NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

Tumour profiling tests to guide adjuvant chemotherapy decisions in people with breast cancer (update of DG10)

Final scope

February 2017

1 Introduction

In August 2016 a surveillance review decision proposed to update the NICE guideline on early and locally advanced breast cancer (CG80). Topic experts advised the guidelines surveillance team that there had been changes in clinical practice relating to the use of tools to guide adjuvant chemotherapy treatment decisions. It was therefore determined that the NICE diagnostics guidance 10 on gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management should be updated alongside the update of NICE guideline 80.

The revised scope was informed by discussions at the scoping workshop on 24 January 2017 and the assessment subgroup meeting held on 8 February 2017. A glossary of terms and a list of abbreviations are provided in appendices A and B.

2 Description of the technologies

This section describes the properties of the diagnostic technologies based on information provided to NICE from the companies and experts. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technologies

Tumour profiling tests are designed to provide information on the activity of genes within tumour samples from people with early breast cancer. The results of the tests provide a risk profile of an individual's breast cancer which can be combined with other clinical risk factors that are routinely assessed, such as nodal status and tumour size, to better predict the risk of disease

recurrence in the future. Some tests may also predict the benefit a patient may receive from chemotherapy. This information is intended to help treatment decision-making with regard to adjuvant chemotherapy use.

The use of tumour profiling tests may improve the identification of people with early breast cancer who may not benefit from having adjuvant chemotherapy because they have a low risk of disease recurrence. These people could potentially avoid unnecessary treatment, and therefore they would not be exposed to the co-morbidities and negative impacts on quality of life that are associated with chemotherapy. The tests may also identify people with early breast cancer who have been identified as low risk of disease recurrence based on current clinical practice, but would actually benefit from chemotherapy. People with breast cancer and clinicians may also benefit from improved confidence in the appropriateness of the treatment they are having or recommending.

2.2 Product properties

2.2.1 EndoPredict (Myriad Genetics)

EndoPredict is a CE marked assay that is designed to predict the likelihood of metastases developing within 10 years of an initial diagnosis of breast cancer. The test is intended for use in pre- and post-menopausal women with early stage breast cancer with all of the following clinical features:

- oestrogen receptor (ER)-positive
- human epidermal growth factor 2 (HER2)-negative
- lymph node (LN)-negative or LN-positive (up to 3 positive nodes).

EndoPredict measures the expression of 12 genes: 3 proliferation associated genes, 5 hormone receptor associated genes, 3 reference (normalisation) genes and 1 control gene.

EndoPredict requires RNA samples extracted from formalin-fixed, paraffin-embedded (FFPE) breast cancer tissue. The test can be performed in a local laboratory using a VERSANT kPCR AD module (Siemens Healthcare Diagnostics). Alternatively, FFPE samples can be submitted to a Myriad Genetics pathology laboratory in Munich that is accredited by the Deutsche Akkreditierungsstelle, a national accreditation body for Germany.

The test process involves using a reverse transcription-quantitative polymerase chain reaction (RT-qPCR), in which target messenger RNAs are reverse transcribed, amplified and simultaneously detected. The raw data are then exported to online evaluation software (EndoPredict Report Generator)

which performs a quality check and calculates the EP score and the EPclin score.

The EP score is a number on a scale between 0 and 15. An EP score of less than 5 indicates low risk of distant disease recurrence reoccurring in the next 10 years. An EP score of 5 or more indicates a high risk of distant disease recurrence in the next 10 years.

The EPclin score is calculated by adding clinical data about tumour size and nodal status to the EP score. From the EPclin score, the probability of metastasis formation within 10 years is estimated, assuming 5 years of hormonal treatment. If the EPclin 10 year risk is less than 10% the patient is classed as low risk for metastases recurring in the next 10 years. If the EPclin 10 year risk is 10% or greater the patient is classed as high risk for metastases recurring in the next 10 years.

It takes approximately 2 days to receive the test results if a local pathology laboratory is used. The turnaround time is longer if samples are sent away for testing.

2.2.2 MammaPrint (Agendia)

MammaPrint is a CE marked microarray that is designed to assess the risk of distant recurrence within 5 years and whether a woman would benefit from chemotherapy. The test is intended for use in pre- and post-menopausal women with stage I or II breast cancer with the following clinical features:

- tumour size less than or equal to 5cm,
- LN-negative or LN-positive (up to 3 positive nodes)

The test can be used irrespective of ER and HER2 status, that is, it can be used for tumours that are ER-negative or ER-positive, and HER2-negative or HER2-positive.

MammaPrint measures the expression of 70 genes, including genes associated with 7 different parts of the metastatic pathway: growth and proliferation, angiogenesis, local invasion, entering the circulation, survival in the circulation, entering organs from the circulation, and adaption to the microenvironment at a secondary site.

The MammaPrint test is offered as an off-site service. In Europe, samples are sent for analysis at the Agendia laboratory in Amsterdam, the Netherlands. The test requires a FFPE breast cancer tissue sample from a surgical specimen or core needle biopsy.

The test process involves isolation of RNA from FFPE sample followed by reverse transcription of the RNA to get cDNA. The cDNA is amplified and labelled before being hybridised to the diagnostic microarray. The microarray is washed and then scanned using an Agilent DNA microarray scanner. The scan file is analysed using Agilent Feature Extraction Software and an algorithm is used to calculate the correlation of the sample profile to a "Low Risk" template profile on a scale of -1.000 to +1.000 with a cut off at 0. Pre-defined cut-off values are then used to determine the prognostic profile of the sample as low risk or high risk. The threshold was set such that women with a low risk result have a 10% risk of developing distant metastases over the next 10 years without any adjuvant hormone or chemotherapy.

Test results are available to healthcare professionals within 10 days of submitting the sample.

2.2.3 Oncotype DX Breast Recurrence Score (Genomic Health)

Oncotype DX Breast Recurrence Score (Oncotype DX) is designed to quantify the 10-year risk of distant recurrence and predict the likelihood of chemotherapy benefit. The test also reports the underlying tumour biology: ER, progesterone receptor (PR) and HER2 status. The test is intended for use in pre- and post-menopausal women with stage I or II breast cancer that has the following clinical features:

- LN-negative or LN-positive (up to 3 positive nodes),
- ER-positive
- HER2-negative.

Oncotype DX quantifies the expression of 21 genes. Of these, 16 are cancer-related genes correlated with distance recurrence-free survival, and 5 are reference genes for normalising the expression of the cancer-related genes. This information is used to calculate the breast recurrence score.

Oncotype DX is offered as a test service to the NHS. Samples are processed centrally at the Genomic Health Inc. laboratory in the US, which is accredited by the American Association for Laboratory Accreditation and the College of American Pathologists. The test requires a FFPE breast cancer tissue sample from a biopsy or surgical resection, which can be sent as a paraffin embedded block or as 15 unstained charged slides. The test process is based on RT-qPCR.

The test gives a recurrence score of between 0 and 100, which is used to quantify the 10 year risk of distant recurrence, assuming 5 years of hormonal therapy. A score below 18 indicates low risk of distant recurrence, a score

between 18 and 30 indicates intermediate risk of recurrence, and a score of 31 or more indicates high risk of recurrence.

The breast recurrence score also predicts the benefit of chemotherapy. A score below 18 predicts little to no chemotherapy benefit, a score between 18 and 30 predicts no substantial chemotherapy benefit, and a score of 31 or more predicts a large benefit from chemotherapy.

The breast recurrence score can be combined with clinical and pathological factors using the recurrence score-pathology-clinical (RSPC) calculator, however this calculator has not been validated.

The Oncotype DX Breast Recurrence Score results are typically reported within 7 to 10 calendar days after the sample is received at the laboratory.

2.2.4 Prosigna (NanoString technologies)

Prosigna is a CE marked assay designed to provide information on breast cancer subtype and to predict distant recurrence-free survival at 10 years. The test is intended for use in postmenopausal women with early stage breast cancer that is:

- LN-negative or LN-positive (up to 3 positive nodes)
- ER-positive
- HER2-negative.

Prosigna is based on the PAM50 gene signature. It measures the expression levels of 50 genes used for the intrinsic subtype classification algorithm. It also measures the expression of 8 housekeeping genes used for signal normalisation, 6 positive controls, and 8 negative controls.

The test requires RNA extracted from a FFPE breast tumour tissue sample and is done using the NanoString nCounter analysis system. The test process involves fluorescent probe pairs that hybridise to the mRNA, the fluorescence is then detected by the nCounter Digital Analyser.

Prosigna classifies samples into the following breast cancer subtypes based on their PAM50 gene expression signatures: luminal A, luminal B, HER2-enriched or basal-like. Risk of distant recurrence within 10 years, assuming 5 years of hormonal treatment, is then derived from an algorithm which is based on the results of the PAM50 gene signature, breast cancer subtype, tumour size, nodal status and proliferation score. The proliferation score is determined by evaluating multiple genes associated with the proliferation pathway. The risk of recurrence score is provided as a numerical score on a 0

to 100 scale that estimates the probability of distant recurrence over 10 years. Based on this score and the nodal status, samples are classified into risk categories:

- Node negative: low risk (0 to 40), intermediate risk (41 to 60), or high risk (61 to 100)
- Node positive (up to 3 positive nodes): low risk (0 to 15), intermediate risk (16 to 40), or high risk (41 to 100)

2.2.5 IHC4

The immunohistochemistry 4 (IHC4) test is a laboratory developed test that combines the results of 4 immunohistochemistry measured parameters with clinical and pathologic features. It is sometimes called the IHC4+C test. It is designed to quantify the risk of distant disease recurrence of breast cancer patients, assuming 5 years of hormone therapy. The test is intended for use in post-menopausal women with early stage breast cancer with the following clinical features:

- ER-positive
- LN-negative or LN-positive (up to 3 positive nodes)

The components of the test are 4 immunohistochemical assays: oestrogen receptor (ER), progesterone receptor (PR), HER2 and the proliferation marker Ki67. The IHC4 test is currently used within the Royal Marsden Breast Cancer Unit service, but the test could be run in local NHS laboratories if quality assurance programmes for the individual assays are in place. It uses FFPE breast tumour tissue samples and immunohistochemistry techniques that are universally available in NHS pathology departments. ER and HER2 markers are commonly measured in NHS laboratories. PR and Ki67 markers are not routinely measured in breast tumour tissue samples, but assays are commonly available for use when needed. The quantitative assessment of Ki67 required for the IHC4 test is not currently performed in most NHS laboratories and therefore further training for pathologists and biomedical scientists is likely to be needed.

The IHC4 test has an algorithm that calculates a risk score for distant recurrence based on the results of the 4 assays and clinical factors such as age, nodal status, tumour size, and grade. The algorithm has been published and is freely available, and a calculator is available for use on request. A distant recurrence score of less than 10% is categorised as low risk for distant recurrence at 10 years; a score of 10% or more but less than 20% is categorised as intermediate risk, and a score of 20% or more is categorised as high risk for distant recurrence at 10 years.

At the Royal Marsden NHS foundation trust the test is processed with an average estimated turnaround time of 1 week, however results may be made available in 2 working days if they are required urgently.

Table 1 Summary of technologies

Test	EndoPredict	MammaPrint	Oncotype DX Breast Recurrence Score	Prosigna	IHC4
Purpose	Recurrence risk	Recurrence risk and chemotherapy benefit	Recurrence risk and chemotherapy benefit	Intrinsic subtype and recurrence risk	Recurrence risk
Description	12 gene assay (RT-qPCR) + clinical factors	Microarray 70 gene array	RT-qPCR 21 gene assay	Direct mRNA counting + clinical factors 50 gene assay	4 IHC tests + clinical factors
Testing location	Local laboratory or test service (Germany)	Test service (the Netherlands)	Test service (US)	Local laboratory or test service (UK)	Local laboratory
Stage	Early stage	Early stage (stage I or II)	Early stage (stage I or II)	Early stage (stage I to IIIA)	Early stage
Lymph node status	LN- and LN+ (up to 3 positive)	LN- or LN+ (up to 3 positive)	LN- or LN+ (up to 3 positive)	LN- and LN+	LN- and LN+ (1 to 3 positive nodes)
Hormone receptor status	ER+	ER+ or ER-	ER+	ER+	ER+
HER2 status	HER2-	HER2- or HER2+	HER2-	HER2-	HER2-
Menopausal status	Pre- and post-menopausal	Pre- and post-menopausal	Pre- and post-menopausal	Post-menopausal	Post-menopausal
Test result	Low risk, high risk	Low risk, high risk	Low risk, intermediate risk, high risk	Low risk, intermediate risk, high risk Intrinsic subtype	Low risk, intermediate risk, high risk
Assumptions	Scores assume 5 years of hormonal treatment		Score assumes 5 years of hormonal treatment	Score assumes 5 years of hormonal treatment	Score assumes 5 years of hormonal treatment
Abbreviations: ER+/- oestrogen receptor positive or negative; LN+/- lymph node positive or negative; PR Progesterone receptor; HER2 human epidermal growth factor; IHC immunohistochemistry					

3 Target conditions

3.1 Early stage and locally advanced breast cancer

Breast cancer is the most common cancer and the third most common cause of cancer related deaths in the UK. One in 8 women and 1 in 870 men will be diagnosed with breast cancer during their lifetime (Cancer Research UK 2016). In 2014, 46,085 women and 332 men were diagnosed with new cases of breast cancer in England (Office for National Statistics 2016). The majority of cases develop in women that are over the age of 50 (Cancer Research UK 2016).

In 2014, 11,360 women and 73 men died from breast cancer in the UK (Cancer Research UK 2016). Breast cancer survival depends on the stage of the disease at diagnosis, treatment received and the biology of the tumour. More than 90% of women diagnosed with early breast cancer survive for at least 5 years, and 78% survive for 10 years (Cancer Research UK 2016). In contrast, only 13% of those diagnosed with advanced disease survive for more than 5 years.

A person's risk of developing breast cancer depends on many factors, including age, genetics and exposure to risk factors, including some preventable lifestyle factors. Preventable risk factors include obesity, alcohol use and exposure to oestrogen or ionising radiation. Factors that contribute to determining the success of treatment and prognosis include the tumour size, the molecular makeup of the tumour and whether the cancer has spread to other parts of the body, particularly the lymph nodes

3.2 Diagnostic and care pathway

3.2.1 Diagnosis and staging

Breast cancer may be diagnosed following an abnormal result in the NHS breast cancer screening programme, or after referral for further investigation because of signs or symptoms that could be associated with breast cancer. The referral criteria for suspected breast cancer are described in further detail in the NICE guideline on suspected cancer. People with suspected breast cancer will have further assessment in secondary care; initial tests may include mammography and/or ultrasound, and core biopsy and/or fine needle aspiration cytology. Tests to stage the cancer and determine how advanced it is may include magnetic resonance imaging, CT scans and bone scans.

Breast cancer is categorised into the following stages, stage I, II (A or B), III (A, B, or C), or IV, based on the tumour size and whether it has spread. Stages I, IIA, IIB and IIIA are classed as early stage breast cancer (Cancer Research UK 2014). Early stage breast cancer is cancer that has not spread beyond the breast or the lymph nodes in the armpit on the same side of the body. Early breast cancer can be locally advanced; this means that the cancer has not spread to distant parts of the body but has at least 1 of the following features:

- bigger than 5cm across
- growing into the skin or muscle of the chest
- present in the lymph nodes in the armpit.

3.2.2 Tumour tests and molecular breast cancer subtypes

When cancer cells have been detected in a biopsy sample, further tests are done to provide more information on the characteristics of the tumour. The results of these tests are used to classify the cancer and to determine which types of treatment it is most likely to respond to. Tumour tests can include hormone receptor and human epidermal growth factor receptor 2 (HER2) tests. Although not routinely done, some laboratories may also test for Ki67.

The NICE guideline on early and locally advanced breast cancer makes the following recommendations on tumour testing:

- Assess oestrogen receptor (ER) status of all invasive breast cancers, using immunohistochemistry with a standardised and qualitatively assured methodology, and report the results quantitatively.
- Do not routinely assess progesterone receptor (PR) status of tumours in patients with invasive breast cancer.
- Test HER2 status of all invasive breast cancers, using a standardised and qualitatively assured methodology.

The results of the test on ER status can be reported as the percentage of cancer cells that stain positive for oestrogen receptors, as an Allred score which is a scale between 0 and 8 that takes into account the proportion of cells staining positive and the intensity of staining, or as positive or negative using a threshold determined by the laboratory. Depending on the threshold used, if a cancer has cells that have oestrogen receptors it is classified as ER-positive and if it doesn't it is classified as ER-negative. ER-positive cancers may respond to hormone (endocrine) therapy which blocks the release of, or prevents the uptake of oestrogen and stops the cancer growing. Progesterone receptors may be tested using similar techniques.

HER2 is an oncogene which encodes for a cell-surface receptor. Cancer cells may have additional copies of *HER2* which leads to an increased number of HER2 receptors and growth of the cancer. HER2 status is assessed using either immunohistochemistry for HER2 protein overexpression or tests which detect *HER2* gene amplification such as fluorescence in situ hybridisation (FISH) or chromogenic in situ hybridisation (CISH). HER2 positive cancers may respond to treatment with trastuzumab, a biological treatment which targets HER2 receptors.

Although not routinely assessed to determine the most appropriate treatment, Ki67 may be measured to provide additional prognostic information. Ki67 is a marker of cell proliferation and is assessed using immunohistochemistry. When a greater number of cells are identified as Ki67 positive it is an indication that a cancer is growing more quickly.

These tumour tests can help to categorise a breast cancer into one of the molecular subtypes shown in table 2. These subtypes can be used to provide additional prognostic information which may help a clinician to determine the likely benefit of further systemic treatment (described in more detail in section 3.2.4) and radiotherapy.

Table 2 breast cancer molecular subtypes

Subtype	Hormone receptor status	HER2 status	Ki67	Prognosis
Luminal A	Positive (ER and/or PR)	Negative	Low levels	Low grade, tend to be slow growing and have good prognosis.
Luminal B	Positive (ER and/or PR)	Positive or negative	High levels	Grow slightly faster than luminal A and prognosis is slightly worse.
Basal-like (triple negative)	Negative (ER and PR)	Negative	-	Worse prognosis.
HER2-enriched	Negative (ER and PR)	Positive	-	Grow faster than luminal types and can have a worse prognosis.

3.2.3 Initial treatment

The NICE guideline on early and locally advanced breast cancer describes the care pathway. Surgery is often the initial treatment for early and locally advanced breast cancer. During surgery the sentinel axillary lymph nodes may be removed and subsequently assessed to detect whether breast cancer

cells are present. Surgical options include breast conserving surgery or a mastectomy, where the whole breast is removed. Some people may opt to have the breast reconstructed, which can be done at the time of the initial surgery or at a later date. Neoadjuvant treatment may be used before surgery, with the aim of reducing the size of the tumour to enable breast conserving surgery.

3.2.4 Adjuvant treatment selection and assessing risk of recurrence

After surgery, further treatment (adjuvant treatment) might be needed and this can include one or a combination of: radiotherapy, chemotherapy, hormone therapy or biological therapy. The decision to offer, and the selection of, adjuvant therapy is made taking into account the clinical history, stage of disease, the likely course of the disease (prognosis), the molecular characteristics of the tumour and a patient's preferences. The NICE guideline on early and locally advanced breast cancer makes the following recommendations on adjuvant therapy planning:

- Consider adjuvant therapy for all patients with early invasive breast cancer after surgery at the multidisciplinary team meeting and ensure that decisions are recorded.
- Decisions about adjuvant therapy should be made based on assessment of the prognostic and predictive factors, the potential benefits and side effects of the treatment. Decisions should be made following discussion of these factors with the patient.
- Consider using Adjuvant! Online to support estimations of individual prognosis and the absolute benefit of adjuvant treatment for patients with early invasive breast cancer.
- Start adjuvant chemotherapy or radiotherapy as soon as clinically possible within 31 days of completion of surgery in patients with early breast cancer having these treatments.

A variety of calculators that can help to predict the likelihood of breast cancer recurrence are available. These may be used to provide prognostic information to a patient and to guide the selection of adjuvant therapy. Expert advice suggests that PREDICT is the most widely used tool to calculate risk of recurrence, which is an online prognostic and treatment benefit calculator. The calculators are described in more detail in section 4.

3.2.5 Adjuvant treatments

Chemotherapy

Adjuvant chemotherapy often involves the use of multiple drugs in combination, known as regimens. The most commonly used chemotherapy drugs for breast cancer include: cyclophosphamide, doxorubicin, docetaxel, epirubicin, fluorouracil and methotrexate. The NICE guideline on early and locally advanced breast cancer makes the following recommendations on adjuvant chemotherapy:

- Offer docetaxel to patients with lymph node-positive breast cancer as part of an adjuvant chemotherapy regimen.
- Do not offer paclitaxel as an adjuvant treatment for lymph node-positive breast cancer.

In addition to the risk calculators, tumour profiling tests may be used to determine whether adjuvant chemotherapy is given. The Oncotype DX test is recommended as an option for guiding adjuvant chemotherapy decisions in NICE diagnostics guidance on gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management for people with ER-positive, HER2-negative, LN-negative breast cancer, who are assessed as being at intermediate risk. Expert advice suggests that clinical practice varies and the test is sometimes offered to those with a 3% benefit from chemotherapy or more, as defined by the PREDICT tool.

The use of tumour profiling tests including, EndoPredict, MammmaPrint, Prosigna and Oncotype DX is recommended in the European clinical practice guideline produced by the European society for medical oncology (Senkus et al. 2015). It states that these tests may be used to gain additional prognostic information to complement pathology assessment and to predict the benefit of adjuvant chemotherapy. The guideline does not recommend one test over another.

A guideline produced by the American society for clinical oncology on the use of biomarker assays to guide decisions on adjuvant systemic therapy for early-stage invasive breast cancer, recommends the use of gene expression profiling tests, that is Endopredict and Oncotype DX, for women with ER-positive, HER2-negative breast cancer if they are lymph node-negative, but not if they are lymph node-positive. Other biomarker assays with sufficient evidence of clinical utility in specific subgroups of breast cancer included: PAM50, Breast Cancer Index, urokinase plasminogen activator and

plasminogen activator inhibitor type 1. IHC4 test was not recommended (Harris et al 2016).

Hormone therapy

Hormone (or endocrine) therapy may be offered to people who have ER-positive or PR-positive cancers. The aim of hormone therapy is to stop the growth of the cancer by blocking the availability of hormones such as oestrogen and progesterone. The selection of hormonal therapy also takes into account a person's menopausal status. The NICE guideline on early and locally advanced breast cancer makes the following recommendations on hormone therapy:

- Do not offer adjuvant ovarian ablation/suppression to premenopausal women with ER-positive early invasive breast cancer who are being treated with tamoxifen and, if indicated, chemotherapy.
- Offer adjuvant ovarian ablation/suppression in addition to tamoxifen to premenopausal women with ER-positive early invasive breast cancer who have been offered chemotherapy but have chosen not to have it.
- Postmenopausal women with ER-positive early invasive breast cancer who are not considered to be at low risk should be offered an aromatase inhibitor, either anastrozole or letrozole, as their initial adjuvant therapy. Offer tamoxifen if an aromatase inhibitor is not tolerated or contraindicated.
- Offer an aromatase inhibitor, either exemestane or anastrozole, instead of tamoxifen to postmenopausal women with ER-positive early invasive breast cancer who are not low risk and who have been treated with tamoxifen for 2–3 years.
- Offer additional treatment with the aromatase inhibitor letrozole for 2–3 years to postmenopausal women with lymph node-positive ER-positive early invasive breast cancer who have been treated with tamoxifen for 5 years.
- The aromatase inhibitors anastrozole, exemestane and letrozole, within their licensed indications, are recommended as options for the adjuvant treatment of early ER-positive invasive breast cancer in postmenopausal women.

Biological therapy

Trastuzumab (Herceptin) is a recombinant humanised IgG1 monoclonal antibody directed against human epidermal growth factor receptor 2 (HER2). The aim of treatment with trastuzumab is to stop the growth of the cancer by blocking the HER2 receptors. Trastuzumab is licensed for the treatment of patients with early-stage HER2+ breast cancer, following surgery,

chemotherapy (adjuvant or neoadjuvant) and radiotherapy (if applicable). The NICE guideline on early and locally advanced breast cancer makes the following recommendations on using trastuzumab:

- Offer trastuzumab, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), as an adjuvant treatment to women with HER2+ early invasive breast cancer following surgery, chemotherapy, and radiotherapy when applicable.
- Assess cardiac function before starting treatment with trastuzumab. Do not offer trastuzumab treatment to women who have any of the following:
    - a left ventricular ejection fraction (LVEF) of 55% or less
    - a history of documented congestive heart failure
    - high-risk uncontrolled arrhythmias
    - angina pectoris requiring medication
    - clinically significant valvular disease
    - evidence of transmural infarction on electrocardiograph (ECG)
    - poorly controlled hypertension.
- Repeat cardiac functional assessments every 3 months during trastuzumab treatment. If the LVEF drops by 10 percentage (ejection) points or more from baseline and to below 50% then trastuzumab treatment should be suspended. Restart trastuzumab therapy only after further cardiac assessment and a fully informed discussion of the risks and benefits with the woman.

The guideline development group also made a recommendation for further research to assess how effective trastuzumab is as an adjuvant therapy without chemotherapy.

Radiotherapy

Radiotherapy may also be offered, depending on the type of surgery done and the risk of recurrence. The NICE guideline on early and locally advanced breast cancer makes the following recommendations on radiotherapy:

- Radiotherapy after breast conserving surgery:
    - Patients with early invasive breast cancer who have had breast conserving surgery with clear margins should have breast radiotherapy.
- Radiotherapy after mastectomy:
    - Offer adjuvant chest wall radiotherapy to patients with early invasive breast cancer who have had a mastectomy and are at a high risk of local recurrence. Patients at a high risk of local recurrence include those with four or more positive axillary lymph nodes or involved resection margins.

- Do not offer radiotherapy following mastectomy to patients with early invasive breast cancer who are at low risk of local recurrence (for example, most patients who are lymph node-negative).

3.3 Patient issues and preferences

Adjuvant treatments for breast cancer can cause side-effects, such as persistent fatigue, pain and nausea. Adjuvant chemotherapy is associated with additional side-effects, such as infections, osteoporosis, hair loss and temporary or permanent infertility. In addition to the adverse physical effects caused by breast cancer and its treatment, patients may experience psychological effects which may also extend to their families and carers. These effects can have an impact on quality of life. Most people will have surgery which can be associated with pain and scarring.

People may experience anxiety while waiting for tumour profiling test results, and about making a treatment decision after the results come back. Providing information which explains the purposes of the tests and the test results in an accessible format can help people to make an informed decision about whether they wish to have the test and whether they want to have adjuvant chemotherapy.

The use of the tumour profiling tests may enable some people to avoid the adverse effects of adjuvant chemotherapy. However, some people may want to have chemotherapy even if they are identified as low risk. Other people may decide that, regardless of the disease prognosis, they do not want to have chemotherapy, due to age, comorbidities or other factors.

4 Comparator

The comparator for this assessment is current decision making for adjuvant chemotherapy prescribing, which is based on clinical and pathological features or the results of tools used to assess risk. Features may include the stage of the disease, nodal status, ER or PR status, HER2 status and any previous treatment (for example, neoadjuvant therapy). Risk assessment tools are often available as online calculators. Expert advice suggests that the most commonly used online risk calculator is PREDICT. The Nottingham Prognostic Index (NPI) and Adjuvant! Online have also been used previously.

4.1 PREDICT

The PREDICT calculator is an online prognostic and treatment benefit tool that presents 5 and 10 year survival estimates following surgery both with and

without adjuvant therapy (hormone therapy, chemotherapy and trastuzumab). It uses information on patient age, tumour size, tumour grade, number of positive nodes, ER status, HER2 status, Ki67 status and mode of detection (screening or symptomatic).The decision rule for the calculator is based on the 10-year survival benefit from chemotherapy. If the benefit is less than 3% then chemotherapy is not recommended, if the benefit is between 3% and 5% chemotherapy is discussed as a possible option and if the benefit is more than 5% chemotherapy is recommended. The tool has been validated using data from 5000 people from the West Midlands Cancer Intelligence unit and from a data set that had previously been used to validate Adjuvant! Online.

4.2 Adjuvant! Online

The Adjuvant! Online tools are intended to estimate the risk of negative outcomes (cancer mortality or relapse) both with and without systemic adjuvant therapy. To use the tools, patient age and comorbidities are required to be input in addition to the following tumour characteristics: size, ER status and number of involved lymph nodes. Results may be displayed and printed in graphical form to aid shared decision-making. Adjuvant! Online is temporarily unavailable as it is being updated with new information. It is not certain when the service will be reinstated, at present the website directs people to use the PREDICT tool.

4.3 Nottingham Prognostic Index (NPI)

The NPI is a validated equation which predicts 5 year survival for operable primary breast cancer. The NPI takes into account grade as well as size and spread of the tumour. Better prognosis is associated with small tumour size, younger age, lymph node-negative, ER-positive and progesterone receptor-positive status.

5 Scope of the assessment

Table 3 Scope of the assessment

Decision question	Do tumour profiling tests used for guiding adjuvant chemotherapy decisions for people with early stage breast cancer (described in section 1.6 of NICE CG80) represent a clinically- and cost-effective use of NHS resources?
Populations	People with ER-positive (and/or PR-positive), HER2-negative, early stage breast cancer (stages I or II) with 0 to 3 positive lymph nodes.

	Where data permits, the following subgroups may be considered: • People with lymph node negative cancer; people with micro-metastases in the lymph nodes; and people with 1 to 3 positive lymph nodes • Premenopausal women and postmenopausal women • People predicted to be at low, intermediate or high risk using a risk assessment tool, or using clinical and pathological features • Males and females • People of different ethnicities
Interventions	• EndoPredict • MammaPrint • Oncotype DX Breast Recurrence Score • Prosigna • IHC4 In combination with current decision making.
Comparators	• Current decision making, which may include any tool, or clinical and pathological features, used to assess risk
Healthcare setting	Secondary and tertiary care
Outcomes	Intermediate measures for consideration may include: • Time to test results • Analytical validity • Prognostic ability • Ability to predict benefit from chemotherapy • Impact of test results on decision making
	Clinical outcomes for consideration may include: • disease free survival • overall survival • distant recurrence • disease-related morbidity and mortality • chemotherapy-related morbidity and mortality
	Patient-reported outcomes for consideration may include: • Health related quality of life • Anxiety
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include:

	• Costs of treating breast cancer, including: drug cost, administration cost, outpatient appointments, and treatment of adverse events • Costs of the tests, including equipment costs and reagents when relevant • Costs of staff and associated training
	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

6 Other issues for consideration

NICE is updating guidance on early and locally advanced breast cancer (CG80), this update will look at several different areas of the care pathway, including: adjuvant systemic therapy planning using risk assessment tools such as Adjuvant! Online and PREDICT; and the optimal adjuvant endocrine therapy for people with ER-positive breast cancer. This guidance is expected to publish in July 2018.

The risk scores from EndoPredict, Oncotype DX Breast Recurrence Score, Prosigna and IHC4 all assume 5 years of hormonal treatment. If this treatment is not adhered to, then the risk of recurrence may be different. In key trials the hormonal treatment used was tamoxifen, however, recent guidance recommends the use of an aromatase inhibitor instead of tamoxifen. The difference in hormonal treatment may have an effect on the risk of recurrence.

In the base case analysis, tests should be assessed in line with their intended use (see table 1). Three of the tests included in the scope incorporate clinical and pathological features into the test results (EndoPredict, Prosigna and IHC4). However, evidence may be available on test results or versions of the test which do not formally incorporate clinical and pathological features. The other 2 tests do not formally include clinical and pathological features (MammaPrint and Oncotype DX Breast Recurrence Score). However, evidence may exist in which additional algorithms have been used to formally incorporate clinical and pathological features. Where such studies are identified, the differences between the versions of the tests or the information it provides should be noted and, where appropriate, the impact of this could be explored in narrative or sensitivity analyses. For all tests, clinicians would interpret the test results alongside clinical and pathological features when making treatment decisions.

Several trials of tumour profiling tests are currently ongoing, including:

- TAILORx - a 10 year prospective randomised trial on the use of chemotherapy in women. Results from an analysis of data from the lowest-risk group have been reported. Data collection and analysis from women who had an intermediate Oncotype DX Breast Recurrence Score (11 to 25) is due to complete by December 2017.
- RxPONDER - a randomised trial for people with 1 to 3 positive nodes with an Oncotype DX Breast Recurrence Score of 25 or less. It is due to complete by February 2022.
- MINDACT - a prospective randomised trial comparing the use of MammaPrint with standard clinical practice for people with node-negative breast cancer. The first results were published in 2016, and the ongoing trial is due to complete by March 2020.

7 Potential equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

All people with cancer are covered under the disability provision of the Equality Act (2010) from the point of diagnosis. Breast cancer is less common in men than women, 1 in 870 men and 1 in 8 women will have breast cancer over their lifetime. Breast cancer is underdiagnosed and often undertreated in men.

Women of African family origin are more likely to develop breast cancer at an earlier age and to have a more aggressive form of the disease compared with other women.

8 Potential implementation issues

Oncotype DX Breast Recurrence Score (Oncotype DX) is currently widely used in clinical practice in the NHS. Therefore, it is likely that major adoption issues would not occur if other tumour profiling tests were to be recommended for use.

8.1 Clinician confidence

Oncotype DX is well adopted in clinical practice in the NHS, indicating a good level of clinician awareness and acceptability. EndoPredict, MammaPrint, Prosigna and IHC4 are not currently widely use in the NHS.

8.2 Capacity

Clinical experts noted that there is a national shortage of pathologists (particularly with an interest in breast cancer), and therefore it may be difficult for local laboratories to adopt tumour profiling tests due to limited capacity.

8.3 Patient acceptance

Clinical experts noted that tumour profiling tests help involve people with breast cancer and their carers in treatment decision making.

8.4 Patient selection

Different oncologists use different risk assessment tools to decide who should be offered a tumour profiling test, for example the Nottingham Prognostic Index (NPI), Adjuvant!Online or PREDICT. The choice of the initial decision making tool may influence subsequent treatment options.

8.5 Location of testing

Some tumour profiling tests have the option of testing samples in a local laboratory or sending samples away for testing in a centralised laboratory. The location of the testing may impact on factors such as test throughput, processing errors, quality assurance and the level of training required.

8.6 Interpreting and acting on the results

Some tumour profiling tests provide results as low risk, intermediate risk or high risk of distant recurrence, whereas others report a binary risk level of either low or high. Clinical expert noted that intermediate risk results can be problematic as they introduce uncertainty about optimal treatment planning.

When trusts are new to tumour profile testing, agreement would need to be reached on who will take responsibility for acting on the test result. Training on interpretation would also be required to support safe adoption.

8.7 Costs

The volume of samples processed affects cost efficiency, so consideration would need to be given to whether testing is done locally or samples are sent away for testing.

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Appendix A Glossary of terms

Adjuvant therapy
Additional cancer treatment given after primary treatment to lower the risk that cancer will come back. Adjuvant therapy may include chemotherapy, radiotherapy, hormone therapy or biological therapy.

Cell surface receptors
Molecules on the surface of a cell which receive chemical signals from outside the cell, causing a cellular response. Cell surface receptors important in breast cancer development include hormone receptors (which respond to oestrogen or progesterone) and HER2 receptors. Blocking the activity of these receptors can prevent the cancer growing

Cell proliferation
An increase in the number of cells which occurs because of increased cell growth and division. Cancers which show increased cell proliferation may be more aggressive.

Distant recurrence
Cancer that comes back in a different area to the original cancer after initial treatment.

Hormone (endocrine) therapy
Hormones such as oestrogen and progesterone can fuel the growth of breast cancer. Hormone therapies, such as tamoxifen and aromatase inhibitors, aim to block the availability of hormones such as oestrogen and progesterone and prevent the cancer growing.

Local recurrence
Cancer that comes back in the same place as the original cancer after initial treatment.

Appendix B Abbreviations

ASCO	American society for clinical oncology
EP	EndoPredict
ER	Oestrogen receptor
EPclin	EndoPredict clinical
ESMO	European society for medical oncology
FDA	US food and drug administration
FFPE	Formalin-fixed paraffin-embedded
HER2	Human epidermal growth factor 2
IHC4	Immunohistochemistry 4
LN	Lymph node
NICE	National Institute for Health and Care Excellence
NPI	Nottingham prognostic index
PCR	Polymerase chain reaction
PR	Progesterone receptor
RNA	Ribonucleic acid
RT-qPCR	Reverse transcription-quantitative polymerase chain reaction

Appendix C References

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