In response to an enquiry from the Scottish Cancer Network

Tumour profiling tests to guide adjuvant chemotherapy decisions for patients with early breast cancer

Recommendations for NHSScotland

In patients* with oestrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-), early-stage breast cancer with 0-3 positive lymph nodes, the use of tumour profiling tests:

• is unlikely to provide additional benefit for decision making about adjuvant chemotherapy for patients who have a low or high clinical risk of distant recurrence, as defined using a validated tool such as PREDICT or the Nottingham Prognostic Index (NPI)

• is recommended as set out in the decision tree on page 2 for patients who have an intermediate risk of distant recurrence, as defined using a validated tool such as PREDICT or the NPI

When tumour profiling tests are indicated, their use should be limited to patients in whom there is uncertainty from both the patient and the clinician as to the benefit of chemotherapy. The tests are intended to be used in addition to existing tools to increase clarity around adjuvant chemotherapy decision making. A shared decision-making discussion should take into account clinical and pathological risk factors alongside patient characteristics and preferences.

There should be ongoing data collection on the impact of using tumour profiling tests on patient outcomes and return on investment in NHSScotland.

* NHSScotland is required to consider the Scottish Health Technologies Group (SHTG) recommendations.

* This SHTG recommendation applies to all patients with ER+, HER2- early-stage breast cancer, including women, men, trans and non-binary people.
Decision tree: Tumour profiling tests to guide adjuvant chemotherapy decisions for patients with early breast cancer

**Patients** with ER+, HER2-, early-stage breast cancer with 0-3 positive lymph nodes

- **Premenopausal**
  - Node negative (LN-)
    - Oncotype DX® is recommended as an option for guiding adjuvant chemotherapy decisions in patients:
      - with an intermediate risk of distant recurrence
      - who are informed that premenopausal patients have a higher propensity to benefit from chemotherapy even when their genomic risk score is low
  - Node positive (LN+)
    - Tumour profiling tests not recommended for routine use

- **Postmenopausal**
  - Node negative (LN-)
    - Oncotype®, EndoPredict®, MammaPrint® and Prosigna® are recommended as options for guiding adjuvant chemotherapy decisions in patients with an intermediate risk of distant recurrence only
  - Node positive (LN+)
    - Tumour profiling tests not recommended for routine use

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1. The general subtypes of breast cancer are identical in men and women, but the evidence base for tumour profiling tests is based on trials with women. Clinical judgement should be used when applying the decision tree with male patients.
2. In some studies, participants were categorised by age (50 and under and over 50) rather than menopausal status. Age 50 was also used as a cut-off in some studies for patients that did not meet the definitions of pre and postmenopausal.
3. Intermediate risk of distant recurrence should be established using a validated tool such as PREDICT or the Nottingham Prognostic Index.
What were we asked to look at?

We were asked by the Scottish Cancer Network to look at the clinical and cost effectiveness, and patient and clinical experience, of tumour profiling tests for guiding chemotherapy decisions for patients with oestrogen receptor positive (ER+), human epidermal growth factor receptor 2-negative (HER2-), early-stage breast cancer with 0-3 positive lymph nodes.

Why is this important?

The Scottish Cancer Strategy (2023) states that allied to systemic anticancer therapy delivery, and in order to maximise the opportunities of precision medicine, comprehensive genomic tests should be offered as appropriate to people with cancer at an earlier stage in their clinical pathway.¹

In Scotland, breast cancer is the most common cancer in women and accounts for 28% of all cancers diagnosed in women, excluding non-melanoma skin cancer. Incidence of breast cancer is increasing over time with 4,297 new cases being diagnosed in 2020 in women in Scotland.² The incidence of ER+, HER2- breast cancer is rare in men, but it does occur. While the studies reported were undertaken in women, there is no reason to believe that these tests would be any less useful in men and this guidance should apply to all patients with ER+, HER2-, early-stage breast cancer with 0-3 positive lymph nodes, regardless of sex or gender.

In most types of breast cancer, surgery is the first-line treatment. Adjuvant therapy, including chemotherapy, may be needed following surgery to reduce risk of recurrence and/or metastasis. While chemotherapy can reduce risk of recurrence, not all patients with early-stage breast cancer require it. Chemotherapy can cause short- and long-term adverse events, and it is important to take this into account. Clinicopathological factors such as tumour size, disease stage and age are used to guide choices on the most appropriate treatment strategy. Tumour profiling tests may be used alongside these factors to inform adjuvant chemotherapy decisions.³

What was our approach

We produced an SHTG Recommendation based on a review of published evidence on the clinical and cost effectiveness, and patient and clinical experience, of tumour profiling tests for guiding chemotherapy decisions for patients with ER+, HER2-, early-stage breast cancer with 0-3 positive lymph nodes.

What next?

This SHTG Recommendation will be used to inform the use of tumour profiling tests for guiding chemotherapy decisions for patients with early-stage breast cancer in NHSScotland. The recommendation will be shared with colleagues in the Scottish Cancer Network, and will be made available to clinicians and the public via the SHTG website.
Key points from the evidence

1. This SHTG Recommendation considers the evidence on the use of tumour profiling tests (Endopredict®, MammaPrint®, Oncotype DX® and Prosigna®) in patients with ER+, HER2-negative, early-stage breast cancer with 0-3 positive lymph nodes. Most patients with this type of breast cancer will be offered surgery as their first-line treatment. Adjuvant therapies, including chemotherapy and endocrine therapy, may be needed following surgery to reduce the risk of recurrence and/or metastases. Chemotherapy may be associated with adverse events, and not all patients will benefit from it. Prognostic tools are available that can help facilitate the decision on whether or not to have chemotherapy. Where uncertainty remains, tumour profiling tests are intended to be used alongside these prognostic tools to help patients and clinicians with adjuvant chemotherapy decision making.

2. In 2018, The National Institute for Health and Care Excellence (NICE) published diagnostic guidance (DG34) on the use of tumour profiling tests to guide adjuvant chemotherapy decisions in patients with ER+, HER2-, early breast cancer. The Molecular Pathology Consortium in Scotland endorsed this guidance for NHSScotland. New evidence has become available since 2018 and clinical experts have advised that variation in practice remains in NHSScotland. This SHTG Recommendation updates the evidence review and recommendations from the NICE guidance.

Clinical-effectiveness evidence

3. The RxPONDER randomised controlled trial (RCT) was published after the NICE guidance. The RxPONDER trial evaluated the use of Oncotype DX® in predicting the benefit of adjuvant chemotherapy in women with lymph node positive (LN+) disease. In addition, updated results (median follow up of 8.7 years) of an RCT, which evaluated the clinical utility of MammaPrint® in women with early-stage breast cancer (the MINDACT trial) were published after the NICE guidance.

4. The collective evidence suggests that all four tumour profiling tests provide prognostic information on a patient’s future risk of cancer recurrence and/or survival. The tests add prognostic value over other prognostic clinical and pathological information available to clinicians and patients. The evidence is weaker and more variable in patients with LN+ disease, compared with those who have LN- disease.

5. Predictive ability relates to the ability of the tests to identify those patients who are most likely to benefit from chemotherapy. Three of the tests are indicated for predictive use (Oncotype DX®, MammaPrint® and EndoPredict®), but there is considerable uncertainty within the evidence that the tests are predictive of improved outcomes with chemotherapy.
Patient and social aspects

6. A qualitative study published after the NICE guidance explored ways in which women in the UK interpret and discuss the Oncotype DX® test. In addition, a patient organisation submission was received from Breast Cancer Now.

7. Patients generally view tumour profiling tests positively, as they are perceived as providing ‘personalised’ information, which is seen as more reliable and informative than risk scores calculated from online algorithms. Low- and high-risk scores from the tumour profiling tests are generally viewed as providing more clarity around the decision to have or forgo chemotherapy, compared with intermediate-risk scores. Waiting for test results prolongs patient anxiety, and so the results of tumour profiling tests should be made available to patients in a timely manner.

Cost-effectiveness evidence

8. SHTG’s updated literature review of the cost-effectiveness evidence highlighted six economic evaluations that were published after the NICE guidance, though these were more limited than the analyses presented by NICE at addressing the decision problem faced by NHSScotland.

9. The manufacturers of the four tests were invited to submit economic evaluations, and were received from the manufacturers of MammaPrint®, Oncotype DX® and Prosigna®. The results of economic analyses submitted by test manufacturers strengthened the conclusions of the NICE recommendation from 2018, that tumour profiling tests (Oncotype DX®, Prosigna® and EndoPredict®) are likely cost effective in patients with LN+ disease who have an intermediate risk of recurrence using a validated algorithm. The MammaPrint® test is also likely cost effective in this population. Cost effectiveness in this subgroup is driven by the avoidance of unnecessary chemotherapy and reducing distant recurrence.

10. Tumour profiling tests are unlikely to be cost effective for patients with LN- disease and a low risk of recurrence based on a validated algorithm as this subgroup have low rates of chemotherapy in current clinical practice without a test.

11. While three of the tumour profiling tests under consideration (EndoPredict®, MammaPrint® and Oncotype DX®) may be cost effective in patients with LN+ (1-3 nodes) disease, these results should be treated with caution because of uncertainty in the clinical evidence base for tumour profiling tests in this subgroup.
1. The recommendations in the NICE guidance were not split by menopausal status. The SHTG Recommendations have considered pre- and postmenopausal patients separately because several studies, including the three main RCTs, noted a greater treatment effect from adjuvant chemotherapy in younger (premenopausal) women, even with low-risk scores from tumour profiling tests. This benefit may be partly explained by an antioestrogenic effect associated with premature menopause induced by chemotherapy. Until this question has been answered by the evidence, SHTG considered that greater caution around the use of tumour profiling tests is needed in premenopausal patients. The Council asked a clinical expert about the applicability of the evidence to men with breast cancer. The expert advised that the recommendations could apply to men and application of the decision tree with male patients should be based on clinical expertise.

2. The SHTG Council considered the decision tree (page 2), and noted the justifications given by the SHTG research team for the recommendation in each of the four main patient groups:

2.1. Premenopausal patients with LN- disease

There is insufficient evidence to support the use of EndoPredict® and MammaPrint® in this patient group, and Prosigna® is only indicated for use in postmenopausal patients.

The TAILORx trial suggested that patients aged 50 years and younger who are LN-, with an Oncotype DX® Recurrence Score (RS) of 15 or lower, may be spared chemotherapy. SHTG Council noted concerns about:

- the generalisability of the participants in the TAILORx study
- a general trend in the literature that suggests premenopausal women benefit more from chemotherapy, even when genomic risk scores are low

As a result of these concerns, the recommendation for use in this subset of patients was restricted.

2.2. Premenopausal patients with LN+ disease

There is insufficient evidence to support the use of EndoPredict®, Oncotype DX® and MammaPrint® in this patient group, and Prosigna® is only indicated for use in postmenopausal patients.

The RxPONDER trial, not included in the NICE guidance, evaluated the use of Oncotype DX® in predicting the benefit of adjuvant chemotherapy in women with LN+ disease, and in premenopausal women a chemotherapy benefit was seen across subgroups. This suggests that premenopausal patients may still benefit from chemotherapy, even with a lower Oncotype DX® RS.
2.3. Postmenopausal patients with LN- disease

In this patient group the recommendations from the NICE (2018) guidance for EndoPredict®, Oncotype DX® and Prosigna® still apply to postmenopausal patients. SHTG identified new clinical- and cost-effectiveness evidence that strengthens NICE’s recommendation.

NICE did not recommend the use of MammaPrint® because it was not found to be cost effective. An updated cost-effectiveness model submitted to SHTG by Agendia demonstrated that the MammaPrint® test may be cost effective in LN- patients with intermediate clinical risk. SHTG concluded that MammaPrint® could be recommended in this patient group because of changes in the availability of the evidence to inform the parameters of the economic model.

2.4. Postmenopausal patients with LN+ disease

SHTG Council concluded that there was insufficient evidence to support the use of tumour profiling tests in postmenopausal patients with LN+ disease. Until more research is available, routine use of tumour profiling tests cannot be recommended in this patient group.

SHTG Council considered the RxPONDER trial and acknowledged the finding that there was no chemotherapy benefit in patients with LN+ disease who had an Oncotype DX® RS of 0-25. SHTG Council expressed the following concerns.

- The majority of participants had cancer that had spread to one lymph node only (65.3%). Only 9% of participants had cancer that had spread to three lymph nodes, meaning the trial mainly reflected the ‘lower risk’ LN+ patients.
- NICE in 2018 raised concerns that, based on the OPTIMA Prelim study, there was a lack of agreement between the tests in risk categorising the groups with LN+ disease and limited their recommendations to LN- populations. No evidence was identified to alleviate this concern.

3. SHTG Council acknowledged that the evidence base in this area is rapidly evolving and this SHTG Recommendation may change as more evidence and health technology assessments (HTAs) become available. The OPTIMA trial was highlighted as having the potential to address gaps in the evidence.

4. SHTG Council noted that the genes that are mapped by the four tests varied considerably, suggesting that the different tests capture different aspects of prognostic drivers. This would suggest that future improvements and refinements in the tests remain possible.

5. The Council heard from a clinical expert who talked about the use of these tests in NHSScotland, noting current variation in practice. The clinical expert reiterated that tumour profiling tests should not replace existing prognostic tools, but be used alongside them. The
Council noted that every patient has different experiences and preferences, which will influence the value of tumour profiling tests to them.

6. The Council heard from Breast Cancer Now about the devastating impact a breast cancer diagnosis can have on a person and the people close to them. When discussing the impact of tumour profiling tests on patients, the Council agreed that timeliness is important. Waiting for test results not only prolongs anxiety for patients, but may also delay chemotherapy. This is a factor that should be considered when deciding which test should be used in NHSScotland.
## Contents

Recommendation................................................................................................................... 1

Decision tree .......................................................................................................................... 2

What were we asked to look at? ............................................................................................... 3

Why is this important? ............................................................................................................. 3

What was our approach.......................................................................................................... 3

What next? ............................................................................................................................... 3

Key points from the evidence ................................................................................................. 4

SHTG Council considerations ................................................................................................. 6

Contents .................................................................................................................................. 9

Definitions ............................................................................................................................... 11

Introduction ............................................................................................................................ 11

Literature search ...................................................................................................................... 12

Health technology description ............................................................................................... 13

Epidemiology ........................................................................................................................... 18

Inequalities .............................................................................................................................. 19

Patient care pathway .............................................................................................................. 19

Recommendations from guidelines and HTAs ..................................................................... 20

NICE diagnostics guidance ................................................................................................... 20

Other guidelines and HTAs ................................................................................................... 21

HIQA’s summary of HTAs ..................................................................................................... 21

HIQA’s summary of guidelines ............................................................................................. 22

Clinical-effectiveness evidence .............................................................................................. 28

RCTs ....................................................................................................................................... 28

MINDACT ............................................................................................................................... 28

TAILORx ............................................................................................................................... 30

RxPONDER ............................................................................................................................ 33

Secondary evidence .............................................................................................................. 34

Prognostic ability of tumour profiling tests ......................................................................... 34

Predictive ability of tumour profiling tests .......................................................................... 38

Decision impact of tumour profiling tests ............................................................................ 40

Ongoing trials ........................................................................................................................ 41
Definitions

**Hormone receptor negative (HR-)** breast cancer: the cells of this type of breast cancer have no (or very few) receptors for the hormones oestrogen and progesterone.

**Hormone receptor positive (HR+)** breast cancer: the cells of this type of breast cancer have receptors that allow them to use the hormones oestrogen and progesterone to grow.

**Human epidermal growth factor receptor 2-negative (HER2-)** breast cancer: the cells of this type of breast cancer do not have higher than normal levels of the receptors HER2.

**Human epidermal growth factor receptor 2-positive (HER2+)** breast cancer: the cells of this type of breast cancer have higher than normal levels of the receptors HER2.

**Lymph node negative (LN-)** breast cancer: this means that the cancer has not spread to the lymph nodes.

**Lymph node positive (LN+)** breast cancer: this means that the cancer has spread to the lymph nodes. In this review, we use ‘LN+’ to describe cancer than has spread to one to three lymph nodes.

**Oestrogen receptor negative (ER-)** breast cancer: the cells of this type of breast cancer have no (or very few) oestrogen receptors.

**Oestrogen receptor positive (ER+)** breast cancer: the cells of this type of breast cancer have receptors that allow them to use the hormone oestrogen to grow.

**Progesterone receptor negative (PR-)** breast cancer: the cells of this type of breast cancer do not have receptors that allow them to use the hormone progesterone to grow.

**Progesterone receptor positive (PR+)** breast cancer: the cells of this type of breast cancer have receptors that allow them to use the hormone progesterone to grow.

**Prognosis**: refers to the likely outcome or course of a disease, including the likelihood of recovery or recurrence. A prognostic factor provides information on the likely clinical outcome at the time of diagnosis independent of or in the absence of further therapy.³

Introduction

Endopredict®, MammaPrint®, Oncotype DX® and Prosigna® are all tumour profiling tests. These tests are used in patients with early breast cancer to give information on the activity of genes in tumour samples. The results provide a risk profile of a person's breast cancer, which can be used with other
routinely assessed clinical risk factors, such as nodal status and tumour size, to predict the risk of disease recurrence. Some tests also claim to predict relative treatment effects for chemotherapy. The test results are intended to help patients and clinicians make informed decisions about the potential value of adjuvant chemotherapy use.

This report summarises the evidence that was used to inform the SHTG Recommendations. SHTG assessed evidence that was published subsequent to the NICE 2018 guidance on tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer.

Research question:

What is the clinical and cost effectiveness, and patient and clinical experience, of tumour profiling tests for guiding chemotherapy decisions for patients with ER+, HER2-, early-stage breast cancer with 0-3 positive lymph nodes?

Literature search

A systematic search of the secondary literature was carried out between 6 and 12 December 2022 to identify systematic reviews, meta-analyses, HTAs and other evidence-based reports. Databases used included: Medline, Medline in process, Embase and the Cochrane Library.

The primary literature was systematically searched between 6 and 12 December 2022 using the following databases: Medline, Medline in process and Embase. Results were limited to English language publications.

Key websites were searched for guidelines, policy documents, clinical summaries, economic studies and ongoing trials.

Concepts used in all searches included: early-stage breast cancer (stages I or II), Oncotype DX®, MammaPrint®, EndoPredict®, Prosigna®, BCI (Breast Cancer Index). A full list of resources searched, and terms used is available on request.

All search results were limited to studies published from 2017 onwards in the English language. Results were also limited using the following criteria (Table 1):

Table 1: PICO criteria (Population, Intervention, Comparator, Outcomes)

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with ER+, HER2-, early-stage breast cancer with 0 to 3 positive lymph nodes.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subgroups: lymph node negative/positive, pre/postmenopausal patients, different ethnicities.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Oncotype DX®, MammaPrint®, EndoPredict®, Prosigna®</td>
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<tr>
<td>--------------------</td>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td>Comparator</td>
<td>Current decision making tools (to assess risk) in Scotland i.e. PREDICT, the NPI</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Invasive disease-free survival</td>
</tr>
<tr>
<td></td>
<td>Overall survival</td>
</tr>
<tr>
<td></td>
<td>Distant recurrence</td>
</tr>
<tr>
<td></td>
<td>Quality of life (health-related, disease-related morbidity and chemotherapy-related)</td>
</tr>
<tr>
<td></td>
<td>Costs (test, medicines, healthcare utilisation, training etc)</td>
</tr>
<tr>
<td></td>
<td>Test accuracy/prognostic ability</td>
</tr>
<tr>
<td></td>
<td>Impact on decision making</td>
</tr>
<tr>
<td></td>
<td>Time to results</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy benefit prediction</td>
</tr>
</tbody>
</table>

**Health technology description**

The use of tumour profiling tests in patients with early-stage breast cancer is intended to optimally apply adjuvant therapy, both adding therapy to otherwise unrecognised high-risk disease and forgoing therapy in low-risk disease. The manufacturers claim that the tests have the potential to reduce treatment morbidity while maintaining the trend for reduced breast cancer mortality. The output of each test is a score, and the manufacturers provide risk categories for each score. While risk categories are provided for all the tests, these tests function along a continuum, with continuous worsening of prognosis as scores increase/decrease.

We assessed four tumour profiling tests in this SHTG Recommendation: Oncotype DX®, MammaPrint®, EndoPredict®, Prosigna®. The following technology descriptions have been taken from the NICE guidance and an HTA from the Health Information and Quality Authority (HIQA), Ireland. The technologies are summarised in Table 2.

**EndoPredict® (Myriad Genetics)**

EndoPredict® is a Conformité Européene marked (CE-marked) assay that is designed to predict the likelihood of metastases developing within 10 years of an initial breast cancer diagnosis. The test is for pre and postmenopausal patients with early breast cancer with ER+, HER2- and LN- or LN+ disease (up to three positive nodes). EndoPredict® measures the expression of 12 genes: three proliferation-associated genes, five hormone receptor-associated genes, three reference (normalisation) genes and one control gene. EndoPredict® needs RNA extracted from a formalin-fixed, paraffin-embedded (FFPE) breast cancer tissue sample. The test can be done in a local laboratory or the Myriad Genetics pathology laboratory in Germany. It takes approximately 2 days from receipt of the tissue sample to get the results from a local laboratory, although the turnaround time may be longer if samples are tested in full batches. The turnaround time is also longer if
samples are sent to Germany. The test involves a reverse transcription-quantitative polymerase chain reaction. Online evaluation software calculates an ‘EP score’ and an ‘EPclin score’. An EP score of zero to less than five indicates low risk of distant disease recurrence in the next 10 years. An EP score of five to 15 indicates high risk of distant disease recurrence in the next 10 years. The EPclin score estimates the probability of metastases developing within 10 years (assuming 5 years of endocrine therapy). It is calculated by adding clinical data about tumour size and nodal status to the EP score. An EPclin score of less than 3.3 indicates low risk (less than 10%) of metastases in the next 10 years. An EPclin score of 3.3 or more indicates high risk of metastases in the next 10 years.

**MammaPrint® (Agendia NV)**

MammaPrint® is a CE-marked assay that is designed to assess the risk of distant recurrence within 5 and 10 years and whether a patient would benefit from chemotherapy. The test is for pre and postmenopausal patients with stage 1 or 2 breast cancer, with a tumour size of 5 cm or less, and LN- or LN+ disease (up to three positive nodes). The test can be used irrespective of ER and HER2 status. MammaPrint® measures the expression of 70 genes, including genes associated with seven 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 needs RNA extracted from an FFPE breast cancer tissue sample. The test is offered as an off-site service. Samples are analysed at the Agendia NV laboratory in Irvine, California, USA. Results are on average available in less than 5 days after the sample is received in the laboratory. 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.

**Oncotype DX® Breast RS (Genomic Health)**

Oncotype DX Breast RS® (Oncotype DX®) is a CE-marked test designed to quantify the 10-year risk of distant recurrence and predict relative treatment effects for chemotherapy. The test also reports the underlying tumour biology: ER, progesterone receptor (PR) and HER2 status. The test is for pre and postmenopausal patients with stage 1 or 2 breast cancer and ER+, HER2-, LN- or LN+ disease (up to three positive nodes). Oncotype DX® quantifies the expression of 21 genes: 16 cancer-related genes correlated with distant recurrence-free survival, and five reference (normalisation) genes. The Oncotype DX® test needs RNA extracted from a FFPE breast cancer tissue sample. Samples are processed centrally at a Genomic Health laboratory in the US. Results are usually available 7 to 10 days after the sample is received. The test is based on a reverse transcription-quantitative polymerase chain reaction. It gives a Recurrence Score (RS) result of between 0 and 100, which is used to quantify the 10-year risk of distant recurrence, assuming 5 years of endocrine therapy.
In women aged over 50 years with LN- or LN+ disease, the RS is interpreted as follows:
- RS of ≤25 indicates a lack of benefit from chemotherapy treatment
- RS of ≥26 indicates a benefit from chemotherapy treatment

In women aged 50 years or younger with LN- disease, the RS is interpreted as follows:
- 0-15 indicates a lack of benefit from chemotherapy treatment
- 16-20 and 21-25 is an intermediate-risk score
- 26-100 indicates a benefit from chemotherapy treatment

In women aged 50 years or younger with LN+ disease, the RS is interpreted as follows:
- 0-13 and 14-25 is an intermediate-risk score
- 26-100 indicates a benefit from chemotherapy treatment

The breast RS result can be combined with clinical and pathological factors using the recurrence score-pathology-clinical (RSPC) calculator. The calculator has not been validated in a cohort independent of that used to derive Oncotype DX® RS.

**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 postmenopausal patients with early breast cancer that is ER+, HER2- and LN- or LN+ (up to three positive nodes). Prosigna® measures the expression of 50 genes used for intrinsic subtype classification, eight housekeeping genes used for signal normalisation, six positive controls and eight negative controls. The test needs RNA extracted from a FFPE breast tumour tissue sample. It is based on direct mRNA counting using fluorescent probes and an nCounter Digital Analyser. 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: LN-: low risk (0 to 40), intermediate risk (41 to 60) or high risk (61 to 100); LN+ (up to three positive nodes): low risk (0 to 15), intermediate risk (16 to 40), or high risk (41 to 100).
Table 2: Summary of the four tests: Oncotype DX®, MammaPrint®, EndoPredict®, Prosigna® (information taken from HIQA³)

<table>
<thead>
<tr>
<th></th>
<th>Oncotype DX®</th>
<th>MammaPrint®</th>
<th>EndoPredict®</th>
<th>Prosigna®</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Genomic Health, Inc. (a wholly owned subsidiary of Exact Sciences Corporation)</td>
<td>Agendia NV</td>
<td>Myriad International GmbH</td>
<td>Veracyte</td>
</tr>
<tr>
<td><strong>Description (genes)</strong></td>
<td>21-gene assay (16 cancer-related, 5 reference)</td>
<td>70-gene assay (70 cancer-related, 465 reference)</td>
<td>12-gene assay (8 cancer-related, 4 reference)</td>
<td>50-gene assay (50 cancer-related, 22 reference)</td>
</tr>
<tr>
<td><strong>Indication(s)</strong></td>
<td>Stage I-IIIa, ER+, HER2−, LN−, micrometastases or LN+ for prognostic and predictive use</td>
<td>Stage I-II (and operable stage III), ER+ or ER−, LN− or LN+ for prognostic and predictive use</td>
<td>Stage I-II, ER+, HER2−, LN− or LN+ for prognostic and predictive use</td>
<td>Stage I-II, LN− and stage II-IIla, LN+ (both in ER+, postmenopausal women only) for prognostic use</td>
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<tr>
<td><strong>Clinicopathological factors considered</strong></td>
<td>Not specified</td>
<td>Not specified</td>
<td>Tumour size, LN status</td>
<td>Breast cancer subtype, tumour size, LN status, proliferation score</td>
</tr>
<tr>
<td><strong>Result measurement</strong></td>
<td>Recurrence Score® result (RS): 0 to 100</td>
<td>MammaPrint® Index (MPI): -1 to 1</td>
<td>12-gene molecular score: 0 to 15 EPclin score: 1 to 6</td>
<td>Risk of Recurrence (ROR): 0 to 100</td>
</tr>
<tr>
<td><strong>Categories for risk measurement</strong></td>
<td>Age&gt;50 years Low risk: 0 to 25 High risk: 26 to 100</td>
<td>Ultra-low risk: 0.355 to 1 Low risk: 0 to 0.354 High risk: −1 to 0</td>
<td>EPclin risk score Low risk: &lt; 3.32867 High risk: ≥ 3.32867</td>
<td>LN- patients Low risk: 0 to 40 Intermediate risk: 41 to 60 High risk: 61 to 100</td>
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<tr>
<td></td>
<td>Ages≤50 years and LN- Low risk: 0 to 15 Intermediate risk: 16 to 20 and 21 to 25 High risk: 26 to 100</td>
<td></td>
<td></td>
<td>LN+ patients Low risk: 0 to 15 Intermediate risk: 16 to 40 High risk: 41 to 100</td>
</tr>
<tr>
<td>Testing location</td>
<td>Test service only (US)</td>
<td>Test service only (US)</td>
<td>Local laboratory or test service (US; only for orders outside of the EU) or Germany</td>
<td>Local laboratory</td>
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</table>
Epidemiology

In Scotland, breast cancer is the most common cancer in women and accounts for 28% of all cancers diagnosed in women, excluding non-melanoma skin cancer. Incidence of breast cancer is increasing over time with 4,297 new cases being diagnosed in 2020 in women in Scotland. One in eight women in Scotland will develop breast cancer over their lifetime. It is the second most common cause of cancer death in women. Over the 10 years 2011-2020 the mortality rate decreased by 2.8%. In Scotland, 86% of women survive at least 5 years after their breast cancer diagnosis. Breast cancer is far rarer in men, but it does occur. The general subtypes of breast cancer are identical in men and women.

Many of the known risk factors for breast cancer relate to a woman’s reproductive history, for example early menarche, late first pregnancy, low parity, not breastfeeding and late menopause. Breast cancer risk is largely determined by lifetime exposure to oestrogens and risk increases substantially with age.

Breast cancer is most commonly classified using the ‘tumour, node and metastasis’ (TNM) staging system from the American Joint Committee on Cancer. T describes the size of the tumour and any spread of cancer into nearby tissue; N describes spread of cancer to nearby lymph nodes; and M describes metastasis (spread of cancer to other parts of the body). Number staging systems use the TNM system to divide cancers into stages, normally I to IV. Early-stage breast cancer is variably defined in the literature, but is generally categorised as stage I-II or I-IIIa.

The presence of hormone receptors and/or HER2 in cancerous cells can affect the treatment course and potentially the outcome of breast cancer. Hormone receptor positive (HR+) breast cancers have receptors for oestrogen and or progesterone. Breast cancers that have very low levels of or no oestrogen receptors are called oestrogen receptor negative or ER- breast cancers. Some breast cancers also have receptors for progesterone, and these are progesterone receptor positive (PR+) breast cancers. Breast cancers that do not have higher than normal levels of the receptors HER2 are referred to as HER2- breast cancers. HR+, HER2- breast cancers represent approximately 70% of all breast cancers diagnosed in patients with breast cancer in western countries, with an estimated 40% of these cancers having spread to the lymph nodes by the time of diagnosis.

Patients with HR+ breast cancer have better survival outcomes than those with HR- breast cancer, largely because of additional treatment options available to them. Endocrine therapy is only likely to work for cancers that are ER+ or PR+. Without the use of chemotherapy, it is estimated that 15% of women with HR+ breast cancer will develop a recurrence within 10 years if treated with adjuvant endocrine therapy alone. If all women with HR+ breast cancer were to receive chemotherapy most of these women could be considered to be over-treated; this is because of the relatively low risk of recurrence and the partial effectiveness of chemotherapy in these patients.

Most breast cancers diagnosed in patients in Scotland are ER+ (76%) and HER2- (65-85%). We would expect to see approximately 2,000 cases of HR+, HER2- stage I-IIIa breast cancer cases diagnosed in Scotland each year. It is in this population that the use of tumour profiling tests may be beneficial.
Inequalities

There are inequalities in the risk factors for breast cancer, in the uptake of breast cancer screening and in survival rates. Postmenopausal obesity, alcohol consumption, inactivity and a high-fat diet increase the risk of breast cancer. Each of these factors is socially patterned, with a higher prevalence in people living in deprived areas. Women from lower socioeconomic groups are less likely to go for breast cancer screening. Breast cancer is more common in women living in affluent areas but survival rates are worse in women from more deprived areas, in part as a result of the lower uptake of breast cancer screening.""}/n

Results from the TAILORx trial highlight the inequalities facing people from ethnic minorities. While Black patients only represented 7.1% of the eligible participants, they had higher rates of distant recurrence [hazard ratio 1.60; 95% confidence interval (CI) 1.07 to 2.41] and inferior overall survival (OS) in the Oncotype DX® RS 11 to 25 cohort (hazard ratio 1.51; 95% CI 1.06 to 2.15) compared with non-hispanic white patients. However, similar to non-hispanic white patients, Black participants did not benefit from the addition of chemotherapy if the RS was 11-25. Hispanic or Asian ethnicity were both associated with improved clinical outcomes. These data demonstrate the need for further interpretation of the clinical utility of RS testing in various races and ethnicities, and this is also needed in other biomarker test studies.8

Patient care pathway

Breast cancer may be diagnosed following an abnormal result in the NHS breast screening programme. The Scottish Breast Screening Programme invites women aged between 50 and 70 years for screening every 3 years. Breast cancer can also be diagnosed after referral for further investigation because of signs or symptoms that could be associated with breast cancer. The Scottish Referral Guidelines for Suspected Cancer sets out the referral criteria for breast cancer in Scotland.9

The breast screening test involves taking breast images using an X-ray (mammogram) and checking them for changes. About five out of 100 people who take the test have a positive result, that is changes in the breast that need investigating.10

A person will be invited for further tests in the case of a positive result in the initial screening. This can include: a breast examination, more mammograms and ultrasound scans. Some people will have a biopsy. The results of these tests can lead to a breast cancer diagnosis. Only one in five people who have further tests will receive a positive breast cancer diagnosis. Once a positive breast cancer diagnosis is made, the patient will be referred to a team of breast cancer specialists for treatment.

The most common treatments for breast cancer are surgery, chemotherapy, radiotherapy and endocrine therapy. The type of treatment offered will depend on individual circumstances.11

In most types of breast cancer, surgery is the first-line treatment. Adjuvant therapy, including chemotherapy and endocrine therapy, may be needed following surgery to reduce risk of recurrence and/or metastasis. Studies have shown that in patients with early-stage, ER+ breast cancer, endocrine therapy for 5 years substantially reduces recurrence rates during and after treatment.
After 5 years of endocrine therapy, one study suggested that breast cancer recurrences occur at a steady rate in the subsequent 15 years.\textsuperscript{12}

Chemotherapy can also reduce risk of recurrence, but not all patients with early-stage breast cancer require it. Chemotherapy is associated with significant short- and long-term adverse events.\textsuperscript{13}

The benefits of chemotherapy are not uniform, and the presence or absence of certain receptors in the cancer (for example, oestrogen receptors) can affect treatment course.\textsuperscript{14} One meta-analysis reported a reduction in new contralateral breast cancer (a tumour in the opposite breast which was diagnosed more than 6 months following the detection of the first cancer) with dose-intensive compared with standard schedule chemotherapy seen in years 0–4 with no significant additional benefit beyond this period. This may be explained by chemotherapy eradicating or delaying the emergence of subclinical contralateral breast cancers but having little impact on the development of future contralateral disease.\textsuperscript{15}

Clinicopathological factors such as age, tumour size and disease stage are used to guide choices on the most appropriate treatment strategy. Prediction tools can provide prognostic information to help clinicians and patients with early-stage breast cancer make decisions about adjuvant therapies, for example PREDICT and the NPI. In NHSScotland, both PREDICT and the NPI are used routinely.

- In patients with LN- disease, a NPI of 3.4 or less is classed as low risk, and a NPI of more than 3.4 and up to or equal to 5.4 is classed as intermediate risk.
- If using the PREDICT tool, an absolute 10-year survival benefit from chemotherapy of less than 3% is classed as low risk; between 3% and 5% is classed as intermediate risk; and more than 5% is classed as high risk.

Tumour profiling tests may be used alongside these factors and tools to inform adjuvant chemotherapy decisions. Tumour profiling tests are intended to provide additional, ‘personalised’, information on disease prognosis (that is, distant recurrence and survival) and the predicted benefit of chemotherapy (that is, identify the patients who are most likely to benefit from chemotherapy).\textsuperscript{3}

**Recommendations from guidelines and HTAs**

**NICE diagnostics guidance**

NICE published diagnostics guidance on the use of tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer in 2018\textsuperscript{4} and recommended:

1. **EndoPredict (EPclin score)**, Oncotype DX Breast Recurrence Score and Prosigna are recommended as options for guiding adjuvant chemotherapy decisions 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, only if:
   - they have an intermediate risk of distant recurrence using a validated tool such as PREDICT or the NPI
information provided by the test would help them choose, with their clinician, whether or not to have adjuvant chemotherapy taking into account their preference

- the companies provide the tests to the NHS with the discounts agreed in the access proposals and
- clinicians and companies make timely, complete and linkable record-level test data available to the National Cancer Registration and Analysis Service as described in the data collection arrangements agreed with NICE.

2. MammaPrint is not recommended for guiding adjuvant chemotherapy decisions for people with ER-positive, HER2-negative and LN-negative early breast cancer because it is not cost effective.

3. IHC4+C is not recommended for guiding adjuvant chemotherapy decisions for people with ER-positive, HER2-negative and LN-negative early breast cancer because the analytical validity of the test is uncertain.

SHTG looked at the literature published after the NICE 2018 guidance to see what developments have been made in tumour profiling research.

Other guidelines and HTAs

Our literature search identified six guidelines[^8] and four HTAs[^3,4,21,22]. Guidelines submitted to SHTG by the manufacturers of the tests were not based on systematic review methodology and were not included in our synthesis.[^23-28]

The most recent HTA was published by HIQA in February 2023.[^3] The patient group considered was patients with HR+, HER2-, early-stage (I, II or IIIa) invasive breast cancer. The HTA is described as a ‘rapid’ assessment, focusing on the clinical-effectiveness evidence over cost effectiveness, patient issues and organisational issues. The HIQA report includes details of the recommendations in existing HTAs and guidelines. The HIQA report notes that despite being grounded in broadly the same evidence base, these recommendations vary substantially. They are summarised in Table 3 and Table 4.

HIQA’s summary of HTAs

HIQA identified nine relevant HTAs, published between 2016 and 2022, from Canada, USA, Australia, France, Sweden and the UK (NICE guidance). One HTA was a pan-European assessment conducted by the European Network for Health Technology Assessment (EUnetHTA). HIQA concluded that these had contrasting recommendations on the use of tumour profiling tests, with several recommending their use in LN- patients, but there was less consistency with respect to LN+ patients. The main recommendations from the HTAs are summarised in Table 3.

Our literature search did not identify any HTAs that were not included by HIQA. The recommendations from HIQA are included at the end of Table 3.
HIQA’s summary of guidelines
HIQA identified six relevant guidelines, published between 2017 and 2022 that used varying methodological approaches. The recommendations from the international guidelines are summarised in Table 4. The HIQA search was not systematic and may have missed some guidelines. Our literature search identified four additional guidelines. Three were from 2017 or 2018 and have not been discussed further. The remaining guideline, from 2022, has been added to Table 4.¹⁶
Table 3: Summary of recommendations for use of tumour profiling tests from previously published HTAs (information taken from HIQA3)

<table>
<thead>
<tr>
<th>Agency (year)</th>
<th>Oncotype DX®</th>
<th>MammaPrint®</th>
<th>EndoPredict®</th>
<th>Prosigna®</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUnetHTA (2018)²⁹</td>
<td>Not assessed</td>
<td>Insufficient evidence to demonstrate clinical utility improved patient outcomes</td>
<td>Not assessed</td>
<td>Not assessed</td>
</tr>
<tr>
<td>HAS (2019)³⁰</td>
<td>Evidence of clinical utility was insufficient to recommend routine use of any of the tumour profiling tests. However, recommended that temporary and conditional research and innovation programme be extended (no date specified) for future review of evidence.</td>
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<tr>
<td>Institute of Health Economics Alberta (2019)³¹</td>
<td>MammaPrint®: Not assessed EndoPredict®: Not assessed Oncotype DX® and Prosigna® may be prognostic in HR+, HER2-, LN- and LN+ populations, but evidence is weaker in LN+ population. Results from the clinical and economic evaluation generally support the predictive ability of Oncotype DX®, and the likely cost effectiveness of Prosigna® compared with Oncotype DX® across a range of scenarios…. ‘Decision-makers must weigh the evidence for the predictive ability of Oncotype DX® in certain populations with the increased cost effectiveness of Prosigna®…’</td>
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<tr>
<td>MSAC (2019, 2022)³²,³³</td>
<td>For all four tests, there was insufficient evidence of predictive ability.</td>
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<tr>
<td>Swedish MTP Council (2021)³⁴</td>
<td>Can be used to inform adjuvant chemotherapy decisions in patients where there is uncertainty</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Can be used to inform adjuvant chemotherapy decisions in patients where there is uncertainty</td>
</tr>
<tr>
<td>NICE (2018)⁴</td>
<td>Recommended as an option in ER+, HER2-, LN- population (subject to criteria as detailed on page 3)</td>
<td>Not recommended</td>
<td>Recommended as an option in ER+, HER2-, LN- population (subject to criteria as detailed on page 3)</td>
<td>Recommended as an option in ER+, HER2-, LN- population (subject to criteria as detailed on page 3)</td>
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<tr>
<td>Agency (year)</td>
<td>Tumour profiling test</td>
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<tr>
<td>**Ontario Health (Quality) (2020)**22</td>
<td>May be prognostic in HR+, HER2-, LN- and LN+ populations, but evidence is weak in LN+ population. No evidence assessing the predictive benefit of EndoPredict® or Prosigna® was identified.</td>
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<tr>
<td>**Oregon Health Authority (2018)**35</td>
<td>Strong recommendation for breast tumours that are ER+, HER2-, LN-</td>
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<td></td>
<td>Weak recommendation for breast tumours that are ER+, HER2-, with 1-3 positive nodes</td>
<td>Weak recommendation for breast tumours that are ER+ or PR+, HER2-, LN-, and only in those cases categorised as high clinical risk</td>
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<tr>
<td></td>
<td></td>
<td>Weak recommendation for breast tumours that are ER+, HER2-, LN-</td>
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<td></td>
<td></td>
<td>Weak recommendation for breast tumours that are ER+, HER2-, LN-</td>
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<tr>
<td>**Washington State Health Authority (2018)**36</td>
<td>Evidence supports use (non-specific)</td>
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<td>Women at high clinical risk that receive a low MammaPrint® risk score may forgo chemotherapy</td>
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<td></td>
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<td>Not assessed</td>
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<td></td>
<td></td>
<td>Not assessed</td>
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<tr>
<td>**HIQA (2023)**3</td>
<td>Among LN- patients:</td>
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<td></td>
<td>- All four commercially available tests examined provide prognostic information.</td>
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<td></td>
<td>- Considering predictive ability, although there are limited data to differentiate between the tests, the available evidence supports the continued use of Oncotype DX®.</td>
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<td>Among LN+ patients:</td>
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<td></td>
<td>- All four commercially available tests were found to provide prognostic information.</td>
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<td></td>
<td>- Considering predictive ability, the evidence most strongly supports the continued use of Oncotype DX® in postmenopausal women, based on available 5-year follow-up data.</td>
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<tr>
<td>Agency (year)</td>
<td>Oncotype DX®</td>
<td>MammaPrint®</td>
<td>EndoPredict®</td>
<td>Prosigna®</td>
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<tr>
<td><strong>American Society of Clinical Oncology (2022)</strong></td>
<td>Recommended in LN- patients:</td>
<td>May be used in patients aged ≥50 years (LN- or LN+) that have high clinical risk (based on a modified version of Adjuvant! Online)</td>
<td>May be used in postmenopausal (LN- or LN+) patients</td>
<td>May be used in postmenopausal, LN- patients</td>
</tr>
<tr>
<td></td>
<td>May be used in postmenopausal patients who are LN+</td>
<td>Should not be used in patients aged ≥50 years (LN- or LN+) that have high clinical risk (based on a modified version of Adjuvant! Online)</td>
<td>Should not be used in patients who have low clinical risk (based on a modified version of Adjuvant! Online)</td>
<td>Evidence is inconclusive for postmenopausal, LN+ patients</td>
</tr>
<tr>
<td></td>
<td>Should not be offered to premenopausal patients who are LN+</td>
<td>Should not be used in patients aged ≥50 years (LN- or LN+) that have high clinical risk (based on a modified version of Adjuvant! Online)</td>
<td>Should not be used in patients who have low clinical risk (based on a modified version of Adjuvant! Online)</td>
<td>Should not be used in premenopausal (LN- or LN+) patients</td>
</tr>
<tr>
<td><strong>European Commission Initiative on Breast Cancer (2021)</strong></td>
<td>Recommended in LN-</td>
<td>Recommended in LN- patients at high clinical risk and LN+ patients at high clinical risk, but not in those at low clinical risk</td>
<td>No recommendation</td>
<td>No recommendation</td>
</tr>
<tr>
<td><strong>European Group on Tumor Markers (2017)</strong></td>
<td>All four tests recommended in LN- and LN+</td>
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<tr>
<td><strong>European Society of Medical Oncology (2019)</strong></td>
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<tr>
<td><strong>National Comprehensive Cancer Network (2022)</strong></td>
<td>Recommended in LN- and LN+ preferred</td>
<td>Recommended in LN- and LN+ (evidence for prognostic)</td>
<td>Recommended in LN- and LN+ (evidence for prognostic)</td>
<td>Recommended in LN- and LN+ (evidence for prognostic)</td>
</tr>
<tr>
<td>Agency (year)</td>
<td>Tumour profiling test</td>
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<tr>
<td>St. Gallen (2021)</td>
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<tr>
<td>Use of tumour profiling tests (non-specific) should be considered in the vast majority of cases when chemotherapy is being considered for people with ER+, HER2- breast cancers with limited LN involvement (1-3 nodes), irrespective of tumour grade or menopausal status.</td>
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<table>
<thead>
<tr>
<th>Cancer Care Ontario (2022)</th>
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<tbody>
<tr>
<td><strong>Premenopausal or &lt;50 years LN-</strong> Clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Clinicians may use a high-risk result to support a decision to offer chemotherapy. A high Oncotype DX® RS is capable of predicting adjuvant chemotherapy benefit. Results should be interpreted more cautiously as a benefit from adjuvant chemotherapy may still exist despite a low-risk score</td>
<td></td>
</tr>
<tr>
<td><strong>Premenopausal or &lt;50 years LN+</strong> Perform Oncotype DX® testing. Results should be interpreted with caution as a significant benefit from adjuvant chemotherapy exists despite a low-risk score</td>
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<tr>
<td><strong>Postmenopausal or ≥50 years LN-</strong> Clinicians may use a low-risk result from Oncotype DX® to support a decision not to use adjuvant chemotherapy</td>
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<tr>
<td><strong>Premenopausal or &lt;50 years LN-</strong> Clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy</td>
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</tr>
<tr>
<td><strong>Premenopausal or &lt;50 years LN+</strong> Perform MammaPrint® testing. Results should be interpreted with caution as a significant benefit from adjuvant chemotherapy exists despite a low-risk score</td>
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<tr>
<td><strong>Postmenopausal or ≥50 years LN-</strong> Clinicians may use a low-risk result from MammaPrint® to support a decision not to use adjuvant chemotherapy</td>
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<tr>
<td><strong>Postmenopausal or ≥50 years LN+</strong> Clinicians may use a low-risk result from EndoPredict® to support a decision not to use adjuvant chemotherapy</td>
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</tr>
<tr>
<td><strong>Postmenopausal or ≥50 years LN+</strong> Not recommended</td>
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<tr>
<td><strong>Premenopausal or &lt;50 years LN-</strong> Clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy</td>
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<tr>
<td><strong>Premenopausal or &lt;50 years LN+</strong> Not recommended</td>
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<tr>
<td><strong>Postmenopausal or ≥50 years LN-</strong> Clinicians may use a low-risk result from EndoPredict® to support a decision not to use adjuvant chemotherapy</td>
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<tr>
<td><strong>Postmenopausal or ≥50 years LN+</strong> Not recommended</td>
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<tr>
<td><strong>Premenopausal or &lt;50 years LN-</strong> Clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy</td>
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<tr>
<td><strong>Premenopausal or &lt;50 years LN+</strong> Not recommended</td>
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<tr>
<td><strong>Postmenopausal or ≥50 years LN-</strong> Clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy</td>
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<tr>
<td><strong>Postmenopausal or ≥50 years LN+</strong> Not recommended</td>
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<tr>
<td><strong>Premenopausal or &lt;50 years LN-</strong> Clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy</td>
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<tr>
<td><strong>Premenopausal or &lt;50 years LN+</strong> Not recommended</td>
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<tr>
<td><strong>Postmenopausal or ≥50 years LN-</strong> Clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy</td>
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<tr>
<td><strong>Postmenopausal or ≥50 years LN+</strong> Not recommended</td>
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<tr>
<td><strong>Premenopausal or &lt;50 years LN-</strong> Clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy</td>
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<tr>
<td><strong>Premenopausal or &lt;50 years LN+</strong> Not recommended</td>
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<tr>
<td><strong>Postmenopausal or ≥50 years LN-</strong> Clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy</td>
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<tr>
<td><strong>Postmenopausal or ≥50 years LN+</strong> Not recommended</td>
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<tr>
<td><strong>Premenopausal or &lt;50 years LN-</strong> Clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy</td>
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<tr>
<td><strong>Premenopausal or &lt;50 years LN+</strong> Not recommended</td>
<td></td>
</tr>
<tr>
<td><strong>Postmenopausal or ≥50 years LN-</strong> Clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy</td>
<td></td>
</tr>
<tr>
<td><strong>Postmenopausal or ≥50 years LN+</strong> Not recommended</td>
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<tr>
<td><strong>Premenopausal or &lt;50 years LN-</strong> Clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy</td>
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<tr>
<td><strong>Premenopausal or &lt;50 years LN+</strong> Not recommended</td>
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<tr>
<td><strong>Postmenopausal or ≥50 years LN-</strong> Clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy</td>
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</tr>
<tr>
<td><strong>Postmenopausal or ≥50 years LN+</strong> Not recommended</td>
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<tr>
<td><strong>Premenopausal or &lt;50 years LN-</strong> Clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy</td>
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<tr>
<td><strong>Premenopausal or &lt;50 years LN+</strong> Not recommended</td>
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<tr>
<td><strong>Postmenopausal or ≥50 years LN-</strong> Clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy</td>
<td></td>
</tr>
<tr>
<td><strong>Postmenopausal or ≥50 years LN+</strong> Not recommended</td>
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<tr>
<td>Agency (year)</td>
<td>Tumour profiling test</td>
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<tr>
<td><strong>Oncotype DX®</strong></td>
<td>MammaPrint®</td>
</tr>
<tr>
<td>Clinicians may use a high-risk result from Oncotype DX® to support a decision to offer chemotherapy. A high Oncotype DX® score is capable of predicting adjuvant chemotherapy benefit.</td>
<td>risk MammaPrint® score if the decision is supported by other clinical, pathological or patient-related factors.</td>
</tr>
<tr>
<td>Postmenopausal or ≥50 years LN+</td>
<td>Clinicians may withhold chemotherapy based on a low-risk Oncotype DX® score if the decision is supported by other clinical, pathological or patient-related factors.</td>
</tr>
<tr>
<td>High-risk Oncotype DX® score can be used to recommend adjuvant chemotherapy and endocrine therapy.</td>
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</tbody>
</table>
Clinical-effectiveness evidence

The secondary evidence (systematic reviews, guidelines and HTAs) refers to the same three RCTs on tumour profiling tests (MINDACT, TAILORx and RxPONDER). The recommendations in the guidelines and HTAs were all largely informed by these trials (although some trials were published after the guidelines). Given the importance of these trials to understanding the existing evidence base, they have been summarised first in this section. The remaining studies, as described by the secondary evidence, have been summarised subsequently.

RCTs

Three of the tests are indicated for predictive use (Oncotype DX®, MammaPrint® and EndoPredict®), and RCT evidence is available for two of these MammaPrint® (MINDACT) and Oncotype DX® (TAILORx and RxPonder).

MINDACT

The clinical utility of the 70-gene signature MammaPrint® was evaluated in a prospective non-inferiority RCT (MINDACT), which included 6,693 women aged 18-70 years with node-negative (79% of participants) or 1-3 node-positive (21% of participants), early-stage breast cancer. Patients were eligible irrespective of breast cancer subtype, but the majority had ER+ tumours (90% of participants). The trial was carried out across 112 hospitals in nine European countries, and took place from 2007-2011.

Each patient had their genomic risk determined using the MammaPrint® 70-gene signature, and their clinical risk determined using a modified version of Adjuvant! Online. Adjuvant! Online is an algorithm which incorporates data on oestrogen receptor status, HER2 status, nodal status, tumour grade and tumour size. In the trial, patients with a low clinical and low genomic risk result did not have chemotherapy (41%). Patients with a high clinical risk and high genomic risk did receive chemotherapy (27%). The remaining patients (32%) with discordant risk results (in other words, high genomic risk and low clinical risk, or high clinical risk and low genomic risk) were randomly assigned to receive chemotherapy or not based on either the clinical risk or the genomic risk.

The primary objective was to test whether the lower boundary of 95% CI for the 5-year distant metastases-free survival (DMFS) was above 92% in patients with clinically high-risk and genomic low-risk tumours, who did not receive adjuvant chemotherapy (all patients with HR+ breast cancer received endocrine therapy). The initial publication reported that the trial met its primary objective. The 5-year DMFS was 94.4% (95% CI 92.5 to 96.2) in the population of interest. In this initial report, a non-statistically significant absolute difference of 1.5% was observed in the 5-year DMFS between patients treated or not with adjuvant chemotherapy, and presenting with a clinically high-risk, genomic low-risk breast cancer. The study authors reported that the MINDACT trial was not powered for a reliable comparison of these two treatment strategies in 2016 at a 5-year median follow up, and so the small DMFS advantage in those who received chemotherapy could not be formally excluded. Based on this finding, NICE concluded it raises the possibility of avoiding chemotherapy in
this group of patients, stating that chemotherapy would usually only be indicated where it is likely to provide an absolute improvement in 5-year distant recurrence-free survival (DRFS) of at least 2-3%.

A recent update of MINDACT reported follow-up results (median follow up of 8.7 years), an exploratory analysis of potential age effect (≤50 or >50 years), and an analysis by nodal status for patients with HR+ and HER2- disease. The main results are summarised below.

- The updated 5-year DMFS rate for patients with high clinical risk and low genomic risk receiving no chemotherapy (primary test population, n=644) was 95.1% (95% CI 93.1 to 96.6) compared with 94.4% (95% CI 92.5 to 96.2) in the initial publication.

- In patients with low clinical risk and high genomic risk (n=690) the 8-year estimates for DMFS were 92.3% (95% CI 88.7 to 94.5) for the group that received chemotherapy versus 90.8% (95% CI 86.9 to 93.6) for the group that did not receive chemotherapy (HR 0.85, 95% CI 0.53 to 1.37).

  **SHTG interpretation:** In patients with low clinical and high genomic risk, no significant difference was detected in metastasis-free survival rate at 8-year follow up between those who had chemotherapy and those that did not. Mammaprint® may not be useful in this group of patients, as it could potentially increase chemotherapy rates without improving patient outcomes.

- Patients with high clinical risk and low genomic risk (n=1,497) were randomly assigned to receive chemotherapy (n=749) or not (n=748). The 8-year estimates for DMFS were 92% (95% CI 89.6 to 93.8) for the group that received chemotherapy versus 89.4% (95% CI 86.8 to 91.5) for the group that did not receive chemotherapy (HR 0.66, 95% CI 0.48 to 0.92).

  **SHTG interpretation:** In patients with high clinical and low genomic risk, those that received chemotherapy had a statistically significant higher metastasis-free survival rate at 8-year follow up (absolute difference 2.6 percentage points). An exploratory analysis described below suggests this benefit is age-dependent as it was only seen in women younger than 50 years.

- An analysis of the subset of patients with HR+, HER2- disease with high clinical risk and low genomic risk (n=1,358, 90.7% of the included patients) suggested that the effects of chemotherapy on 8-year DMFS varied according to age and nodal status. This analysis was exploratory and underpowered, and so the results should be interpreted with caution.

  - In women aged 50 years and younger, DMFS was 93.6% (95% CI 89.3 to 96.3) in the group who received chemotherapy versus 88.6% (95% CI 83.5 to 92.3) in the group who did not receive chemotherapy (absolute difference 5 percentage points, SE 2.8, 95% CI -0.5 to 10.4; adjusted HR 0.54, 95% CI 0.30 to 0.98).

    **SHTG interpretation:** In women aged 50 years and younger with high clinical risk and low genomic risk, 8-year metastasis-free survival was higher in those who received chemotherapy.

  - In women aged over 50 years, DMFS was 90.2% (95% CI 86.8 to 92.7) in the group who received chemotherapy versus 90% (95% CI 86.6 to 92.6) in the group who did
not receive chemotherapy (absolute difference 0·2 percentage points, SE 2·1, 95% CI –4·0 to 4·4; adjusted HR 0·82, 95% CI 0·55 to 1·24).

**SHTG interpretation:** In women aged over 50 years with high clinical risk and low genomic risk, there was no difference in 8-year metastasis-free survival between those who received chemotherapy and those that did not.

- In LN- patients, DMFS was 91.7% (95% CI 88.1 to 94.3) in the group who received chemotherapy versus 89.2% (95% CI 85.2 to 92.2) in the group who did not receive chemotherapy (absolute difference of 2·5 percentage points (SE 2·3, 95% CI –2·1 to 7·2; HR 0·60; 95% CI 0·38 to 0·96).

**SHTG interpretation:** In LN- patients with high clinical risk and low genomic risk, 8-year metastasis-free survival was statistically significantly higher in those who received chemotherapy.

- In LN+ patients (one to three positive nodes), DMFS was 91.2% (95% CI 87.2 to 94.0) in the group who received chemotherapy versus 89.9% (95% CI 85.8 to 92.8) in the group who did not receive chemotherapy [absolute difference of 1·3 percentage points (SE 2·4, –3·5 to 6·1; HR 0·84, 95% CI 0·51 to 1·37)].

**SHTG interpretation:** In LN+ patients with high clinical risk and low genomic risk, there was no statistical difference in 8-year metastasis-free survival between those who received chemotherapy and those that did not.

Based on these finding, the MINDCAT trial authors concluded that there is ‘excellent survival’ for women with high clinical risk and low genomic risk treated without chemotherapy at 5 years. They also report that the magnitude of benefit from adding chemotherapy to endocrine therapy remains small at 8-years (absolute difference 2.6 percentage points), and is not enhanced by nodal positivity. Based on underpowered exploratory analyses, the updated results of MINDACT indicate that relying on the genomic signature to forgo adjuvant chemotherapy is safer in women who are postmenopausal with a high clinical risk than in women who are premenopausal.

Limitations of the MINDACT study include its open-label nature, and high drop-out rates (22%, 481 out of 2,187 patients who were randomised). Participants were eligible for inclusion in the trial regardless of breast cancer subtype, so it includes a broader population than is the focus of this SHTG review, for example those with HER2+ tumours or triple negative breast cancer. HIQA noted that molecular diagnostic testing was performed on frozen samples of the resected tumour, rather than a FFPE tissue sample, although in preparing this review, the manufacturer highlighted a study which suggests that FFPE results are substantially equivalent to results derived from fresh tissue.\(^3\)\(^,\)\(^{39}\)

**TAILORx**

The TAILORx trial aimed to evaluate whether there was a benefit for chemotherapy for patients who have a midrange score as determined with the Oncotype DX\(^8\)\(^,\)\(^{40}\). The trial included 10,273 women for at least 5 years (median of 7.5 years), and was carried out at 1,182 sites in the United States,
Australia, Canada, Ireland, New Zealand and Peru. The trial took place between 2006 and 2010. Participants were women aged between 18 and 75 years, who had HR+, HER2-, axillary node-negative (LN-) breast cancer. All participants met National Comprehensive Cancer Network guidelines for the recommendation or consideration of adjuvant chemotherapy.

Based on the 21-gene RS, women were assigned to one of four treatment groups. Women with a RS of 10 or lower were assigned to receive endocrine therapy only, and women with a score of 26 or higher were assigned to receive chemotherapy plus endocrine (chemoendocrine) therapy. Women with a midrange score of 11 to 25 were randomised to receive either endocrine therapy alone or chemoendocrine therapy. The trial was designed to show noninferiority of endocrine therapy alone for invasive disease-free survival.

Among the women with a RS of 11 to 25, the main results are summarised below.

- **Endocrine therapy was noninferior to chemoendocrine therapy in the analysis of invasive disease-free survival (HR 1.08, 95% CI 0.94 to 1.24, p=0.26).**

- **At 9 years, the two treatment groups had similar rates on invasive disease-free survival (83.3% in the endocrine therapy group and 84.3% in the chemoendocrine therapy group), freedom from disease recurrence at a distant site (94.5% and 95.0%) or at a distant or local–regional site (92.2% and 92.9%), and OS (93.9% and 93.8%).**

- **The chemotherapy benefit for invasive disease-free survival varied with the combination of RS and age (p=0.004), with some benefit of chemotherapy found in women 50 years of age or younger with a RS of 16 to 25.**

- **When all RS cohorts (≤10, 11 to 25, and ≥26) and treatment-group assignments were considered, there were significant differences in the rates of invasive disease-free survival, recurrence and death (p<0.001), driven largely by the higher likelihood of having an event in the cohort with a RS of 26 or more.**

- **For patients age ≤50 years, the absolute benefit increased as the RS increased (invasive disease-free survival rate at 5 years: 92% v 94.7% for RS 16-20, and 86.3% v 92.1% for RS 21-25) for endocrine versus chemoendocrine therapy, respectively.**

The authors concluded that trial results suggest that the 21-gene assay may identify up to 85% of women with early breast cancer who can be spared adjuvant chemotherapy, especially those who are older than 50 years of age and have a RS of 25 or lower, as well as women 50 years of age or younger with a RS of 15 or lower.

Limitations of this RCT include an unbalanced drop out of participants randomised to each group (32% of women assigned to the chemotherapy plus endocrine therapy arm did not complete the study protocol, compared with 17% of patients assigned to the endocrine therapy alone arm), and the lack of comparator for Oncotype DX®. The authors of the study acknowledged the potential impact of nonadherence to assigned treatments on the results, and attempted to account for this. For example, they increased the sample size that underwent randomisation, and reported that as-
treated analyses produced similar results to intention-to-treat analyses. NICE suggests that the results from TAILORx may not be generalisable to practice in the UK because it was not clear how many of the participants who were offered chemotherapy in the trial would have been offered chemotherapy in an NHS pathway. HIQA noted that 29% of women within the TAILORx trial had Grade 1 tumours, which typically may not have been treated with chemotherapy in Ireland. Additionally, 74% of women randomised to chemoendocrine therapy were classified as clinically low risk based on a modified Adjuvant! Online algorithm. These limitations may have biased the results towards finding non-inferiority of chemoendocrine therapy compared with endocrine therapy alone.

Two peer reviewers for this evidence summary also questioned the primary outcome used in the TAILORx study (invasive disease-free survival). They suggested that this was a broad endpoint, which includes new non-breast cancer primaries. Given that the primary purpose of chemotherapy is for the prevention of distant metastases, they argue that using such a broad outcome might have diluted the findings around potential benefits of chemotherapy.

In 2019 (after the publication of the NICE guidance), the results of a secondary analyses of the TAILORx trial were reported. The aim of the analyses were to determine whether clinical risk, as assessed with a modified version of Adjuvant! Online, adds prognostic information to the Oncotype DX® RS and predictive information regarding the benefit of chemotherapy. The authors provided further analyses examining the relationship between age and the absolute benefit of chemotherapy in women aged 50 years or less with an intermediate RS (16 to 25). Data was available for 9,427 participants, or whom 6,615 (70.2%) had low clinical risk and 2,812 (29.8%) had high clinical risk.

The main results were are summarised below.

- The level of clinical risk was prognostic of distant recurrence in women with RS 11-25 who were randomly assigned to endocrine therapy or chemoendocrine therapy, and in women with an RS 26-100 (who were all assigned to chemoendocrine therapy).
  - The hazard ratio for the comparison of high versus low clinical risk in women with RS 11-25 in the endocrine therapy group was 2.73 (95% CI 1.93 to 3.87) and was 2.41 (95% CI 1.66 to 3.48) in the chemoendocrine therapy group.
  - The hazard ratio for the comparison of high versus low clinical risk in women with RS 26-100 was 3.17 (95% CI 1.94 to 5.19).

- Among younger women (aged 50 years and less)
  - with a low RS (0-10), the estimated rate (± standard error, SE) of distant recurrence at 9 years was less than 5% (≤1.8 ± 0.9%) irrespective of clinical risk
  - with an intermediate RS (11-25), the estimated rate of distant recurrence at 9 years was 4.7 ± 1.0% with low clinical risk
  - with an intermediate RS (11-25), the estimated rate of distant recurrence at 9 years exceeded 10% with high clinical risk who received endocrine therapy alone (12.3 ± 2.4%) and chemoendocrine therapy (15.2 ± 3.3%)
Based on these findings, the authors concluded that clinical-risk stratification provided prognostic information that, when added to the Oncotype DX® RS, could be used to identify premenopausal women who could benefit more from effective therapy.

**RxPONDER**

The RxPONDER trial aimed to evaluate the value of the Oncotype DX® RS in predicting the benefit of adjuvant chemotherapy in women with LN+ disease. A total of 5,083 women (33.2% premenopausal and 66.8% postmenopausal) underwent randomisation, and 5,018 participated in the trial. Participants with ER+, HER2- breast cancer, with 1-3 axillary lymph nodes positive, and an Oncotype DX® RS of 0-25 were randomly assigned to endocrine therapy alone or taxane and/or anthracycline-based chemoendocrine therapy. The trial was conducted at 632 sites in nine countries (United States, Canada, Mexico, Colombia, Ireland, France, Spain, South Korea and Saudi Arabia), and took place between 2011-2017.

In the overall population of participants with RS 0-25, there was no improvement in 5-year invasive disease-free survival with the addition of adjuvant chemotherapy to endocrine therapy. At the third planned interim analysis, chemotherapy benefit for invasive disease-free survival differed by menopausal status in a prespecified analysis, leading to separate analyses.

In the 67% of participants who were postmenopausal, 5-year invasive disease-free rates were 91.9% and 91.3%, for endocrine and chemoendocrine therapy respectively, with no chemotherapy benefit (HR=1.02, 95% CI 0.82 to 1.26, p=0.89). In premenopausal women (33.2% of RxPONDER participants), the 5-year invasive disease-free survival rates were 89.0% and 93.9% for endocrine therapy and chemoendocrine therapy (HR=0.60, 95% CI 0.43 to 0.83, p=0.002), with similar improvement in distant disease-free survival (HR=0.58, 95% CI 0.39 to 0.87, p=0.009). In premenopausal women, chemotherapy benefit was seen across RS categories.

The relative chemotherapy benefit did not increase with higher RS, that is the trial did not show that Oncotype DX® RS is predictive of improved outcomes with chemotherapy. There was greater absolute chemotherapy benefit observed with higher RS in premenopausal women with RS 0-25. The RxPONDER trial suggested that postmenopausal LN+ women with an RS 0-25 could be safely spared chemotherapy. These findings are only from the first 5 years of data of a planned 15-year follow up, and may change with time, although Scottish clinical experts have advised that most chemotherapy benefit is seen in the first 5 years. A peer reviewer for this review questioned the conclusion of non-inferiority of chemotherapy in this population, given that the trial was not designed as a non-inferiority trial. In addition, as with the TAILORx trial, the RxPONDER trial did not compare Oncotype DX® with another risk prediction method, and used invasive disease-free survival as the primary endpoint. Finally, the majority of participants had cancer that had spread to one lymph node only (65.3%). Only 9% or participants had cancer that had spread to three lymph nodes, and so this trial represents the ‘lower risk’ LN+ patients.
Secondary evidence

The guidelines and HTAs identified by our literature search included comprehensive and robust reviews of the published evidence and the literature reviews on which they were based consisted of largely the same evidence base. Given this overlap in the included studies, we have focused on three sources of secondary evidence in this section, which together give a comprehensive overview of the evidence:

- an HTA by HIQA (2023) which included a systematic review of the clinical-effectiveness evidence for tumour profiling tests in guiding the use of adjuvant chemotherapy in early-stage invasive breast cancer;
- the clinical-effectiveness evidence that was reported on by the NICE guidance (2018);
- a well-conducted systematic review from 2022 (Lemij et al), which included the same studies as NICE and HIQA, but focused on the use of tumour profiling tests as a tool in adjuvant treatment decision making in older patients (aged 65 and above) with breast cancer.

As it is the most recent and comprehensive, the HIQA review has been used as the main source of secondary evidence. The HIQA review included 87 relevant studies. These considered the prognostic ability (n=49), predictive ability (n=24) and decision impact (n=14) of tumour profiling tests (some studies reported data in more than one category).

Prognostic ability of tumour profiling tests

The NICE guidance from 2018 reported that for patients with LN- disease, the four tests had statistically significant prognostic accuracy over clinical and pathological features or risk assessment tools (results summarised in Table 5). NICE also reported that the evidence was weaker and more variable in patients with LN+ disease, although there was some evidence of prognostic accuracy for all four tests over clinical and pathological features or risk assessment tools (Table 5).

The overall conclusions from the more recently published HIQA review, which includes more up-to-date evidence, mirror the NICE guidance from 2018. HIQA note that large observational studies provide the highest certainty of evidence regarding the prognostic ability of tumour profiling tests. In their review, evidence for prognostic factors came from retrospective analyses of RCTs and data registries (n=49). Oncotype DX® was the most studied test in both LN- and LN+ populations. Based on all the evidence, the HIQA authors concluded that each of the four tests likely has modest prognostic value for providing an estimate of a patient’s future risk of cancer recurrence and/or survival, with greater consistency of evidence about LN- populations than LN+. HIQA reported additional observations with regard to the evidence on prognostic ability, summarised below.

- As a result of high heterogeneity across studies (for example in study design, analytic approaches, cut-off scores used, eligible populations and outcome measures) each test’s ability to predict cancer recurrence and survival could not be meaningfully quantified.
- Some studies suggested that the prognostic ability of tests might vary between pre- and postmenopausal women, and perform better among white patients compared with African American patients (further research would be required to confirm this).
Few studies directly compared the tumour profiling tests, so the evidence does not allow conclusions to be drawn on the relative prognostic ability of each test.

Tumour profiling tests may add prognostic value beyond that of other prognostic information available to clinicians and patients, although the evidence is limited.

HIQA considered the results for LN- and LN+ patients separately. Their high-level conclusions have been summarised below.

**HIQA conclusions for patients in the LN- population**

HIQA identified 30 studies that considered the prognostic ability of tumour profiling tests in the LN-population (16 for Oncotype DX®, six for MammaPrint®, nine for Prosigna® and three for EndoPredict®). Outcomes were freedom from distant recurrence, disease-free survival and less commonly overall survival.

Four studies compared the different tests. All were retrospective analyses of trials designed for other purposes. The certainty of the comparative evidence was judged to be very low because of imprecision and a high risk of bias. These studies found EndoPredict’s® EPIClin score and Prosigna® to be more prognostic for distant recurrence than Oncotype DX®. HIQA noted that Sestak et al was the closest fully comparative study they identified, and the only one of the four comparative studies that was published after the NICE guidance from 2018. It compared the prognostic accuracy of six multigene signatures, including Oncotype DX®, Prosigna® and EndoPredict®. This was a retrospective secondary analysis of data from an RCT (TransATAC trial) that compared the efficacy of adjuvant treatment approaches in postmenopausal women with early-stage, operable breast cancer. The biomarker analysis included 774 postmenopausal women with ER+, HER2- breast cancer (591 had node-negative disease) who had received endocrine therapy for 5 years. HIQA’s summary of the results for the LN- population is below.

All of the tests were found to predict, with statistical significance, distant recurrence during years 0 to 10 (and also years 5 to 10), though Prosigna® and EndoPredict® had the highest strength of prediction...all tests also provided independent prognostic information beyond the clinicopathologic score when this was included as an additional variable in the model. When the three tests were combined with the clinicopathologic score, the Prosigna® ROR score provided the highest prognostic value, although differences across tests were not tested for statistical significance.

The non-comparative studies included by HIQA are available in the HIQA report. They do not alter the conclusions made by NICE in 2018 on the prognostic accuracy of tumour profiling tests in the LN-population.

**HIQA conclusion for patients in the LN+ population and mixed lymph node status population**

HIQA included 30 studies that evaluated the prognostic ability of tumour profiling tests in LN+ patients (19 for Oncotype DX®, three for MammaPrint®, nine for Prosigna® and six for EndoPredict®).
A further nine studies evaluated the prognostic ability of tumour profiling tests in mixed LN status populations. Outcomes were mostly freedom from distant recurrence and less commonly disease-free survival and commonly OS.

Six studies considered head-to-head comparisons of the prognostic accuracy of the tumour profiling tests. Five studies compared different two different tumour profiling tests, and one compared three (Oncotype DX®, Prosigna® and EndoPredict®). As with the LN- population, the certainty of the comparative evidence was judged to be very low or low because of imprecision and a high risk of bias.

The study that compared three of the tests (Sestak et al) concluded that for the LN+ population, all the tests provided significant prognostic information among endocrine-treated women during years 0 to 10. They also noted that the prognostic ability of all three tests was weaker for the LN+ population compared with the LN- population.44

The non-comparative studies included by HIQA are available in the HIQA report. They do not alter the conclusions made by NICE in 2018 on the prognostic accuracy of tumour profiling tests in the LN+ population.

Lemij et al reported that there was some evidence supporting the clinical validity of the prognostic performance of Oncotype DX® and Prosigna® in older patients (aged 65 years and older) with HR+, LN- and LN+ breast cancer. They included four studies in LN- patients (all evaluating Oncotype DX®) and three in LN+ patients (two on Oncotype DX® and one on Prosigna®).43

Both NICE And HIQA noted concerns about bias in the studies reporting prognostic ability. For example, some studies/analyses included participants whether or not they had chemotherapy. Some studies excluded tumour samples with insufficient tissue, and some included participants with HR- or HER2+ disease. The studies included by Lemij et al, were assessed as having a moderate risk of bias.
Table 5: Summary of findings from NICE literature review (2018) – prognostic ability

<table>
<thead>
<tr>
<th>Tumour profiling test</th>
<th>Evidence included</th>
<th>Main results</th>
<th>Adjusted analyses*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oncotype DX®</strong></td>
<td>11 datasets (seven reanalyses of RCT data and four retrospective studies of routinely collected data)</td>
<td>Prognostic accuracy (statistically significant differences between low-risk and high-risk groups) across various recurrence outcomes, regardless of LN status. Hazard ratios between the intermediate-risk group and the high or low-risk groups were not always statistically significant, particularly in the group with LN+ disease.</td>
<td>Statistically significant additional prognostic information over most commonly used clinical and pathological variables (age, grade, size, nodal status), regardless of LN status. A bespoke analysis of TransATAC study data showed that Oncotype DX provided additional prognostic information over clinical and pathological tools to assess risk.</td>
</tr>
<tr>
<td><strong>MammaPrint®</strong></td>
<td>10 datasets (one reanalysis of RCT data and nine retrospective studies of routinely collected data)</td>
<td>Prognostic accuracy in six of seven unadjusted analyses, (statistically significant differences between low-risk and high-risk groups) for 10 year DRFS or interval, regardless of LN status.</td>
<td>Statistically significant prognostic accuracy for 10-year DRFS in patients with LN- and LN+ disease. In patients with LN- disease, a statistically significant prognostic accuracy for 10-year distant recurrence-free interval when adjusted for Adjuvant! Online, NPI or clinical and pathological variables. In patients with LN+ disease, borderline statistically significant prognostic accuracy for 10-year distant metastasis-free survival when adjusted for clinical and pathological variables.</td>
</tr>
<tr>
<td><strong>EndoPredict®</strong></td>
<td>three datasets (all were reanalyses of RCT data)</td>
<td>Statistically significant prognostic accuracy for 10-year DRFS and interval in patients with LN- and LN+ disease.</td>
<td>Statistically significant increases in likelihood ratio for 10-year distant recurrence-free interval over clinical and pathological variables or tools, regardless of LN status.</td>
</tr>
<tr>
<td><strong>Prosigna®</strong></td>
<td>eight datasets (six reanalyses of RCT data and three retrospective analyses of two prospective cohort studies)</td>
<td>Statistically significant prognostic accuracy for 10-year DRFS and interval in all unadjusted analyses of patients with LN- and LN+ disease.</td>
<td>Statistically significant prognostic accuracy for 10-year distant metastasis-free survival and DRFS in patients with LN- disease. In patients with LN+ disease the results were statistically or borderline significant.</td>
</tr>
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</table>

* Unadjusted analyses look at differences in the event rates among low, intermediate and high-risk groups without adjusting for clinical and pathological variables. Adjusted analyses show whether the test has prognostic value over clinical and pathological variables.
Predictive ability of tumour profiling tests
Three of the tests are indicated for predictive use (Oncotype DX®, MammaPrint® and EndoPredict®). HIQA noted that the strongest evidence for the predictive ability of the three tests comes from the TAILORx, RxPONDER and MINDACT RCTs (described in the ‘RCTs’ section starting on page 29).³

HIQA included 15 publications that evaluated the predictive ability of tumour profiling tests (13 on Oncotype DX®, and two on MammaPrint®), although their conclusions are largely based on the three RCTs. For patients with LN- disease, their conclusions are below.

- MammaPrint® does not offer predictive value beyond that of a modified Adjuvant! Online algorithm, which incorporates data on oestrogen receptor status, HER2 status, nodal status, tumour grade and tumour size.
- The TAILORx trial suggested that patients with an Oncotype DX® RS 11-25 could be safely spared chemotherapy, although exploratory analyses indicate that there may be some chemotherapy benefit for women aged under 50 years with an RS of 16-25.

HIQA notes a high degree of uncertainty with these conclusions because of limitations within the trials, and concerns around lack of generalisability to the Irish setting. Their conclusion for MammaPrint® was based on two publications on the MINDACT trial. In the MINDACT 8-year follow-up paper, an exploratory analysis was done on nodal status, which suggested there was a chemotherapy benefit in patients with high clinical, low genomic risk and LN- disease. While it is statistically significant, the clinical significance of this result (absolute difference in metastasis-free survival of 2.5 percentage points) is unclear. Despite being considered small by the MINDACT trial authors, it falls between the 2-3% proposed by NICE, which likely explains HIQA’s conclusion for the LN- population. HIQA noted that in the low clinical, high genomic risk LN- population, there was no difference in distant metastasis-free survival between those who did or did not receive chemotherapy. HIQA’s overall conclusion for Oncotype DX® in this group of patients is based on the TAILORx trial, though they note limitations with this.

For patients with LN+ disease, HIQA’s conclusions are summarised below.

- Evidence supports the predictive utility of MammaPrint® in patients aged over 50 years, with a high clinical risk and low genomic risk. The MINDACT trial suggested that this group might be safely spared chemotherapy.
- Postmenopausal patients with an Oncotype DX® RS 0-25 can be safely spared chemotherapy, although these findings are derived from the first 5 years of data from the RxPONDER trial with a planned 15-year follow up.

As with the LN- population, HIQA notes a high degree of uncertainty with these conclusions. Their conclusion for MammaPrint® was based on the exploratory analyses done in the
MINDACT trial on nodal status, which suggested no chemotherapy benefit in patients with high clinical, low genomic risk and LN+ disease. Their conclusion for Oncotype DX® in this group of patients is based on the RxPONDER trial.

In 2018, NICE also considered the evidence on the ability of the tests to predict which patients have disease that will respond to chemotherapy. They considered five datasets (two reanalyses of RCT data, three observational studies) for Oncotype DX® and two studies on MammaPrint®. NICE similarly noted a high degree of uncertainty with the evidence, but concluded that Oncotype DX® may be able to predict who will respond to chemotherapy. They reported that there was some evidence of differential chemotherapy benefit between risk groups for Oncotype DX® as shown by significant interaction tests between risk group and chemotherapy treatment in unadjusted analyses, but interaction tests sometimes became non-significant when clinicopathological factors were adjusted for. They also noted that the evidence relating to the ability of MammaPrint® to predict benefit from chemotherapy was extremely limited.

NICE considered the evidence on clinical utility, that is, the ability of the tumour profiling tests to affect patient outcomes. Included in this were the 5-year results from the MINDACT study and the TAILORx study (RxPONDER was not published). Overall, NICE concluded that none of the tests had strong enough evidence to demonstrate an effect on subsequent patient outcomes.

Lemij et al included the TAILORx and RxPONDER trials, and similarly concluded that there was some evidence that Oncotype DX® was predictive for older patients with an intermediate-risk RS in both LN- and LN+ patients. Their results are summarised below.

- The predictive ability of Oncotype DX® in older patients with LN- disease was addressed in four studies. Two publications were based on the TAILORx trial and three studies were based on retrospective analyses of registry data. The TAILORx trial demonstrated no benefit from the addition of chemotherapy in patients aged 65–75 years of age with an intermediate-risk RS in terms of distant recurrence-free interval, invasive disease-free survival and relapse free interval. One of the retrospective studies, with a high risk of bias, showed that patients aged 66–80 years had a better OS when treated with chemotherapy compared to those who did not receive chemotherapy, for both the intermediate-risk RS (p=0.031) and high-risk RS groups (p=0.042), but not in patients over 80 years of age. The other two retrospective studies, with a high risk of bias, showed no beneficial effect of chemotherapy on breast cancer specific mortality in patients who had an intermediate- and high-risk RS, when using the TAILORx thresholds.

- The predictive ability of Oncotype DX® in older patients with LN+ disease was addressed in three studies. One study was the RxPONDER trial and two studies were retrospective studies based on registry data. A subgroup analysis of approximately 1,100 patients from the RxPONDER trial, aged 65 years and older who had either a low-risk or intermediate-risk RS, showed no statistically significant difference in 5-
year invasive disease-free survival between the two treatment strategies (HR 1.05, 95% CI 0.75 to 1.47). The two retrospective studies, with a high risk of bias, included patients with a high-risk RS who had either LN- or LN+ disease. One study showed that patients aged 65 years and older receiving adjuvant chemotherapy had a decrease in breast cancer specific mortality compared with patients not receiving chemotherapy (HR 0.63, 95% CI 0.60 to 0.67, p<0.001). The number of older patients with LN- disease was not mentioned, but 70% of the whole cohort (including the younger patients) had negative lymph nodes. The other retrospective study found no breast cancer specific survival and OS advantage of chemotherapy for patients aged 70 years and older. Eighteen percent of patients had LN+ disease.

Lemij et al noted that the studies included relatively young older patients (between 65 and 75 years old), and this may not be reflective of the true older population, in whom decisions around chemotherapy may be more difficult. They also noted that there was a need for further research in older patients (aged over 65 years) with high-risk tumours before tumour profiling tests can be implemented in clinical practice as a prediction tool for adjuvant chemotherapy decision making.43

**Decision impact of tumour profiling tests**
HIQA identified 24 studies, which evaluated the impact of tumour profiling test results on treatment decisions, and reported that approximately 20% to 50% of treatment decisions were observed to have changed based on the results of these tests. Evidence in LN+ specific populations was sparse. They noted that these studies did not assess whether the changes in treatment recommendations led to improved patient outcomes. Similar findings were reported by NICE.

**Concordance between tests**
This refers to the extent to which the tests assign the same patients to the same risk groups. Within this context, HIQA and NICE both discuss the OPTIMA Prelim study. The OPTIMA trial is an ongoing trial from the UK, which aims to test the effectiveness of multiparameter testing in identifying patients who can be spared chemotherapy. The OPTIMA Prelim study was designed to help select the tests to include in the trial. It included 302 women aged over 40 years with HER2-, ER+, early-stage breast cancer with either 1-9 positive lymph nodes or a tumour of ≥30 mm. It included three of the four tumour profiling tests covered by this review (Oncotype DX®, MammaPrint®, and Prosigna®). The authors concluded that the three tests showed moderate agreement when dichotomising results between high versus low/intermediate risk (kappa range: 0.40 to 0.53), with concordance higher in the low-/intermediate-risk groups than in the high-risk groups. In comparing Oncotype DX® with Prosigna®, 9.7% of tumours were classified as high risk by one test and low risk by the other. HIQA concluded that this discordance suggests that no one test should be the ultimate discriminator of risk for individual patients.3
NICE stated that their decision to only consider the cost effectiveness of tumour profiling tests in LN- patients was partly because of this lack of agreement between the tests in risk categorising the group with LN+ disease (there was also the lack of data to inform any modelling). \(^4\)

A peer reviewer for this SHTG evidence review also highlighted a study not included in the NICE or HIQA reviews (Bartlett et al. 2021)\(^{45}\), which suggested that different tests may provide different risk estimates at the individual patient level. Comparing the genes that are mapped in Oncotype DX\(^8\), MammaPrint\(^9\), and Prosigna\(^8\), the authors concluded that the different tests capture different aspects of prognostic drivers, and that future improvements in prognostic testing remain achievable. Subgroup analyses suggested that the interaction between clinical risk, treatment, and molecular risk profiling may differ depending on the test chosen, and this might provide support for the use of different testing strategies in different patient risk strata.

**Ongoing trials**

**Table 6: Summary of ongoing trials**

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Population</th>
<th>Intervention and comparator(s)</th>
<th>Primary outcomes</th>
<th>Estimated completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03904173</td>
<td>Adults (18+) with primary non-metastatic, node-negative (pN0), hormone receptor positive, HER2 negative breast cancer. Patients with pT1pN1(mi) status may also be included</td>
<td>Prosigna(^8) compared to standard adjuvant treatment recommendations (based on clinicopathological variables only)</td>
<td>Treatment decision differences with or without Prosigna(^8) test; Distant disease-free survival</td>
<td>Primary completion date: June 2027 Study completion date: December 2043</td>
</tr>
<tr>
<td>OPTIMA: Optimal Personalised Treatment of early breast cancer using Multi-parameter Analysis</td>
<td>Adults (40+), HR+, HER2-, with cancer that is: LN+ (1-9 lymph nodes) or LN- that is at least 3 cm in size</td>
<td>Group 1: Prosigna(^8) test will not be used to guide treatment decision – this group will go straight to chemotherapy Group 2: Prosigna(^8) test will be used to guide</td>
<td>Cancer recurrence within 5 years</td>
<td>Recruitment end: 31 December 2024, then a 10 year follow up</td>
</tr>
</tbody>
</table>
Patient and social aspects

Our literature search identified one qualitative study that explored the ways in which women in the UK interpret and discuss tumour profiling tests for breast cancer treatment decision making, as articulated in online accounts. The study focused on discussions of Oncotype DX®. Accounts were taken from online forums hosted by two UK cancer charity websites, comprising 132 discussion threads from seven forums.

The main findings are summarised below.

- Many of the discussions focused on how the test had been useful to help guide decision making. Some people talked about the test providing ‘personalised’ information, which was perceived as more reliable than risk scores calculated from online algorithms.
- Many people valued Oncotype DX®’s production of a single figure to indicate recurrence risk, and corresponding recommendation to proceed (or not) to chemotherapy. Test scores were often seen as authoritative, particularly amongst women attaining low scores. Women with intermediate scores were more likely to describe decision making following Oncotype DX® as complex and fraught.
Some people talked about no test being able to provide a definitive answer as to whether their cancer would recur, and as to whether chemotherapy was an appropriate option. Some users discussing Oncotype DX® results articulated that the onus was on themselves to make the final decision with regards chemotherapy. The authors noted that this uncertainty could be linked to posts emphasising the ability of cancer to evade detection.

Some people, particularly those with intermediate results, talked of basing their decision on a ‘gut feeling’, on the possibility of future regret, or on a perceived vulnerability to ‘rogue’ cancer cells.

The authors concluded that the women represented in the research ‘did not always interpret Oncotype DX scores straightforwardly, with these results taking on varying significance according to factors including personal encounters with cancer, and potential regret for declining treatment. This emphasises the importance of holistic treatment decision making between patients and clinicians, which may engage with loved ones’ experiences of the disease, “gut feelings,” emotions and anticipated futures.’

Guidance from the American Society of Clinical Oncology (ASCO) says patients should be provided with a copy of their pathology report and ER, HER2, and, if available, Oncotype DX®, EndoPredict®, Prosigna®, or other test results when useful.

Submission from Breast Cancer Now

To inform this work, SHTG engaged with Breast Cancer Now, who completed a patient organisation submission. They drew on their organisational experience and expertise, and specifically referred to the experience of three people who had breast cancer, two of whom had tumour profiling tests (Oncotype DX® and Prosigna®). Some of the main points from the submission are presented below. The full submission is available from the SHTG website.

The submission states that a breast cancer diagnosis can be devastating for a person and the people close to them. As well as concerns around survival, people worry about the impact disease will have on their body, the financial implications from not being able to work, the side effects of treatment and whether the cancer will return. Chemotherapy can be viewed with particular concern because of the side effects. Patients also report high levels of stress and anxiety, and many find life after breast cancer to be challenging.

The submission included the following patient quotes:

“The shock was tremendous. I hadn’t felt ill or felt any lumps. For me, all I had noticed was dimpling in my left breast and nothing had shown on either mammogram or ultrasound. It was only as a result of biopsies that it was confirmed I had lobular breast cancer ER+ HER2-. None of this meant anything to me and the 3 weeks following diagnosis which were filled with various diagnostics
(MRI/Tomosynthesis) were a mental battle which had me fearing a death sentence and feeling very lonely.”

“The constant worry about a recurrence or developing a secondary is also an ongoing issue. Dealing with the constant thoughts of ‘will I be around for that’ or ‘is there any point in paying into a pension’ is definitely on my mind a lot.”

“The main issue I have day to day is the medication I take to reduce a recurrence. In my case this is a monthly zoladex injection and a daily exemestane tablet. The muscles aches and joint pain can sometimes be unbearable. I’m 33 years old and some days feel 100!”

“Until I started chemotherapy I actually still felt well. I recovered well from surgery, but chemo is so much more systemic, and the loss of my hair was a notice to the world that I had cancer. I felt like I was no longer “normal” and was very fatigued. At times, I could hardly walk the length of myself.”

With respect to the tumour profiling tests, Breast Cancer Now say that they provide an opportunity to offer a more personalised treatment approach. They state that the decision on whether or not chemotherapy is needed is often a top concern for patients, so having more information to inform discussions and provide reassurance can be an important step forward.

“I think it helps people who get a low score to not worry as much and also not have treatment they don’t need and for people who score high I feel it allows them to take any action necessary to reduce their reoccurrence risk.”

“I felt it put my mind at rest as to whether it was highly likely it would come back or not. I do take comfort in the fact I didn’t get a high score on the test and also had all treatments I could have to stop it from coming back.”

Someone who did not have tumour profiling testing said:

“I question whether I needed to go through chemo and whether it has actually made any difference. I have since found out that lobular cancer tends to respond less to chemo than other cancer types (not always but in general terms). I have questioned why I didn’t get oncotype testing and was told I didn’t qualify due to the size of my tumour (12.5 cm).”

The submission notes the importance of people receiving their test results in a timely manner, as waiting for test results can cause considerable anxiety.
Organisational issues

Currently in NHSScotland, Oncotype DX® is the only genomic test widely available for use in patients with early breast cancer. The topic experts who peer reviewed this evidence review reported that there is disparity in use of Oncotype DX® across NHSScotland health board areas resulting in inequity of access. Prosigna® is only used within the context of research in NHSScotland.

Until August 2022, the Molecular Pathology Evaluation Panel (MPEP) assessed and evaluated molecular pathology tests for the NHS in Scotland against set criteria and made recommendations to the Molecular Pathology Consortium (MPC) on the clinical validity, analytical validity and clinical utility of tests [this is now done by the Scottish Genomics-Test Advisory Group (SG-TAG)]. MPEP/MPC reviewed the NICE Diagnostics Guidance [DG34] regarding tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer. The MPEP/MPC jointly endorsed NICE Diagnostics Guidance [DG34] regarding tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer. It was beyond the remit of MPC to make recommendations as to selecting which test to provide at Health Board level. MPC stated that it is for health professionals within NHS boards in Scotland to make clinical decisions regarding the care of patients. There is no national funding within the MPC to meet the cost of the tests. Costs would fall to the NHS board of residence of patients referred for testing. The expectation is that NHS boards will fund the test should a specialist clinician consider it is required to inform case management for a patient who meets the criteria. [link]

Scotland’s cancer networks report against a national breast cancer quality performance indicator (QP17) on genomic testing (QPI title: Patients with breast cancer should be offered genomic testing where appropriate).

Cost effectiveness

NICE independent economic analysis – DG34 2018

The most recent UK-based HTA of tumour profiling tests to guide adjuvant chemotherapy decisions in women with early-stage breast cancer was conducted by NICE in 2017 and informed the diagnostic guidance (DG34) recommendations. A summary and critical appraisal of this economic analysis is available in Appendix 1.

The NICE Committee did not consider the cost-effectiveness results in the LN+ population, as the clinical evidence to inform these was considered highly uncertain. Of particular concern was evidence that individual patients with LN+ disease received different risk classification from different tests in this population.
NICE concluded that, when a confidential discount had been applied for the tests, the EPclin®, Oncotype DX® and Prosigna® tests were likely cost effective in patients with LN-disease with an intermediate clinical risk score using a validated tool.

Cost effectiveness of tumour profiling tests in the NICE economic evaluation for the LN-NPI>3.4 subgroup was driven by reduced chemotherapy use without significant increases in distant recurrence. The results in this group were sensitive to the costs of the test.

The NICE analysis found that none of the tests were likely to be cost effective in patients with LN- disease and low clinical risk. Patients in the LN- NPI≤3.4 subgroup are unlikely to receive chemotherapy in routine clinical practice without a test and in the NICE analysis, the tests were found to increase the use of chemotherapy. For the low clinical risk subgroup in the base-case analysis, incremental cost-effectiveness ratios (ICERs) were all over £91,000 per quality adjusted life year (QALY) gained without a discount. So in the model, tests improved patient outcomes by identifying patients with a high risk of recurrence who would not normally be recommended adjuvant chemotherapy using clinicopathological risk alone, but this was not cost effective using conventional willingness-to-pay thresholds (£20,000 to £30,000 per QALY gained).

The NICE analysis used a bespoke analysis of data from the TransATAC study (academic in confidence) for distant metastases-free interval (DMFI) and test-risk classification for three of the four tests in the review. Using these data maintained correlation between these parameters, which reduced the risk that spectrum bias could affect the results. The analysis also incorporated data from the NHS England Access Scheme for the probability of receiving chemotherapy with or without a test in the LN- intermediate-risk subgroup. This meant that these probabilities were likely to reflect how the tests would influence clinical decision making in practice.

Significant uncertainties that were unresolved in the NICE analysis included weaker evidence for the decision impact of tests in LN- NPI≤3.4 and LN+ subgroups, lack of evidence about tools more commonly used in routine clinical practice to define risk of recurrence (for example, PREDICT) and that evidence for the MammaPrint® test was only available in comparison to modified Adjuvant! Online (mAOL), a risk prediction tool that is not routinely used routinely in the NHS. Whether tests could offer a predictive factor for the benefit of chemotherapy had a significant impact on the results of the analysis for the Oncotype DX® test. If predictive benefit was assumed for the Oncotype DX® test, it became more cost effective. The NICE Committee concluded that the evidence that Oncotype DX® provided predictive benefit was highly uncertain.
The SHTG systematic search identified a number of economic evaluations of tumour profiling tests to guide chemotherapy in people with early breast cancer published since the previous UK-based HTA agency appraisal of tumour profiling tests in 2017 and potentially relevant for inclusion in the review. The review was undertaken to assess the impact of evidence published since the previous appraisal on estimates of cost effectiveness. Six unique cost-effectiveness studies were identified that were considered relevant to the decision problem. A manufacturer identified an additional study that was not found in the initial search. The analytic scope of each economic evaluation study is summarised and a brief summary of how each study incorporated clinical evidence with the overall results are available in Appendix 2.

The economic evaluations published since NICE DG34 are heterogeneous in their methodology, population under consideration and application of the evidence. Six of the eight studies assessed the cost effectiveness of the Oncotype DX® test. One study assessed the cost effectiveness of the Prosigna® test and another assessed the MammaPrint® test. Four studies adopted a cost-utility analysis (CUA), two studies adopted a cost-minimisation analysis (CMA) approach and two studies were a cost comparison as part of a cohort study. A CUA conducted from a US-payer perspective using US registry data to inform key model parameters and a model structure closely aligned to NICE DG34 indicated that Oncotype DX® was cost effective in LN- patients clinically intermediate or high risk. A CUA conducted from the perspective of the national insurance system in Türkiye using Turkish registry data, reported that Oncotype DX® was cost effective in LN- patients. Another CUA in the review was conducted from the perspective of the NHS and Personal Social Services (PSS) and found that the Oncotype DX® test was dominant over clinical risk tools alone amongst LN+ patients. A CUA conducted from the perspective of the healthcare systems of six countries including the UK using data from the MINDACT study, reported that the MammaPrint® was more costly but more effective than current clinical practice and likely cost effective. One CMA considered a societal perspective in the Netherlands and reported that Oncotype DX® was cost saving versus MammaPrint® or no test in LN- patients with high clinical risk. The other CMA in the review was from the perspective of the German healthcare system and assumed that Oncotype DX® correctly identified the adjuvant chemotherapy decision for patients with LN- early breast cancer and used this as a baseline to compare the cost false-positives and false-negatives using other tests (EndoPredict®, MammaPrint® and Prosigna®), reporting that Oncotype DX® was cost saving against all the comparators. One cost comparison comparing the Prosigna® test to guide adjuvant chemotherapy decisions versus a decision to provide chemotherapy to all patients at intermediate clinical risk, found the Prosigna® to be cost saving using data from a France-based observational study. The other cost comparison compared the Oncotype DX® test to guide adjuvant chemotherapy decisions versus a decision to provide chemotherapy to all patients calculated to have a >3% OS benefit using PREDICT found the test to be cost saving using data from a UK-based observational study.
All of the economic evaluations identified in the search were more limited than that conducted by NICE for DG34 at addressing the decision problem faced by NHSScotland. These limitations were varied and included modelling approaches that did not consider the appropriate range of patient outcomes affected by the adjuvant chemotherapy decision, use of registry data from other countries’ health systems that may not be generalisable to the Scottish population/clinical setting and/or an analysis that did not include all relevant subgroups stratified according to clinical risk.

Review and critical appraisal of economic analyses provided to SHTG by test manufacturers

The manufacturers of the four tests under review for helping guide adjuvant chemotherapy decisions in women with HR+, HER2- early breast cancer were invited to submit economic evaluations to SHTG for consideration. Three manufacturers submitted economic evaluations (Agendia NV, MammaPrint®; Exact Sciences, Oncotype DX®; and Veracyte, Prosigna®), these analyses are summarised and critically appraised in Appendix 3.

Overall, each manufacturers’ submission used a similar model structure to that used by NICE, implementing a hybrid decision-tree Markov model. The manufacturers’ submissions considered the respective tumour profiling tests to help guide adjuvant chemotherapy decisions in women with HR+, HER2- early breast cancer versus current practice without a test. Some companies also provided an analysis versus one or more of the other tests. Subgroups considered varied between the manufacturers’ submissions, though most considered LN- and LN+ populations separately. Some provided analysis by NPI subgroup, menopausal status and tumour characteristics not included in clinical risk profiling tools.

The Exact Sciences economic evaluation used evidence published since NICE DG34 from the RxPONDER and TAILORx studies to inform estimates of tumour profiling test-risk classifications in the LN+ population, the probability of distant recurrence without adjuvant chemotherapy and the probability of distant recurrence with adjuvant chemotherapy.40, 42 Academic-in-confidence data was available to the company from a UK-based decision impact study56 to estimate the pre- and post-test chemotherapy probabilities for the LN+ population. These sources of evidence may contribute to more accurate estimation of longer-term survival and the safety of forgoing chemotherapy in LN- and LN+ patients, and of how the Oncotype DX® test results would be used in practice in the LN+ population. There is some uncertainty around how generalisable the RxPONDER42 and TAILORx40 study populations are to the Scottish population eligible for tumour profiling tests and that the decision impact study results may be biased because of the non-randomised study design. Another limitation of the evidence from TAILORx and RxPONDER is that they do not provide randomised data for distant recurrence-free interval (DRFI) for patients in the LN- subgroup or the LN+ subgroups with a high-risk test score, respectively. To estimate the distant recurrence probabilities in the subgroups with missing data from the TAILORx and
RxPONDER studies, the company used the chemotherapy benefit hazard ratio from the NSABP B-20 study, which was from a heterogeneous study population and estimated from an unadjusted analysis, making this approach highly uncertain.57 The company assumed that Oncotype DX® predicts chemotherapy benefit in its analysis, which is also uncertain. A further limitation of data from TAILORx and RxPONDER is that they do not provide evidence by clinical risk subgroup, meaning that results do not reflect the clinical utility of information provided by Oncotype DX® above clinicopathological risk factors, particularly in the LN-patient population where clinically low-risk patients are unlikely to be eligible for chemotherapy.

The Agenda NV economic evaluation used more recent evidence from the MINDACT study than was available to inform the NICE DG34 analysis (8-years versus 5-years).38 These data add more certainty to the estimates of long-term survival for patients who were clinical-high risk but received a low-risk MammaPrint® test and did not receive chemotherapy. The company’s access to patient-level data from the MINDACT trial meant that data more applicable to the decision problem were available to inform the model compared with NICE DG34. This included only using data from MINDACT for patients with HR+/HER2- disease and using DMFI for calculating the risk of distant recurrence versus DMFS used in NICE DG34. The company’s base-case analysis was restricted to patients who would be considered for a tumour profiling test according to the most recent NICE guidance (DG34) plus LN+ patients. The only source of comparative data for risk classifications probabilities and probability of distant recurrence without chemotherapy by NPI score and tumour profiling test score is the data published in NICE DG34 from the TransATAC study. As the TransATAC data analysis did not report MammaPrint® test scores, the company assumed that mAOL low risk was equivalent to LN- NPI≤ 3.4 and created a composite LN- NPI>3.4 and LN+ (1-3 nodes) by using a weighted average of TransATAC data. This adjustment somewhat allows for MammaPrint® to be considered in a context closer to that of routine clinical practice, however the indirect comparison appeared to be unadjusted so may be confounded by heterogeneous study populations. Although the company was unable to identify empirical evidence for chemotherapy allocation according to mAOL high risk, the probability of receiving chemotherapy without the test was based on clinical expert opinion, which although uncertain was similar to the approach taken by NICE for DG34. The company also assumed that patients with a high-risk MammaPrint® test score obtain all of the chemotherapy benefit from the relative risk reported by the EBCTCG (Early Breast Cancer Trialists’ Collaborative Group) meta-analysis that was used to estimate chemotherapy treatment effect in the NICE DG34 analysis. The company justified this approach counterfactually, by asserting that the results of MINDACT show that patients with a low-risk MammaPrint® test score obtain no clinically significant benefit from chemotherapy. The MINDACT study reported a statistically significant chemotherapy treatment effect for patients with LN- disease and a high clinical risk but low MammaPrint® test score (2.5 percentage points) making this approach uncertain.58

The Veracyte (Prosigna®) economic evaluation was the most similar to that published by NICE in both structure and evidence parameters, with some important differences. The
company did not conduct an additional analysis for patients who were low clinical risk (LN-NPI≤3.4), instead considering a combined LN-population (low plus intermediate risk) assuming 38.2% of patients in the TransATAC data published in NICE DG34 were intermediate clinical risk. Risk tapering of the long-term risk of distant recurrence also differed from the assumption made in economic evaluation for NICE DG34.

Each company’s analysis used utility weights for health states that were broadly similar to those used by NICE in DG34, except Agendia NV’s model (MammaPrint®) that assumed lower utility values for patients who received chemotherapy for up to three years versus 6-months in the other manufacturers’ submissions and NICE DG34. All the companies assumed higher costs associated with chemotherapy than was assumed in NICE DG34, including higher use of granulocyte-colony stimulating factor (G-CSF), beyond uprating of prices to the current price year. The distribution and composition of chemotherapy regimens came from clinical expert opinion for each submitted analysis but varied between them. It is uncertain whether the cost of the adjuvant chemotherapy regimens used in patients with early breast cancer in Scottish clinical practice are increasing above the rate of price increases over time. For instance, according to some clinical experts consulted by SHTG, the use of G-CSF as neutropenia prophylaxis with adjuvant chemotherapy has increased because of the coronavirus pandemic but its use may reduce again over time. NHS guidelines do not recommend the routine use of G-CSF.59

Exact Sciences (Oncotype DX®) micro-costed the treatment of distant recurrence, approximately tripling this cost versus NICE DG34. This approach may be reasonable given the new, more costly, treatments (CDK4/6 inhibitors) available to treat patients with advanced breast cancer, though it is uncertain whether these are the costs that would be faced by NHSScotland in practice. Agendia NV and Exact Sciences also included terminal care costs unlike Prosigna® or NICE DG34.

SHTG requested scenario analyses from the test manufacturers to address a number of key uncertainties, align assumptions across the models that were most reflective of Scottish clinical practice and for greater comparability of the cost-effectiveness results. The results of these analyses were used to draw the cost-effectiveness conclusions of this review.

Most manufacturers did not provide cost-effectiveness analysis in the low clinical risk LN-population (LN-NPI≤3.4). Exact Sciences did provide results for the LN-NPI≤3.4 subgroup where the Oncotype DX® test was associated with an ICER above conventional willingness-to-pay thresholds even with a confidential discount and the uncertain assumption that the test predicts chemotherapy benefit. Myriad did not submit an economic evaluation however the NICE guidance from 2018 reported that the EPclin test was associated with an ICER of £147,419 per QALY gained.

With the modelling assumptions requested by SHTG in the LN-NPI>3.4 subgroup and compared with current clinical practice using clinicopathological risk factors alone, the
MammaPrint® test was associated with an ICER of £4,392 per QALY gained; the Oncotype DX® test dominated usual practice and; the Prosigna® test was associated with an ICER that was within conventional willingness-to-pay thresholds. NICE reported that the EPclin test was cost effective in this subgroup when a confidential discount was included.

In the overall LN+ population two of the manufacturers’ submissions found their tests to be cost saving and more effective than current practice (MammaPrint® and Oncotype DX®) in the LN+ subgroup. For this population the model submitted by Veracyte found that the Prosigna® test was associated with an ICER above conventional willingness-to-pay thresholds. EPclin® was associated with a central estimate of cost effectiveness of £21,458 per QALY gained in the LN+ population. In 2018, the NICE Committee stated that evidence of different test results between LN+ patients meant that cost-effectiveness results in this population were ignored because of insufficient clinical evidence. Since NICE DG34, results from the RxPONDER study suggest that premenopausal LN+ patients with a low-risk Oncotype DX® RS result may still benefit from chemotherapy.

Overall, these results support the conclusions in NICE DG34, that tumour profiling tests are likely to be cost effective in LN- patients with an intermediate clinical risk using a tool such as NPI, including the MammaPrint® test.

**Discussion**

The literature evaluating the use of tumour profiling tests to guide adjuvant chemotherapy decisions in people with early-stage breast cancer is heterogeneous and complex. Several high-quality HTAs and guidelines have been published but there is a lack of concordance between their recommendations. This reflects a confusing evidence base, and makes drawing confident conclusions challenging.

NICE guidance from 2018 recommended the use of Oncotype DX®, EndoPredict® and Prosigna® as options for guiding adjuvant chemotherapy decisions for patients with ER+, HER2-, LN- early breast cancer who have an intermediate risk of recurrence using a validated tool (and subject to certain criteria). MammaPrint® was not recommended. The clinical evidence base has evolved since the publication of this guidance. The 5-year results of the RxPONDER trial published in 2021 evaluated the value of the Oncotype® RS in predicting the benefit of adjuvant chemotherapy in people with LN+ disease. Updated results of the MINDACT study (median follow up of 8.7 years) were published in 2021, including an exploratory analyses of potential effects by age and nodal status for patients with HR+ and HER2- disease.

Some studies, including the three RCTs, noted a greater treatment effect from adjuvant chemotherapy in younger (premenopausal, or aged 50 years and younger) women, even with low-risk scores from tumour profiling tests. This may make the tumour profiling tests less useful in this group of patients, or mean that different thresholds need to be used.
Some authors propose that the chemotherapy benefit in younger patients may be partly explained by an anti-oestrogenic effect associated with premature menopause induced by the treatment. It remains unclear whether similar benefits could be achieved with ovarian suppression plus an aromatase inhibitor instead of chemotherapy.  

Six economic evaluations were identified that were published after the NICE guidance. These were more limited than the analyses presented by NICE at addressing the decision problem faced by NHSScotland due to issues such as the modelling approaches that did not consider an adequate range of patient outcomes, sources of data that may not be generalisable to a Scottish context and/or the analysis that did not include all relevant subgroups. In developing this SHTG Recommendation, three manufacturer economic evaluations of the four tumour profiling tests were received (for MammaPrint®, Oncotype DX® and Prosigna®). The results of analyses submitted by test manufacturers strengthened the conclusions of the NICE recommendation that some tumour profiling tests are likely cost effective in patients with LN- disease who have an intermediate risk of recurrence using a validated tool. Cost effectiveness in this subgroup is driven by the avoidance of unnecessary chemotherapy and reducing distant recurrence. Tumour profiling tests are unlikely to be cost effective for patients with LN- disease and a low risk of recurrence using a validated tool as this subgroup has low rates of chemotherapy in current clinical practice without a test.

A qualitative study and submission from a patient organisation highlighted that tumour profiling tests are viewed by patients as providing ‘personalised’ information, which is generally perceived as being more reliable and informative than risk scores calculated from online algorithms. A low-risk score was described as providing ‘reassurance’ that chemotherapy was not required whereas a high-risk score enabled greater confidence around the decision to have chemotherapy. For people with intermediate scores, their decision making around chemotherapy was likely to be more complex and fraught. The qualitative study emphasised the importance of ‘holistic treatment decision making between patients and clinicians’, which will likely include discussions around ‘gut feelings’, emotions, perceptions of the disease and treatment, and anticipated futures. Waiting for test results is anxiety inducing for patients, so receiving them in a timely manner and being provided with a copy (along with other clinical and pathological information) is important. A peer reviewer for this report suggested that information on tumour profiling tests should be made available to patients in NHSScotland earlier in the breast cancer treatment pathway.

A summary of the research findings for each of the tumour profiling tests is presented below.

Summary: Oncotype DX®

The NICE conclusion that Oncotype DX® provides statistically significant additional prognostic information over most commonly used clinical and pathological variables, in both patients with LN- and LN+ disease remains valid. This updated literature review has not identified any evidence to alter this conclusion.
The uncertainty reported by NICE in 2018 regarding the evidence that Oncotype DX® may be able to predict who will respond to chemotherapy remains following this updated literature review.

Two RCTs have evaluated the use of Oncotype DX® in patients with early-stage breast cancer. In patients with LN- disease, the TAILORx trial reported that there was no chemotherapy benefit in:

- patients aged over 50 years who have an Oncotype DX® RS of 25 or lower
- patients aged 50 years or younger with an Oncotype DX® RS of 15 or lower

In patients with LN+ disease, the RxPONDER trial reported that:

- there was no chemotherapy benefit in postmenopausal patients who have an Oncotype DX® RS of 25 or lower
- in premenopausal women, a chemotherapy benefit was seen across Recurrence Score categories
- the relative chemotherapy benefit did not increase with higher RS.

The results of economic analyses submitted by test manufacturers strengthened the conclusions of the NICE recommendation (DG34) that Oncotype DX® is likely cost effective in patients with LN- disease who have an intermediate risk of distant recurrence using a validated tool. Cost effectiveness in this subgroup is driven by the avoidance of unnecessary chemotherapy and reducing distant recurrence.

Oncotype DX® may be cost effective in patients with LN+ (1-3 nodes) disease, however these results should be treated with caution because of uncertainty in the clinical evidence base for tumour profiling tests in this subgroup. The cost-effectiveness analysis provided by Exact Sciences suggest that amongst LN+ patients the Oncotype DX® test was more cost effective when considered in postmenopausal patients.

**Summary: MammaPrint®**

NICE reported that based on pooled adjusted analyses, in patients with LN- disease, MammaPrint® had statistically significant prognostic accuracy for 10-year DRFI when adjusted for Adjuvant! Online, NPI or clinical and pathological variables. In patients with LN+ disease, MammaPrint® had borderline statistically significant prognostic accuracy for 10-year distant metastasis-free survival when adjusted for clinical and pathological variables.

The evidence relating to the ability of MammaPrint® to predict benefit from chemotherapy was limited.
The recently published updated results of the MINDACT trial (median follow up 8.7 years) concluded that in those with LN- and LN+ disease:

- The 5-year survival was 95.1% (95% CI 93.1 to 96.6) in patients who were assessed as having a high clinical risk (as determined using a modified version of Adjuvant! online) but low genomic risk (as determined by the MammaPrint® score) who are not treated with chemotherapy.
- Underpowered exploratory analyses indicated that relying on the genomic signature to forgo adjuvant chemotherapy is safer in older women (aged over 50 years) with a high clinical risk than in younger women (aged 50 years and younger).
- Underpowered exploratory analysis by nodal status indicated that among patients with high clinical risk but low genomic risk who have LN- disease, a chemotherapy benefit was noted, although the magnitude of difference was small (absolute difference in metastasis-free survival of 2.5 percentage points). In the same population with LN+ disease, a statistically significant chemotherapy benefit was not found.
- In patients with low clinical and high genomic risk, no significant difference was detected in metastasis-free survival rate at 8-year follow up between those who had chemotherapy and those that did not. Mammaprint® may not be useful in this group of patients, as it could potentially increase chemotherapy rates without improving patient outcomes.

The results of economic analyses submitted by Agendia suggest that MammaPrint® is likely cost effective in patients with LN- disease who have an intermediate risk of recurrence using a validated tool. Cost effectiveness in this subgroup is driven by the avoidance of unnecessary chemotherapy and reducing distant recurrence.

MammaPrint® may be cost effective in patients with LN+ (1-3 nodes) disease, however these results should be treated with caution because of uncertainty in the clinical evidence base for tumour profiling tests in this subgroup.

Summary: EndoPredict®

NICE reported than based on adjusted analyses, EndoPredict® had statistically significant increases in likelihood ratio for 10-year DRFI over clinical and pathological variables or tools, regardless of LN status. This was based on a reanalysis of data from an RCT (TransATAC) that was limited to postmenopausal women.

No evidence evaluating the predictive ability of EndoPredict® was identified.

No evidence was identified that would change the conclusion of the economic analyses presented in the NICE guidance from 2018; EndoPredict® is likely cost effective in patients
with LN- disease who have an intermediate risk of recurrence using a validated tool. Cost effectiveness in this subgroup is driven by the avoidance of unnecessary chemotherapy. The NICE guidance also reported that EndoPredict® might be cost effective in patients with LN+ (1-3 nodes) disease, however these results should be treated with caution because of uncertainty in the clinical evidence base for tumour profiling tests in this subgroup.

**Summary: Prosigna®**

Prosigna® is only indicated for use in postmenopausal women. NICE reported that adjusted analyses showed that Prosigna® had prognostic accuracy for 10-year distant metastasis-free survival and DRFS. In patients with LN- disease, the results were statistically significant. In patients with LN+ disease, the results were statistically or borderline significant.

Prosigna® is not indicated for predictive use.

The results of economic analyses submitted by test manufacturers strengthened the conclusions of the NICE recommendation (DG34) that Prosigna® is likely cost effective in patients with LN- disease who have an intermediate risk of recurrence using a validated tool. Cost effectiveness in this subgroup is driven by the avoidance of unnecessary chemotherapy and reducing distant recurrence.

**Identified research gaps**

While the evidence on the use of tumour profiling tests in patients with LN+ breast cancer has evolved since the publication of the NICE guidance in 2018, notably with the publication of the RxPONDER trial, there is still considerable uncertainty. This may be partly addressed with ongoing follow up of the MINDACT and RxPONDER trials, and publication of the OPTIMA trial.

Further evidence is required on how the prognostic and predictive abilities of the tumour profiling tests compare with one another.

The evolving evidence suggests that the tests may perform differently in premenopausal and postmenopausal women, and further research and data collection is required before confident conclusions can be made on this.

Further research is needed to establish whether the clinical utility of the tests differs depending on a patient’s race or ethnicity.

The existing evidence tends to include relatively young ‘older patients’ (between 65 and 75 years old), and this may not be reflective of the population aged over 75, in whom decisions around chemotherapy may be more difficult (especially in those with comorbidities). Further research and data collection in this patient group will be beneficial.
A manufacturer presented evidence from their commercial database that some clinicopathological risk factors, such as tumour grade, may not be adequately quantified by validated tools when estimating recurrence risk. There may be subgroups within the LN-population with a low risk of recurrence using a validated tool for whom the use of a tumour profiling test may be cost effective for reducing chemotherapy under-treatment.

There should be ongoing data collection on the impact of using tumour profiling tests on patient care and patient outcomes within the Scottish context.
# Appendix 1

## Table 7: Summary and critical appraisal of NICE DG34 economic analysis

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis type</td>
<td>Cost-utility analysis</td>
</tr>
<tr>
<td>Time horizon</td>
<td>Lifetime</td>
</tr>
<tr>
<td>Population</td>
<td>Women with HR+, HER2-, early breast cancer (LN0-3)</td>
</tr>
<tr>
<td></td>
<td>Subgroups considered for the Oncotype DX®, Prosigna® and EPclin® tests were:</td>
</tr>
<tr>
<td></td>
<td>- LN- NPI≤3.4 (clinical-low risk)</td>
</tr>
<tr>
<td></td>
<td>- LN- NPI&gt;3.4 (clinical intermediate risk)</td>
</tr>
<tr>
<td></td>
<td>- LN+ (1-3 nodes)</td>
</tr>
<tr>
<td></td>
<td>Subgroups considered for the MammaPrint® test were:</td>
</tr>
<tr>
<td></td>
<td>- intention-to-treat population from MINDACT</td>
</tr>
<tr>
<td></td>
<td>- mAOL clinical-low risk</td>
</tr>
<tr>
<td></td>
<td>- mAOL clinical-high risk</td>
</tr>
<tr>
<td>Intervention*</td>
<td>1) Oncotype DX®</td>
</tr>
<tr>
<td></td>
<td>2) Prosigna®</td>
</tr>
<tr>
<td></td>
<td>3) EPclin®</td>
</tr>
<tr>
<td></td>
<td>4) MammaPrint®</td>
</tr>
<tr>
<td>Comparators</td>
<td>Current practice, including a mix of risk prediction tools and diagnostic guidelines.</td>
</tr>
<tr>
<td>Model description</td>
<td>A hybrid decision-tree Markov model was used as the economic model in the evaluation. The model stratifies patients according to their tumour profiling test-risk classification and adjuvant chemotherapy decision using a decision tree (Figure 1), then models costs and the longer-term effects of the treatment decision using a Markov model (Figure 2). Figure 1 illustrates the decision tree component for three-level tests. Two-level tests had a similar structure without the intermediate-risk stratum.</td>
</tr>
</tbody>
</table>
Patients’ probability of receiving adjuvant chemotherapy depended on their clinical risk subgroup and tumour profile test score for the three-level tests (OncoType DX® and Prosigna®), tumour profile test score alone for the two-level tests (EPclin® and MammaPrint®), and by clinical risk subgroup alone in the current practice arm.

The Markov model included four discrete health states: recurrence free, distant recurrence, long-term adverse events and an all-absorbing dead state.

In both arms, patients’ risk of recurrence was dependent on their clinical risk and tumour profiling test score, modified by a chemotherapy treatment effect for those that received adjuvant chemotherapy. A proportion of patients who entered the distant metastases health state were assumed to have also experienced a local recurrence and were allocated a one-off cost and QALY loss.

Patients who received chemotherapy could enter the long-term adverse event state (acute myeloid leukaemia).
Clinical data

*Risk classification probabilities*
For Oncotype DX®, Prosigna® and EPclin® test-risk classification by clinical risk subgroup came from a reanalysis of data from the TransATAC study. For the MammaPrint® test, these data came from the MINDACT study.38

*Probability of receiving chemotherapy - current practice*
In the current practice arm of the model, the probability of receiving chemotherapy depended on clinical risk subgroup. For the Oncotype DX®, Prosigna® and EPclin® tests these data came from a bespoke analysis of data for NICE DG34 from the National Cancer Registration and Analysis Service (NCRAS) database for the low and high clinical risk subgroups and from the NHS England Oncotype DX® Access Dataset for the intermediate clinical risk subgroup. For the MammaPrint® test, this parameter was estimated based on clinical expert opinion.

*Probability of chemotherapy – three-level tests (Oncotype DX® and Prosigna®)*
For the Oncotype DX® and Prosigna® tests, the probability of chemotherapy by test-risk classification came from different sources for each clinical risk subgroup:
Criterion | Overview
--- | ---
• Low clinical risk (LN- NPI≤3.4): UKBCG survey (panel of expert clinical opinion)
• Intermediate clinical risk (LN- NPI>3.4): NHS England Oncotype DX® Access Dataset
• High clinical risk (LN+ 1-3 nodes): UK-based decision impact pilot study

*Probability of chemotherapy – two-level tests (EPclin® and MammaPrint®)*
For the EPclin® and MammaPrint® tests, the probability of chemotherapy by test-risk classification came from a UK-based prospective study investigating the decision impact of the EPclin® test. These probabilities were applied to all clinical risk subgroups.

*Probability of distant recurrence (without chemotherapy)*
10-year distant recurrence rates by test-risk classification and clinical risk subgroup were calculated from 10-year DMFI data reported by the TransATAC study for the Oncotype DX®, Prosigna® and EPclin® tests. For the MammaPrint® test, these were calculated using 5-year distant metastases survival data reported by the MINDACT study.

*Chemotherapy treatment effect (Oncotype DX®, Prosigna® and EPclin®)*
Evidence for the adjuvant chemotherapy treatment effect on distant recurrence for the Oncotype DX®, Prosigna® and EPclin® tests came from the EBCTCG 2012 meta-analysis. 58 10-year risk of distant recurrence for chemotherapy and no chemotherapy was estimated by projecting forward the annualised risk of distant metastases. The relative risk (RR) for chemotherapy versus no chemotherapy was then calculated based on the difference between the projected 10-year DMFS probabilities for the two groups. The same RR was applied to all the clinical risk subgroups.

*Chemotherapy treatment effect (MammaPrint®)*
Evidence for the adjuvant chemotherapy treatment effect on distant recurrence for the MammaPrint® test came from the MINDACT study. 38

*Probability of local recurrence*
The proportion of those who develop distant metastases who also experience a local recurrence was based on a reanalysis of data from
three studies of women who had been treated for early breast cancer (LN- and LN+).

**Probability of death following distant recurrence**
A 6-month probability of death following distant recurrence was based on evidence from a UK-based analysis of hospital records that reported a median survival following distant recurrence and fitting an exponential distribution with a constant rate assumed.\(^5\)

**Probability of acute myeloid leukaemia (AML)**
10-year risk of developing AML following chemotherapy was taken from a US-based study.\(^6\)

**Probability of death following AML**
A mean survival following the onset of AML of 8 months was taken from evidence included in a NICE appraisal of azacitidine for myelodysplastic syndromes.\(^7\)

**Extrapolation**
The long-term risk of recurrence (beyond 10 years), up to 15-years, is assumed to be half the rate between 1-10 years. Beyond 15-years, the risk of distant recurrence is assumed to be zero.\(^8\)

5-year DMFS probabilities from MINDACT (MammaPrint®) were extrapolated to 10 years using a constant rate.\(^9\)

**Quality of life**
Health state specific quality of life values were taken from published literature:

```
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Source</th>
<th>Value used in base case (mean (SE))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence free</td>
<td>Lidgren et al.(^6)</td>
<td>0.824 (0.018)</td>
</tr>
<tr>
<td>Distant recurrence (disutility per cycle)</td>
<td>Lidgren et al.(^6)</td>
<td>-0.14 (0.11)</td>
</tr>
<tr>
<td>AML</td>
<td>Younis et al.(^8)</td>
<td>0.26 (0.04*)</td>
</tr>
<tr>
<td>Local recurrence (one-off disutility)</td>
<td>Campbell et al.(^8)</td>
<td>-0.108 (0.04*)</td>
</tr>
</tbody>
</table>
```
<table>
<thead>
<tr>
<th>Criterion</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy adverse events disutility (first cycle only)</strong></td>
<td>Campbell et al.(^{65}) -0.038 (0.004*)</td>
</tr>
</tbody>
</table>

**Costs and resource use**

Costs included in the model were for the tumour profiling tests, adjuvant chemotherapy (acquisition and administration), endocrine therapy (acquisition), additional medications (including acquisition and administration of zoledronic acid), routine follow up (mammograms and face-to-face appointments), a one-off cost for a local recurrence for a proportion of patients entering the distant metastases health state, and a per cycle cost in the distant metastases health state.

**Results**

Table 9: Cost-effectiveness results, tumour profiling tests pairwise vs current practice by clinical risk subgroup (list price for tests)

<table>
<thead>
<tr>
<th>Test</th>
<th>ICER in NPI subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LN- NPI(\leq3.4)</td>
</tr>
<tr>
<td><strong>Oncotype DX</strong>(^\circ)</td>
<td>£122,725</td>
</tr>
<tr>
<td><strong>Prosigna</strong>(^\circ)</td>
<td>£91,028</td>
</tr>
<tr>
<td><strong>EPclin</strong>(^\circ)</td>
<td>£147,419</td>
</tr>
</tbody>
</table>

**MINDACT subgroup**

<table>
<thead>
<tr>
<th>Test</th>
<th>ITT population</th>
<th>mAOL high risk</th>
<th>mAOL low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MammaPrint</strong>(^\circ)</td>
<td>£131,482</td>
<td>Dominated</td>
<td>£414,202</td>
</tr>
</tbody>
</table>

**Key scenarios**

The analysis for NICE DG34 implemented extensive scenario analyses to test assumptions in the base case. In summary:

**Oncotype DX**\(^\circ\)

The only scenarios that changed the conclusions of the analysis for the Oncotype DX\(^\circ\) test were those that assumed that the test could predict chemotherapy benefit (ICER £34,245/QALY in the LN- NPI\(\leq3.4\) subgroup and dominating in the LN- NPI\(>3.4\) and LN+ 1-3 nodes).
<table>
<thead>
<tr>
<th>Criterion</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prosigna®</strong></td>
<td>In all scenarios the ICER for the Prosigna® test remained &gt;£70,000/QALY in the LN- NPI≤3.4 subgroup; in the LN- NPI&gt;3.4 subgroup the ICER remained below £30,000 QALY except when the starting age in the model was increased or the RR of distant metastases for chemotherapy versus no chemotherapy was set equal to 0.80; in the LN+ (1-3 nodes) subgroup the ICER was below £38,000/QALY in all scenarios tested.</td>
</tr>
<tr>
<td><strong>EPclin®</strong></td>
<td>In all scenarios the ICER for the EPclin® test remained &gt;£91,000/QALY in the LN- NPI≤3.4 subgroup; in the LN- NPI&gt;3.4 subgroup the ICER remained in excess of £30,000/QALY except when alternative assumptions informed the probability of receiving chemotherapy conditional on the result of the EPclin® test were used though these were &gt;£25,000/QALY; in the LN+ (1-3 nodes) subgroup the ICER remained below £30,000/QALY across all scenarios.</td>
</tr>
<tr>
<td><strong>MammaPrint®</strong></td>
<td>Within the overall MINDACT population the ICER remained &gt;£76,000 in all scenarios tested; in the mAOL clinical-high subgroup MammaPrint® was dominated across all scenarios; in the mAOL clinical-low subgroup the ICER remained &gt;£161,000/QALY in all scenarios tested.</td>
</tr>
</tbody>
</table>

**Key strengths**

- The model structure was similar to those used in other published economic evaluations of gene-profiling tests to guide adjuvant chemotherapy in early breast cancer.
- Subgroup analysis by NPI or mAOL clinical risk allowed the cost effectiveness of the tests in providing information for guiding adjuvant chemotherapy beyond that available from these tools to be explored.
- Evidence for risk classification probabilities for four of the five tests were taken from the same source (TransATAC).
- The use of data from the NHS England Access Scheme data set (for the 3-level tests) for baseline probabilities of chemotherapy (current practice) and the probability of receiving chemotherapy based on the results of the test is likely to reflect how the tests are used in Scottish clinical practice.
### Criterion

<table>
<thead>
<tr>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive scenario analyses allowed the exploration of uncertainties in the clinical evidence base on the model’s results.</td>
</tr>
</tbody>
</table>

### Key uncertainties

<table>
<thead>
<tr>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test-risk classification probabilities and distant recurrence probabilities taken from TransATAC are for postmenopausal patients only but are assumed to apply to the premenopausal population too.</td>
</tr>
<tr>
<td>NPI subgroups may not be representative of other tools used to define clinical risk that are more routinely used in clinical practice such as PREDICT.</td>
</tr>
<tr>
<td>The analysis of MammaPrint® using data from the MINDACT trial compares the test only against mAOL and therefore may not reflect clinical practice in Scotland.</td>
</tr>
<tr>
<td>Data to inform distant recurrence probabilities for the MammaPrint® analysis were based on 5-year DMFI data from the MINDACT study which was a much shorter follow up than for the other tests and thus more uncertain.</td>
</tr>
<tr>
<td>The evidence for pre- and post-test chemotherapy use for the LN- NPI≤3.4 and LN+ (1-3 nodes) subgroups was subject to considerable uncertainty.</td>
</tr>
<tr>
<td>The assumption of predictive benefit for the Oncotype DX® test is uncertain but has a large impact on the results of the analysis, potentially changing the conclusions for all subgroups.</td>
</tr>
</tbody>
</table>

*IHC4+C immunohistochemical test also included as an intervention but is not considered in this review.*
### Appendix 2

#### Table 10: Cost-effectiveness analyses since NICE DG34 – analytic scope

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Age</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Country</th>
<th>Perspective</th>
<th>Time horizon</th>
<th>Discount rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loncaster* (2017)</td>
<td>HR+/HER2-early breast cancer considered for chemotherapy</td>
<td>55.2</td>
<td>Oncotype DX*</td>
<td>Chemotherapy for all</td>
<td>UK</td>
<td>NHS</td>
<td>1 year</td>
<td>N/A</td>
</tr>
<tr>
<td>Wang (2018)</td>
<td>HR+/HER2-LN-early breast cancer</td>
<td>≥60</td>
<td>Oncotype DX*</td>
<td>PREDICT</td>
<td>US</td>
<td>US payer</td>
<td>Lifetime (50 years)</td>
<td>5%</td>
</tr>
<tr>
<td>Özmen (2019)</td>
<td>HR+/HER2-LN- and LN1-3 early breast cancer</td>
<td>49.9</td>
<td>Oncotype DX*</td>
<td>Current practice</td>
<td>Turkey</td>
<td>National insurance</td>
<td>30 years</td>
<td>Not reported</td>
</tr>
<tr>
<td>Retèl* (2020)</td>
<td>ER+/HER2 “high risk”</td>
<td>Uncle</td>
<td>MammaPrint</td>
<td>Current practice</td>
<td>Belgium, France, Germany, Netherlands, UK and US</td>
<td>Health care</td>
<td>10 years</td>
<td>3-4% (country specific)</td>
</tr>
<tr>
<td>Hequet (2021)</td>
<td>HR+/HER2-early breast cancer at intermediate risk of recurrence in whom a test was performed during the study in a real-life setting</td>
<td>57</td>
<td>Prosigna*</td>
<td>Chemotherapy for all</td>
<td>France</td>
<td>National health insurance</td>
<td>1 year</td>
<td>N/A</td>
</tr>
<tr>
<td>Berdov* (2022)</td>
<td>HR+/HER2-LN1-3 early breast cancer</td>
<td>Not reported</td>
<td>Oncotype DX*</td>
<td>Clinical risk tools alone</td>
<td>UK</td>
<td>NHS and PSS</td>
<td>Lifetime</td>
<td>3.5%</td>
</tr>
<tr>
<td>Author</td>
<td>Population</td>
<td>Age</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Country</td>
<td>Perspective</td>
<td>Time horizon</td>
<td>Discount rate</td>
</tr>
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<td>---------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>De Jongh* (2022)52</td>
<td>HR+/HER2-LN breast cancer with high clinical risk who are eligible for chemotherapy</td>
<td>Not reported</td>
<td>Oncotype DX* or MammaPrint*</td>
<td>Chemotherapy for all</td>
<td>Netherlands</td>
<td>Societal</td>
<td>10 years</td>
<td>Not reported</td>
</tr>
<tr>
<td>Lux* (2022)53</td>
<td>HR+/HER2-LN early breast cancer</td>
<td>Not reported</td>
<td>Oncotype DX*</td>
<td>EndoPredict*, MammaPrint*, Prosigna*</td>
<td>Germany</td>
<td>German health care system</td>
<td>10 years</td>
<td>Not reported</td>
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</tbody>
</table>

*known or potential conflict of interest declared

Table 11: Cost-effectiveness analyses since NICE DG34 – methodological approach, evidence sources and results
<table>
<thead>
<tr>
<th>Author</th>
<th>Model approach</th>
<th>Test-risk classification distribution</th>
<th>Evidence sources</th>
<th>Pre-/post-test chemotherapy probability</th>
<th>Distant recurrence</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Özmen (2019)</td>
<td>CUA: Markov</td>
<td>Turkish Oncotype DX® decision impact study</td>
<td>Turkish Oncotype DX® decision impact study</td>
<td>NSABP B-20</td>
<td></td>
<td>PREDICT high risk US $20,400/QALY</td>
</tr>
<tr>
<td>Retèl* (2020)</td>
<td>CUA: Hybrid decision-tree Markov</td>
<td>MINDACT</td>
<td>Dutch decision impact study/expert clinical opinion</td>
<td>MINDACT</td>
<td></td>
<td>US $7,208/QALY</td>
</tr>
<tr>
<td>Hequet (2021)</td>
<td>No model: Cost comparison</td>
<td>French cohort study</td>
<td>French cohort study</td>
<td>N/A</td>
<td></td>
<td>Cost saving of €2,742/patient</td>
</tr>
<tr>
<td>Berdonov* (2022)</td>
<td>CUA: Hybrid decision-tree Markov</td>
<td>RxPONDER</td>
<td>With test: Israeli registry data Without test: UK registry data</td>
<td>DRFI from RxPONDER (modified with HR from TransATAC/SWOG-8814)</td>
<td>Dominant (0.02 QALY gain and cost saving of £989)</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Model approach</td>
<td>Test-risk classification distribution</td>
<td>Pre-/post-test chemotherapy probability</td>
<td>Distant recurrence</td>
<td>Result</td>
<td></td>
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<td>----------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Lux* (2022)</td>
<td>CMA: Decision tree</td>
<td>N/A – model assumed that chemotherapy allocation based on test-risk distribution from TAILORx for Oncotype DX® and used data from IQWiG Rapid Report to calculate the number of false-positives/false-negatives for the other tests.</td>
<td>High: all</td>
<td></td>
<td>Oncotype DX® cost saving: vs EndoPredict® €2,500 vs MammaPrint® €1,936 vs Prosigna® €649</td>
<td></td>
</tr>
</tbody>
</table>

*known or potential conflict of interest declared

Abbreviations: CUA, cost-utility analysis; CMA, cost-minimisation analysis; DRFI, distant recurrence-free interval
### Table 12: Summary and critical appraisal of economic evaluation submitted by Exact Sciences – Oncotype DX® test

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis type</td>
<td>Cost-utility analysis</td>
</tr>
<tr>
<td>Time horizon</td>
<td>Lifetime</td>
</tr>
<tr>
<td>Population</td>
<td>Women with HR+, HER2-, early breast cancer (LN0-3)</td>
</tr>
<tr>
<td></td>
<td><strong>Subgroups analysed were:</strong></td>
</tr>
<tr>
<td></td>
<td>• Lymph node negative (LN-)</td>
</tr>
<tr>
<td></td>
<td>• Micrometastastic disease (N1mi)</td>
</tr>
<tr>
<td></td>
<td>• Lymph node positive (LN+)</td>
</tr>
<tr>
<td></td>
<td>• LN+ postmenopausal only</td>
</tr>
<tr>
<td>Intervention</td>
<td>Oncotype DX®</td>
</tr>
<tr>
<td>Comparator</td>
<td>Current practice, including a mix of risk prediction tools and diagnostic guidelines.</td>
</tr>
<tr>
<td>Model description</td>
<td>The same model structure was used as in NICE DG34.</td>
</tr>
<tr>
<td></td>
<td>Patients’ probability of receiving adjuvant chemotherapy depended on their nodal subgroup and tumour profile test score, or nodal subgroup alone in the current practice arm.</td>
</tr>
<tr>
<td>Clinical data</td>
<td><strong>Risk classification probabilities</strong></td>
</tr>
<tr>
<td></td>
<td>Test-risk classifications came from the TAILORx\textsuperscript{40} study for the LN- subgroup, the RxPONDER\textsuperscript{42} study for the LN+ (overall and postmenopausal) subgroup and from an Israel-based cancer registry for the N1mi subgroup.\textsuperscript{66}</td>
</tr>
<tr>
<td></td>
<td><strong>Probability of receiving chemotherapy - current practice</strong></td>
</tr>
<tr>
<td></td>
<td>The probability of receiving adjuvant chemotherapy without a test came from aggregated NCRAS data reported in NICE DG34 for the LN- subgroup (same chemotherapy allocation was assumed for the N1mi subgroup). For the LN+ subgroup this was estimated using academic-in-confidence data from a UK-based prospective study investigating the decision impact of the Oncotype DX® test.\textsuperscript{56}</td>
</tr>
<tr>
<td></td>
<td><strong>Probability of receiving chemotherapy with the test</strong></td>
</tr>
</tbody>
</table>
The probability of receiving chemotherapy with the test depended on subgroup and test-risk score. Data for this parameter came from an Israel-based cancer registry study for LN- subgroup\textsuperscript{66}, a US-based cancer registry\textsuperscript{67} for the N1mi subgroup and academic-in-confidence data from a UK-based prospective study investigating the decision impact of the Oncotype DX\textsuperscript{®} test in the LN+ subgroup.

**Probability of distant recurrence without chemotherapy**

Risk of recurrence without chemotherapy was assumed vary by nodal subgroup and tumour profiling test score. Recurrence risk without chemotherapy was assumed equal for the LN- (overall) and N1mi subgroups.

In the LN- subgroups probabilities for distant recurrence were based on 9-year DRFI data from the TAILORx study for the low- and intermediate-risk patients.\textsuperscript{40} As all patients in the TAILORx study with a high-risk test score were allocated to adjuvant chemotherapy, by adjusting these patients’ DRFI with adjuvant chemotherapy with the estimated hazard ratio for chemotherapy from the NSABP B-20 study.\textsuperscript{57}

In the LN+ subgroups (overall and postmenopausal), the probabilities for distant recurrence were based on 5-year DRFI data from the RxPONDER study for those with low- and intermediate-risk test scores.\textsuperscript{42} Patients with a high-risk test score were excluded from the RxPONDER study, so probability of distant recurrence without chemotherapy was taken from TransATAC data published in NICE DG34.

**Probability of distant recurrence with chemotherapy**

The risk of distant recurrence with chemotherapy was assumed to vary by nodal subgroup and tumour profiling test score, implying that Oncotype DX\textsuperscript{®} has the ability to predict the benefit of chemotherapy. Recurrence risk with chemotherapy was assumed equal for the LN- (overall) and N1mi subgroups.

In the LN- subgroup, the probability of distant recurrence for patients with an intermediate- or high-risk test score were based on 9-year distant recurrence-free interval data from the TAILORx study.\textsuperscript{40} As all patients with a low-risk test score were assigned to endocrine therapy alone (no chemotherapy) in the TAILORx study, these patients’ DRFI with endocrine therapy alone was adjusted using the HR for chemotherapy benefit from the NSABP B-20 study.\textsuperscript{57}

In the LN+ subgroup, the probability of distant recurrence for patients with a low- and intermediate-risk test score were based on 5-year DRFI data from the RxPONDER study. As patients with a high-risk test score were excluded from the RxPONDER study, these patients’ risk of recurrence was based on data published
<table>
<thead>
<tr>
<th>Criterion</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>from TransATAC in NICE DG34 for endocrine therapy alone and adjusted using the HR for chemotherapy benefit from the SWOG-8814 study.</td>
</tr>
<tr>
<td>Probability of local recurrence</td>
<td>Same as NICE DG34</td>
</tr>
<tr>
<td>Probability of death following distant recurrence</td>
<td>Data from the MONARCH2 study were used to estimate the probability of death following a distant recurrence.</td>
</tr>
<tr>
<td>Probability of AML</td>
<td>The probability of AML came from a 2012 meta-analysis of leukaemic risk and cardiovascular toxicity of adjuvant anthracycline and taxane chemotherapy in breast cancer.</td>
</tr>
<tr>
<td>Probability of death following AML</td>
<td>The probability of death following AML came from a NICE technology appraisal (TA552) of treatments for AML reporting OS.</td>
</tr>
<tr>
<td>Extrapolation</td>
<td>Same as NICE DG34</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Same approach as NICE DG34. Same values as DG34 except for AML utility, 0.550 per cycle from NICE TA552.</td>
</tr>
<tr>
<td>Costs and resource use</td>
<td>The cost of the Oncotype DX® test was provided by the company. The list price was £2,580. A confidential discount is available to NHSScotland but was not disclosed by the company, although the company did provide the results of analysis using each price.</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy regimens and distributions were taken from expert clinical opinion. Chemotherapy distributions varied by nodal status. Costs of chemotherapy trended higher than these costs in NICE DG34. All patients received G-CSF (filgrastim) which comprised a large proportion of chemotherapy costs.</td>
</tr>
<tr>
<td></td>
<td>Distant recurrence costs were micro-costed (including first through third line endocrine, chemotherapy and CDK4/6 inhibitor treatments) and appeared approximately triple those reported in NICE DG34.</td>
</tr>
<tr>
<td></td>
<td>AML was costed using a one-off cost upon entering the adverse event health state and an ongoing per cycle cost, whereas NICE DG34 applied a one-off cost.</td>
</tr>
</tbody>
</table>
Similarly to the approach taken by NICE DG34, other costs included in the model were chemotherapy administration, endocrine therapy acquisition, routine follow-up costs (same as NICE DG34) and costs of local recurrence (same as NICE DG34).

Terminal care costs were also included in the model.

### Results

**Table 13: Summary of base-case results, Oncotype DX® (list price)**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Incremental costs</th>
<th>Incremental QALYs</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>-£550</td>
<td>0.171</td>
<td>Dominant</td>
</tr>
<tr>
<td>N1mi</td>
<td>£1,513</td>
<td>0.089</td>
<td>£16,992</td>
</tr>
<tr>
<td>N1 (overall)</td>
<td>-£1,114</td>
<td>0.037</td>
<td>Dominant</td>
</tr>
<tr>
<td>N1 postmenopausal</td>
<td>-£2,596</td>
<td>0.125</td>
<td>Dominant</td>
</tr>
</tbody>
</table>

**Key scenario/subgroup analysis**

The company provided additional analysis based on NPI clinical risk subgroups in the LN- population.

**Table 14: Oncotype DX® model using NPI subgroups for LN-**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Inc.costs (discounted)</th>
<th>Inc. costs (list)</th>
<th>Inc.l QALYs</th>
<th>ICER (discounted)</th>
<th>ICER (list)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LN- NPI≤3.4</td>
<td>£2,037</td>
<td>£2,037</td>
<td>0.033</td>
<td>£62,205</td>
<td>Dominant</td>
</tr>
<tr>
<td>LN- NPI&gt;3.4</td>
<td>-£1,043</td>
<td>-£1,043</td>
<td>0.209</td>
<td>Dominant</td>
<td>Dominant</td>
</tr>
</tbody>
</table>

The company also provided additional analysis based on a clinicopathological risk factor that is not accounted for by NPI or other clinical risk profiling tools but according to data from the Exact Sciences commercial database of test orders that appears to identify a group of patients with G2 T1c tumours who would be clinical low risk but may be undertreated without the test as a significant proportion (17%) have a high-risk Oncotype DX® test result.

**Table 15: Additional clinical risk subgroup suggested by Exact Sciences**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Inc.l costs (discounted)</th>
<th>Inc. costs (list)</th>
<th>Incremental QALYs</th>
<th>ICER (discounted)</th>
<th>ICER (list)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Scenario using SHTG preferred assumptions

Additional scenario analyses were requested by SHTG to test assumptions made in the company’s base-case analysis that were considered uncertain. These included matching the starting age in the model with that used in the NICE DG34 analysis, excluding G-CSF costs, using the same approach as NICE DG34 for chemotherapy costs (inflated to 2023 prices) and using the same approach to costing distant recurrence as used in NICE DG34.

Table 16: Combined scenario analysis, Oncotype DX® requested by SHTG

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Inc. costs (list price)</th>
<th>Inc. costs (test discount)</th>
<th>Inc. QALYs</th>
<th>ICER (list price)</th>
<th>ICER (test discount)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall LN-</td>
<td>£931</td>
<td></td>
<td>0.154</td>
<td>£6,044</td>
<td>Dominant</td>
</tr>
<tr>
<td>LN- NPI≤3.4</td>
<td>£2,335</td>
<td></td>
<td>0.029</td>
<td>£80,609</td>
<td></td>
</tr>
<tr>
<td>LN- NPI&gt;3.4</td>
<td>£532</td>
<td></td>
<td>0.187</td>
<td>£2,580</td>
<td>Dominant</td>
</tr>
<tr>
<td>LN- G2 T1c</td>
<td>£2,611</td>
<td></td>
<td>0.082</td>
<td>£31,676</td>
<td></td>
</tr>
<tr>
<td>N1mi</td>
<td>£2,204</td>
<td></td>
<td>0.080</td>
<td>£27,674</td>
<td></td>
</tr>
<tr>
<td>Overall LN+</td>
<td>£374</td>
<td></td>
<td>0.035</td>
<td>£10,610</td>
<td>Dominant</td>
</tr>
<tr>
<td>LN+ postmenopausal</td>
<td>-£550</td>
<td></td>
<td>0.123</td>
<td>Dominant</td>
<td>Dominant</td>
</tr>
</tbody>
</table>

Key strengths

- The probability of chemotherapy (with or without the test) in the LN+ subgroup is from a UK-based decision impact study.
- Scenario analysis provided results to that explored stratifying patients by clinicopathological risk, though this was at the expense of not utilising data from RxPONDER and TAILORx.
<table>
<thead>
<tr>
<th>Criterion</th>
<th>Overview</th>
</tr>
</thead>
</table>
|           | • Risk of distant recurrence is from the most up-to-date evidence from RxPONDER trial for the LN+ subgroup for patient with low or intermediate Oncotype DX® RS.  
• Micro-costing of distant recurrence treatment may better reflect plausible increases in these costs faced by NHSScotland over time because of treatment advances in advanced breast cancer.  
• Inclusion of terminal care costs may better reflect all the costs faced by NHSScotland resulting from adjuvant chemotherapy decisions in early breast cancer than their exclusion. |

<table>
<thead>
<tr>
<th>Key uncertainties</th>
<th></th>
</tr>
</thead>
</table>
| • The Oncotype DX® to be predictive of chemotherapy benefit in addition to providing prognostic information. It is likely that the results of the analysis will be highly sensitive to this assumption (as in NICE DG34) but its clinical evidence base is uncertain.  
• RxPONDER data is immature (5-years) and required extrapolation which adds uncertainty to the results of the analysis.  
• TAILORx data used to model LN- population may not reflect the Scottish early breast cancer population eligible for adjuvant chemotherapy.  
• As a result of the trial design of TAILORx and RxPONDER, it was not possible for the company to use these data in a model that fully accounts for the use of clinicopathological risk factors that reflect chemotherapy decision making in Scottish clinical practice.  
• Patients with LN- and N1mi disease were modelled to have a higher risk of recurrence with adjuvant chemotherapy, which lacks biological plausibility.  
• The estimated HR from the NSABP B-20 study is from a heterogeneous study population to the TAILORx population, this adjustment adds uncertainty to the results of the analysis. Indeed, the results of this analysis estimates 10-year DMFI for the overall node-negative population with a high-risk Oncotype DX® score treated with endocrine therapy alone as 55.8% compared with 83.8% and 74.9% in the low and intermediate-risk groups stratified by NPI in the TransATAC data used by NICE in DG34, respectively. Therefore, the approach used by the company is likely to favour Oncotype DX® in analyses that allocate more of this group to chemotherapy.  
• Costs for chemotherapy are uncertain as they are based on clinical expert opinion and appear much higher than those assumed in NICE DG34. The assumption that all patients receive G-CSF is highly uncertain and significantly increases costs for patients receiving chemotherapy, potentially biasing the results in favour of chemotherapy reducing strategies. |
Table 17: Summary and critical appraisal of economic evaluation submitted by Agendia NV – MammaPrint test

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis type</td>
<td>Cost-utility analysis</td>
</tr>
<tr>
<td>Time horizon</td>
<td>Lifetime</td>
</tr>
<tr>
<td>Population</td>
<td>Women with HR+, HER2-, LN- early breast cancer with an intermediate clinical risk according to NPI or high clinical risk according to mAOL, or LN1-3.</td>
</tr>
<tr>
<td>Intervention</td>
<td>MammaPrint®</td>
</tr>
</tbody>
</table>
| Comparators        | • clinical risk tests (NPI/mAOL)  
                    | • Oncotype DX®  
                    | • Prosigna®  
                    | • EndoPredict®                                                                                                                                 |
| Model description  | The model structure submitted for MammaPrint® was similar to NICE DG34, the pink box in figure 3 highlights the population considered in the base case. One significant difference within the Markov state transition portion of the company’s model (figure 3) is how local recurrence was modelled. In the NICE model, a proportion of patients who entered the distant recurrence health state were assumed to have also experienced a local recurrence and a one-off QALY loss and cost were applied. Whereas, in the company’s submission, patients in the recurrence-free health state have a risk of developing a local recurrence and entering the subhealth state ‘local recurrence’ which incurs a one-off QALY loss and cost. Patients in the local recurrence subhealth state subsequently accrue QALYs and costs as though in the recurrence-free health state but have a modified risk of experiencing a distant recurrence or subsequent local recurrences. Subsequent local recurrences are associated with further QALY loss and costs. |

Figure 3: MammaPrint model structure – hybrid decision-tree Markov model
The baseline clinical and tumour profiling test-risk distributions were derived from individual-level patient data from the MINDACT study\textsuperscript{38} for the MammaPrint test and from data published in NICE DG34 from the TransATAC study for its comparators (usual clinical practice, Oncotype DX\textsuperscript{®}, Prosigna\textsuperscript{®} and EPclin\textsuperscript{®}).
As the TransATAC study did not report mAOL risk classification distributions the company integrated the NPI clinical risk groups reported in TransATAC into a single risk group equivalent to mAOL clinical-high. The company assumed equivalence between a composite combined grouping of LN- NPI>3.4 (intermediate risk) and LN+ (1-3) nodes from TransATAC using a weighted average and the mAOL clinical-high group as observed in MINDACT. The mAOL clinical-low group was considered equivalent to the NPI≤ 3.4 (low risk) group.

**Probability of receiving chemotherapy - current practice**
As no empirical data was available for chemotherapy allocation according to mAOL clinical-high, clinical expert opinion was relied upon for the baseline probability of receiving chemotherapy.

**Probability of receiving chemotherapy with the test**
For the MammaPrint® test, a non-UK based decision impact study was used to inform the probability of receiving chemotherapy according to test result.71

For Oncotype DX®, these data came from a retrospective analysis of UK registry data which included LN- NPI>3.4 patients.72

For the Prosigna® and EPclin® tests, these data came from data published in NICE DG34.

**Probability of distant recurrence without chemotherapy**
Data used to inform MammaPrint® and usual care risk of recurrence without chemotherapy were extracted from the MINDACT individual-level patient data. 8-year DMFI probabilities were available from the MINDACT study and were extrapolated to 10-year probabilities to align with TransATAC data. DMFI (without chemotherapy) from both the concordant and discordant clinical-low subgroups in MINDACT were combined and weighted. The DMFI for the clinical-high/genomic-low group was extracted for patients who did not receive chemotherapy. As nearly all the patients in the clinical-high/genomic-high group in MINDACT received chemotherapy, a counterfactual DMFI was estimated for use in the model for this group and combined with the clinical-high/genomic-low non-treated DMFI.

For the Oncotype DX®, Prosigna® and EPclin® tests, the probability of developing distant metastases without chemotherapy were based on TransATAC data published in NICE DG34.
**Probability of distant recurrence with chemotherapy**

For the MammaPrint® test, the company estimated the treatment effect for chemotherapy using the randomised discordant clinical and genomic risk subgroup, clinical-high/genomic-low, from the MINDACT individual-level patient data. As the estimate of chemotherapy treatment effect from this analysis of these data was non-statistically significant, the company applied a RR of 1.00, meaning that patients who had a low genomic risk as per the MammaPrint® test were assumed to have no additional benefit in terms of DMFI from the addition of chemotherapy. Patients who received a high-risk genomic test were assumed to obtain all the chemotherapy benefit RR from the EBCTCG meta-analysis.

For the Oncotype DX®, Prosigna® and EPclin® tests, the company assumed the same RR for chemotherapy versus no chemotherapy from the EBCTCG meta-analysis used in NICE DG34.

**Probability of local recurrence**

The company used evidence from a Dutch registry study that reported local/regional recurrence over 10-years.

**Probability of death following distant recurrence**

The company used data from a US-based registry to estimate the 6-month probability of death following distant recurrence. This resulted in a higher probability (~30% higher) than assumed in the NICE DG34 analysis. This evidence source was better matched to the population in the model, though may not be generalisable to the Scottish population because of structural differences between the health care systems.

**Probability of AML**

Same as NICE DG34

**Probability of death following AML**

Same as NICE DG34

**Extrapolation**

MINDACT DMFI extrapolated from 8-year data to 10-years.

Distant recurrence beyond 10-years was the same as NICE DG34.

**Quality of life**

Health state utilities were broadly in line with the NICE DG34 model, however, the company argued that chemotherapy disutility was underestimated so implemented utility values from the same source but
where patients who received chemotherapy had a lower per cycle utility for the first three years of being recurrence free in the model.

Table 18: Recurrence-free utilities used in MammaPrint model

<table>
<thead>
<tr>
<th>Health state</th>
<th>Mean utility value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence-free adjuvant chemotherapy (year 1)</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Recurrence-free adjuvant chemotherapy (year 2-3)</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Recurrence-free adjuvant chemotherapy after year 3</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Recurrence-free no chemotherapy (year 1)</td>
<td>0.74</td>
<td>Lidgren 2007(^{63})</td>
</tr>
<tr>
<td>Recurrence-free no chemotherapy after year 1</td>
<td>0.82</td>
<td></td>
</tr>
</tbody>
</table>

Costs and resource use

The cost of the MammaPrint® test was provided by the company. The list price was £2,616. A confidential discount may be available but was not disclosed.

Chemotherapy regimens and their distribution in Scottish clinical practice came from clinical expert opinion. The costs of acquisition and administration of chemotherapy were also included. The total weighted costs for chemotherapy in the model were nearly twice that of that in the NICE DG34 model.

The frequency of health care resource utilisation was from expert clinical opinion and depended on whether patients had received adjuvant chemotherapy. Health care resource utilisation was assumed to be more intensive for those who had received chemotherapy.

G-CSF and bisphosphonates (supportive medications for patients receiving adjuvant chemotherapy) use appeared to be high.

Costs were also included for endocrine therapy acquisition (similar to NICE DG34), end of life costs, one-off cost for entering the loco/regional recurrence sub-state (similar to NICE DG34) and a one-off cost for entering the long-term adverse event health state (high cost compared with other models).
### Results

**Table 19: Summary of pairwise base-case results (mAOL 2 level high, LN- and LN+)**

<table>
<thead>
<tr>
<th>Technology</th>
<th>Incremental costs</th>
<th>Incremental QALYs</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>MammaPrint®</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Usual care</td>
<td>£3,742</td>
<td>0.55</td>
<td>MammaPrint®</td>
</tr>
<tr>
<td>Oncotype DX®</td>
<td>-£256</td>
<td>0.28</td>
<td>MammaPrint®</td>
</tr>
<tr>
<td>Prosigna®</td>
<td>-£2,982</td>
<td>0.37</td>
<td>MammaPrint®</td>
</tr>
<tr>
<td>EPClin®</td>
<td>-£2,525</td>
<td>0.25</td>
<td>MammaPrint®</td>
</tr>
</tbody>
</table>

### Key scenario analysis

The company also presented a scenario analysis that used test-risk classification probabilities for the Oncotype DX® test from the TAILORx study. As TAILORx only reported results for the LN- population, the company conducted this analysis for the LN- population only. The company used MINDACT individual patient-level data to estimate the test-risk classifications for patients who were LN- and mAOL clinical-high risk.

**Table 20: MammaPrint® vs. Oncotype DX® and usual care in LN- mAOL clinical-high risk population, equivalent to LN- NPI>3.4, using data from TAILORx and MINDACT individual patient-level data**

<table>
<thead>
<tr>
<th>Technology</th>
<th>Incremental costs</th>
<th>Incremental QALYs</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotype DX®</td>
<td>-£132</td>
<td>0.06</td>
<td>MammaPrint®</td>
</tr>
<tr>
<td>Usual care</td>
<td>-£524</td>
<td>0.13</td>
<td>MammaPrint®</td>
</tr>
</tbody>
</table>

The company provided a number of scenarios that tested certain base-case assumptions.

**Table 21: Selected scenario analysis, MammPrint® vs usual care**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Incremental Costs</th>
<th>Incremental QALYs</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>-£3,742</td>
<td>0.55</td>
<td>MammaPrint®</td>
</tr>
</tbody>
</table>
### AML costs excluded

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Inc QALYs</th>
<th>Inc. Costs</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>LN- NPI&gt;3.4</td>
<td>0.02</td>
<td>£107</td>
<td>£4,392</td>
</tr>
<tr>
<td>LN+</td>
<td>0.13</td>
<td>-£1,499</td>
<td>MammaPrint® Dominant</td>
</tr>
</tbody>
</table>

### Health care resource use costs excluded

- £3,377

### NICE DG34 utility set

- £3,743

### Drug administration costs excluded

- £2,126

### Scenario using SHTG preferred assumptions

Additional scenario analyses were requested by SHTG to test assumptions made in the company’s base-case analysis that were considered uncertain. These included: applying a treatment effect for chemotherapy using the 10-year relative risk of recurrence for chemotherapy versus no chemotherapy derived from the 2012 meta-analysis by the EBCTCG (RR=0.76); disutility to account for short-term chemotherapy-related adverse events is for 6-months; frequency of health care resource use (HCRU) does not vary by chemotherapy allocation and; the same approach to modelling local recurrence as NICE DG34 (10.5% of patients entering the distant recurrence health state have also experienced local recurrence).

### Key strengths

- Incorporates up-to-date data from the MINDACT study\(^3\) which were not available when NICE DG34 was published.
- Use of DMFI from MINDACT to estimate rates of recurrence.
- Use of individual-level patient data from MINDACT patients with HR+/HER2- disease.
- The company attempted to compare the use of MammaPrint® to usual Scottish clinical practice in the absence of direct evidence.

### Key uncertainties

- The results of the indirect comparison between the TransATAC and MINDACT study\(^3\) data may be confounded because of baseline imbalances between the study populations that did not appear to have been adjusted for in the presented evidence.
- As a result of a lack of evidence, the company relied upon clinical expert opinion for the baseline probability of chemotherapy.
- Redefinition of clinical risk of mAOL to NPI breaks randomisation and creates imbalance between the discordant clinical and genomic risk groups, which may bias the results and introduce uncertainty to the model. The direction and magnitude of this bias is also uncertain.

- The company have combined the intermediate and high clinical risk groups (LN- NPI>3.4 and LN+ 1-3 nodes, respectively). This may conceal differential cost effectiveness between these subgroups, which could be significant for decision making. The company did disaggregate these groups in other presented analyses.

- For patients receiving usual care (no tumour profiling test), the risk of distant recurrence was derived from a DMFI that did not take into account their genomic risk. This could confound the results of the analysis as patients would have the same risk of distant recurrence whether the results of their tumour profiling test were known or not. The cost effectiveness of the tests should be evaluated based on their ability to effect clinical decision making and their impact on patient outcomes. The company state that the structure of data from MINDACT informed the approach to estimating DMFI in the usual care arm.

- The assumption that MammaPrint® can predict the benefit of chemotherapy is based on limited evidence and is thus uncertain. It is likely that the results of the analysis would be sensitive to this assumption, however it has not been tested in sensitivity analysis.

- It is not clear whether the risk of patients entering the local/regional recurrence health state is modified by chemotherapy treatment effect and whether patients within the health state continue to obtain the benefit of chemotherapy with respect to their risk of distant recurrence. This approach adds uncertainty to the model results as it could overestimate the number of patients experiencing a local/regional recurrence.

- The approach to estimating recurrence-free health state utility for those who received chemotherapy is uncertain. NICE assumed a chemotherapy disutility that was limited to 6-months. The company have assumed chemotherapy will have a detrimental effect on an individual for a much longer period of time. This assumption could bias the results of the analysis in favour of a strategy that reduces chemotherapy use. In the scenario requested by SHTG this assumption was aligned with NICE DG34.

- HCRU costs were assumed to be higher for patients who had received adjuvant chemotherapy that reduces chemotherapy use, without empirical evidence and is thus uncertain. Although HCRU may vary by chemotherapy allocation, the extent of this is highly uncertain. This
The overall costs of chemotherapy appeared high compared to these costs in the NICE DG34 analysis. This may bias the results in favour of a strategy that reduces chemotherapy use. In a scenario analysis that removed drug administration costs, this had a large impact on the results for incremental costs versus usual care. Although this is a crude method for testing the uncertain chemotherapy costs in the base case, if combined with testing the other favourable or uncertain assumptions it may alter the conclusions of the analysis.

Table 23: Summary and critical appraisal of economic evaluation submitted by Veracyte – Prosigna® test

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis type</td>
<td>Cost-utility analysis</td>
</tr>
<tr>
<td>Time horizon</td>
<td>Lifetime</td>
</tr>
<tr>
<td>Population</td>
<td>Women with HR+, HER2-, early breast cancer. Subgroups considered were:</td>
</tr>
<tr>
<td></td>
<td>• LN-</td>
</tr>
<tr>
<td></td>
<td>• Luminal B like pT1c-pT2 pN0 (“luminal B”)</td>
</tr>
<tr>
<td></td>
<td>• LN+</td>
</tr>
<tr>
<td>Intervention</td>
<td>Prosigna®</td>
</tr>
<tr>
<td>Comparators</td>
<td>• Current practice (without a test, using a mix of risk prediction tools and diagnostic guidelines)</td>
</tr>
<tr>
<td>Model description</td>
<td>The company utilised the same model structure adopted by NICE in DG34.</td>
</tr>
<tr>
<td>Clinical data</td>
<td>Risk classification probabilities</td>
</tr>
<tr>
<td></td>
<td>The risk classification probabilities used in the model were taken from the TransATAC bespoke analysis published in the NICE DG34 analysis. The company have assumed that 38.2% of patients were LN- NPI&gt;3.4 to estimate a combined risk classification probability for the node-negative (all) subgroup and used the LN- NPI&gt;3.4 risk classification probabilities for the luminal B subgroup, assuming these were equivalent.</td>
</tr>
<tr>
<td></td>
<td>Probability of receiving chemotherapy - current practice</td>
</tr>
<tr>
<td></td>
<td>Probabilities of receiving chemotherapy without a test (current practice) were based on the NICE DG10 analysis. The company have combined the</td>
</tr>
</tbody>
</table>
probability of chemotherapy without a test with the same assumptions regarding the proportion of patients categorised as NPI>3.4 as elsewhere in their analysis.

An alternative analysis using the probabilities reported in NICE DG34 was requested and provided by the company.

**Probability of receiving chemotherapy – with a test**
The probability of receiving chemotherapy dependent on the Prosigna® test results were taken from the UKBCG survey, also utilised in NICE DG34.

**Probability of distant recurrence without chemotherapy**
The probability of distant recurrence without chemotherapy was based on 10-year distant metastases-free intervals published in NICE DG34 from the TransATAC study which were dependent on clinical risk subgroup and tumour profiling test-risk classification. The data were combined for the LN-patients assuming 38.2% of patients were NPI>3.4 as elsewhere in the analysis.

**Probability of distant recurrence with chemotherapy**
Same as NICE DG34

**Probability of local recurrence**
Same as NICE DG34

**Probability of death following distant recurrence**
Same as NICE DG34

**Probability of AML**
Same as NICE DG34

**Probability of death following AML**
Same as NICE DG34

**Extrapolation**
Risk tapering of the long-term risk of distant recurrence after 10-years to 50% of the preceding period for the remaining lifetime of patients was applied in the model.

An alternative analysis using the tapering assumptions used in NICE DG34 was requested and provided by the company.

**Quality of life**
Same as NICE DG34
Costs and resource use

The cost of the Prosigna® test was provided by the company. The list price was £1,896. A confidential discount is available.

The weighted mean cost of adjuvant chemotherapy acquisition and delivery was less than that in NICE DG34, however 80% of patients were assumed to receive G-CSF, which was associated with very high administration costs.

Other costs included in the model were for endocrine therapy acquisition (similar to NICE DG34), routine HCRU and follow up (similar to NICE DG34) and health state specific costs (distant recurrence, AML one-off and local recurrence one-off) that were from the same sources as NICE DG34, uplifted to the current price year.

Results

The company’s base case includes the adjustments to parameters at the request of SHTG during consultation. These include, the probability of chemotherapy without a test and tapering recurrence risk according to the assumptions in NICE DG34.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Inc. costs (list)</th>
<th>Inc. costs (discounted)</th>
<th>Inc. QALYs</th>
<th>ICER (list)</th>
<th>ICER (discounted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LN-</td>
<td>£1,608</td>
<td></td>
<td>0.07</td>
<td>£24,724</td>
<td></td>
</tr>
<tr>
<td>LN- NPI&gt;3.4</td>
<td>£1,653</td>
<td></td>
<td>0.08</td>
<td>£20,312</td>
<td></td>
</tr>
<tr>
<td>LN+</td>
<td>£4,183</td>
<td></td>
<td>0.11</td>
<td>£37,283</td>
<td></td>
</tr>
</tbody>
</table>

Key scenarios

None presented by the company

Key strengths

- Model structure and data for parameter values largely from the same evidence base as NICE DG34 making for easy comparison of results where values have been updated or changed.

Key uncertainties

- The use of data from NICE DG1073 as the source of data for the probability of receiving chemotherapy without the test appears to overestimate chemotherapy use in the LN- NPI>3.4 subgroup (luminal B in the analysis). This would lead to higher chemotherapy costs and disutility in the usual practice arm of the model for this subgroup and may bias the results in favour of the test.
- Costs of chemotherapy appear high because of the use of G-CSF. The true cost of adjuvant chemotherapy in early breast cancer facing the NHS in Scotland is a source of uncertainty.
Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex and sexual orientation.

About SHTG Recommendations

SHTG Recommendations are produced to inform a decision at a particular point in time and are not routinely updated. The recommendations will be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the advice given. For further information about the SHTG Recommendations process see our webpage on the range of products we provide.

To propose a topic for SHTG consideration, email his.shtg@nhs.scot

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

A glossary of commonly used terms in HTAs is available from htaglossary.net.

Acknowledgements

SHTG would like to thank the following individuals who provided comments on the draft review of evidence:

- Ms Sandra Auld, Director, Healthcare Public Affairs
- Ms Anne-Marie Barry, Policy And Public Affairs Lead, Breast Cancer Now
- Professor David Cameron, Professor of Oncology, University of Edinburgh
- Dr Judith Fraser, Medical Oncology Consultant, Beatson West of Scotland Cancer Centre
- Professor Lee Jordan, Consultant Cellular (Breast) Pathologist, NHS Tayside
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- Ms Heather Rankine, Patient/Business Lead, Exact Sciences
- Professor Rob Stein, Professor of Breast Oncology, University College London
- Dr Rosemary Stevens, Consultant Medical Oncologist, NHS Greater Glasgow and Clyde
- Professor Robert Van Der Meer, Professor of Management Science, University of Strathclyde
Mr Adrian Wood, UK Country Manager, Veracyte®

SHTG would like to thank the following individuals who provided comments on the draft recommendations:

- Dr Judith Fraser, Medical Oncology Consultant, Beatson West of Scotland Cancer Centre
- Professor Lee Jordan, Consultant Cellular (Breast) Pathologist, NHS Tayside
- Dr Noelle O’Rourke, National Clinical Lead Scottish Cancer Network, NHS Scotland
- Dr Frances Yuille, Consultant in Clinical Oncology, Edinburgh Cancer Centre

Declarations of interest were sought from all reviewers. All contributions from reviewers were considered by the HIS Evidence Review Team and the SHTG Council. Reviewers had no role in authorship or editorial control and the views expressed are those of HIS and the SHTG Committee.

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SHTG Council

The SHTG Executive would like to thank the following individuals on the SHTG Council for developing the recommendation for NHSScotland:

- Mr Edward Clifton, SHTG Unit Head, Healthcare Improvement Scotland
- Mr Mark Cook, Director of Reimbursement and Government Affairs, Association of British Healthcare Industries
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- Mr Colin Marsland, Director of Finance, NHS Shetland
- Mr Jim Miller, Chief Executive, NHS 24
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- Dr Neil Smart, SHTG Council Chair, Healthcare Improvement Scotland, and Consultant Anaesthetist, NHS Greater Glasgow and Clyde

Comments were sent in advance of the meeting by:

- Dr Fatim Lakha, Consultant in Public Health Medicine, Public Health Scotland

The SHTG Executive would like to thank the following topic experts who attended SHTG Council and provided their input to the discussion of the evidence:

- Professor Peter Hall, Consultant Medical Oncologist, NHS Lothian
- Ms Anna Lewis, Policy Manager (Regional and Devolved), Breast Cancer Now

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References