
1408

Protocol to guide the
assessment of a
prognostic RT-qPCR
test for ER+ve,
HER2-ve primary
breast cancer

January 2016

1. Title of Application

A prognostic RT-qPCR test run locally for ER+ve /HER2-ve breast cancer that determines the risk of early and late metastasis in node negative and positive cancer under endocrine treatment.

2. Purpose of application

An application was received from Myriad Genetics Australia Pty Ltd (a distributor for Sividon Diagnostics GmbH) requesting the listing of *A prognostic RT-qPCR test run locally for ER+ve /HER2-ve¹ breast cancer that determines the risk of early and late metastasis in node negative and positive cancer under endocrine treatment.* The prognostic gene profiling test is claimed to determine the risk of distant recurrence or metastases in primary breast cancer patients and assist in the selection of appropriate therapy.

Patients with primary breast tumours who fall into the subtype ER+ve, HER2-ve often do not have clear-cut treatment options. While clinical factors and immunohistochemistry (IHC) may predict risk of recurrence for those at the low and high risk ends of the spectrum, many patients fall into an intermediate risk group, for whom treatment options could be better informed. The proposed new test claims to provide additional information to aid the decision for treatment.

The test and algorithm referred to in the application is registered outside and within Australia as EndoPredict®. The quantitative real-time polymerase chain reaction (RT-qPCR) gene profiling test determines the expression level of eight genes, three of which are associated with tumour cell proliferation and five with hormone receptor function. Risk of distant recurrence or metastases is calculated from the RT-qPCR gene expression profile combined with classical clinical markers of tumour size and nodal status to calculate the score in patients who have undergone surgical tumour removal (EPclin Score).

Beside providing the continuous EPclin risk score patients with ER+ve, HER2-ve tumours are classified by the prognostic tool as *low* or *high* risk of distant recurrence or metastases. As there is no *intermediate* risk classification, the treatment decision is simplified. The applicant claims EndoPredict® is useful in both node negative and positive patients (up to 3 nodes). It is proposed that more patients will benefit by being classified as low risk and *avoiding* chemotherapy, than is currently the case.

For further description of the EndoPredict® tool and its clinical application refer to the following articles which describe its design and use in a European setting (Brase JC 2013; Muller et al. 2013).

¹ ER+ve = tumours testing positive for expression of oestrogen receptor and either positive or negative for expression of progesterone receptor; HER2-ve = tumours testing negative for expression of human epidermal growth factor receptor 2 oncogene

3. Population and medical condition eligible for the proposed medical services

Description of the medical condition relevant to the proposed service.

Breast cancer is the most common cancer type among women, representing 28% of all reported cancer in females in Australia (AIHW 2012). The incidence of breast cancer in Australia is increasing, and has risen from 5303 new cases in 1982 to 14181 new cases in 2010 (Cancer Australia 2015). There are multiple classifications of breast cancer. The most important primary tumour markers in terms of prognosis and metastatic disease are now considered to be the epidermal growth factor gene (HER2) and hormone receptor genes (ER and PgR) (Coates et al. 2015; Rossi et al. 2015). These markers categorise disease into four basic groups through in situ hybridisation (ISH) and IHC definition, and are described in an American retrospective study by Onitilo et al (2009) of 1134 invasive breast cancer patients (Onitilo et al. 2009). The categories and survival rates published by the study are shown in Table 1. The population for the study included patients with primary breast tumours (stages 1-111) categorised as ER+ve, HER2-ve as determined by IHC (highlighted in green in Table 1). This is the largest category, making up 65-70% of all breast cancer according to published evidence (Voduc et al. 2010; Wang-Lopez et al. 2015).

Another way of defining breast cancer is by classification of the level of Ki67 gene expression. Luminal cell tumours which express low levels of Ki67 are called luminal A type and tend not to be responsive to chemotherapy. Those expressing high levels of Ki67 are called luminal B type tumours (Coates et al. 2015). There is some overlap of HER2+ve and -ve expression between luminal A and B groups. While most Luminal A type cancers will be HER2-ve, some will be HER2+ve. Some HER2-ve patients may fall into the luminal B type cancer group. For the proposed new service, only HER2-ve tumours will be eligible (either luminal A or B type).

Table 1 Five-year overall and disease-free survival by tumour subtype, ER/PgR and HER2 status for US breast cancer patients (Onitilo et al. 2009)

Subtype	Overall survival, % (95% CI)	Disease-free survival
ER/PgR+, HER2- (luminal A)*	90.3% (87.6, 92.5)	86.8% (83.8, 89.4)
ER/PgR+, HER2+ (luminal B)*	88.7% (79.2, 94.1)	83.2% (74.0, 89.6)
ER/PgR-, HER2+	78.8% (66.0, 87.7)	66.0% (53.9, 76.3)
ER/PgR-, HER2-	79.0% (70.8, 85.3)	73.5% (65.0, 80.5)
ER/PgR status		
ER/PgR+	90.1% (87.5, 92.2)	86.5% (83.6, 88.8)
ER/PgR-	79.0% (72.4, 84.4)	70.8% (63.9, 76.8)
HER2 status		
Positive	84.6% (77.3, 89.9)	75.9% (68.6, 81.9)
Negative	88.5% (85.9, 90.6)	84.7% (81.9, 87.2)
Overall	87.8% (85.4, 89.9)	83.1% (80.5, 85.5)

CI = confidence interval; ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; PgR = progesterone receptor; + = positive; - = negative

* According to 4/5ths of the 2015 St Gallen's consensus panel Luminal A tumours are those expressing low Ki-67 activity (<20-29%) and Luminal B tumours expressing high Ki-67 activity (>20-29%)(Coates et al. 2015)

Tumour grade is another important prognostic factor for breast cancer. The grade of a cancer is a qualitative assessment of the degree of differentiation of the tumour. Although criteria can vary, grade reflects the extent to which a tumour resembles normal tissue at that site, where tumour tissue that is well differentiated is classified as Grade 1, moderately differentiated is Grade 2, and poorly differentiated is Grade 3 (AJCC 2012). The American Joint Committee of Cancer (AJCC) recommend that all invasive breast cancer should be graded using the Nottingham combined histologic grade (Elston-Ellis modification of Scarf-Bloom-Richardson grading system) (Elston & Ellis 2002).

In recent years additional prognostic tests have been developed that provide multi-parameter molecular markers for hormone receptor and proliferation related genes in individual breast cancer patients. These tests act as tools for the selection of patients who are unlikely to benefit from chemotherapy by assessing their gene expression profile as a means of predicting the risk of recurrence within 1-5 years and beyond 5 years. Tests currently available internationally include OncotypeDX[®], MammaPrint[®], PAM-50 ROR[®] score, Breast Cancer Index[®] and EndoPredict[®] (Coates et al. 2015).

Additional information on the assay techniques and application of currently available gene expression profiling tools may be found in the publication by Cobain and Hayes, 2015 (Cobain EF & Hayes DF 2015). A systematic review of effectiveness and cost-effectiveness of available breast cancer gene profiling tools was conducted by Ward et al (2013) and provides useful information on their analytic validity, clinical validity and clinical utility in the UK (Ward et al. 2013).

Patient population that would benefit from the proposed service

The AJCC Tumour (T), Lymph Nodes affected (N) and Metastases (M) TNM breast cancer staging classifications are outlined in Table 2 (AJCC 2012). This application applies to primary breast cancer patients who fall into the category of HER2-ve determined by ISH and ER+ve (either PgR positive or negative), as determined by IHC, have an operable class T1, T2 or T3 tumour, with or without lymph node involvement (up to 3 nodes). Stages which apply to primary operable tumours with size classifications of T1 - T3 (but not Stage III), involvement of 0-3 lymph nodes (N0 or N1) and without distant metastases (classification M0) are highlighted. Alternatively, tumours assessed as Grade2 are eligible.

Table 2 TNM staging for breast cancer (AJCC 2012)

Stage	T classification	N classification	M classification
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

is = in situ; mi – micrometastases; T = tumour; N = node; M = metastases

* T1 includes T1mi

** T0 and T1 tumours with nodal micrometastases only are excluded from Stage IIA and are classified Stage IIB

The *intermediate risk* patient population eligible for this application (to receive an EPclin score from EndoPredict®) is described as:

Patients with primary tumours who have undergone surgical tumour removal, are determined to be ER+ve, HER2-ve (by IHC/ISH on surgically removed tumour tissue), and are assessed as having a pre-test intermediate risk of distant metastases by pathological post-surgical examination of the tumour tissue defined as tumours with at least one of the following characteristics: tumour size > 2cm; or Grade 2; or one to three lymph nodes involved in metastatic disease (nodes include micrometastases but not isolated tumour cells). Patients may be pre or post-menopausal, and tumours may be of any type, and may be multicentric or multifocal.

To determine if there is a maximum tumour size for which patients of intermediate risk would benefit from EndoPredict®, a subgroup analysis of patients with tumours > 5cm in size should be included.

Note that the pre-test definitions for the *high risk* and *low risk* groups (excluded from eligibility) are the following:

High risk: tumours classified as Stage II and greater than 5 cm in size, or Stage III, or have more than 3 lymph nodes involved (including micrometastases, but excluding isolated tumour cells).

Low risk: tumours classified as Stage I (less than 2cm in size) *and* Grade 1 *and* zero nodes involved.

Optimal treatment for these patients can be difficult to determine and can vary between therapists and patients (Coates et al. 2015). The proposed test can be used for pre and post-menopausal women with breast cancer, and women with and without lymph node involvement. Only patients who have been assessed by an oncologist as not requiring neoadjuvant chemotherapy and are suitable for adjuvant chemotherapy need undergo EndoPredict® as factors such as older age, comorbidity or advanced stage of cancer may rule patients out for chemotherapy. Some women may choose not to undergo chemotherapy even if they are eligible due to its toxicity and side effects. For patients who are not suitable or choose not to undergo chemotherapy it would be unnecessary to be classified as high or low risk using EndoPredict® as their treatment would be the same as that given to those classified as low risk.

The EndoPredict® tool is used in conjunction with markers currently used to decide on treatment and provides additional information to assist that decision. To calculate an EPclin score using the EndoPredict® tool, tumour size and nodal status must be determined by a pathologist and can only be performed on surgically removed tumours.

The eligibility criteria for calculation of an EPclin score are:

- new primary breast cancer;
- no prior adjuvant treatment;
- suitable for adjuvant treatment and not requiring neoadjuvant chemotherapy;
- undergone surgical tumour removal or mastectomy;
- ER+ve, HER2-ve diagnosed by ISH and IHC respectively;
- tumour size (operable, no metastases) and nodal involvement (up to 3 nodes) determined post surgically; and
- have a pre-test 'intermediate' risk of distant recurrence or metastases.

Summary of population included in the evidence

Table 3 provides a summary of the populations in which EndoPredict® has been tested for test accuracy and change in management. *Please note, this table is not intended to provide a comprehensive summary of what evidence may be available, but to give an early indication to PASC that there is evidence in the population of interest.*

Table 3 Summary of the populations tested with EndoPredict® for test accuracy and change in management

Country Investigation	Population	Test	Source
Austria and Germany Prognostic test accuracy	Participants of the ABCSG-6 and ABCSG-8 trials who received endocrine therapy only. <u>ABCSG-6 inclusion criteria</u> Post-menopausal women with surgical tumour removal Histologically confirmed ER or PR positive tumour Stage I or II unilateral breast cancer Negative or positive axillary nodes <u>ABCSG-8 inclusion criteria</u> Post-menopausal women aged 80 years or younger Histologically verified, invasive or minimally invasive, breast tumour, surgically removed ER or PR positive tumour	EP score and EPclin Score, conducted on FFPE samples	(Filipits et al. 2011) (Dubsky et al. 2013)
Germany Patient management	Patients with primary invasive ER+ve or PR+ve, HER2-ve breast cancer. Median age 55 years (range: 30-76 years)	EP Score and EPclin Score, conducted on FFPE samples	(Muller et al. 2013)

ABCSG = Austrian Breast and Colorectal Cancer Study Group; EP = EndoPredict®; ER = oestrogen receptor; FFPE = formalin fixed paraffin-embedded; HER2 = human epidermal growth factor receptor; PR progesterone receptor

Expected utilisation if the new service is publicly funded

The number of new breast cancer cases detected in 2011 and 2014 in Australia are reported in Table 4, as well as Cancer Australia's prediction of what the incidence is likely to be in 2020 (Cancer Australia). Of these, it is assumed that 65% of new cases would be classified as being ER+ve, HER2-ve (Voduc et al. 2010; Wang-Lopez et al. 2015). The applicant estimates that 80% of new primary breast cancer patients have localised cancer suitable for adjuvant therapy. Approximately 75% of these have no comorbidity and are of a suitable age for therapy. It is estimated that 50% of patients are at intermediate risk and therefore EndoPredict® may be undertaken in approximately 20% of primary breast cancer patients. It would be expected that some women may choose not to receive chemotherapy due its toxicity and side effects.

Table 4 Estimated breast cancer incidence for Australia

Statistic	2011	2014	2020
New cases	14 568*	15 270**	17 210**
New ER+ve, HER2-ve cases (assuming 65% of total) ^a	9469	9925	11 187
New ER+ve, HER2-ve cases eligible for EndoPredict® (assuming 30%) [#]	2840	2978	3356

* Australian Institute of Health and Welfare in 2015 (AIHW 2015)

** (Cancer Australia 2015)

[^]Estimated from recent publications (Voduc et al. 2010; Wang-Lopez et al. 2015)

[#]Applicant provided estimate that 30% of ER+ve, HER2-ve primary breast cancer patients would be offered EndoPredict® (localised cancer – 80%; no comorbidity and suitable age – 75%; intermediate risk according to conventional prognostic factor – 50%; Note: this equates to 19.5% of all new cases)(Kronenwett R 2014)

4. Intervention – proposed medical service

Description of the proposed medical service

EndoPredict® is an *in vitro* prognostic product which uses RT-qPCR technology in combination with clinical markers (assessed by the pathologist) to score individual breast cancer patients for risk of distant recurrence or metastases. RT-qPCR is conducted in a laboratory setting using the test EndoPredict® Kit manufactured by Sividon Diagnostics and distributed by Myriad Genetics, and the device manufactured by Siemens and listed with the ARTG (number 10282939)². To perform the RT-qPCR an RNA sample required. This is prepared from a sample of the formalin-fixed, paraffin-embedded (FFPE) block using the kit reagents. Alternatively a tissue sample from the core biopsy or excised tumour can be used to prepare the RNA. The FFPE block may need to be retrieved from pathology store as the test is not performed in conjunction with histopathology but following the determination of ER and HER2 status and clinical assessment.

Online software is used in conjunction with the qPCR module, analyses expression data and calculates a score (EP score) for this element of the test. When clinical information (node status and tumour size) is entered into the software a second score is produced (EPclin score). Information on nodal status and tumour size would be provided by the pathologist assessing the surgically removed tumour. A patient's EPclin score is then used to provide an estimate of the risk of recurrence or metastases (on a continuous scale), as well categorising the patient as low or high risk for distant recurrence or metastases. According to the Sividon online tool³ the EPclin score uses a scale of 1-8, and a score of 3.3 determines the threshold between low and high risk. The cut-off is based on a 10 per cent risk of distant recurrence or metastases within 10 years, which is considered to be the point at which the absolute benefit from adjuvant chemotherapy is outweighed by the risks and adverse events affecting quality of life (Brase et al 2013; Cardoso et al 2008; Harbeck et al 2013). The oncologist will decide on treatment of endocrine therapy alone, extended endocrine therapy or endocrine and chemotherapy, based on the calculated risk.

Evidentiary standard

The proposed new service is a *prognostic* test, therefore the reference standard for EndoPredict® is the rate of development of long term disease recurrence (10 years).

In the assessment of prognostic tests the only reference standard is the development of the outcome of interest. This characteristic of prognostic tests is supported by comments made in a recent systematic review conducted by the United Kingdom National Health Service, in which gene expression tests for breast cancer were compared (Ward et al. 2013). In addition, an evaluation of

² PASC has advised that the evaluation should provide evidence that there is a fixed definition of the EndoPredict® package that has not changed significantly overtime since the discovery sample, to ensure that the same package has been used in clinical trials, subsequent validation sample and will be used in regular clinical practice.

³ Sividon online tool available at the link: [EndoPredict online tool](#)

genetic testing by Lin et al agreed that a prognostic test should be measured through strength of association between the test results and the development of the outcome (Lin et al. 2012).

Registration details for the proposed service

EndoPredict® has a registered trademark. The test is registered by Sividon Diagnostics GmbH with the Registered/Protected trademarks -

AUS: 1672186 filed February 3, 2015, registered February 5, 2016

EU: 009612409 filed December 20, 2010; registered April 29, 2011

US: 85520009 filed 1/2012; registered January 5, 2016

Delivery setting for the proposed service

EndoPredict® requires reagents, RT-qPCR instrumentation and access to online evaluation software (EndoPredict® Report Generator). The RT-qPCR test would be conducted within a laboratory setting. The service will be available to primary breast cancer patients who meet the eligibility criteria i.e. who have ER+ve, HER2-ve tumours determined by IHC/ISH analysis, are assessed as being suitable for adjuvant treatment after tumour removal, and at intermediate risk by clinical assessment. A separate tissue sample for the test would not need to be collected from the patient, rather a sample of the routine FFPE, biopsy or excised tumour would be requested from pathology for conducting the RT-qPCR testing. The service could therefore be offered to patients in a public or private hospital following surgery or biopsy, or when they attend a hospital outpatient service or consulting room.

The proposed service can be conducted in local public or private pathology laboratories if they have the appropriate equipment and training. A 10 µm section of the FFPE is used to prepare ribonucleic acid (RNA) for RT-qPCR using the EndoPredict® Kit reagents. The prepared tissue sample along with quality control samples are run on the RT-qPCR instrumentation and produce data which are exported into reporter software. The reporter software generates the EPclin risk assessment score. Results may be produced within 8 hours in an ideal setting.

Clinical delivery of the proposed service

A core biopsy is performed by an oncology surgeon, and then sent to the laboratory for testing and routine FFPE embedding. Patients with new primary breast cancer will be assessed for suitability for surgery. Following surgical removal of the tumour, a pathologist assesses the surgically removed tissue for ER/HER status (by IHC/ISH staining), tumour size and nodal status. The pathologist then reports the results to the oncologist or surgeon.

Patients with tumours that are classified ER+ve, HER2-ve are assessed by the patient's oncologist or surgeon regarding their risk of recurrence or metastases, and regarding their suitability for treatment with endocrine therapy alone (low risk patients), or endocrine combined with chemotherapy (high risk patients). To make this decision in patients with an intermediate risk, the EndoPredict® tool can be used to calculate an EPclin Score to provide an estimate of the risk of recurrence or metastases (on a continuous scale) and to categorise the patient as low risk or high risk for developing distant recurrence or metastases within 10 years. To use the tool the oncologist or surgeon would request the EndoPredict® test be performed. RNA would be prepared from the sample for the RT- qPCR gene profiling test by a molecular pathologist. Data on tumour size and nodal status may be determined from laboratory reports and entered into the EndoPredict® algorithm. The molecular pathologist would interpret and report on the results to the oncologist or surgeon. The pathologist may

recommend the gene profile analysis once ER+ve, HER2-ve status has been established through IHC/ISH. PASC suggested that, if possible, the definition of intermediate risk could be varied (i.e. using categories recommended by international guidelines), and the consequences of any variation in definition of the population could be examined in the assessment.

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

The test is being recommended for primary breast cancer patients, and would be expected to be delivered once per primary cancer diagnosis per patient at the point of primary tumour analysis. For the majority of patients the test would be requested once in their lifetime, but in the instance where primary breast cancer is detected a second or additional time (in either breast), the test may be requested more than once. The test is a prognostic tool to assist in treatment decision making as a means of preventing distant recurrence or metastases up to 10 years post diagnosis/surgery. Should there be recurrence or metastases, it is expected that an alternate decision pathway would be used.

5. Co-dependent information (if not a co-dependent application go to Section 6)

Not applicable.

6. Comparator – clinical claim for the proposed medical service

Current clinical practice

The Australian National Breast and Ovarian Cancer Centre (NBOCC) published *Recommendations for use of Endocrine Therapy* for the treatment of hormone receptor positive advanced breast cancer in June 2008, incorporating evidence to July 2007. While these guidelines are not specific to the population in this application, they indicate that current treatment of primary breast cancers in Australia is largely determined by the IHC/ISH analysis of tumour type, i.e. hormone receptor (ER/PR) positive or negative, and HER2 positive or negative. In the case of ER/PgR+ve tumours the 2007 Guideline recommends endocrine therapy in preference to chemotherapy except in the presence of rapidly progressing visceral disease (for which HER2+ve is a marker).

In Australia HER2 status is determined by ISH rather than IHC, as it is a requirement for access to trastuzumab under the Pharmaceutical Benefits Scheme (PBS) (MBS item 73332), although the result may be confirmed by IHC. MBS items 72848 and 73061 provide for the IHC analysis of oestrogen, progesterone and HER2 receptor status. However treatment benefit cannot be totally predicted by these subtypes. Other standard markers used in the risk assessment process are the molecular marker Ki67, and tumour grade.

The use of further markers varies amongst clinicians, and some may use a combination of guidelines markers and predictive tools. In Australia the recommendations of the St. Gallen International Expert Consensus (Coates et al. 2015) or National Comprehensive Cancer Network guideline (NCCN 2015), European Society for Medical Oncology (ESMO 2015) may be considered, along with clinical factors

such as age, menopausal status, lymph node involvement, tumour size, and comorbidities. The Adjuvant! Online tool may be used by some clinicians.

As the group who are defined as being at intermediate risk of metastases is defined differently in different guidelines, the base case scenario for current practice should be based on IHC/ISH analysis of tumour tissue (ER and HER2 status; MBS items 72847 and 72848), Ki67 status, tumour grade and any additional markers most likely to be used.

Additional comparators

Endopredict® should be further compared with the alternative prognostic tools OncotypeDX® and MammaPrint® as applications have been received by MSAC for these interventions.

MammaPrint® is a 70-gene microarray gene expression profile analysis which quantifies the risk of disease recurrence for patients with stage I-II early breast cancer classed as oestrogen or progesterone positive. Patients may have tumours of any histological grade and may be either HER2 positive or negative.

OncotypeDX® uses RT-qPCR to produce an expression panel of 21 genes and calculate a Recurrence Score® (10 year risk of distant recurrence for node negative patients, 5 year risk of recurrence or death for node positive patients) to determine the likelihood of benefiting from combined adjuvant chemotherapy and endocrine therapy. The eligible population are those with early stage breast tumours classified as oestrogen or progesterone positive, and HER2 negative.

PASC considered that the assessment could also include different international guidelines as comparators, as alternative means of decision which treatment patients are most likely to derive the best outcomes from. Examples of relevant international guidelines are:

- [*NCCN 2015, Breast Cancer, NCCN Clinical Practice Guidelines in Oncology National Comprehensive Cancer Network.*](#)
- *Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, Zackrisson S, Cardoso F; ESMO Guidelines Committee. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2015;26 Suppl 5:v8-v30.* [*ESMO Guidelines Committee. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*](#)
- *Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, Thürlimann B, Senn HJ; Panel Members. -Tailoring therapies-improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015;26:1533-46.* [*http://annonc.oxfordjournals.org/content/26/8/1533.long*](http://annonc.oxfordjournals.org/content/26/8/1533.long)
- [*Wockel, A & Kreienberg, R 2008, 'First Revision of the German S3 Guideline 'Diagnosis, Therapy, and Follow-Up of Breast Cancer', Breast Care \(Basel\), vol. 3, no. 2, pp. 82-86.*](#)

7. Expected health outcomes relating to the medical service

Impact of patient relevant outcomes

The proposed service is not expected to change current adjuvant treatment options or treatment algorithms. EndoPredict® is expected to change the decision patterns of treating clinicians and the recommendations for patient treatments. The proportions of patients receiving endocrine therapy alone and chemotherapy with endocrine therapy would be expected to change. The EndoPredict® test classifies women into low or high risk groups, with no intermediate risk classification.

Patients who receive the same treatment following risk classification with EndoPredict® as they did with current clinical practice alone will not be affected by the new service. The new service has a short turnaround time (ideally 8 hours when the test is performed within Australia) and should not result in a delay to treatment. Even if the test is not performed immediately following IHC and a FFPE block needs to be requested, this is unlikely to cause a delay in treatment. There is a gap of approximately 6 weeks between surgery and adjuvant treatment for patients who have undergone surgical tumour removal.

Women who would previously have been classified as intermediate risk and treated as high risk and received chemotherapy may be classified as low risk under the new service and therefore receive only endocrine therapy. Should this therapy be successful, these patients will avoid the risks and side-effects of chemotherapy. If the patients are wrongly classified as low risk, they may *develop* recurrence of cancer when previously they may not have done so, having been treated with chemotherapy.

Women who would previously have been classified as intermediate risk and treated as low risk but would now be classified as high risk with the new service, may receive endocrine and chemotherapy treatments rather than endocrine therapy alone. Should the new classification be correct, these patients may *avoid* metastases or cancer recurrence as a result of the treatments. If the new classification is incorrect, the patients will have undergone chemotherapy, and been at risk of side-effects unnecessarily.

Ideally, direct evidence in the correct population assessing long-term survival (10-15 years post diagnosis), disease free survival, and metastasis-free survival, comparing the current and proposed decision pathways, would provide the best evidence for the proposed service. In the absence of satisfactory direct evidence, linked evidence should be sought. Linked evidence may answer questions of the additional prognostic ability of EndoPredict® compared to current clinical practice, the impact of the new test on management of patients, and the impact of change in management on patient outcomes.

If more patients are classified as low-risk using the proposed service compared to the current treatment pathway, there will be fewer patients treated with chemotherapy. This would be expected to lead to a cost saving to Medicare, provided that the cost of testing the number of patients required to prevent one person from undergoing chemotherapy, is less than the cost of chemotherapy. If the new service leads to improved safety and/or effectiveness, the economic evaluation required would be a *cost-effectiveness* analysis.

8. Fee for the proposed medical service

The applicant is seeking Medicare subsidy for the new service. It is proposed that the new service would be listed as *RT-qPCR gene expression profiling for ER+ve /HER2-ve breast cancer to determine the risk of early and late metastasis in node negative and positive cancer under endocrine treatment* under Pathology services (category 6) in Group P7 (Genetics). The proposed item descriptor is shown in Table 5.

Table 5 Item descriptor for the proposed new pathology service

Category 6 – PATHOLOGY SERVICES
Group P7 - GENETICS
<p>MBS XXXXX</p> <p>RT-qPCR gene expression profiling of FFPE, core needle biopsy or surgical tumour sample in primary breast cancer tissue.</p> <p>The test may be used when all of the following criteria are met:</p> <ul style="list-style-type: none"> - New primary breast cancer, suitable for adjuvant chemotherapy, and not requiring neoadjuvant chemotherapy - Oestrogen positive and HER2 negative as determined by IHC and ISH respectively on surgically removed tumour - Node negative or positive (up to 3 nodes) and tumour size determined by histopathology on surgically removed tumour - Pre-test <i>intermediate</i> risk of distant metastases defined by at least one of the following characteristics: tumour size \geq 2cm*; or Grade 2; or one to three lymph nodes involved in metastatic disease (nodes include micrometastases but not isolated tumour cells) <p>The test may be used once per new primary breast cancer diagnosis.</p> <p>Fee: REDACTED Benefit: 75% = REDACTED; 85% = REDACTED</p>

* Maximum tumour size for intermediate risk group to be determined by subgroup analysis.

The applicant lists the resources required for carrying out the test as:

- Real Time PCR Instrumentation,
- standard laboratory equipment for molecular diagnostics,
- onsite training,
- staff and labour to conduct the test,
- the EndoPredict® Kit, and
- preparation of the tissue sample.

There would also be additional future costs associated with equipment service agreements when the instrument warranty expires.

The applicant has proposed a fee of REDACTED for the new service when performed within Australian laboratories. As the proposed test is provided as a packaged item, there are no breakdown costs for individual components of the service.

9. Clinical Management Algorithm - clinical place for the proposed intervention

Clinical management pathways for the comparators

Using the current clinical pathway, patients have a diagnosis of primary breast cancer confirmed by core needle biopsy. The patient would be placed under the care of an oncologist and assessed for surgery suitability. Following surgical tumour removal or mastectomy, a pathologist will conduct a histological examination, assess ER and HER2 status and tumour size and nodal status, and report results to the oncologist. The oncologist will further assess other clinical factors and classify the patient as low, intermediate or high risk of disease recurrence. For the base case scenario, this decision should be based on (in addition to ER+ve, HER2-ve status, tumour size and nodal status) Ki67 status, tumour size, tumour grade and other markers most likely to be used in the Australian population. Treatment with endocrine therapy is given to all patients, and adjuvant chemotherapy is administered to high risk and some intermediate risk patients. The current clinical management algorithm for patients who have ER+ve, HER2-ve primary breast cancer is shown in Figure 1.

Although the main comparator to be assessed is “current clinical practice” (as outlined above), PASC requested that the proposed prognostic pathway also be compared with recommendations of current international clinical guidelines. In addition, PASC requested that management using the EndoPredict® tool be compared with the alternative prognostic tools OncotypeDX® and MammaPrint® as submissions on these tests may be considered in the near future. These pathways are shown in Figure 2.

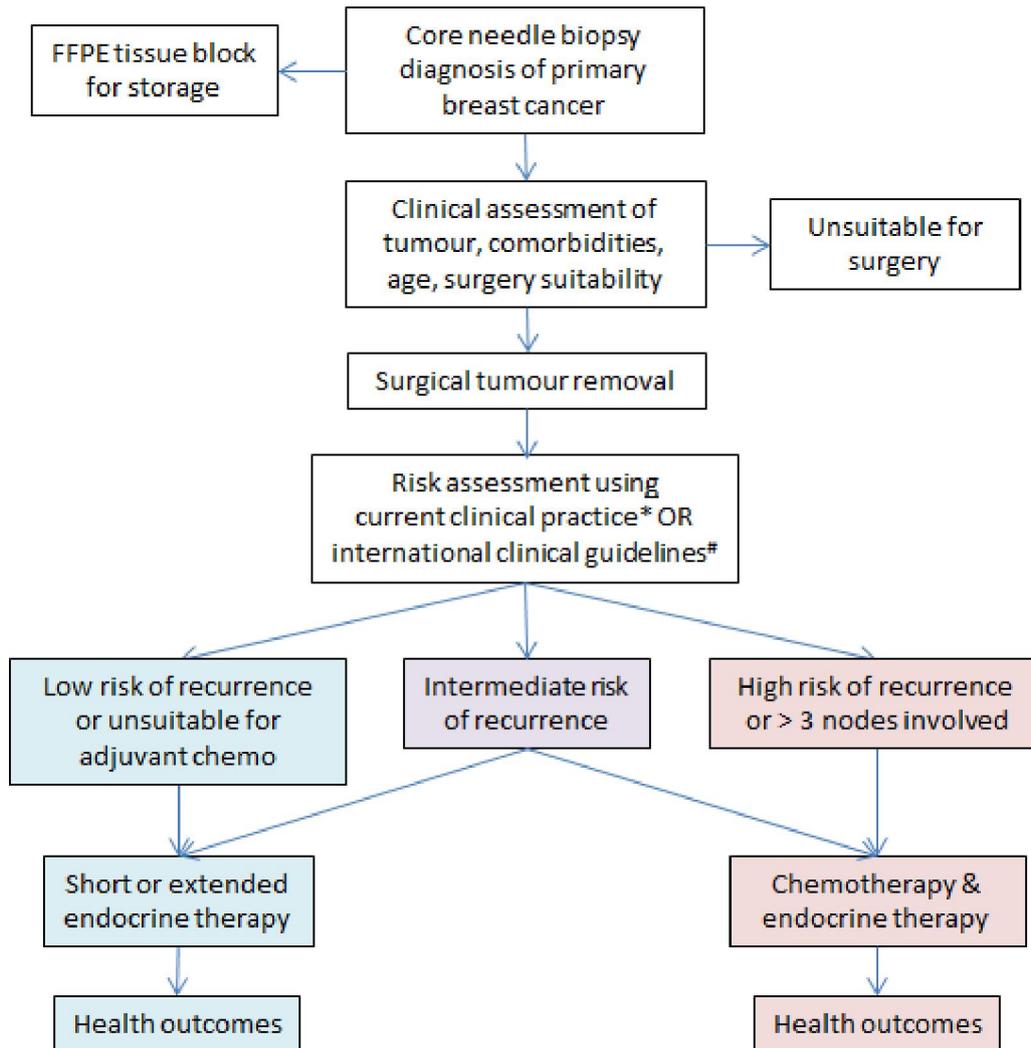


Figure 1 Management algorithm using current clinical practice (base case scenario) or international clinical guidelines for patients with ER+ve, HER2-ve primary breast cancer

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

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

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

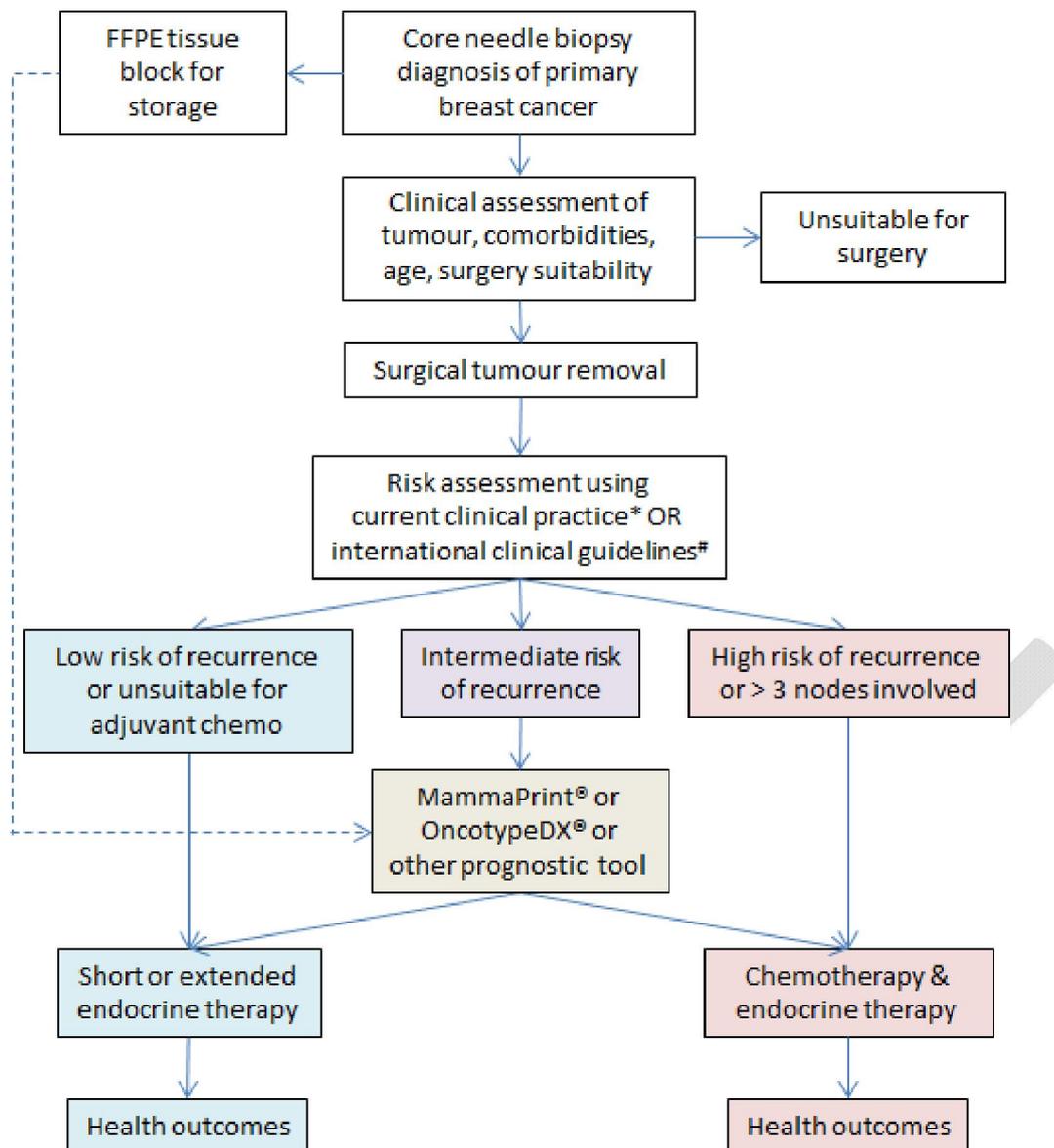


Figure 2 Management algorithm using current clinical practice or international clinical guidelines and alternative comparator prognostic tools for patients with ER+ve, HER2-ve primary breast cancer

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

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

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

Proposed clinical management pathway

In the proposed management pathway (Figure 3) patients with primary breast cancer diagnosed by core needle biopsy would have the sample sent to pathology for analysis, in the same manner as is performed in current clinical practice (see Figure 1). Patients who are assessed as suitable for surgery will undergo tumour removal. Following surgery, a pathologist will determine ER and HER2 status, and assess tumour size and nodal status histologically and report results to the treating oncologist. The oncologist will further assess all clinical markers and for patients who are ER+ve, HER2-ve and determined to be at intermediate risk, and the EndoPredict® test will be requested (or the alternative prognostic tools MammaPrint® or Oncotype DX®), provided the patient is suitable for

adjuvant chemotherapy. Alternatively patients may be assessed for risk using markers specified in an international guideline, and this assessment will be followed by a request for the EndoPredict® test for the appropriate (intermediate risk) patients.

Risk of disease recurrence is scored using the EndoPredict® tool in an algorithm which combined information on the gene expression profile with tumour size and nodal status (EPclin Score). The EndoPredict® software produces a graph, showing the risk of recurrence or metastases within 10 years, as well as a classification of high or low risk. The oncologist and patient will use this to guide the decision regarding therapy.

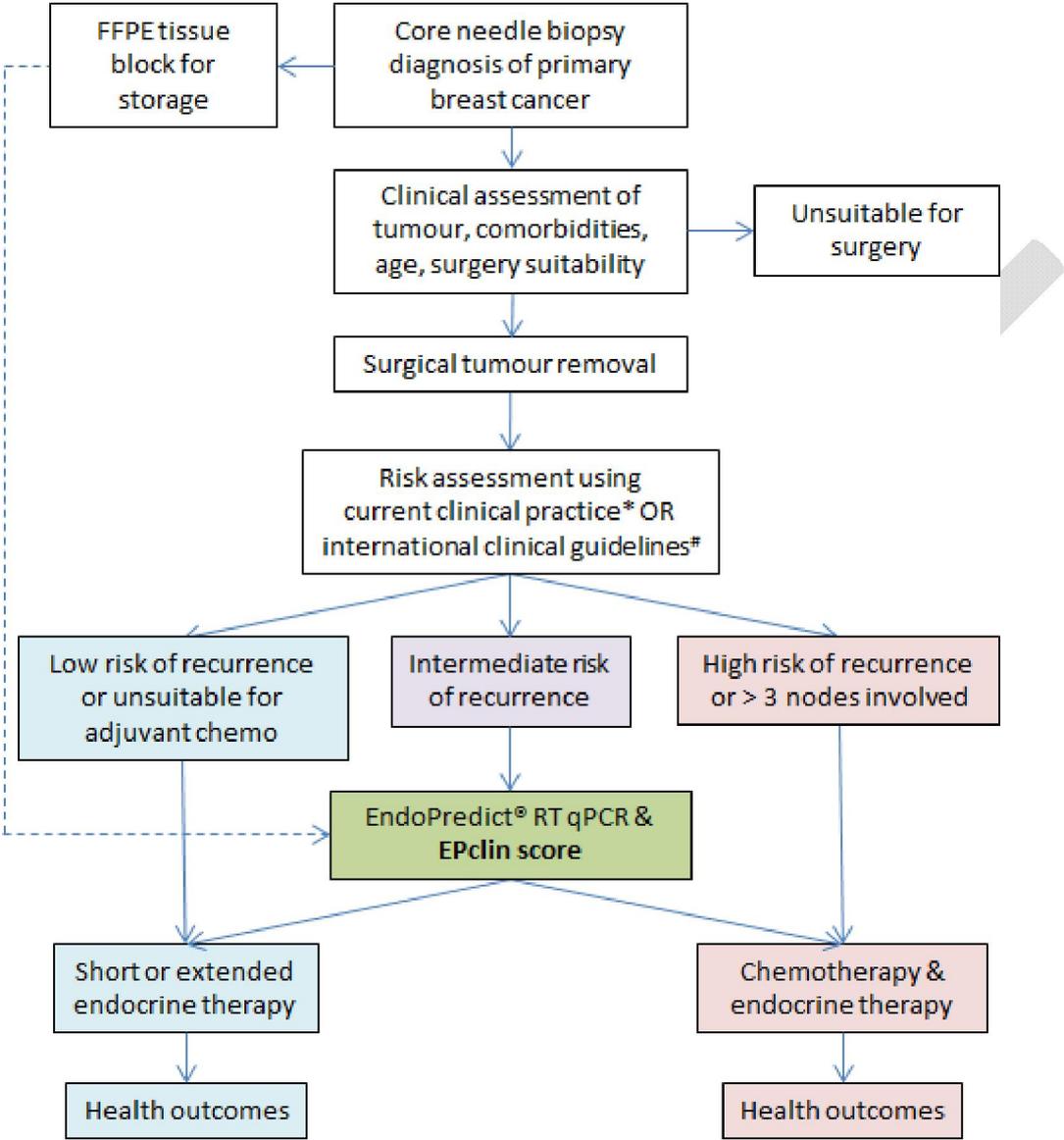


Figure 3 Algorithm for the proposed clinical management of patients with ER+ve, HER2-ve primary breast cancer

ER+ve = oestrogen receptor positive; FFPE = formalin-fixed paraffin –embedded; HER2-ve human epidermal growth receptor negative; IHC = immunohistochemistry; ISH = in situ hybridisation; RTqPCR = real time quantitative polymerase chain reaction

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

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

10. Regulatory Information

The proposed new service uses RT-qPCR methodology to produce a gene expression profile, and as such is classified as an *in vitro* diagnostic test (IVD), which must be registered and approved by the TGA. As a registered IVD it comes under the regulation of the National Pathology Accreditation Advisory Council (NPAAC). NPAAC have published the following guidelines which are relevant to the regulation of IVDs and genetic testing:

- Requirements for medical pathology services (1st edition 2013) (NPAAC 2013a), and
- Requirements for medical testing of human nucleic acids (2nd edition 2013) (NPAAC 2013b).

Myriad Genetics has stated that EndoPredict® will be undergoing registration with the Therapeutic Goods Administration (TGA) (ARTG TBC, class 3 IVD). In addition, a submission to the TGA for approval has been made for the medical device 10282939 kPCR Amplification/Detection (AD Module), which is manufactured by Siemens (ARTG identifier 175890).

On the recommendation of their TGA consultant, the applicant completed an external audit and has gained the International Standardisation Organisation certification 13485 (with appropriate recognition through the International Accreditation Forum) in conjunction with Canada Medical Devices Conformity Assessment System and third party US Food and Drug Association inspection requirements.

11. Decision analytic

If funded the proposed new service would be added to the current decision pathway for treatment of ER+ve, HER2-ve primary breast cancer, and would be an alternative to MammaPrint® or Oncotype DX®. The cost of the new prognostic test would be in addition to current costs to the MBS. However there is likely to be a cost saving if fewer patients undergo chemotherapy as a result of the new test. Cost savings of fewer chemotherapy treatments will need to be weighed against the cost of the new test. The questions to be considered in this analysis are regarding the safety, effectiveness and cost-effectiveness of EndoPredict® in addition to current clinical practice compared to current clinical practice alone for the prognosis of disease recurrence in ER+ve, HER2-ve primary breast cancer.

PICO criteria

The criteria for assessment of the proposed test are defined through a description of the relevant population, intervention, comparator, and outcomes (PICO), and any prior tests required to define the population. The PICO criteria detailed in Table 6:

- (1) define the question for public funding,
- (2) guide selection of the relevant evidence to assess the safety, and effectiveness of EndoPredict® in conjunction with current clinical practice for determining the prognosis of patients with primary ER+ve, HER2-ve breast cancer, to assist the decision in regards to which treatment patients should receive;

- (3) provide the evidence-based inputs for any decision-analytical modelling to determine the cost-effectiveness of EndoPredict® in the prognosis of ER+ve, HER2-ve patients.

Table 6 PICO criteria for evaluating safety, effectiveness and cost effectiveness of gene expression profiling alone or in combination with classical clinical factors to determine the risk of early and late metastases in primary breast cancer patients at intermediate risk of distant recurrence or metastases

Prior tests	Patients	Intervention	Comparators	Outcomes to be assessed
IHC and ISH for ER and HER2 status, histopathology for tumour size and nodal status following surgery	Patients with primary breast cancer, suitable for adjuvant chemotherapy, and who have ER+ve, HER2-ve status, tumour size and nodal status determined following tumour removal, at intermediate risk of distant recurrence or metastases*	EndoPredict® - RT-qPCR gene expression profiling in combination with classical clinical markers (tumour size and node status) as an adjunct to current clinical practice as a prognostic tool to determine the risk of distant recurrence and metastases plus subsequent treatments (short or extended endocrine therapy or chemotherapy plus endocrine therapy)	<ol style="list-style-type: none"> 1. Base case: Prognosis based on ER/HER2 status, current clinical practice (including Ki67 status and Grade) plus subsequent treatments (short or extended endocrine therapy or chemotherapy plus endocrine therapy) 2. Prognosis based on international breast cancer clinical guidelines, plus treatments: NCCN St Gallen Consensus German S3 3. Prognosis based on other tools plus treatments: MammaPrint OncotypeDX 	<p>Safety</p> <p>Effectiveness</p> <p>Survival, disease free survival, metastases free survival, quality of life</p> <p>Cost effectiveness</p> <p>Financial implications</p>

IHC = immunohistochemistry; ISH = in situ hybridisation; ER+ve = oestrogen receptor positive; HER2-ve = human epidermal growth receptor negative; NCCN = National Comprehensive Cancer Network; RT-qPCR = qualitative real time polymerase chain reaction

*Intermediate risk is defined as tumour size \geq 2cm; or Grade 2; or one to three lymph nodes involved in metastatic disease (nodes include micrometastases but not isolated tumour cells). Maximum tumour size for intermediate risk group to be determined by subgroup analysis.

Direct research questions for safety, effectiveness and cost-effectiveness

Is EndoPredict® (EPclin Score) when used in conjunction with current clinical practice, as safe, effective and cost-effective as current clinical practice alone for determining the prognosis of distant recurrence and metastases in ER+ve, HER2-ve primary breast cancer patients at intermediate risk who have undergone surgical tumour removal?

Is EndoPredict® (EPclin Score) when used in conjunction with current clinical practice, as safe, effective and cost-effective as international guidelines (NCCN, St Gallen, German S3) for determining the prognosis of distant recurrence and metastases in ER+ve, HER2-ve primary breast cancer patients at intermediate risk who have undergone surgical tumour removal?

Is EndoPredict® (EPclin Score) when used in conjunction with current clinical practice, as safe, effective and cost-effective as MammaPrint or Oncotype DX when used in conjunction with current clinical practice, for determining the prognosis of distant recurrence and metastases in ER+ve, HER2-ve primary breast cancer patients at intermediate risk who have undergone surgical tumour removal?

Table 7 PICO criteria for evaluating predictive value for recurrence in patients at intermediate risk who have been classified as high risk or low risk by EndoPredict®

Prior tests	Patients	Intervention	Comparators	Outcomes to be assessed
IHC and ISH for ER and HER2 status, histopathology for tumour size and nodal status following surgery	Patients with primary breast cancer, suitable for adjuvant chemotherapy, and who have ER+ve, HER2-ve status, tumour size and nodal status determined following tumour removal, at intermediate risk of distant recurrence or metastases* Subgroups as determined by EndoPredict: 1. Low risk 2. High risk	Endocrine therapy plus chemotherapy	Endocrine therapy alone	Predictive value for distant recurrence or metastases i.e. the interaction between low and high risk status and treatment

IHC = immunohistochemistry; ISH = in situ hybridisation; ER+ve = oestrogen receptor positive; HER2-ve = human epidermal growth receptor negative

*Intermediate risk is defined as tumour size ≥ 2 cm, ; or Grade 2; or one to three lymph nodes involved in metastatic disease (nodes include micrometastases but not isolated tumour cells). Maximum tumour size for intermediate risk group to be determined by subgroup analysis.

Direct research question for predictive value

Is EndoPredict able to predict which patients will benefit from chemotherapy plus endocrine therapy compared with endocrine therapy alone in patients who are intermediate risk of recurrence or metastases?

Note: Evidence from a randomised controlled trial is required for this question due to the high risk of selection bias in observational studies.

Questions to consider – linked evidence

If inadequate direct evidence for effectiveness is identified then linked evidence should be sought. Additional literature searches may be required to provide the evidence. These are the questions to consider in the assessment of linked evidence of effectiveness.

Table 7 PICO criteria for evaluating linked evidence for gene expression profiling alone or in combination with classical clinical factors to determine the risk of early and late metastases in primary breast cancer patients at intermediate risk of distant recurrence or metastases

Patients	Intervention	Comparators	Reference standard	Outcomes to be assessed
Patients with primary breast cancer, suitable for adjuvant chemotherapy, and who have ER+ve, HER2-ve status, tumour size and nodal status determined following tumour removal, at intermediate risk of distant recurrence or metastases*	EndoPredict® RT-qPCR gene expression profiling in combination with classical clinical markers (tumour size and node status) as a prognostic tool to determine the risk of distant recurrence and metastases	1. EndoPredict® RT-qPCR gene expression profiling conducted at a different time, in a different laboratory or with a different operator, protocol or instrument 2. Prognosis based on other tools (if data are available): MammaPrint OncotypeDX	N/A	Analytic validity Consistency of repeat testing within and between laboratories, protocols, operators and instruments
Patients with primary breast cancer, suitable for adjuvant chemotherapy, and who have ER+ve, HER2-ve status, tumour size and nodal status determined following tumour removal, at intermediate risk of distant recurrence or metastases*	EndoPredict® - RT-qPCR gene expression profiling in combination with classical clinical markers (tumour size and node status) as an adjunct to current clinical practice as a prognostic tool to determine the risk of distant recurrence and metastases	1. Prognosis based on ER/HER2 status, and current clinical practice (including Ki67 status) 2. Prognosis based on international breast cancer clinical guidelines: NCCN St Gallen German S3 3. Prognosis based on other tools: MammaPrint OncotypeDX	Metastases free survival	Prognostic value Comparative incremental prognostic accuracy (sensitivity, specificity, PPV, NPV), relative risk, etiologic fraction, odds ratio, hazard ratio
Patients with primary breast cancer, suitable for adjuvant chemotherapy, and who have ER+ve, HER2-ve status, tumour size and nodal status determined following tumour removal, at intermediate risk of distant recurrence or metastases*	EndoPredict® - RT-qPCR gene expression profiling in combination with classical clinical markers (tumour size and node status) as an adjunct to current clinical practice as a prognostic tool to determine the risk of distant recurrence and metastases	1. Treatment decisions based on ER/HER2 status, and current clinical practice (including Ki67 status) 2. Treatment decisions based on international breast cancer clinical guidelines: NCCN St Gallen German S3 3. Treatment decisions based on other tools: MammaPrint OncotypeDX	N/A	Therapeutic efficacy Proportion of patients referred for, or treated with, chemotherapy or endocrine therapy alone
Patients with primary breast cancer, suitable for adjuvant chemotherapy, and who have ER+ve, HER2-ve	Endocrine therapy alone	Endocrine therapy plus chemotherapy	N/A	Therapeutic effectiveness: Safety Effectiveness: Survival, disease

Patients	Intervention	Comparators	Reference standard	Outcomes to be assessed
status, at intermediate risk# of distant recurrence or metastases*, who would be classified as low risk with EndoPredict, but receive chemotherapy through current clinical practice				free survival, metastases free survival, quality of life
Patients with primary breast cancer, suitable for adjuvant chemotherapy, and who have ER+ve, HER2-ve status, at intermediate risk# of distant recurrence or metastases*, who would be classified as high risk with EndoPredict, but not receive chemotherapy through current clinical practice	Endocrine therapy plus chemotherapy	Endocrine therapy alone	N/A	Therapeutic effectiveness: Safety Effectiveness: Survival, disease free survival, metastases free survival, quality of life

IHC = immunohistochemistry; ISH = in situ hybridisation; ER+ve = oestrogen receptor positive; HER2-ve = human epidermal growth receptor negative; NPV = negative predictive value; PPV = positive predictive value; RT-qPCR = qualitative real time polymerase chain reaction

#Note that if the EndoPredict scores are prospectively used to determine treatment, then this would be the same as direct evidence. However, as the EndoPredict scores may be determined retrospectively (and not used to influence what treatment was used) it is possible this information may be available to use as the last step of linked evidence. If these subgroups are not available, then the evaluation should provide evidence of the effectiveness and safety of endocrine therapy plus chemotherapy versus endocrine therapy alone in the broader intermediate risk population.

*Intermediate risk is defined as tumour size ≥ 2 cm; or Grade 2; or one to three lymph nodes involved in metastatic disease (nodes include micrometastases but not isolated tumour cells). Maximum tumour size for intermediate risk group to be determined by sub-group analysis.

Analytic validity (reliability of testing within and between laboratories, protocols, operators and instruments)

What is the analytic validity of EndoPredict® (EPclin Score) for the assessment of prognosis of distant recurrence and metastases in ER+ve, HER2-ve primary breast cancer patients at intermediate risk?

What is the analytic validity of EndoPredict® (EPclin Score) compared with MammaPrint® or OncotypeDX® for the assessment of prognosis of distant recurrence and metastases in ER+ve, HER2-ve primary breast cancer patients at intermediate risk? *(If data are available)*

Prognostic accuracy

What is the incremental prognostic accuracy of EndoPredict® in conjunction with current clinical practice compared with current clinical practice alone in ER+ve, HER2-ve primary breast cancer patients at intermediate risk who have undergone surgical tumour removal?

What is the incremental prognostic accuracy of EndoPredict® in conjunction with current clinical practice compared with international clinical guidelines (NCCN, St Gallen, German S3) in ER+ve, HER2-ve primary breast cancer patients at intermediate risk who have undergone surgical tumour removal?

What is the comparative prognostic accuracy of EndoPredict® in conjunction with current clinical practice compared with the prognostic tools MammaPrint® and OncotypeDX® in ER+ve, HER2-ve primary breast cancer patients at intermediate risk who have undergone surgical tumour removal?

Therapeutic efficacy

What is the proportion of ER+ve, HER2-ve primary breast cancer patients at intermediate risk referred for adjuvant chemotherapy combined with endocrine therapy and endocrine therapy alone using EndoPredict® in conjunction with current clinical practice compared with current clinical practice alone?

What is the proportion of ER+ve, HER2-ve primary breast cancer patients at intermediate risk referred for adjuvant chemotherapy combined with endocrine therapy and endocrine therapy alone using EndoPredict® in conjunction with current clinical practice compared with international guidelines (NCCN, St Gallen, German S3)?

What is the proportion of ER+ve, HER2-ve primary breast cancer patients at intermediate risk referred for adjuvant chemotherapy combined with endocrine therapy and endocrine therapy alone using EndoPredict® in conjunction with current clinical practice compared with prognostic tools MammaPrint® and OncotypeDX®?

Therapeutic effectiveness

What is the safety and effectiveness of endocrine therapy alone compared with chemotherapy combined with endocrine therapy in ER+ve, HER2-ve primary breast cancer patients at intermediate risk, who would be classified as low risk by EndoPredict®, but would receive chemotherapy combined with endocrine therapy when assessed by current clinical practice?

What is the safety and effectiveness of endocrine therapy plus chemotherapy compared with endocrine therapy alone in ER+ve, HER2-ve primary breast cancer patients at intermediate risk, who would be classified as high risk by EndoPredict®, but would receive endocrine therapy alone when assessed by current clinical practice?

If there is no evidence specifically in these patients, then therapeutic effectiveness will have to be inferred from the evidence available about the clinical validity/prognostic accuracy of the EndoPredict versus other prognostic tools and the relative effectiveness of endocrine therapy alone versus chemotherapy combined with endocrine therapy in a broader population of those at intermediate risk.

12. Healthcare resources

The proposed test would be used in addition to current clinical practice for disease prognosis. There would be no impact on patients with regards to conducting the test as no additional sampling or attendance with a clinician would be required. There would be costs associated with purchasing the EndoPredict® Kit and the RT-qPCR module needed, for pathology laboratories providing the service. The cost of these components would not be charged separately but would be covered by the service fee. There may also be costs associated with training molecular laboratory staff to use the test and to interpret the results. In the scenario where a patient consults a private clinician the test is likely to be conducted within private pathology laboratories. Pathology laboratories may claim reimbursement directly from patients, or through MBS funding should the test be approved, or through a combination of both sources.

Should the test be conducted on patients attending a public hospital outpatient clinic, the costs may be covered by public hospital funds.

Should the proposed test prove to be more accurate than current clinical practice alone, there may be a reduction in patients receiving chemotherapy, which could result in a cost saving, as chemotherapy is a more expensive treatment option than endocrine therapy.

It is expected that under the proposed new service more patients will be classified as low-risk compared to the current treatment pathway. If that is the case and fewer patients are treated with chemotherapy under the proposed service, it would be expected to lead to a cost saving to Medicare, assuming that the cost of the number of patients you need to test to save one person receiving chemotherapy is less than the fee for chemotherapy. The proportion of breast cancer patients under the care of an oncologist in the private sector is not likely to be affected should the proposed service be funded through Medicare. If the new service is not approved, the cost would need to be borne by the patient should the oncologist request the service. This extra cost may lead to a shift of patients to the public system.

There may be some additional costs to the Pathology sector for training, qualification and accreditation requirements.

Table 8 List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Resources provided to deliver EndoPredict® and current clinical practice										
RT-qPCR Instrumentation	Molecular pathologist	Pathology laboratory								
Online software	Molecular pathologist	Pathology laboratory								
EndoPredict® Kit (reagents)	Molecular pathologist	Pathology laboratory								
Report on EP score/EPclin score	Molecular pathologist	Pathology laboratory								
Resources provided in association with EndoPredict® and current clinical practice										
FFPE block retrieval (occasional)	Pathologist	Pathology laboratory								
Equipment service agreements	Pathology provider	Pathology laboratory								
Chemotherapy										
Aftercare, treatment of side effects and adverse events										
Resources provided in association with current clinical practice										
(e.g., pre-treatments, co-administered interventions, resources used to monitor or in follow-up, resources used in management of adverse events, resources used for treatment of down-stream conditions)										

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Chemotherapy										
Treatment of side effects and adverse events										
Resources used to manage patients who are unsuccessfully treated with EndoPredict® and current clinical practice										
Chemotherapy										
Treatment of side effects and adverse events										
Palliative care										
Resources used to manage patients who are unsuccessfully treated with comparator 1										
Chemotherapy										
Treatment of side effects and adverse events										
Palliative care										

ER = Oestrogen receptor; HER2 = human epidermal growth factor receptor 2; FFPE = formalin-fixed, paraffin embedded; IHC = immunohistochemistry

* Include costs relating to both the standard and extended safety net.

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