NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

Tumour profiling tests to guide adjuvant chemotherapy decisions in lymph node-positive early breast cancer (provisional title)

Draft scope

March 2023

1 Introduction

The topic selection oversight panel identified tumour profiling tests to guide adjuvant chemotherapy decisions in lymph node-positive early breast cancer as suitable for evaluation by the Diagnostics Assessment Programme based on a topic briefing. This was developed following a specific request from NHS England to re-examine the use of these tests in people with lymph node-positive early breast cancer.

Questions for consultation on this draft scope are set out in appendix A. A glossary of terms is provided in appendix B.

2 Description of the technologies

This section describes the properties of the technologies based on information provided to NICE by manufacturers 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. This assessment will not assess using the tests to inform neoadjuvant chemotherapy, endocrine or biological therapy treatment decisions.

The use of tumour profiling tests may improve the identification of people with lymph node-positive 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 lymph node-positive 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.

NICE diagnostics guidance 34 makes recommendations on the use of tests for people with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative and lymph node (LN)-negative (including micrometastatic disease) early breast cancer. This guidance will assess use of the tests for people whose ER-positive, HER2-negative cancer has spread to the lymph nodes (LN-positive early breast cancer).

2.2 Product properties

2.2.1 EndoPredict (Myriad Genetics)

EndoPredict is a CE marked assay that is designed to predict the likelihood of distant recurrence within 10 years of an initial diagnosis of breast cancer, as well as the absolute benefit of chemotherapy. The test is for pre- and postmenopausal people with early breast cancer with all of the following clinical features:

- ER-positive
- HER2-negative
- 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 done in a local laboratory or the Myriad Genetics pathology laboratory in the USA. 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.

The test process uses reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Online evaluation software (EndoPredict Report Generator) performs a quality check and calculates the EPclin score. The EPclin score is calculated by adding clinical data about tumour size and nodal status to the EP score. This can be used to estimate the likelihood of distant recurrence, assuming 5 years of endocrine therapy. An EPclin score of less than 3.3 indicates low risk (less than 10%) of distant recurrence in the next 10 years. An EPclin score of 3.3 or more indicates high risk of distant recurrence in the next 10 years. These categories can also be used to estimate absolute chemotherapy benefit, in which people with an EPclin score of less than 3.3 are less likely to benefit from adjuvant chemotherapy.

2.2.2 MammaPrint (Agendia)

MammaPrint is a CE marked microarray that is designed to assess the risk of distant recurrence within 10 years and whether a person would benefit from chemotherapy. The test is intended for use in people with primary stage 1, 2 or operable stage 3 breast cancer with the following clinical features:

- Hormone receptor (HR)-positive
- HER2-negative
- tumour size less than or equal to 5 cm
- LN-negative or LN-positive (up to 3 positive nodes).

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.

The test is based on diagnostic microarray. Software is used to calculate the MammaPrint result on a scale of −1 to +1. The score indicates the risk of developing distant metastases over the next 10 years without any adjuvant endocrine therapy or chemotherapy. A MammaPrint result of 0 or less indicates high risk of metastases in the next 10 years and a result of more than 0 indicates low risk (10% or less) of metastases in the next 10 years. Test results are available to healthcare professionals within 10 days of submitting the sample.

2.2.3 Oncotype DX Breast Recurrence Score (Exact Sciences)

Oncotype DX Breast Recurrence Score (Oncotype DX) is designed to quantify the 9-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 people with early breast cancer that has the following clinical features:

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

Oncotype DX quantifies the expression of 21 genes. Of these, 16 are cancer-related genes correlated with distant 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 Exact Sciences 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 uses RT-qPCR.

The test gives a recurrence score of between 0 and 100, which is used to estimate the 9-year risk of distant recurrence, assuming 5 years of hormonal therapy. The company states that the recurrence score also predicts the benefit of chemotherapy (in terms of reducing risk of distant recurrence). For LN-positive disease (1 to 3 positive nodes), the instructions for use state that a score below 18 predicts little to no chemotherapy benefit, a score between 18 and 30 predicts a potential chemotherapy benefit, and a score of 31 or more predicts a large benefit from chemotherapy. However, the company's website [accessed 27 February 2023], states that a recurrence score of 25 or less predicts no chemotherapy benefit for post-menopausal women and 2.9% benefit at 5 years for pre-menopausal women. In both groups, a score of 26 to 100 is stated to predict substantial chemotherapy benefits.

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 (Veracyte)

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 for post-menopausal women with early breast cancer that is:

- HR-positive
- HER2-negative
- LN-negative or LN-positive (up to 3 positive nodes, or 4 or more positive nodes).

Prosigna measures the expression of 50 genes used for intrinsic subtype classification, 8 housekeeping genes used for signal normalisation, 6 positive controls, and 8 negative controls. The test uses RNA extracted from a FFPE breast tumour tissue sample, and can be performed in local laboratories provided they have access to the NanoString nCounter Dx Analysis System. The company state that results are usually available within 3 days.

Prosigna classifies the risk of distant recurrence within 10 years, assuming 5 years of endocrine therapy, based on 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 test gives a score between 0 and 100. Based on this score and the nodal status, samples are classified into risk categories. For LN-positive disease (up to 3 positive nodes), 0 to 15 indicates low risk, 16 to 40 intermediate risk, and 41 to 100 high risk. For 4 or more positive nodes, any score is assigned high risk.

Table 1: Overview of tumour profiling tests

Test	EndoPredict EPClin score	MammaPrint	Oncotype DX Breast Recurrence Score	Prosigna
Purpose	Recurrence risk and chemotherapy benefit	Recurrence risk and chemotherapy benefit	Recurrence risk and chemotherapy benefit	Intrinsic subtype and 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
Testing location	Local laboratory or test service (USA)	Test service (the Netherlands)	Test service (USA)	Local laboratory
Stage	Early stage	Early stage (stage 1, 2 or operable stage 3)	Early stage (stage 1 to 3A)	Early stage (stage 1 to 3A)
Lymph node status	LN− or LN+ (up to 3 positive nodes)	LN− or LN+ (up to 3 positive nodes)	LN− or LN+ (up to 3 positive nodes)	LN− and LN+ (up to 3 positive nodes, and 4+ nodes)
Hormone receptor status	ER+	HR+	HR+	HR+
HER2 status	HER2−	HER2−	HER2−	HER2−
Menopausal status	Pre- and post-menopausal	Pre- and post-menopausal	Pre- and post-menopausal	Post-menopausal
Test result	Low risk, high risk Chemotherapy benefit	Low risk, high risk Chemotherapy benefit	Risk of recurrence Chemotherapy benefit	Low risk, intermediate risk, high risk Intrinsic subtype
Assumptions	Assumes 5 years of endocrine treatment	Assumes no therapy	Assumes 5 years of endocrine treatment	Assumes 5 years of endocrine treatment

Abbreviations: ER, oestrogen receptor; HER2, human epidermal growth factor; HR, hormone receptor; LN, lymph node; RT-qPCR, reverse transcription-quantitative polymerase chain reaction

3 Target conditions

3.1 Early 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 7 women will be diagnosed with breast cancer during their lifetime (Cancer Research UK 2021). In 2020, 44,943 women and 348 men were diagnosed with new cases of breast cancer in England (NHS Digital 2022). The majority of cases develop in women who are over the age of 50 (Cancer Research UK 2020).

In 2020, 9,639 women and 95 men died from breast cancer in the UK (NHS Digital 2022). Breast cancer survival depends on the stage of the disease at diagnosis, treatment received and the biology of the tumour. Around 98% of women diagnosed with stage 1 breast cancer survive for at least 5 years (Cancer Research UK 2020). In contrast, only 25% of those diagnosed with stage 4 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 (Cancer Research UK 2020). 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.

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

3.2 Diagnostic and care pathway

3.2.1 Diagnosis

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.

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.

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

- Request the ER, PR and HER2 status of all invasive breast cancers simultaneously at the time of initial histopathological diagnosis.
- Assess the ER, PR and HER2 status of all invasive breast cancers using standardised and quality-assured techniques and report the results quantitatively.
- Ensure that the ER, PR and HER2 statuses are available and recorded at the preoperative and postoperative multidisciplinary team meetings when systemic treatment is discussed.

ER- or PR-positive cancers may respond to endocrine (hormone) therapy which blocks the release of or prevents the uptake of oestrogen and stops the cancer growing.

Receptor statuses 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 sections 3.2.4 and 3.2.5) and radiotherapy.

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 then 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, endocrine 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 the patient's preferences. The NICE guideline on early and locally advanced breast cancer makes the following recommendations on adjuvant therapy planning:

- Consider adjuvant therapy after surgery for people with invasive breast cancer, and ensure that recommendations are recorded at the multidisciplinary team meeting.
- Base recommendations about adjuvant therapy on multidisciplinary team assessment of the prognostic and predictive factors, and the possible risks and benefits of the treatment. Make decisions with the person after discussing these factors.
- Use the PREDICT tool to estimate prognosis and the absolute benefits of adjuvant therapy for women with invasive breast cancer.
- When using version 2.0 of the PREDICT tool, be aware that:

- it is less accurate for:
  - women under 30 with ER-positive breast cancer
  - women aged 70 and over
  - women with tumours larger than 5 cm
- it has not been validated in men and
- the validation may have under-represented some ethnic groups.

Note the potential limitations in versions of PREDICT after 2.0 may differ from those listed here.

A variety of calculators such as PREDICT are available that can help to predict the likelihood of breast cancer recurrence. These may be used to provide prognostic information to a patient and to guide the selection of adjuvant therapy. The calculators are described in more detail in section 4.

3.2.5 Adjuvant treatments

3.2.5.1 Chemotherapy

Adjuvant chemotherapy often involves the use of multiple drugs in combination, known as regimens.

The NICE guideline on early and locally advanced breast cancer has recommendations on adjuvant chemotherapy use. These include:

- For people with breast cancer of sufficient risk that chemotherapy is indicated, offer a regimen that contains both a taxane and an anthracycline. Please refer to the summaries of product characteristics for individual taxanes and anthracyclines because there are differences in their licensed indications.
- Discuss with people the benefits and risks of adding a taxane to anthracycline-containing regimens (further detail is provided in the guidance).
- Weekly and fortnightly paclitaxel should be available locally because these regimens are tolerated better than 3-weekly docetaxel, particularly in people with comorbidities.

Tumour profiling tests

In addition to the risk calculators, tumour profiling tests may be used to determine whether adjuvant chemotherapy should be offered. NICE diagnostics guidance on tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer provides recommendations on using the tests for people with ER-positive, HER2-negative and LN-negative (including micrometastatic disease) early breast cancer.

The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for early breast cancer recommend that gene expression assays such as MammaPrint, Oncotype DX, Prosigna, EndoPredict or Breast Cancer Index can be used in cases of uncertainty regarding indications for adjuvant chemotherapy, after consideration of all clinical and pathological factors.

The American Society for Clinical Oncology (ASCO) guideline on Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer recommends that various tumour profiling tests can be used for specific populations (Table 2).

Table 2: ASCO recommendations on using tumour profiling tests to guide decisions on adjuvant chemotherapy for people with LN-positive breast cancer

Test	Recommended population
Oncotype DX	Post-menopausal, 1 to 3 positive nodes
EndoPredict	Post-menopausal, 1 to 3 positive nodes
MammaPrint	Age 51 or over, high clinical risk, 1 to 3 positive nodes
Prosigna	No LN-positive population recommendations
IHC4	1 to 3 positive nodes, if the assay has been validated and if multigene assays are not available

3.2.5.2 Endocrine therapy

Endocrine (or hormone) therapy may be offered to people who have ER-positive or PR-positive cancers. The aim of endocrine therapy is to stop the growth of the cancer by blocking the availability of hormones such as oestrogen and progesterone. The selection of endocrine 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 adjuvant endocrine therapy:

- Offer tamoxifen as the initial adjuvant endocrine therapy for men and premenopausal women with ER-positive invasive breast cancer.
- Offer an aromatase inhibitor as the initial adjuvant endocrine therapy for postmenopausal women with ER-positive invasive breast cancer who are at medium or high risk of disease recurrence. Offer tamoxifen to women who are at low risk of disease recurrence, or if aromatase inhibitors are not tolerated or are contraindicated.
- Offer extended therapy (total duration of endocrine therapy of more than 5 years) with an aromatase inhibitor for postmenopausal women with ER-positive invasive breast cancer who are at medium or high risk of disease recurrence and who have been taking tamoxifen for 2 to 5 years. Medium or high risk may include people who have lymph node-positive breast cancer, with tumours that are T2 or greater and higher grade.
- Consider extended therapy (total duration of endocrine therapy of more than 5 years) with an aromatase inhibitor for postmenopausal women with ER-positive invasive breast cancer who are at low risk of disease recurrence and who have been taking tamoxifen for 2 to 5 years. Low risk may include people with lymph node-negative breast cancer, with smaller or lower-grade tumours.
- Consider extending the duration of tamoxifen therapy for longer than 5 years for both premenopausal and postmenopausal women with ER-positive invasive breast cancer.
- Discuss the benefits and risks of extended endocrine therapy with women.

Another form of endocrine therapy is ovarian function suppression. This is a treatment that stops or lowers the amount of oestrogen made by the ovaries through surgery, radiotherapy or drugs. The NICE guideline on early and locally advanced breast cancer makes the following recommendations on ovarian function suppression:

- Consider ovarian function suppression in addition to endocrine therapy for premenopausal women with ER-positive invasive breast cancer.
- Discuss the benefits and risks of ovarian function suppression in addition to endocrine therapy with premenopausal women with ER-positive invasive breast cancer. Explain to women that ovarian function suppression may be most beneficial for those women who are at sufficient risk of disease recurrence to have been offered chemotherapy.

3.2.5.3 Bisphosphonate therapy

Bisphosphonates are a class of drugs used to slow down or prevent damage to bone. The NICE guideline on early and locally advanced breast cancer makes the following recommendations on adjuvant bisphosphonate therapy for people with LN-positive breast cancer:

- Offer bisphosphonates (zoledronic acid or sodium clodronate) as adjuvant therapy to postmenopausal women with node-positive invasive breast cancer.
- Discuss the benefits and risks of bisphosphonate treatment with women, particularly the risk of osteonecrosis of the jaw, atypical femoral fractures and osteonecrosis of the external auditory canal. Follow the Medicines and Healthcare products Regulatory Agency/Commission on Human Medicines (MHRA/CHM) advice on bisphosphonates.

Bisphosphonates are usually given alongside chemotherapy.

3.2.5.4 Radiotherapy

Radiotherapy may also be offered, depending on the type of surgery done and the risk of recurrence. Recommendations on radiotherapy for people with LN-positive breast cancer can be found in the NICE guideline on early and locally advanced breast cancer.

3.2.5.5 Biological therapy

NICE's technology appraisal guidance TA810 recommends that the biological drug abemaciclib with endocrine therapy is an option for adjuvant treatment of HR-

positive, HER2-negative, node-positive early breast cancer in adults whose disease is at high risk of recurrence, defined by the following clinical and pathological features:

- at least 4 positive axillary lymph nodes, or
- 1 to 3 positive axillary lymph nodes, and at least one of the following criteria:
  - grade 3 disease (defined as at least 8 points on the modified Bloom–Richardson grading system or equivalent), or
  - primary tumour size of at least 5 cm.

If adjuvant chemotherapy is given, clinical experts advised that abemaciclib would normally be started after completion of the chemotherapy course. Decisions on biological therapy are made independently of decisions about chemotherapy.

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, infertility, and increased risk of cardiomyopathy and leukaemia. People with comorbidities may be particularly susceptible to these side effects and so have more reason to avoid chemotherapy, such as those with cardiac conditions. Dose reductions or delays to treatment because of side effects may have an effect on the efficacy of chemotherapy.

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.

Using 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 they do not want or are not able to have chemotherapy regardless of the disease prognosis, due to age, comorbidities or other factors. In these cases, risk profiles from tumour profiling tests may only result in anxiety if they predict high risk of recurrence without the possibility of further treatment.

4 Comparator

The comparator for this assessment is decision making for adjuvant chemotherapy prescribing (without use of the technologies being assessed), 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) is also used in some areas.

4.1 PREDICT

The PREDICT calculator is an online prognostic and treatment benefit tool that presents 5-, 10- and 15-year survival estimates following surgery both with and without adjuvant therapy (endocrine therapy, chemotherapy, bisphosphonates and trastuzumab). It uses information on age, tumour size, tumour grade, number of positive nodes, menopausal status, ER status, HER2 status, Ki67 status and mode of detection (screening or symptomatic).

The PREDICT website [accessed 6 March 2023] states the following about interpreting the risk score produced and the need for further treatment: “the Cambridge Breast Unit uses the absolute 10-year survival benefit from chemotherapy to guide decision making. 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 5,000 people from the West Midlands Cancer Intelligence unit and from a data set of 3,140 people from British Columbia, Canada. There are limitations to the validation set (see section 3.2.4), for example that it did not include men. Future versions of the tool are planned to include the effects of PR status and the benefits of radiotherapy, as well as the potential harms of treatments.

4.2 Nottingham Prognostic Index (NPI)

The Nottingham Prognostic Index (NPI) is a validated equation which predicts 5-year survival for operable primary breast cancer. The NPI incorporates tumour grade, size and number of positive nodes. Experts advised that the NPI is used in some centres where access to the internet is not available or consistent. The NPI can be used to define 3 prognostic groups:

- Less than 3.4: good prognosis
- 3.5 to 5.4: moderate prognosis
- 5.5 or higher: poor prognosis.

People with moderate or poor prognosis are usually considered for adjuvant chemotherapy.

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 lymph node-positive early breast cancer represent a clinically- and cost-effective use of NHS resources?
Populations	People with ER-positive, HER2-negative, early breast cancer with 1 to 3 positive lymph nodes, who are deciding whether to have adjuvant chemotherapy. Where data permits, the following subgroups may be considered: • Premenopausal women and postmenopausal women • People predicted to be in low, intermediate or high risk groups using a risk assessment tool (such as PREDICT or NPI), or using clinical and pathological features

	• Sex • People of different ethnicities • People with comorbidities which mean that they could be particularly affected by the side effects of chemotherapy
Interventions	• EndoPredict EPclin score • MammaPrint • Oncotype DX Breast Recurrence Score • Prosigna in combination with current decision making.
Comparator	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	Intermediate measures for consideration may include: • Prognostic ability • Ability to predict benefit from chemotherapy • Impact of test results on decision making
Outcomes: clinical	Clinical outcomes for consideration may include: • disease free survival • overall survival • distant recurrence • disease-related morbidity and mortality • chemotherapy-related morbidity and mortality
Outcomes: patient-reported	Patient-reported outcomes for consideration may include: • Health related quality of life • Anxiety
Outcomes: costs	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
Measuring cost-effectiveness	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

6.1 Previous assessments

The external assessment group for NICE's diagnostics guidance on tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer created an economic model that included the LN-positive population. It is possible that this model could also be used in this assessment, provided it is updated to account for changes to clinical practice and the evidence base since the previous guidance was published.

6.2 Current use

Clinical experts highlighted that some NHS trusts are already offering tumour profiling tests to inform chemotherapy decisions for people with LN-positive early breast cancer. Many began doing so during the COVID-19 pandemic to help relieve pressure on infusion services. Outputs from decision-analytic models of the expected impact of using the technologies (compared to current practice) on chemotherapy services are likely to be beneficial for decision-making.

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: in 2020, 44,943 women and 348 men were diagnosed with new cases of breast cancer in England (NHS Digital 2022). Breast cancer is underdiagnosed and often undertreated in men. Some tests may not be validated for use in men with breast cancer.

Women from South Asian, Black African or Caribbean family backgrounds are more likely to have less favourable breast tumour characteristics at diagnosis (stage, grade, ER or HER2 status) compared with white women, and are more likely to be diagnosed younger (Gathani et al. 2021; Breast Cancer Now 2021).

As described in section 6.3, there is a level of geographic inequality in access to tumour profiling tests in the LN-positive population.

8 Potential implementation issues

Oncotype DX, EndoPredict and Prosigna are all currently used in clinical practice in the NHS (see section 3.2.5.1). Therefore, it is unlikely that major adoption issues would occur if other tumour profiling tests were to be recommended for use, or if the population for use was expanded.

8.1 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), or PREDICT. The choice of the initial decision-making tool may influence subsequent treatment options.

8.2 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.

8.3 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 experts 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.

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Appendix A Questions for consultation

Introduction and product properties

1 Are these sections accurate and complete?

Care pathway

2 Is the care pathway as outlined in the scope accurate?

3 Are there any other clinical guidelines for the management of early breast cancer that NICE should be aware of?

4 Does the availability of abemaciclib affect adjuvant chemotherapy use for people with LN+ early breast cancer?

Population

5 Is the population outlined in the draft scope appropriate?

   a. Is limiting to people with cancer with involvement of 1 to 3 lymph nodes appropriate?

6 Are the listed subgroups appropriate? Are there any other subgroups that should be included?

   a. The presence of which comorbidities are most likely to influence decisions on whether to offer adjuvant chemotherapy?

Interventions

7 Are the descriptions of the technologies accurate?

   a. Are there any other tools or methods that can be used alongside the test outputs to further inform decisions about treatment?

   b. Can the tests be used for men with breast cancer?

8 Are there any other technologies that should be included in this assessment?

9 The IHC4 and IHC4+C tests have not been included in this draft scope. This is because clinical experts have advised that uncertainty about the analytical validity of the test remains (for example about the reproducibility of test results as described in NICE diagnostics guidance 34). Any comments on this decision would be welcomed during the scope consultation.

Comparator

10 Is this the most appropriate comparator for the assessment?

Outcomes and costs

11 Are all the outcomes and costs suitable for inclusion in the assessment? Are there any additional outcomes or costs which should be included?

Equality

12 NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed scope may need changing in order to meet these aims. In particular, please tell us if the proposed scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Adoption and implementation

13 Are there any potential barriers to implementation of tumour profiling tests in NHS clinical practice? For example, testing capacity, time for testing, interpretation of intermediate results.

Provisional stakeholder list

14 Are there any stakeholders who should be invited to participate in the assessment?

General

15 Please tell us if there are any other key points that are important and relevant to consider for this assessment that are not currently included in this draft scope.

Appendix B Glossary of terms

Adjuvant therapy

Additional treatment given as well as the primary treatment to improve outcomes.

Distant recurrence

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

Endocrine therapy

Hormones such as oestrogen and progesterone can fuel the growth of some breast cancers. 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.

Formalin-fixed paraffin-embedded (FFPE)

A method of preserving samples for biopsy. Tissue is fixed in formalin (formaldehyde) and then embedded in paraffin wax to create a stable sample that can be sent to a laboratory for analysis.

HER2

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 or tests which detect HER2 gene amplification. HER2-positive cancers may respond to treatment with trastuzumab, a biological treatment which targets HER2 receptors**.**

Hormone receptor

Hormone receptors include both oestrogen and progesterone receptors. So, a tumour that is hormone receptor-positive may be ER-positive, PR-positive or both.

IHC4 and IH4+C

An test that combines the results of 4 immunohistochemistry measurements (ER, PR, HER2 and Ki67) to quantify the 10-year risk of distant disease recurrence in

post-menopausal people with early breast cancer. The IHC4+C also includes clinical and pathological factors such as age, nodal status, tumour size, and grade.

Lymph node

A small structure that contains white blood cells, and acts as a filter for foreign particles like cancer cells. There are several lymph nodes in the armpit or near the breastbone where breast cancer cells may be found in people with early breast cancer.

Microarray

A laboratory tool used to detect the expression of thousands of genes at the same time.

Micrometastatic disease

Occurs when very small metastatic tumours have formed that are too small to detect on a scan.

Neoadjuvant therapy

Treatment given before surgery that aims to shrink the tumour beforehand. This could be chemotherapy, radiation therapy or endocrine therapy.

Oestrogen receptor

Cancer cells that have oestrogen receptors can use the hormone oestrogen to grow. See also endocrine therapy.

PAM50

A 50-gene signature that classifies breast cancer into 4 intrinsic molecular subtypes (see Table 2).

Reverse transcription quantitative polymerase chain reaction (RT-qPCR)

A laboratory technique used to amplify RNA which can be used for a number of purposes, including measuring the level of expression of a particular gene.

Appendix C References

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