et al (2020). Earlier results of these two studies were reported in the 1408 application.

The change in management outcomes for the two European studies are compared with the Australian outcomes in Table 9.



Penault-Llorca et al (2020) provided change in management evidence for patients who met the criteria of grade 2, or grade 3 and pT <2 cm, or lobular histology, based on current guidelines. This patient cohort more closely aligns with the likely intermediate risk population eligible for a GEP test in Australia. The primary outcomes were the change in treatment recommendation following EPclin, and the impact of the treatment decision on patient anxiety and psychological distress.

Increased anxiety levels were associated with the change in treatment at the second decision point. As patients had already received a treatment recommendation, it was not possible to determine whether performing EndoPredict® itself had an impact on decision-related anxiety, or whether it was related to changing their treatment plan. There was notable heterogeneity across recruitment sites in the rate of decision changes ( $\chi^2$  p=0.003). The decision to withdraw chemotherapy varied from 12% to 70%, and to add chemotherapy varied between 0% and 24% at the Multidisciplinary Team Meeting 2 (MTM2) time point. This variation was thought to reflect a variation in the application of intermediate criteria to the patient cohort. It could also reflect the clinician-patient relationship and how the clinician responded to the information provided by EndoPredict®.

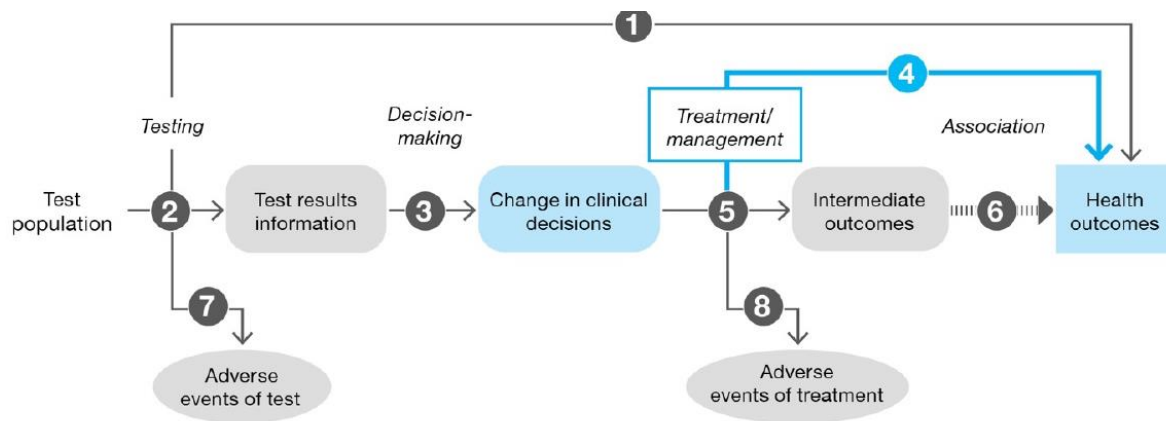
Ettl et al reported outcomes for a group of breast cancer patients whose treatment was directed by their EPclin score. There was no treatment decision recorded before EPclin was performed. Therapy recommendations were made by an MDT primarily based on EPclin risk classification taking comorbidities into account. Patient compliance rates were also measured. The authors reported that the rate of non-compliance of 28.1% (36 of 128 patients recommended for chemotherapy) for the high-risk group is similar to rates reported in other articles, for which estimates reach as high as 50% for not successfully completing adjuvant therapy over 5-year treatment periods. Reasons for non-compliance in the study were not reported.

The proportion of patients recommended for adjuvant chemotherapy and the final treatment decisions for the non-Australian studies are illustrated in Table 9. In the French study, there was an overall reduction in uptake of chemotherapy, after MTM2 recommendations and patient choice were taken into account. Fifty-four out of 200 (27.0%) patients had chemotherapy removed from their treatment, and 15 of 200 (7.5%) patients had chemotherapy added to their treatment as a result of their EPclin result (Penault-Llorca et al, 2020). These proportions compare with 13.5% and 7.0% respectively in the MBS eligible group of the PROSPER study. Patient choice reduced the number of changes following EndoPredict® recommendations. Of the 200 patients, eight (4.0%) opted for no chemotherapy when it was recommended, and one (0.5%) opted to add chemotherapy when it was not recommended following their EPclin result.

In the German study there was a change in management after treatment recommendations, as a result of patient choices. Of those recommended chemotherapy, 36 of 373 (9.7%) patients refused the recommended chemotherapy, and three of 373 (0.8%) patients decided to undergo chemotherapy when it was not recommended following their EPclin result.

## Health outcomes

Evidence showing consequences for health outcomes following treatment decisions that were directed by the test results, was provided in *Step 4 Association* in the assessment framework (Figure 7).



**Figure 7** Linked evidence assessment framework

The health outcomes reported include recurrence and survival rates following treatment directed by EPclin, and psychological impact of EndoPredict®.

### ***Disease free survival following treatment decision using EndoPredict®***

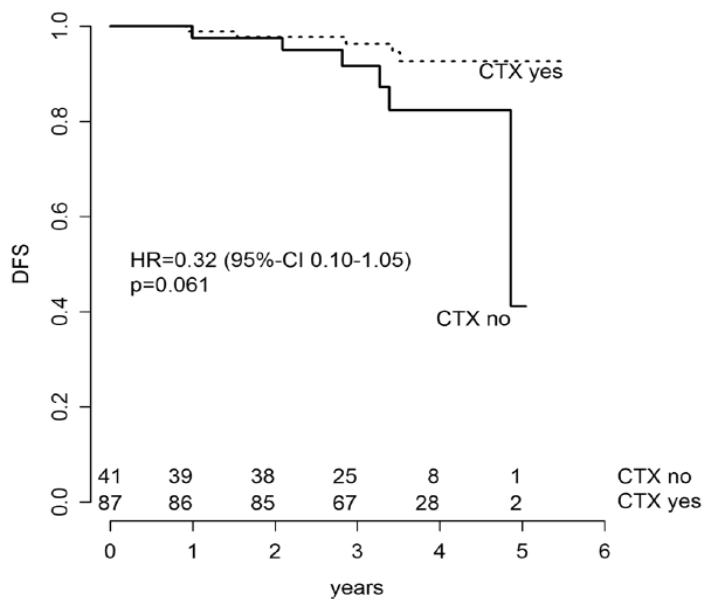
Treatment benefit was reported in Ettl et al (2020) in EPclin risk subgroups at a 3-year follow-up time point. Ettl et al reported outcomes for a case series of breast cancer patients whose treatment was directed by their EPclin score.

In the high-risk group (those with EPclin score over 3.3) the 3-year disease free survival (DFS) and distant metastasis-free survival (DMFS) were 94.9% (95%CI 90.9%, 99.0%) and 97.6% (95%CI 95.0%, 100%) respectively. The hazard ratio (HR) for DR in the high-risk group was significantly higher compared to that in the low-risk group (HR 5.18; 95%CI 1.04, 25.74; p=0.0443) (i.e. the adjuvant chemotherapy used did not completely compensate for the higher baseline risk of DR).

In the low-risk group the DFS and DMFS were 96.6% (95%CI 94.2%, 99.1%) and 99.6% (95%CI 98.7%, 100%) respectively. Authors claimed the data supports the argument that EPclin low-risk patients can safely avoid chemotherapy.

Although all patients received EPclin, a comparison was made in the EPclin high-risk group between those who followed recommendation to undergo chemotherapy, versus those who chose not to undertake the recommended chemotherapy. The authors found that for EPclin high-risk patients who underwent chemotherapy, there was a 68% reduction in relapse, compared to those who decided not to undertake the recommended chemotherapy (HR 0.32; 95%CI 0.10, 1.05; p=0.061). Although this outcome is a positive indicator of the effectiveness of EPclin risk allocation, the result did not reach statistical significance (likely due to the small sample size, as only 36 patients did not receive the recommended adjuvant chemotherapy). The data were only collected for a median follow-up period of 41.9 months (<5 years) so the difference in late DR between high-risk groups cannot yet be determined (Figure 8).

As none of the EPclin low-risk group were given chemotherapy, a comparison of DMFS and DFS between EPclin high- and low-risk groups who were given or withheld from chemotherapy cannot be conducted so a predictive value cannot be shown. The study cohort was not specifically intermediate risk prior to EPclin, the applicability of the results to the Australian early breast cancer population is uncertain. Furthermore, given all patients received EPclin, no comparisons can be made against likely health outcomes resulting from not using EPclin.



**Figure 8** Kaplan-Meier estimates of DFS of EPclin high-risk patients of those who received adjuvant chemotherapy, and for those who were not compliant with recommended chemotherapy

CTX = chemotherapy; DFS = disease free survival; HR = hazard ratio.  
Source: Ettl et al 2020

### **Psychological impact of EndoPredict®**

Penault-Llorca et al (2020) provided change in management evidence for patients who met the criteria of grade 2, or grade 3 and pT <2 cm, or lobular histology, based on current guidelines. This patient cohort more closely aligns with the likely intermediate risk population proposed to be eligible for a GEP test in Australia. One of the primary outcomes was the impact of EndoPredict® on patient anxiety and psychological distress related to treatment decision making.

Patients were given initial treatment recommendations after the first decision time point (MTM 1) after the MDT met. Increased anxiety levels were associated with the change in treatment at the second decision point (MTM 2), which followed the EPclin test. As patients had already been given a treatment recommendation, it was not possible to determine whether performing EndoPredict® itself had an impact on decision-related anxiety, or whether it was related to changing their treatment plan.

### **Treatment benefit predictive value of EndoPredict® in high-risk versus low-risk patients**

Chemotherapy has been reported to reduce the risk of recurrence in breast cancer by approximately one third, but the size of this benefit depends on the absolute risk of recurrence without chemotherapy. Given that the EPclin score can determine which patients are at a low risk of recurrence (and therefore a low absolute benefit of adding chemotherapy), those at low risk should be able to avoid chemotherapy and have non-inferior health outcomes.

During the evaluation of the 1408.1 re-application, particular attention was given to the previously considered article by Sestak et al (2019)<sup>11</sup>, as the article claims to show that EndoPredict® is able to predict the benefit of chemotherapy (i.e. the difference in risk of DR

<sup>11</sup> Sestak I, et al. (2019). Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. *Breast Cancer Res Treat*, **176**(2):377-86.

within 10 years by treatment group). Not only does this study claim that the test predicts the risk of recurrence in patients treated with either endocrine therapy alone or endocrine therapy plus chemotherapy, it also claims that there is also a treatment by EPclin risk group interaction. An EPclin score of 3.3 is used as the threshold between high and low risk of distant recurrence.

The study by Sestak et al (2019) performed a retrospective analysis including five trials, two of which included patients who had been randomised to receive endocrine therapy plus one of two regimens of adjuvant chemotherapy (fluorouracil, epirubicin, and/or cyclophosphamide) (GEICAM 2003-02 and 9906 trials), and three of which included patients who had received endocrine therapy alone (ABCSG-6, ABCSG-8 and TransATAC).

The study reported that women receiving endocrine therapy alone had larger 10-year DR risks with increasing EPclin scores than those who received endocrine and chemotherapy. For example, women given endocrine therapy alone with an EPclin score of 5 had a 10-year risk of DR of 46% compared to 26% for women who were given endocrine and chemotherapy, a relative risk difference of 44%<sup>12</sup>. Based on this risk comparison, women with a EPclin score of 5 should be recommended for chemotherapy. For women with low EPclin scores, ie those at low risk of recurrence (scores 1-3), the differences in 10-year DR were not statistically significant between treatment groups. The relationship between chemotherapy benefit and EPclin as a continuous variable was tested statistically with an interaction test, showing a statistically significant interaction (p=0.022).

Time periods of 0-5 years and 5-10 years were investigated separately. There was a difference in outcomes for women on endocrine therapy alone compared to those on endocrine and chemotherapy. EPclin was more prognostic for late recurrence for those on endocrine therapy alone than for early recurrence (0-5 years: HR 2.76 vs 5-10 years: HR 2.85; p>0.05). In women who received both therapies, EPclin was more prognostic for early than late recurrence (0-5 year: HR 2.49 vs 5-10 years: HR 1.86; p>0.05). These results did not reach statistical significance.

The 10-year risk of recurrence by EPclin score is compared between therapy groups in Table 10.

As previously, these data are retrospective and from an indirect comparison. No new evidence was submitted for the predictive value of EndoPredict®. In particular, no results from prospective randomised trials were provided to support the claim for predictive value.

**Table 10 10-year risk (%; 95%CI), absolute risk differences and relative risk differences in chemotherapy benefit**

EPclin risk class	EPclin score	ET [A]	ET + CTX [B]	Risk difference [A – B] (absolute benefit of CTX)
Low	1	1.0% (0.6, 1.4)	1.1% (0.5, 1.7)	-0.1%
	2	2.8% (2.1, 3.5)	2.5% (1.5, 3.5)	0.3%
	3	7.6% (6.4, 8.8)	5.7% (4.1, 7.2)	1.9%
High	3.3	10.2% (8.9, 11.6)	7.2% (5.4, 8.9)	3.0%
	4	19.8% (17.6, 22.0)	12.4% (10.1, 14.6)	7.4%
	5	46.1% (40.2, 51.4)	25.8% (22.0, 29.5)	20.3%
	6	82.2% (72.1, 88.6)	49.2% (40.5, 56.7)	33.0%

CI = confidence interval; DR = distant recurrence; ET = endocrine therapy; ET + CTX = endocrine therapy plus chemotherapy; EPclin = EndoPredict® + clinical algorithm score.

Source: Modified from Sestak et al (2019)

<sup>12</sup> Relative risk difference = (46-26)/46

### **Comments on Sestak et al 2019**

The previously considered retrospective analysis by Sestak et al (2019) included patients who were postmenopausal and premenopausal, and those who had received either endocrine therapy alone or endocrine plus chemotherapy following 5 years of endocrine treatment, albeit from different trials. Differences in the trials increases uncertainty in between arm comparisons, thereby potentially decreasing the internal validity of the study. Retrospective study design can also introduce selective population bias.

When populations were compared between trial arms, those receiving chemotherapy were more likely to be of younger age, have a later tumour stage and larger number of positive nodes than those receiving endocrine therapy alone. The fact that the population had received five years of endocrine therapy before beginning chemotherapy also differentiates this study population from the indicated population.

As with the incremental prognostic evidence, those given an EPclin score were not previously stratified by clinical and pathological characteristics into low, intermediate and high risk, and therefore the results cannot be directly applied to the Australian intermediate risk population proposed for the new GEP test. For example, there may be reduced applicability of recurrence estimates, by EPclin score to the proposed population (i.e. would a patient with a score of 6 in the proposed Australian population have a 10-year risk of 82.2% with ET alone, or 49.2% with ET + CTX).

### ***Estimated treatment benefit predictive value of EndoPredict® from the linked evidence approach***

Linking the updated change in management data by Dinh et al. (2022) and the previously considered predictive information by Sestak et al. (2019), if 1000 patients at intermediate risk of breast cancer use EndoPredict®:

- 740 patients receive an EPclin score that is consistent with the treatment recommended by a multidisciplinary team (MDT)
- 149 patients have their classification of high risk (from MDT) downgraded to low risk by EPclin. 135 of these patients follow the EPclin suggestion that they may safely avoid chemotherapy, and avoid adverse events associated with chemotherapy. No additional cases of recurrence are likely due to the avoidance of chemotherapy.
- 112 patients have their classification of low risk (from MDT) upgraded to high risk by EPclin. 70 of these patients follow the EPclin suggestion that they would benefit from chemotherapy. Four patients benefit from the addition of chemotherapy by avoiding distant recurrence within 10 years, which they would have had in the absence of chemotherapy.

The evidence for treatment benefit predictive value comes only from retrospective data from an indirect comparison – a prospective randomised trial directly assessing health outcomes is lacking. Considering the issues with the evidence, no strong conclusions could be drawn, noting that MSAC previously considered that “*the retrospective analysis of three cohorts derived from four randomised clinical trials ... could not be relied upon for decision making*” (1408 PSD, July 2021).

### 13. Economic evaluation

The 1408.1 re-application presented an updated cost-utility analysis that compared treatment decisions with EndoPredict® relative to the current standard of care, where treatment decisions are based on MDT. The analysis was updated to:

- incorporate data from the final analysis of the PROSPER study (compared to the interim analyses considered by MSAC in November 2019);
- apply a lower average fee per service that includes EndoPredict® (reduced from \$█ to \$█), reflecting the volume-based fee structure proposed and expected use over the first five years of listing (see below for further detail on how this was estimated); and
- Incorporate other minor updates to costs and ABS life tables.

The commentary noted that, as described in Table 3, a number of economic matters of concern raised during the previous consideration of EndoPredict® were not addressed in the 1408.1 re-application. The commentary considered this was not reasonable.

A summary of the key components of the economic evaluation is presented in Table 11.

**Table 11: Summary of the economic evaluation**

Component	Description
Perspective	Health care system perspective
Comparator	Standard of care (treatment decisions based on MDT)
Type(s) of analysis	Cost-utility analysis
Outcomes	Quality-adjusted life years
Time horizon	Lifetime (50 years). <i>While this was unchanged from the 1408 application, this was longer than the 30-year time horizons applied in other applications for GEP tests presented to MSAC.</i> <sup>a</sup>
Computational method	Hybrid decision tree-Markov model
Generation of the base case	Modelled. The base case ICER presented in the 1408 application formed the basis of the stepped analysis. The second step incorporated model updates to costs (except EndoPredict®), life tables and PROSPER data. Subsequent steps (3–5) varied the cost of EndoPredict®.
Health states	The decision-tree component of the model separates patients by risk of recurrence (high or low) and by lymph node status (positive or negative) – so four groups are modelled: <ul style="list-style-type: none"> <li>• lymph node negative with a low risk of recurrence;</li> <li>• lymph node negative with a high risk of recurrence;</li> <li>• lymph node positive with a low risk of recurrence; and</li> <li>• lymph node positive with a high risk of recurrence.</li> </ul> For each group, outcomes are generated for two different treatment options: ET alone, or ET + CTX using a Markov model. The Markov health states are: No distant recurrence, Distant recurrence, Cancer death, Natural death.
Cycle length	1 year
Transition probabilities <sup>a</sup>	The decision tree probabilities, which separate patients by risk of recurrence and lymph node status, were updated using the final analysis of the PROSPER study. The EndoPredict® EPclin scores reported for each patient in PROSPER were also updated in line with the final analysis. As per the 1408 application, these scores were transformed for each patient into a 10-year risk of recurrence on ET and ET + CTX, based on Sestak et al. (2019) <sup>b</sup> . ESC previously considered that the assumption of a perfect relationship between EPclin score and 10-year risk of recurrence was inappropriate (PSD November 2019, p18). This approach also

Component	Description
	<p><i>incorporates a predictive effect of EndoPredict<sup>®</sup>, where the relative treatment effect of chemotherapy is higher in those classified as high risk (45% decrease in risk of recurrence) than those classed as low risk (26% decrease in risk of recurrence). This may not be reasonable as MSAC recently confirmed that it did not accept that predictive value had been adequately demonstrated (PSD July 2021, p1).</i></p> <p>The assumption that treatment decisions following EndoPredict<sup>®</sup> aligned with the EPclin risk classification was maintained (i.e. all patients with a high risk classification were assumed to receive ET + CTX, while all patients with a low risk classification were assumed to receive ET alone). <i>ESC previously considered that this may not be supported by the evidence (PSD November 2019, p18).</i></p> <p>Background mortality was based on ABS life tables (2018–2020).</p>
Extrapolation	The transition probabilities derived from the 10-year risks of recurrence were assumed to continue beyond 10 years to the model time horizon (50 years). <i>This approach was unchanged from the 1408 application and is not reasonable, as ESC had previously considered that the extrapolation of the 10-year rate to 50 years was inappropriate (PSD November 2019, p18).</i>
Health-related quality of life	Health state utilities were applied for the 'No distant recurrence' (0.989) and 'Distant recurrence' (0.796) health states, based on Verry et al. (2012) <sup>c</sup> . <i>These were unchanged from the 1408 application. ESC had previously considered that the values used may not be reflective of the health states and were unrealistically high (PSD November 2019, p18). This was not addressed.</i> Utility decrements were applied for adverse events related to adjuvant chemotherapy (0.124) (Lidgren et al. 2007) <sup>d</sup> , and for the development of local recurrence (0.078) (Verry et al. 2012) <sup>c</sup> .
Discount rate	5% for both costs and outcomes
Software	TreeAge Pro

Note: Shaded cells depict components that are unchanged from the 1408 application.

<sup>a</sup> MSAC Application 1376.1, March 2018 MSAC Meeting PSD; MSAC Application 1473, November 2017 MSAC Meeting PSD; and MSAC Application 1342, November 2013 MSAC Meeting PSD.

<sup>b</sup> Sestak I, Martin M, Dubsky P, Kronenwett R, Rojo F, Cuzick J, et al. Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. *Breast Cancer Res Treat.* 2019 Jul;176(2):377-86.

<sup>c</sup> Verry H, Lord SJ, Martin A, Gill G, Lee CK, Howard K, et al. Effectiveness and cost-effectiveness of sentinel lymph node biopsy compared with axillary node dissection in patients with early-stage breast cancer: a decision model analysis. *Br J Cancer.* 2012 Mar 13;106(6):1045-52.

<sup>d</sup> Lidgren M, Wilking N, Jonsson B, Rehnberg C. Health related quality of life in different states of breast cancer. *Qual Life Res.* 2007 Aug;16(6):1073-81.

ET = endocrine therapy; ET + CTX = endocrine and chemotherapy; GEP = gene expression profile; ICER = incremental cost-effectiveness ratio; MDT = multidisciplinary team.

Source: Constructed during the evaluation.

The fee per service that included EndoPredict<sup>®</sup> applied in the base case analysis was \$ [REDACTED]. The applicant proposed a volume-based fee structure, where the total number of services claimed in the previous year determines the fee (see Table 4 for further detail). In the first year of listing, the fee is based on expected use in that year. The fee applied in the economic analysis reflects the average charged over the first five years of MBS listing, assuming that the fee charged in Years 1–3 is \$ [REDACTED] (based on 3,112–4,665 services in the first two years of listing) and \$ [REDACTED] in Years 4 and 5 (based on ≥4,666 services in the third and subsequent years) (Table 12). The commentary noted there is substantial uncertainty in the use of EndoPredict<sup>®</sup> estimated, and so use in the first year of listing may be substantially higher (and exceeding 4,666 services). If use is at this level, the cost in Years 2 and 3 would reduce to reflect the increase in use, and the average charged over the five-year period would decrease to \$ [REDACTED].

**Table 12: Derivation of EndoPredict® fee applied in the economic analysis**

	2023	2024	2025	2026	2027	2023–2027
Expected use	3,276	3,950	4,666	4,823	4,984	21,699
MBS fee <sup>a</sup>						
Total cost						

<sup>a</sup> MBS fee is set based on use in the previous year. In the first year of listing, the fee is set based on expected use within that year.

<sup>b</sup> Total cost divided by the total number of services over 2023–2027.

Source: Constructed during the evaluation using the 'Attachment 6\_EndoPredict\_budget impact.xlsx' workbook included in the 1408.1 re-application.

The commentary considered that costs for treating local and distant recurrences remained based on the Verry et al. (2012) study (updated for inflation). This approach assumes that treatment practices have not changed since publication and reflect current practice. Resource use and unit costs have likely changed over this period, and unit cost changes may not be consistent with changes based on the consumer price index.

The results of the stepped economic analysis are presented in Table 13. The commentary noted the changes that had the most effect on the incremental cost-effectiveness ratio (ICER) were the updated PROSPER data and the reduced fee. The base case analysis was corrected during the evaluation to account for a transcription error in the life table data applied.

**Table 13: Updated incremental costs and effectiveness**

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
<i>Interim analysis of PROSPER (June 2019) (EndoPredict® fee: \$ [REDACTED])</i>					
EndoPredict®			13.878	0.067	
SOC (MDT)	\$23,803.36		13.811		
<i>Final analysis of PROSPER <sup>a</sup></i>					
EndoPredict®			13.935	0.079	
SOC (MDT)	\$23,473.62		13.856		
<i>Inclusion of other model updates (corrected)<sup>b</sup></i>					
EndoPredict®			14.044	0.080	
SOC (MDT)	\$24,182.05		13.964		
<i>Updated model with proposed Year 1 fee (\$ [REDACTED]) (corrected)<sup>b</sup></i>					
EndoPredict®			14.044	0.080	
SOC (MDT)	\$24,182.05		13.964		
<i>Updated model with estimated Year 4 fee onwards (\$ [REDACTED]) (corrected)<sup>b</sup></i>					
EndoPredict®			14.044	0.080	
SOC (MDT)	\$24,182.05		13.964		
<i>Updated model with estimated average fee per service (\$ [REDACTED]) [base case analysis] (corrected)<sup>b</sup></i>					
EndoPredict®			14.044	0.08	
SOC (MDT)	\$24,182.05		13.964		

Note: Text in *italics* reflect modifications made during the evaluation. See specific notes for these additions.

<sup>a</sup> This step was added during the evaluation to allow the effect on the ICER due the updated PROSPER data to be distinguished from the other model updates.

<sup>b</sup> The analysis was corrected during the evaluation to account for an error in the updated life table data where the age of 2 was not included in the index column (and so all subsequent rows were in error).

ICER = incremental cost-effectiveness ratio; MDT = multidisciplinary team; QALY = quality-adjusted life year; SOC = standard of care.

Source: Adapted during the evaluation from Table 7, p24 of the 1408.1 re-application.

The key drivers of the commentary's corrected analysis are presented in Table 14.



**Table 14: Key drivers of the model**

Description	Method/Value	Impact Base case (corrected): \$ [redacted] /QALY gained
Predictive effect for chemotherapy by EPclin score	The modelled ET and ET + CTX risks of recurrence incorporate a predictive effect for chemotherapy benefit by EPclin score (the relative benefit of chemotherapy modelled increases from a 20% reduction in the risk of recurrence with EPclin scores of 2.5, to a 50% reduction with scores >4). <i>MSAC recently confirmed that it did not accept predictive value had been adequately demonstrated for any GEP test (PSD July 2021, p1).</i>	<i>High, favours EndoPredict® Assuming no predictive effect increases the ICER to \$ [redacted] /QALY gained.</i>
Extrapolation of 10-year recurrence rate	The annual transition probabilities derived from the 10-year recurrence rates were assumed to continue beyond 10 years to the model time horizon (50 years). <i>ESC previously considered that this approach was not appropriate (PSD November 2019, p19). Extrapolation of the distant recurrence estimate to 10 years only was used in a previous GEP application to MSAC (MSAC Application 1342.2, November 2015 MSAC Meeting PSD).</i>	<i>High, favours EndoPredict® Assuming extrapolation of recurrence rates to 10 years only increases the ICER to \$ [redacted] /QALY gained.</i>
Transition probabilities derived from the EPclin score	The risks of recurrence on ET and ET + CTX treatment were derived from the EPclin scores. <i>ESC previously considered that this approach assumed a perfect relationship between EPclin score and 10-year rate of recurrence and that this was not considered to be appropriate as no loss of information was assumed during the transformation process (PSD November 2019, p18). Estimates of distant recurrence by EPclin score were based on Sestak et al. (2019). Differences were noted between the modelled and published estimates. Sensitivity analyses were conducted during the evaluation using the central estimates and 95% CI reported in this study.</i>	<i>The analysis is sensitive to changes in this estimate, however it is uncertain to what extent the loss of information would have in the transformation process. ICERs ranged between \$ [redacted] and \$ [redacted] /QALY gained.</i>
Change in management	With EndoPredict®, it was assumed that all patients would be treated as per the EPclin risk classification (i.e. low-risk patients would receive ET alone, while high-risk patients would receive ET + CTX). <i>MDT recommendations (and final patient treatment decisions) in PROSPER were not always concordant with EPclin risk assessment. This approach may overestimate the benefit associated with EndoPredict®.</i>	<i>Moderate, favours EndoPredict® The ICER increased to \$ [redacted] /QALY gained where final patient treatment decisions were considered.</i>
Time horizon	The nominated time horizon (50 years) was unchanged from the 1408 application. <i>This was longer than the 30-year time horizons applied in other applications for GEP tests presented to MSAC (MSAC Application 1376.1, March 2018 MSAC Meeting PSD; MSAC Application 1473, November 2017 MSAC Meeting PSD; MSAC Application 1342, November 2013 MSAC Meeting PSD). While ESC considered that the 50-year time horizon may not be inappropriate, it was noted that longer time horizons appear to favour the intervention.</i>	<i>Moderate, favours EndoPredict® The ICER increased to \$ [redacted] /QALY gained when a 30-year time horizon was assumed.</i>
Utility values	The health state utility values used were unchanged from the 1408 application. <i>This was not reasonable given that ESC had considered that these may not accurately reflect the intended health states and were unrealistically high, favouring EndoPredict® (PSD November 2019, p18).</i>	<i>Moderate, favours EndoPredict® The ICER increased to \$ [redacted] when alternate utility values were used.</i>

ET = endocrine therapy; ET + CTX = endocrine and chemotherapy; GEP = gene expression profile; ICER = incremental cost-effectiveness ratio; MDT = multidisciplinary; QALY = quality-adjusted life year.

Source: Constructed during the evaluation. Text in *italics* reflect comments generated during the evaluation.

In addition to these drivers, the commentary considered that concerns remain in the underlying clinical evidence base:

- Sestak et al. (2019), which was used to inform the 10-year recurrence rates for ET alone and ET + CTX, was a retrospective analysis of the GEICAM, ABCSG and TransATAC studies. Patients included also did not necessarily reflect the proposed intermediate population based on clinical and pathological characteristics. It is unclear what effect these differences would have on the recurrence estimates applied in the model by EPclin score.
- The predictive effect for the benefit of chemotherapy by EPclin score modelled was also based on Sestak et al. (2019). Patients in the studies where chemotherapy was used were more likely to be younger, have a later tumour stage and larger number of positive nodes than those receiving endocrine therapy alone. It is unclear what effect this would have on the comparisons presented.
- While the change in management data used in the economic analysis was based on the MBS-eligible subgroup of PROSPER, previous applicability concerns were raised regarding management practices and decisions in this study. As PROSPER was conducted in a limited number of Australian sites that have a reputation for cancer care, the decisions made may not reflect MDT decisions more broadly.

These issues are likely to affect the accuracy of the results generated from the economic analysis.

As previously noted, the base case analysis did not include changes that addressed concerns previously identified by MSAC and ESC. Some of these were addressed in sensitivity analyses presented in the 1408.1 re-application, though a number remained outstanding. Additional analyses were conducted during the evaluation to address the remaining matters of concern, where able, around the base case analysis (with corrections) (Table 15).

**Table 15: Sensitivity analyses exploring matters of concern previously raised by MSAC**

	Inc. cost	Inc. QALYs	ICER	%
<b>1408.1 re-application base case (corrected)</b>	\$	0.080	\$	
Change in management (base case: all low-risk ET only, all high-risk ET + CTX)				
1. Include MDT decisions that deviate from EP	\$	0.060	\$	25%
2. Including information about what patients receive <sup>a</sup>	\$	0.032	\$	32%
<i>Transition probabilities derived from the EPclin score</i>				
3. DR risk by EPclin score, Sestak et al. (2019) <sup>b</sup> central estimates	\$	0.077	\$	8%
4. DR risk by EPclin score, Sestak et al. (2019) <sup>b</sup> ET alone upper 95% CI and ET + CTX lower 95% CI	\$	0.088	\$	-21%
5. DR risk by EPclin score, Sestak et al. (2019) <sup>b</sup> ET alone lower 95% CI and ET + CTX upper 95% CI	\$	0.052	\$	137%
Predictive effect of EPclin score (base case: relative effect of chemotherapy improves with EPclin score)				
6. Assume constant relative risk reduction from adjuvant chemotherapy used in the NICE model of 0.76 (i.e. no predictive effect)	\$	0.039	\$	267%
<i>Extrapolation of 10-year risk DR rate (base case: extrapolation to 50-year time horizon)</i>				
7. Extrapolation to 10 years only (as used in MSAC Application 1342.2, November 2015 MSAC Meeting PSD)	\$	0.055	\$	148%
8. Extrapolation to 15 years only	\$	0.067	\$	69%
9. Extrapolation to 10 years with a 50% reduction in risk applied between years 10–15 (Ward et al. 2013) <sup>c</sup>	\$	0.061	\$	104%
Health state utility values (base case: No DR 0.989; DR 0.786)				
10. Lidgren et al. (2007) <sup>d</sup> utilities (No DR 0.824; DR 0.685)	\$	0.067	\$	20%
<i>Time horizon (base case: 50 years)</i>				
11. 30 years	\$	0.068	\$	26%

Note: Analyses in *italics* text were conducted during the evaluation.

<sup>a</sup> In patients where the change in management was not likely due to EndoPredict® (as initial and final MDT recommendations did not change with EndoPredict®), it was assumed that the change would have occurred equally across the model arms.

<sup>b</sup> Sestak I, Martin M, Dubsy P, Kronenwett R, Rojo F, Cuzick J, et al. Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. *Breast Cancer Res Treat.* 2019 Jul;176(2):377-86.

<sup>c</sup> Ward S, Scope A, Rafia R, Pandor A, Harnan S, Evans P, et al. Gene expression profiling and expanded immunohistochemistry tests to guide the use of adjuvant chemotherapy in breast cancer management: a systematic review and cost-effectiveness analysis. *Health Technol Assess.* 2013 Oct;17(44):1-302.

<sup>d</sup> Lidgren M, Wilking N, Jonsson B, Rehnberg C. Health related quality of life in different states of breast cancer. *Qual Life Res.* 2007 Aug;16(6):1073-81.

DR = distant recurrence; ET = endocrine therapy; ET + CTX = endocrine and chemotherapy; ICER = incremental cost-effectiveness ratio; MDT = multidisciplinary team; QALY = quality adjusted life year.

Source: Constructed during the evaluation using the 'Attachment 4\_MSAC EndoPredict Economic model.trex' file included in the 1408.1 re-application.

Given the concerns previously raised by MSAC and ESC, and that the changes made did not address these matters of concern, the base case analysis was respecified during the evaluation.

The changes made in the respecified base case included:

- That change in management data from PROSPER, based on treatments patients actually received (with some adjustment where changes in management were not likely due to EndoPredict®) (Analysis #2)
- Using the central estimates of recurrence with ET alone and ET + CTX from Sestak et al. (2019) (Analysis #3)
- Extrapolation of distant recurrence estimates to 10 years only, as per a previous application to MSAC (MSAC Application 1342.2 PSD, November 2015 MSAC Meeting) (Analysis #7)
- Health state utilities from Lidgren et al. (2007)<sup>13</sup> (Analysis #10)

<sup>13</sup> Lidgren M, et al. (2007). Health related quality of life in different states of breast cancer. *Qual Life Res*, 16(6):1073-81.

- Time horizon of 30 years (Analysis #11)
- Assuming no predictive effect for chemotherapy benefit by EPclin score (Analysis #6).

The generation of the respecified base case is presented in a stepped manner to observe the effect of making each additional change on the ICER (Table 16). The main contributors to the final respecified ICER were the extrapolation of distant recurrences to 10 years only, and removing the assumption of a predictive effect for chemotherapy by EPclin score. Disaggregated costs and outcomes are presented for the respecified base case in Table 17.

**Table 16: Generation of the respecified base case analysis**

	Inc. cost	Inc. QALYs	ICER
1408.1 re-application base case (corrected)	\$█	0.080	\$█
<b>Step 1:</b> Change in management from PROSPER (with some adjustment where changes in management were not likely due to EndoPredict®) (Analysis #2) and Using central risk recurrence estimates reported in Sestak et al. (2019) <sup>a</sup> (Analysis #3)	\$█	0.034	\$█
<b>Step 2:</b> Step 1 + Extrapolation of distant recurrence estimates to 10 years only (Analysis #7)	\$█	0.021	\$█
<b>Step 3:</b> Step 2 + Utilities from Lidgren et al. (2007) <sup>b</sup> (Analysis #10)	\$█	0.018	\$█
<b>Step 4:</b> Step 3 + Time horizon of 30 years (Analysis #11)	\$█	0.018	\$█
<b>Step 5:</b> Step 4 + No predictive effect for chemotherapy benefit by EPclin score (Analysis #6). <b>This is the respecified base case.</b>	\$█	<b>0.010</b>	\$█

<sup>a</sup> Sestak I, Martin M, Dubsky P, Kronenwett R, Rojo F, Cuzick J, et al. Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. *Breast Cancer Res Treat.* 2019 Jul;176(2):377-86.

<sup>b</sup> Lidgren M, Wilking N, Jonsson B, Rehnberg C. Health related quality of life in different states of breast cancer. *Qual Life Res.* 2007 Aug;16(6):1073-81.

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

Source: Constructed during the evaluation using the 'Attachment 4\_MSAC EndoPredict Economic model.trex' file included in the 1408.1 re-application.

**Table 17: Disaggregated cost and outcomes, respecified base case analysis**

	EndoPredict®	MDT	Increment
<b>Disaggregated costs</b>			
EndoPredict®	\$█	\$0.00	
ET	\$751.41	\$751.49	-\$0.08
Adjuvant chemotherapy	\$8,270.55	\$9,319.38	-\$1,048.83
Costs related to local recurrence	\$105.64	\$105.86	-\$0.22
Costs related to distant recurrences	\$9,484.82	\$9,504.38	-\$19.56
<b>Total cost</b>	<b>\$█</b>	<b>\$19,681.11</b>	<b>\$█</b>
<b>Disaggregated outcomes</b>			
No distant recurrence LYs	13.504	13.501	0.002
Distant recurrence LYs	0.323	0.324	-0.001
<b>Total LYs</b>	<b>13.827</b>	<b>13.825</b>	<b>0.002</b>
No distant recurrence QALYs	11.127	11.125	0.002
Distant recurrence QALYs	0.220	0.221	-0.000
Adjuvant chemotherapy QALYs	-0.063	-0.072	0.008
<b>Total QALYs</b>	<b>11.284</b>	<b>11.274</b>	<b>0.010</b>

LY = life year; MDT = multidisciplinary team; QALY = quality adjusted life year.

Source: Constructed during the evaluation using the 'Attachment 4\_MSAC EndoPredict Economic model.trex' file included in the 1408.1 re-application.

Sensitivity analyses were presented around the respecified base case analysis (Table 18) and was found to be most sensitive to EndoPredict® test cost (ranging from Dominant [i.e. less costly, more effective] to \$█ per additional quality-adjusted life year [QALY] gained, assuming a fee of \$█ and \$█, respectively). The analyses were also sensitive to the basis for the change in

management modelled, risk of distant recurrence with ET alone and assumptions regarding the extrapolation of distant recurrence estimates beyond 10 years.

**Table 18: Key sensitivity analyses, respecified base case**

	Inc. cost	Inc. QALYs	ICER	%
<b>Respecified base case</b>	\$	0.010	\$	
Change in management				
Based on MDT recommendations	\$	0.010	\$	75%
Transition probabilities derived from the EPclin score				
DR risk by EPclin score, Sestak et al. (2019) <sup>a</sup> ET upper 95% CI	\$	0.010	\$	-4%
DR risk by EPclin score, Sestak et al. (2019) <sup>a</sup> ET lower 95% CI	\$	0.007	\$	42%
Extrapolation of 10-year risk DR rate				
Direct extrapolation to 15 years	\$	0.013	\$	-35%
Direct extrapolation to 10 years, 50% reduction in risk applied between years 10–15 (as per Ward et al. 2013) <sup>b</sup>	\$	0.011	\$	-19%
EndoPredict <sup>®</sup> cost				
\$	\$	0.010	\$	315%
\$	\$	0.010	\$	186%
\$	\$	0.010	\$	58%
\$	\$	0.010	\$	-70%
\$	\$	0.010	\$	-116%

<sup>a</sup> Sestak I, Martin M, Dubsy P, Kronenwett R, Rojo F, Cuzick J, et al. Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. *Breast Cancer Res Treat.* 2019 Jul;176(2):377-86.

<sup>b</sup> Ward S, Scope A, Rafia R, Pandor A, Harman S, Evans P, et al. Gene expression profiling and expanded immunohistochemistry tests to guide the use of adjuvant chemotherapy in breast cancer management: a systematic review and cost-effectiveness analysis. *Health Technol Assess.* 2013 Oct;17(44):1-302.

DR = distant recurrence; ET = endocrine therapy; ICER = incremental cost-effectiveness ratio; MDT = multidisciplinary team; QALY = quality adjusted life year.

Source: Constructed during the evaluation using the 'Attachment 4\_MSAC EndoPredict Economic model.trex' file included in the 1408.1 re-application.

The commentary considered that despite changes made during the evaluation to address some of the concerns previously raised by MSAC, uncertainty remains in the underlying clinical evidence base. In addition to the lack of a prospective randomised trial directly assessing health outcomes, applicability issues remain between the studies included in the linked evidence and between these studies and the proposed Australian population, which would likely affect the accuracy of the results generated.

## 14. Financial/budgetary impacts

The 1408.1 re-application presented an updated financial analysis to reflect the proposed fee structure and updated PROSPER data. AIHW incidence data and MBS and PBS cost information were also updated. The commentary noted MSAC previously considered that the estimate of the eligible patient population presented was inadequately supported, as no justification was provided for many of the input variables. The changes made do not address these areas of concern.

The financial implications to the MBS resulting from the proposed listing of EndoPredict<sup>®</sup> are summarised in Table 19.

**Table 19: Net financial implications of EndoPredict® to the MBS**

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated use and cost of EndoPredict®</b>					
Incident breast cancer cases (3.36% growth)	21,222	21,934	22,670	23,431	24,217
No. with localised cancer (80%)	16,977	17,547	18,136	18,745	19,374
No. that are ER+ (67%)	11,375	11,757	12,151	12,559	12,980
No. that are HER2- (80%)	9,100	9,405	9,721	10,047	10,384
No. suitable for adjuvant therapy (75%)	6,825	7,054	7,291	7,535	7,788
Pre-test intermediate risk of recurrence (80%) (i.e. the population eligible for EndoPredict®)	5,460	5,643	5,833	6,028	6,231
Uptake rate	60%	70%	80%	80%	80%
Number of people who receive EndoPredict®	3,276	3,950	4,666	4,823	4,984
Cost per EndoPredict® service	\$█	\$█	\$█	\$█	\$█
<i>Cost per EndoPredict® service</i>	<i>\$1,200</i>	<i>\$1,200</i>	<i>\$1,200</i>	<i>\$1,200</i>	<i>\$1,200</i>
Cost to the MBS (exc. copayments) <sup>a</sup>	\$█	\$█	\$█	\$█	\$█
<i>Cost to the MBS (exc. copayments) <sup>b</sup></i>	<i>\$3,643,240</i>	<i>\$4,392,795</i>	<i>\$5,189,059</i>	<i>\$5,363,658</i>	<i>\$5,542,706</i>
<b>Change in use and cost of other health technologies *</b>					
Number of people who receive chemotherapy - before EndoPredict® (58.4%) <sup>c</sup>	1,912	2,306	2,724	2,815	2,909
Number of people who receive chemotherapy - after EndoPredict® (54.9%) <sup>c</sup>	1,800	2,170	2,563	2,649	2,738
Net change in people that use chemotherapy	-112	-136	-160	-166	-171
Change in initial specialist consultations (MBS item 104, \$90.35), 1 per patient	-112	-136	-160	-166	-171
Change in subsequent specialist consultations (MBS item 105, \$45.40), 1 per patient	-112	-136	-160	-166	-171
Change in chemotherapy administration (MBS item 13950, \$112.40), 8.7 per patient <sup>d</sup>	-976	-1,177	-1,391	-1,437	-1,485
Net change in costs to the MBS (exc. copayments) <sup>a</sup>	\$█	\$█	\$█	\$█	\$█
<b>Net financial impact to the MBS</b>	<b>\$█</b>	<b>\$█</b>	<b>\$█</b>	<b>\$█</b>	<b>\$█</b>
<b><i>Net financial impact to the MBS *</i></b>	<b><i>\$3,549,480</i></b>	<b><i>\$4,279,738</i></b>	<b><i>\$5,055,515</i></b>	<b><i>\$5,225,633</i></b>	<b><i>\$5,400,049</i></b>

Italics indicate MSAC's revisions to financial analyses to take into account a flat fee of \$1,200, and that the test would typically be provided on an outpatient basis.

\* = Note that MSAC did not accept the evidence had sufficiently demonstrated predictive value, therefore it did not agree that there would be changes in chemotherapy and a resulting reduction in costs to the PBS.

<sup>a</sup> 75% benefit

<sup>b</sup> 85% benefit – note that 85% benefit reflects the 1 November 2021 Greatest Permissible Gap (GPG) of \$87.90. All out-of-hospital Medicare services that have an MBS fee of \$586.20 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).

<sup>c</sup> Based on the final analysis of PROSPER (all patients)

<sup>d</sup> Four services of chemotherapy MBS administration items in all patients, plus a further 12 in 39% of patients.

ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2.

Source: MSAC's revisions to table constructed during the evaluation using the 'Attachment 6\_EndoPredict\_budget impact.xlsx' workbook included in the 1408.1 re-application.

The net financial impact to the MBS remains uncertain, given the lack of justification in a number of the estimates used to determine the size of the eligible population and extent of use:

- The growth rate for breast cancer incidence (3.36%) was updated to reflect the average reported by the AIHW over 2008–2017. The commentary considered this did not take into account estimates projected by the AIHW up to 2021. When these data are considered, the 10-year average decreases to 3.15%.
- The proportion of incident cases that are localised was unchanged from the 1408 application and assumed to be 80%. The commentary considered this remains inadequately justified. Australian<sup>14</sup> and US data (Nelson et al. 2022)<sup>15</sup> reported that approximately 95% of patients are diagnosed with early stage disease.
- The proportion of cancers that were ER+ and HER2– was unchanged from the 1408 application and assumed to be 67% and 80%, respectively. The commentary considered the basis for these were not clear, however were noted to be lower than recently reported in a cohort of Australian women with early breast cancer (85.3% and 87.3%, respectively) (Chan et al. 2021)<sup>16</sup>.
- The proportion of patients suitable for adjuvant chemotherapy was unchanged from the 1408 application and assumed to be 75%. The commentary considered this remains inadequately justified. Suitability to chemotherapy may be weighed against the possible gains from treatment, and so patients who are less able to tolerate chemotherapy may still be offered it if predicted to substantially benefit.
- The proportion of patients with an intermediate risk of recurrence prior to EndoPredict® was unchanged from the 1408 application and assumed to be 80%. The commentary considered that this appears consistent with intermediate risk patients in the ABCSG6&8 cohort (1,371/1,702, 80.6%)<sup>17</sup>. However, high-risk patients may have been underrepresented in this cohort (and intermediate risk patients overrepresented) as the studies did not allow use of adjuvant chemotherapy, nor enrolled pre-menopausal patients.
- Uptake of EndoPredict® was unchanged from the 1408 application and was assumed to increase from 60% in the first year to 80% by the third year of listing. The commentary noted no justification was provided to support these estimates.

The alternate estimates identified during the evaluation suggest that the size of the eligible population may be an underestimate, though substantial uncertainty remains regarding the proportion of patients considered suitable for chemotherapy and the proportion who meet the definition of intermediate risk of recurrence as specified in the proposed MBS item descriptor.

Additional uncertainty was previously raised regarding whether EndoPredict® would be requested in the outpatient or inpatient setting. This was not addressed in the 1408.1 re-application, which maintained the previous assumption that all services would incur the 75% benefit. The MBS benefit applied is a driver of the net impact to the MBS, given that in the outpatient setting, the 85% rebate increases above 85% due to the greatest permissible gap rule.

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<sup>14</sup> Australian Institute of Health and Welfare [AIHW]. Cancer Data in Australia. Canberra: AIHW; 2021 [cited 2022]; Available from: <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/>.

<sup>15</sup> Nelson DR, et al. (2022). Breast cancer-specific mortality in early breast cancer as defined by high-risk clinical and pathologic characteristics. *PLoS One*, **17**(2):e0264637.

<sup>16</sup> Chan A, et al. (2021). BreastSurgANZ members recommendations for adjuvant systemic treatment and patient compliance in Australian breast cancer patients. *ANZ J Surg*, **91**(11):2418-24.

<sup>17</sup> Dubsy P, et al. (2013a). EndoPredict improves the prognostic classification derived from common clinical guidelines in ER-positive, HER2-negative early breast cancer. *Ann Oncol*, **24**(3):640-7. PMID: 23035151.

As per the 1408 application, cost offsets to the MBS were assumed due to a reduction in adjuvant chemotherapy use with EndoPredict®. The commentary noted this was based on the difference in adjuvant chemotherapy recommendations made by the MDT before and after EndoPredict® in all patients enrolled in the final analysis of PROSPER. These data therefore do not reflect what patients would actually have received with and without EndoPredict®, nor reflect treatment changes in the subgroup eligible under the proposed MBS item descriptor.

As per the 1408 application, cost offsets to the PBS were also estimated (Table 20). These included cost offsets due to a reduction in chemotherapy medicines used, consistent with the related MBS cost offsets and so subject to the same uncertainties. In addition, a reduction in ancillary medicines for the treatment of adverse events was included at a cost of \$12,583 per patient. This was derived from Verry et al. (2012)<sup>18</sup> which reported an adjuvant treatment course cost of \$16,160.43 which included consultations, chemotherapy medicines, administration costs and the cost of treating adverse events. Per patient costs of consultations (\$135.75)<sup>19</sup>, chemotherapy medicines (\$2,465.96)<sup>20</sup> and chemotherapy administration (\$975.63)<sup>21</sup> were subtracted from the course cost and the remainder assumed to represent the cost of ancillary medicines due to adverse events. The commentary considered these costs were the main driver of cost offsets to the PBS and are highly uncertain, given that the age of costs reported in Verry et al. (2012).

**Table 20: Net financial implications of EndoPredict® to the PBS and Australian government health budgets**

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5
Change in people that use chemotherapy*	-112	-136	-160	-166	-171
Change in cost of AC (\$379.18 per script) <sup>a</sup>	-\$170,599	-\$205,711	-\$242,988	-\$251,142	-\$259,570
Change in cost of paclitaxel (\$202.83 per script) <sup>b</sup>	-\$106,770	-\$128,745	-\$152,075	-\$157,178	-\$162,453
Change in cost of ancillary medicines (\$12,583.08 per patient that uses chemotherapy) <sup>c</sup>	-\$1,415,332	-\$1,706,632	-\$2,015,889	-\$2,083,538	-\$2,153,457
<b>Net cost to the PBS</b>	<b>-\$1,692,701</b>	<b>-\$2,041,089</b>	<b>-\$2,410,952</b>	<b>-\$2,491,859</b>	<b>-\$2,575,480</b>
Net cost to the MBS	\$	\$	\$	\$	\$
<i>Net cost to the MBS</i>	<i>\$3,549,480</i>	<i>\$4,279,738</i>	<i>\$5,055,515</i>	<i>\$5,225,633</i>	<i>\$5,400,049</i>
Net cost to government health budgets	\$	\$	\$	\$	\$
<i>Net cost to government health budgets*</i>	<i>\$1,856,779</i>	<i>\$2,238,649</i>	<i>\$2,644,563</i>	<i>\$2,733,774</i>	<i>\$2,824,569</i>

Italics indicate MSAC's revisions to financial analyses to take into account a flat fee of \$1,200, and that the test would typically be provided on an outpatient basis.

\* = Note that MSAC did not accept the evidence had sufficiently demonstrated predictive value, therefore it did not agree that there would be changes in chemotherapy and a resulting reduction in costs to the PBS.

<sup>a</sup> 4 scripts per patient in 100% of patients that use chemotherapy. The cost per script of AC was based on the dispensed price for the maximum amount of doxorubicin in a private hospital (\$179.18) and the dispensed price for the maximum amount of cyclophosphamide in a private hospital (\$200.00).

<sup>b</sup> 12 scripts per patient in 39% of patients that use chemotherapy.

<sup>c</sup> Total adjuvant chemotherapy treatment course cost of \$16,160.43 (reported in Verry et al. 2012), minus consultation, chemotherapy medicines and chemotherapy administration costs over the treatment course.

AC = doxorubicin and cyclophosphamide.

Source: Constructed during the evaluation using the 'Attachment 6\_EndoPredict\_budget impact.xlsx' workbook included in the 1408.1 re-application.

<sup>18</sup> Verry H, et al. (2012). Effectiveness and cost-effectiveness of sentinel lymph node biopsy compared with axillary node dissection in patients with early-stage breast cancer: a decision model analysis. *Br J Cancer*, **106**(6):1045-52.

<sup>19</sup> One initial specialist consultation (\$90.35) and one subsequent specialist consultation (\$45.40)

<sup>20</sup> Four cycles each of docetaxel (\$179.18 per cycle) and cyclophosphamide (\$200.00 per cycle) in all patients, plus 12 cycles of paclitaxel (\$202.83 per cycle) in 39% of patients

<sup>21</sup> Four services of chemotherapy MBS administration items in all patients, plus a further 12 in 39% of patients (\$112.40 per service)



## 15. Other relevant information

### *The value of knowing a prognostic test result*

According to the MSAC Guidelines, one of the non-health outcomes of an investigative test is the value of knowing the result. The benefits and harms of receiving the test information versus what would happen in the absence of the test should be discussed in this instance.

Information gained by patients from using EndoPredict® is a high or low risk categorisation. Even in the absence of a known predictive health benefit, knowledge of risk may benefit some patients, enabling them to plan ahead, avoid treatment delays, or consider the alternative of avoiding chemotherapy. On the other hand, the knowledge of risk status may have a negative psychological impact on some patients, increasing their anxiety level, or making decisions more difficult.

No specific evidence was presented by the applicant for the value of knowing.

## 16. Key issues from ESC to MSAC

### **Clinical issues:**

There is some evidence for incremental prognostic value, but no new convincing evidence for predictive value (in terms of effect modification). It may be reasonable to estimate potential absolute benefit of treatment (e.g. chemotherapy) for a patient by multiplying their baseline absolute risk by relative risk reduction from treatment (assuming no effect modification).

There is some new evidence of a modest effect on change in clinical management. The extent to which this translates to clinical benefit remains uncertain.

The target intermediate risk patient population could be better defined through changes to the item descriptor.

The proposed item descriptor would permit both EndoPredict® and Prosigna® GEP tests, however the evidence base of this re-application relates to EndoPredict® alone.

### **Economic issues:**

Most economic issues raised by MSAC in November 2019 have not been addressed by the re-application.

The ICER is most uncertain because of uncertainties in the clinical inputs impacting the accuracy of the economic evaluation (overestimating the transition probabilities in favour of the intervention). Implicit in estimates of clinical inputs is a claim of predictive value for chemotherapy benefit or not by EPclin scores. The ICER is also strongly sensitive to the fee, the implementation of which is uncertain based on the volume-based fee structure proposed. The ICER is also sensitive to transition probabilities (derived from the risk of recurrence predicted by the test) with an impact on health outcomes as well as the cost side of the model (in terms of cost of treatment of distance recurrence).

### **Financial issues:**

The financial impact is highly uncertain due to the uncertain uptake and the volume-based fee structure proposed.

**Other relevant information:**

The product is TGA-approved. The need for NATA and NPAAC accreditation was acknowledged, and an appropriate QAP would be provided if MBS funding proceeds.

**ESC discussion**

ESC noted that this was a re-application for the Medicare Benefits Schedule (MBS) listing of a genetic expression profiling (GEP) test (EndoPredict®) for determining the prognosis (risk of distant recurrence), and for predicting the absolute benefit of chemotherapy in addition to endocrine therapy for patients with primary oestrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) early-stage breast cancer.

ESC noted EndoPredict® is an algorithmic tool that categorises patients as high or low risk of distant recurrence (DR) based on testing the expression of specific genes. ESC noted that, although not specified in the proposed item MBS descriptor, this proposal relates to the “EPclin score”, rather than the “EP score”. The EP score ranges from 0 to 15, and is algorithmically calculated based on the expression levels of eight cancer-related genes and three reference genes, with a low/high threshold score of 5. The EPclin score ranges from 1 to 6, and is calculated by combining the EP score with the clinical factors nodal status and tumour size, with a low/high threshold score of 3.3.

ESC noted that this will be MSAC’s the third consideration of EndoPredict®. ESC noted the re-application examined not only incremental prognostic value (i.e., additional information about a patient’s prognosis without changes in downstream treatments), but also predictive value (i.e., information about differences in downstream treatment effects for a patient or patient group).

ESC noted that, in July 2021, MSAC accepted that the GEP tests provided some modest prognostic information, however advised that no applicant had provided sufficient evidence for additional prognostic value beyond current standard of care. MSAC also did not accept predictive value had been adequately demonstrated for any GEP test. The applicant provided the EndoPredict® instructions for use (IFU) with its pre-ESC response, and ESC noted that both the IFU and the listing on the Australian Register of Therapeutic Goods (ARTG) permit both prognostic and predictive usage.

ESC expressed reservations about the feasibility of the proposed volume-based fee structure, where the MBS item’s fee decreases across 4 tiers as more tests are performed (Table 5). ESC considered the proposed fee structure would be unique for an MBS item, but noted that similar arrangements are commonly used for the Pharmaceutical Benefits Scheme (PBS). ESC considered key issues related to the fee structure are:

- It is uncertain whether any fee reduction (based on annual volume of services) would be passed on from the supplier to the pathology providers. ESC considered there is a risk it may lead to out-of-pocket costs for the patient. This might be mitigated by a guaranteed concomitant reduction in the price of the EndoPredict® product to pathology providers.
- There is a high level of uncertainty in the extent of use estimated over the first 5 years of listing (and hence cost to the MBS) and that this is likely to be an underestimate. The cost of the service is a key driver of the incremental cost-effectiveness ratio (ICER).
- The proposed volume-based fee structure has not been previously implemented in the MBS.

ESC considered that the applicant did not provide a rationale for this genetic testing being sufficiently unique to warrant a novel fee mechanism, and recalled that the applicant for Oncotype DX® had also previously proposed a non-standard approach related to the proposed fee, which MSAC had not supported<sup>22</sup>. Therefore, ESC queried whether a standard fee proposal (similar to other pathology services) might be more appropriate.

ESC noted the method-agnostic nature of the applicant's proposed MBS item descriptor, and the applicant's comment that the proposed item descriptor would permit EndoPredict® and Prosigna®, but that the applicant would agree to EndoPredict® alone being specified in the item descriptor if MSAC considered this appropriate. ESC considered an item descriptor that permitted GEP tests beyond EndoPredict® may be inappropriate, as the evidence being considered for this re-application relates only to EndoPredict®. ESC further considered it may not be feasible to extend the proposed fee structure simultaneously to include other GEP tests.

ESC noted the Department's suggestion to require multidisciplinary team (MDT) determination that GEP test is required. ESC considered that requiring an MDT determination may better define the patient population, and that this would align with both current clinical practice and cohort 2 from the PROSPER study, which ESC noted the commentary considered to be more similar to the intermediate risk population proposed for testing. However, ESC considered that some MDTs comprise only 2–3 clinicians so does not necessarily represent a consensus, the MDT decision may often be driven by the oncologist anyway, and it is more important for the treating oncologist and the patient to make the treatment decision together. On the other hand, ESC noted that the PROSPER study showed a clearly higher proportion of management decisions changed for cohort 2 than cohort 1. Therefore, ESC was uncertain about the value of requiring an MDT determination.

ESC considered it inappropriate for the test to be pathologist-determinable, as patients may not opt for chemotherapy for non-clinical reasons, and it was unclear what the trigger item would be for the pathologist.

ESC considered the MBS item descriptor's frequency restriction "once per new primary breast cancer diagnosis" to be appropriate, as a subsequent contralateral breast cancer diagnosis may have a different risk profile. ESC considered that this restriction would also assist in appropriately preventing patients from undertaking multiple GEP tests per diagnosis.

ESC noted that EndoPredict® is aimed at patients with "intermediate risk", and that different research groups have defined this differently. Therefore, ESC considered that the population could be better defined by adding tumour size upper and lower limits (1–5 cm, based on the PROSPER study) as a mandatory criterion in the MBS descriptor, specifying axillary nodes, and requiring no evidence of distal metastasis.

ESC considered that including the criterion distinguishing neoadjuvant and adjuvant therapy in the MBS descriptor was not necessary. A revised item descriptor incorporating ESC's advice is provided below.

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<sup>22</sup> Page 14, Public Summary Document (PSD) for MSAC Application 1342.3. Available at: <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1342.3-public>

**Table 21 ESC's revised MBS item descriptor**

<p>MBS XXX</p> <p>Clinically validated gene expression profiling test that algorithmically combines tumour size, lymph node status with tumour gene expression of FFPE from core needle biopsy or surgical tumour sample in primary breast cancer tissue to predict <math>\geq 10</math> year prognosis.</p> <p>The test may be used when all the following criteria are met:</p> <p>(a) New primary breast cancer, suitable for adjuvant chemotherapy, <del>and not requiring neoadjuvant chemotherapy.</del></p> <p>(b) Oestrogen receptor positive and HER2 negative as determined by IHC and ISH respectively on surgically removed tumour.</p> <p>(c) <i>Axillary</i> node negative or positive (up to 3 nodes) and tumour size 1-5 cm determined by histopathology on surgically removed tumour.</p> <p>(d) <i>No evidence of distal metastasis.</i></p> <p>(e) Pre-test intermediate risk of distant metastases defined by at least one of the following characteristics: <del>tumour size <math>\geq 2</math> cm; or</del> Grade 2; or Grade 3; or one to three lymph nodes involved in metastatic disease (nodes include micrometastases but not isolated tumour cells).</p> <p><del>Laboratory pathologist can determine if required as a reflex test when criteria are met.</del> The test may be used once per new primary breast cancer diagnosis.</p>
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Strikethrough and italicised text indicate ESC's deletions and additions (respectively) to the item descriptor.

ESC noted the re-application's claims were that EndoPredict® has superior effectiveness and non-inferior safety for targeting use of systemic therapy for patients with ER+, HER2- early breast cancer assessed as intermediate risk of distant recurrence.

ESC noted that the comparative safety claim was unchanged from the 2019 application and that this re-application provided no new evidence in support. ESC noted that the main safety issues related to false positive or false negative results from EndoPredict®, and that these impacts are implicit in the Kaplan-Meier analyses. Patients who are overtreated for their level of risk of recurrence may suffer adverse effects of chemotherapy unnecessarily, and patients who are not offered potentially beneficial chemotherapy may have disease relapse unnecessarily.

ESC noted the clinical evidence base was largely the same studies as were previously considered in November 2019, and that little new clinical evidence was provided for this re-consideration. The two studies used in the modelled evaluation were Sestak et al. 2019 (10-year follow-up) and Dinh et al. 2022 (updated analysis of the PROSPER study). ESC noted the re-application's claims that EndoPredict® has incremental prognostic value over clinical characteristics (including nodal status, tumour grade and tumour size) and standard assessment tools (Adjuvant!Online, IHC4, CTS5 and Ki67), impacts patient management, and predicts treatment benefits.

ESC considered that there is some evidence of an incremental prognostic value because, in the multivariate Cox model including various clinical variables, nodal status and EPclin score had independent prognostic value and, in the bivariable model, Adjuvant!Online and EPclin score both had independent prognostic value. ESC noted the adjusted hazard ratios for these effects are statistically significant. However, ESC considered that this evidence is uncertain due to low level study design and population differences. ESC also considered the gain in c-statistic by adding EPclin to Adjuvant!Online evidenced a modest gain in discrimination, also indicating some incremental prognostic value.

ESC noted the clinical utility evidence came from three studies, all of which have already been considered by MSAC in relation to the first application, and all of which have enlarged populations presented in this re-application: Dinh et al. 2022 (PROSPER – Australia), Ettl et al. 2020 (Germany), and Penault-Llorca et al. 2020 (France). ESC noted that the main new evidence presented in this re-application was the modest enlargement of the PROSPER study

population assessing change in clinical management. ESC noted the commentary's analysis included disaggregating where a change in management occurred that could have been attributable to the EndoPredict® result, and that a final change in clinical management occurred for 20.5% (44/215) patients, and the net change in chemotherapy was a 6.5% decrease.

ESC noted that Ettl et al. (2020) reported clinical outcomes for a case series of breast cancer patients whose treatment was directed by their EPclin score, though only at the 3-year follow-up. ESC noted the study population was not specifically intermediate risk before using EndoPredict®, and considered the study's applicability to the Australian early breast cancer population is uncertain. In addition, ESC noted that all patients received EndoPredict®, so no comparisons can be made against likely health outcomes resulting from not using EndoPredict®. ESC considered the comparison of high-risk patients who did versus did not follow the chemotherapy recommendation had limited relevance because these patients deciding to have or not have chemotherapy are likely to differ from patients at intermediate risk.

ESC noted that Penault-Llorca et al. (2020) reported psychological outcomes for a cohort with grade 2, or grade 3 and pT <2 cm, or lobular histology, which more closely aligns with the intended MBS-eligible population in Australia. Increased anxiety levels were associated with the change in treatment at the second decision point that followed the EndoPredict® test. As patients had already been given a treatment recommendation, ESC noted that it was not possible to determine whether performing EndoPredict® had an impact on decision-related anxiety, or whether the anxiety was related to changing the treatment plan.

ESC noted no new evidence had been provided for treatment benefit predictive value (e.g. effect modification in a prospective randomised controlled trial), to support the claim of predictive value. ESC noted the re-application again provided Sestak et al. (2019)'s retrospective analysis of five trials with indirect comparisons across studies, which showed a statistically significant interaction between chemotherapy benefit and EPclin as a continuous variable ( $p=0.022$ ) – however ESC also noted that MSAC had previously advised that *“the retrospective analysis of three cohorts derived from four randomised clinical trials ... could not be relied upon for decision making”* (1408 PSD, Nov 2019).

ESC considered the lack of the MSAC-requested level of evidence for any effect modification is pivotal to the economic model, and considered it inappropriate to claim that there is predictive value via an effect modification to drive the economic model. ESC considered that an acceptable use of the prognostic value may be to estimate potential absolute benefit using the baseline absolute risk of recurrence for the patient, multiplying by the relative risk reduction from treatment, and assuming this is a constant relative risk reduction was assumed across all groups (i.e. no effect modification). ESC considered this absolute risk approach is consistent with the “stratified care” approach used for management decisions of other conditions. For example, decisions on whether to start primary cardiovascular preventative drugs may be made based on the person's baseline absolute risk and the size of potential reduction in this risk with treatment. This approach assumes a constant relative risk reduction across different subgroups, i.e. no treatment effect modification.

ESC considered that the other economic issues raised by MSAC in November 2019 remained largely unaddressed by this re-application. ESC accepted the decision tree-Markov model as appropriate for the economic evaluation, with the decision tree representing risk classification (high or low), lymph node status (positive or negative) and treatment decision (4 groups), and the Markov model representing patients' progression (“no distant recurrence”, “distant recurrence”, “cancer death” and “natural death”).

ESC noted the main changes to the economic evaluation since the first application were the updated change in management estimates from the PROSPER analysis and the updated cost inputs. ESC considered that the PROSPER updated estimates favoured the intervention. The cost inputs (treatment of recurrences) for the economic evaluation were sourced from Verry et al. (2012), and updated for inflation, though assumed no change to clinical practice since publication.

ESC noted the re-application used a 50-year time horizon during which the intervention effect is assumed to continue, which MSAC regarded as a key concern in its 2019 consideration. ESC considered the most uncertain aspect of the economic evaluation is using the predictive effect as the clinical inputs to populate the Markov model; that is, whether a high EPclin score can predict chemotherapy benefit – an assumption that MSAC did not support in 2019. Similarly ESC noted that the unchanged assumption of complete compliance with treatment decisions based on EPclin scores favoured the application and was not previously accepted by MSAC.

ESC noted the main source of utility values was unchanged from the previous application, which it considered favours the intervention.

ESC noted that the ICER in the first application was \$ [REDACTED] per quality-adjusted life year (QALY) when the EndoPredict® fee was \$ [REDACTED], which has decreased to \$ [REDACTED] at an average EndoPredict® fee of \$ [REDACTED] in this re-application. ESC considered the ICER to be strongly sensitive to the fee, the implementation of which is uncertain based on the volume-based fee structure proposed. ESC also considered that if fee reductions resulted in patients being charged out-of-pocket payments, then the estimated full cost of providing the service should be included in estimating the ICER.

ESC considered that another key driver of the economic evaluation was the costs related to distant recurrences, which is related to an uncertain predictive value.

ESC noted the commentary's re-specified base case comprised five steps, which it considered addressed some of the economic issues raised by MSAC in 2019. ESC noted the re-specified base case provided an updated ICER of \$ [REDACTED]/QALY.

- Step 1: Change in management from PROSPER (based on the treatments patients actually received)
- Step 2: Step 1 + extrapolation of distant recurrence estimates to 10 years only
- Step 3: Step 2 + utilities from Lidgren et al. (2007)
- Step 4: Step 3 + time horizon of 30 years
- Step 5: Step 4 + no predictive effect for chemotherapy benefit by EPclin score.

ESC noted the sensitivity analysis showing that any EndoPredict® fee greater than \$ [REDACTED] would increase the re-specified base case ICER to more than \$ [REDACTED], and considered that if only 165 fewer services were provided in year 1 than the re-application had estimated then the average fee would increase to \$ [REDACTED]. ESC noted if the fee was less than \$ [REDACTED], EndoPredict® becomes dominant.

ESC noted that when adjusted for cost-savings, the estimated total cost to the MBS was \$ [REDACTED] in Year 1 to \$ [REDACTED] in Year 5. ESC considered the uptake to be based on unjustified and therefore uncertain assumptions, making the financial impact uncertain, especially when using the proposed volume-based fee structure. ESC also noted that the uncertainties regarding predictive value flowed to the estimated cost offsets of chemotherapies to the PBS. As a result, ESC queried whether a financial risk-sharing arrangement would be appropriate for EndoPredict®.

ESC noted the pre-ESC response described broad consumer support for this re-application, including a petition to the previous Minister for Health with over 17,000 signatories in support of GEP testing. ESC noted that patients vary in the weight they place on GEP test results, that decisions relating to breast cancer treatments can be complex and difficult, and that there are studies examining how patients negotiate the value of GEP tests. ESC considered that patients placed value in knowing their prognosis, though MSAC does yet not have methods to formally incorporate ‘value of knowing’ in a quantifiable form into an economic evaluation. ESC requested that the applicant take the opportunity to address the value of patients better knowing their prognosis based on an EndoPredict® result. ESC recognised that some clinician groups, at least one Australian laboratory, and various international guidelines make statements describing using GEP tests to assist decision-making regarding the use of chemotherapy in early breast cancer. ESC noted the recent update to ASCO guidelines<sup>23</sup> may provide useful background for MSAC, though ESC has not specifically evaluated it.

Finally, ESC noted that advice from NPAAC was that EQA would need to be addressed using sample exchange with other laboratories, and considered the requirements around TGA approval, NATA and NPAAC accreditation, and an appropriate QAP, to be reasonable.

## **17. Applicant comments on MSAC’s Public Summary Document**

We are very excited that MSAC has recognised variance between GEP tests and has recommended EndoPredict® on its own merit and evidence. Myriad Genetics is committed to resolve this unprecedented substantial out of pocket cost to the patient and will work with all stakeholders in an equitable manner to deliver this service onshore to eligible women diagnosed with breast cancer.

## **18. Further information on MSAC**

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

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<sup>23</sup> Andre F, et al. (2022). Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update. *J Clin Oncol*, **40**:1816-1837.