NICE National Institute for Health and Care Excellence

NICE guidance

Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer

Diagnostics guidance

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Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account, and specifically any special arrangements relating to the introduction of new interventional procedures. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces DG34.

1 Recommendations

This guidance is a partial review of NICE's diagnostics guidance on tumour profiling tests for guiding adjuvant chemotherapy decisions in early breast cancer (DG34) which made recommendations for lymph node-negative (including micrometastatic disease) early breast cancer. This partial review specifically considers tumour profiling tests for lymph node-positive early breast cancer. The recommendations from DG34 have been incorporated into this guidance. To see what NICE did for tumour profiling tests for lymph node-negative and micrometastatic early breast cancer, see the DG34 evidence review.

Oncotype DX is processed in the US and laboratories processing the test must be Clinical Laboratory Improvement Amendments (CLIA)-certified and be accredited to ISO15189 or ISO17025. Use of tests must be in compliance with UK General Data Protection Regulation (GDPR) and the Health and Social Care Act (2012).

Lymph node-positive early breast cancer

Can be used

1.1 Use EndoPredict, Oncotype DX or Prosigna as options alongside consideration of clinical risk factors to guide adjuvant chemotherapy decisions for treating oestrogen receptor (ER)- or progesterone receptor (PR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer with 1 to 3 positive lymph nodes for:

- women who have been through the menopause
- men
- trans, non-binary or intersex people, depending on their hormonal profile.

Use clinical judgement to determine if testing is suitable for men, trans or non-binary or intersex people.

Should not be used

1.2 For women who have not been through the menopause, EndoPredict, Oncotype DX and Prosigna should not be used to guide adjuvant chemotherapy decisions for ER- or PR-positive, HER2-negative early breast cancer with 1 to 3 positive lymph nodes.

1.3 MammaPrint should not be used to guide adjuvant chemotherapy decisions for people with ER- or PR-positive, HER2-negative early breast cancer with 1 to 3 positive lymph nodes.

Lymph node-negative and micrometastatic early breast cancer

Can be used with evidence generation

1.4 EndoPredict, Oncotype DX or Prosigna can be used in the NHS while more evidence is generated, to guide adjuvant chemotherapy decisions for people with ER- or PR-positive, 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 Nottingham Prognostic Index
- clinicians and companies make timely, complete and linkable record-level test data available to the National Cancer Registration and Analysis Service.

Should not be used

1.5 MammaPrint and IHC4+C should not be used to guide adjuvant chemotherapy decisions for people with ER- or PR-positive, HER2-negative and LN-negative early breast cancer.

Conditions for use

1.6 Use EndoPredict, Oncotype DX or Prosigna to guide adjuvant chemotherapy decisions for ER- or PR-positive, HER2-negative early breast cancer only if:

- the person having the test will use the results to help them choose, with their healthcare professional, whether or not to have adjuvant chemotherapy
- the tests are used within their intended purpose:
  - EndoPredict (ER-positive, or both ER- and PR-positive)
  - Oncotype DX (ER- or PR-positive, or both)
  - Prosigna (ER- or PR-positive, or both; only for women who have been through the menopause)
- the companies provide the tests to the NHS with the discounts agreed in the access proposals
- laboratories processing the tests take part in a UK national external quality assurance scheme.

1.7 Use the test and results alongside NICE's guideline on shared decision making. An oncologist should explain to the person what their tumour profiling test results mean, and the risks and benefits of treatment options based on all available risk factors.

Why the committee made these recommendations

People with early breast cancer may have further treatment (adjuvant treatment) after they have surgery. Decisions on adjuvant chemotherapy are made based on several

factors relating to the clinical and pathological profile of the cancer, the risk of the cancer coming back (recurrence) and preference of the person with cancer. Additional information from tumour profiling tests may be helpful when making decisions about chemotherapy.

Evidence suggests that EndoPredict, MammaPrint, Oncotype DX and Prosigna can predict the risk of recurrence in a different part of the body in women who have been through the menopause who have ER- or PR-positive, HER2-negative early breast cancer that has spread to 1 to 3 lymph nodes. There is some evidence that Oncotype DX can also predict whether chemotherapy is likely to prevent recurrence, but this is uncertain.

Clinical trial evidence suggests that chemotherapy is effective at reducing the risk of recurrence in women who have not been through the menopause, regardless of Oncotype DX recurrence score. So, the test should not be used in this population. Evidence for other tests was mostly in women who have been through the menopause or did not distinguish by menopausal status, so it was unclear whether they would be useful for women who have not been through the menopause.

Economic modelling suggests that EndoPredict, Oncotype DX and Prosigna are cost effective compared with standard care in women who have been through the menopause. MammaPrint is likely to be less clinically effective and costs more than standard care.

There is limited evidence on using tumour profiling tests for men, but healthcare professionals should offer testing if it is suitable for the person. There is no evidence for trans, non-binary or intersex people. But healthcare professionals should offer testing if it is suitable based on the person's individual hormonal profile. There is not enough evidence to say whether the ability of tumour profiling tests to predict risk may differ across ethnic groups. Further research is needed to establish the effectiveness of the tests in these populations (see the section on further research).

It is important that results from tumour profiling tests are considered alongside other clinical risk factors such as age and tumour size. People with breast cancer should be involved in decisions about their treatment, and should be well informed about what their test result means, their options, and the associated risks and benefits. Further research is needed on the best ways to communicate this information (see the section on further research). Oncologists should be aware of the limitations of the evidence for tumour profiling tests (see sections 3.7 to 3.10 and sections 3.14 to 3.15).

2 The diagnostic tests

Clinical background

2.1 Breast cancer is the most common cancer in the UK. Around 1 in 7 women will develop breast cancer during their lifetime (Cancer Research UK webpage about breast cancer). In 2020, new cases of breast cancer were diagnosed in 44,943 women and 348 men in England (NHS Digital Cancer Registration Statistics, England 2020). Most cases develop in women who are over 50 years (Cancer Research UK webpage on risk factors for breast cancer).

2.2 Early breast cancer is cancer that has not spread beyond the breast or the lymph nodes in the armpit on the same side of the body. Early breast cancer can be locally advanced; this means that the cancer has spread to the surrounding areas such as the nearby lymph nodes, skin or chest muscle, but not to distant parts of the body.

2.3 When cancer cells have been detected, further tests are done to provide more information on the characteristics of the tumour. The results of these tests are used to classify the cancer and to determine which types of treatment it is most likely to respond to. Typically, tests determine oestrogen receptor (ER), progesterone receptor (PR) and HER2 status.

2.4 The NICE guideline on early and locally advanced breast cancer describes the care pathway. Surgery is often the initial treatment for ER- or PR-positive, HER2-negative early and locally advanced breast cancer. After surgery, further treatment (adjuvant treatment) might be recommended and this can include:

- radiotherapy
- chemotherapy
- endocrine therapy
- targeted therapy.

Some people may have treatment before surgery (neoadjuvant treatment).

Clinical need

2.5 Not all people with early breast cancer will benefit from adjuvant chemotherapy. Decisions on chemotherapy use may be made based on a combination of:

- clinical or pathological factors (such as age or tumour size)
- results from tools such as Predict or the Nottingham Prognostic Index
- personal preferences of the person with early breast cancer.

Additionally, tumour profiling tests may be used.

2.6 Tumour profiling tests provide information on the expression of genes in tumour samples from people with early breast cancer. The test results provide a risk profile of an individual's breast cancer. This can be considered with other clinical risk factors, such as nodal status and tumour size, to better predict the risk of disease recurrence in the future. Some tests may also predict how beneficial chemotherapy may be for the person.

2.7 NICE's guidance on tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer (DG34; replaced by this guidance) made recommendations on using the tests for people with ER-positive, HER2-negative and lymph node (LN)-negative (including micrometastatic disease) early breast cancer (see the DG34 evidence review).

2.8 Tumour profiling tests could also be used to guide decisions on adjuvant chemotherapy for people with ER- or PR-positive, HER2-negative early breast cancer with 1 to 3 positive lymph nodes. This group has a clinically higher risk than people with LN-negative cancer. So, it is more likely that people with LN-positive cancer will be recommended adjuvant chemotherapy. Identifying people who may not benefit from adjuvant chemotherapy could allow them to avoid unnecessary treatment, and so avoid side effects and other impacts on day-to-day life associated with chemotherapy. Alternatively, testing could identify people who would be considered to have a low risk of disease recurrence based on

clinical factors, but who would actually benefit from chemotherapy.

The intervention

2.9 The intervention is any of the tumour profiling tests in sections 2.10 to 2.25, alongside consideration of any other clinical factors usually used to help guide decisions about chemotherapy.

EndoPredict (Myriad Genetics)

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

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

2.11 EndoPredict measures the expression of 12 genes: 3 proliferation-associated genes, 5 hormone receptor-associated genes, 3 reference (normalisation) genes and 1 control gene. This information is used to calculate a 12-gene molecular score (EP score).

2.12 EndoPredict uses RNA extracted from formalin-fixed, paraffin-embedded (FFPE) breast cancer tissue samples. The test can be done in local laboratories. Test results are available about 3 to 5 days after the sample has arrived at the laboratory.

2.13 The test uses reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Online evaluation software (EndoPredict Report Generator) performs a quality check and calculates the EPclin score, which is the final test result. The EPclin score is calculated using clinical data about tumour size and nodal status, and the EP score. This can be used to estimate the likelihood of distant

recurrence, assuming 5 years of endocrine therapy. An EPclin score below 3.3 indicates low risk of distant recurrence in the next 10 years (less than 10%). An EPclin score of 3.3 or more indicates high risk of distant recurrence in the next 10 years. The company claimed that the EPclin score can also be used to estimate chemotherapy benefit, in which people with an EPclin score below 3.3 are less likely to benefit from adjuvant chemotherapy.

MammaPrint (Agendia)

2.14 MammaPrint is a CE-marked microarray that is designed to assess the risk of distant recurrence within 10 years and predict the likelihood of chemotherapy benefit. The test is intended for pre- and postmenopausal people with primary stage 1 or 2, or operable stage 3, breast cancer with the following clinical features:

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

2.15 MammaPrint measures the expression of 70 cancer-related genes and 465 control genes.

2.16 The MammaPrint test is offered as an off-site service. In the UK, samples are sent for analysis at the Agendia laboratory in the US. A decentralised version of the test is also available for local laboratories with next-generation sequencing capability. The test requires a FFPE breast cancer tissue sample.

2.17 The test is based on diagnostic microarray. Software calculates the MammaPrint result on a scale of -1 to +1. The result 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 below indicates high risk of metastases in the next 10 years and a result above 0 indicates low risk (10% or less) of metastases in the next 10 years. A result above 0.355 indicates ultra-low

risk, which the company defines as more than 99% breast cancer-specific survival at 8 years and 97% breast cancer-specific survival at 20 years with 2 to 5 years of tamoxifen treatment. The company states that test results are typically reported within 10 days of receiving the sample at the laboratory and the average turnaround time is less than 5 days.

Oncotype DX (Exact Sciences)

2.18 Oncotype DX is a CE-marked assay designed to quantify the 9-year risk of distant recurrence and predict the likelihood of chemotherapy benefit. The test also reports the underlying tumour biology: ER, PR and HER2 status. The test is intended for pre- or postmenopausal people with early breast cancer that is:

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

2.19 Oncotype DX quantifies the expression of 21 genes. Of these, 16 are cancer-related genes correlated with distant recurrence-free survival, and 5 are reference genes for normalising the expression of the cancer-related genes. This information is used to calculate the Oncotype DX Breast Recurrence Score (RS).

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

2.21 The test gives an Oncotype DX Breast RS of between 0 and 100, which is used to estimate the 5- or 9-year risk of distant recurrence, assuming 5 years of hormonal therapy. The company states that the RS also estimates chemotherapy benefit (in terms of reducing risk of distant recurrence). For premenopausal women with LN-positive cancer (1 to 3 positive nodes), the instructions for use state that:

- RS up to 13 predicts 2.3% chemotherapy benefit at 5 years
- RS between 14 and 25 predicts 2.9% chemotherapy benefit at 5 years.

  For postmenopausal women with LN-positive cancer, the instructions for use state that an RS of up to 25 predicts no apparent chemotherapy benefit (less than 1%) at 5 years. In both groups, the instructions for use state that guidelines recommend chemotherapy in addition to hormone therapy for people with an RS between 26 and 100.

2.22 The company states that Oncotype DX Breast RS results are typically reported within 7 to 10 calendar days after the sample is received at the laboratory.

Prosigna (Veracyte)

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

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

2.24 Prosigna measures the expression of 50 genes (PAM50) used for intrinsic subtype classification, 8 housekeeping genes used for signal normalisation, 6 positive controls, and 8 negative controls. The test uses RNA extracted from a FFPE breast cancer tissue sample, and can be done in local laboratories provided they have access to the NanoString nCounter Dx Analysis System. The company states that results are usually available within 3 days.

2.25 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 an overall risk of recurrence score between 0 and 100. Based on this score and the nodal status, samples are classified into risk categories. For LN-positive cancer (up to 3 positive nodes), 0 to 15 indicates low risk, 16 to 40 intermediate risk, and 41 to 100 high risk. For 4 or more positive nodes, any score is assigned high risk. Clinical advice is that most people with 4 or more positive nodes would be offered chemotherapy under standard care.

The comparator

2.26 The comparator is decision making for adjuvant chemotherapy prescribing (without use of tumour profiling tests) based on clinical and pathological features or the results of tools used to assess risk. Features may include age, the stage of the disease, nodal status, ER or PR status, HER2 status, and any previous treatment. Risk assessment tools such as Predict or the Nottingham Prognostic Index are available as online calculators.

3 Committee discussion

The diagnostics advisory committee considered evidence on tumour profiling tests to guide adjuvant chemotherapy decisions in lymph node (LN)-positive early breast cancer from several sources, including an external assessment report and an overview of that report. Full details are in the project documents for this guidance.

Shared decision making

3.1 The committee agreed that tumour profiling tests may be used as part of a shared decision-making process, and should not be considered a definitive indicator of whether chemotherapy should be offered or not. Patient experts and stakeholders cited evidence and personal experience that results of tumour profiling tests are sometimes considered superior to other prognostic factors and so disproportionately influence decision making. The committee emphasised that tumour profiling tests should form part of a comprehensive management plan. All available information (see section 2.5), including the results of tumour profiling tests and other tools such as Predict or the Nottingham Prognostic Index (NPI), should be considered when making a decision. Clinical experts noted the importance of providing suitable educational materials for healthcare professionals to help them understand the evidence behind tumour profiling test results. This knowledge would allow them to make a nuanced interpretation of the results, considering uncertainty and potential risks and benefits, and explain this to the person with cancer. The committee highlighted that the NICE guideline on shared decision making should be used to support decisions.

3.2 The committee acknowledged there was little comparative data between tumour profiling tests and risk prediction tools like Predict or NPI. The external assessment group (EAG) noted that Predict and NPI are likely to estimate most people with LN-positive breast cancer as having high risk of recurrence, making the comparison with tumour profiling test results less relevant than for people with LN-negative breast cancer. Comments received at consultation highlighted that Predict will soon be updated to reflect changes in breast cancer mortality. The committee re-emphasised that all available information should be considered alongside tumour profiling test results when making decisions (see section 3.1).

3.3 Patient experts highlighted that people with LN-positive breast cancer can be poorly informed on the risks and benefits of different treatment options, or on how tumour profiling tests can inform treatment decisions. In some cases, they may feel left out of the decision-making process entirely. The committee emphasised the importance of accessible patient-focused information and counselling for people making decisions about whether to have chemotherapy, and that ideally discussions of tumour profiling test results should happen with an oncologist.

Anxiety from test results

3.4 The committee heard that tumour profiling test results could increase anxiety for people with breast cancer. Patient experts stated that anxiety could be increased for people with test results that indicate high risk of recurrence. They also said that people who choose to forego chemotherapy based on tumour profiling test results may experience anxiety over whether they have made the right decision. A patient expert suggested that some people may benefit from ongoing support or counselling to help manage this anxiety. The EAG did not find any evidence on anxiety in people with LN-positive breast cancer after chemotherapy decisions were made using tumour profiling test results.

Turnaround time

3.5 The committee concluded that all tests were likely to provide results within a useful timeframe. Some tests are processed outside of the UK, which can increase turnaround time (see sections 2.10 to 2.25). The committee discussed whether turnaround time could affect the availability of results in time for an appointment with an oncologist. It noted that all tests are expected to provide results within 10 days, which should be fast enough for results to be available to inform chemotherapy decisions.

Clinical effectiveness

Prognostic ability

3.6 The prognostic ability of a test describes its ability to differentiate between people who will have good or poor outcomes. There was some evidence that all the tests had statistically significant prognostic ability for distant recurrence within 10 years. Clinical experts noted that the absolute benefit of chemotherapy is dependent on the absolute level of risk, so people with low risk of recurrence will have a lower absolute benefit from chemotherapy than people with a high risk of recurrence. So, tests with prognostic ability are useful to help guide chemotherapy decisions even if they are unable to predict chemotherapy benefit.

Predictive ability

3.7 The predictive ability of a test is determined by whether the relative effect of chemotherapy versus no chemotherapy on clinical outcomes differs between risk groups or ranges. The EAG did not identify any evidence on the predictive ability of EndoPredict or Prosigna in a population that was mostly people with LN-positive breast cancer. So, these tests could only be considered to have prognostic ability.

3.8 The committee concluded that there was not enough evidence to definitively say whether or not MammaPrint is predictive of chemotherapy benefit. Two studies were available that evaluated the predictive ability of MammaPrint. A reanalysis of 2 cohorts reported by Mook et al. (2009) did not find a significant interaction between MammaPrint result and the effect of chemotherapy on breast cancer-specific survival. In the MINDACT trial, people were randomised to chemotherapy or no chemotherapy only if their clinical risk and MammaPrint risk were discordant. Everyone in the clinical high-risk and MammaPrint high-risk group was offered chemotherapy, so the EAG stated that it was not possible to determine whether MammaPrint was predictive of chemotherapy benefit from MINDACT data. The company stated that MINDACT was designed to demonstrate lack of chemotherapy benefit in the clinical high-risk, MammaPrint low-risk group and that chemotherapy benefit on distant recurrence in this group

was non-significant (hazard ratio [HR] 0.84, 95% confidence interval [CI] 0.51 to 1.37). So, people in this group would have low or no benefit from chemotherapy. The EAG responded that a non-significant benefit is not necessarily the same as no benefit, and that there was no evidence to estimate the size of chemotherapy benefit in the MammaPrint high-risk group. A company representative noted that MINDACT was not powered to detect differences in chemotherapy benefit by LN status. So, the predictive ability of MammaPrint remained uncertain.

3.9 The committee thought that it was likely that Oncotype DX has some predictive ability for chemotherapy benefit in postmenopausal women with oestrogen receptor (ER)- or progesterone receptor (PR)-positive, HER2-negative early breast cancer with 1 to 3 positive lymph nodes. There were 2 studies that provided evidence on the predictive ability of Oncotype DX for chemotherapy benefit. A reanalysis of the SWOG-8814 study found a difference in chemotherapy benefit on disease-free survival between people with a recurrence score (RS) of 0 to 17, 18 to 30 and 31 to 100 over 10 years. The statistical significance of this difference was dependent on which factors were adjusted for in the analysis. The RxPONDER trial used Oncotype DX for screening and excluded people with RS 26 to 100, because they were likely to benefit from chemotherapy based on the results of SWOG-8814. So, it was not possible to determine whether Oncotype DX was predictive of chemotherapy benefit with a cutoff of RS 25 using results from RxPONDER alone. People with RS 0 to 25 were randomised to chemotherapy or no chemotherapy. Within this group, the hazard ratio for the effect of chemotherapy was non-significant but favoured no chemotherapy for postmenopausal women (HR 1.12, 95% CI 0.82 to 1.52). A clinical expert noted that RxPONDER was not powered as a non-inferiority trial, so this finding could be considered uncertain.

3.10 The EAG noted that in SWOG-8814, 38% of people had 4 or more positive lymph nodes and 12% had HER2-positive cancer, so the population did not exactly match the scope, and the effect of chemotherapy may be overestimated. In RxPONDER, the overall clinical risk was relatively low for a population with 1 to 3 positive lymph nodes. The EAG noted that of the people randomised, 65% had 1 positive lymph node, 25% 2 positive nodes and 9% 3 positive nodes. Some people had micrometastases and 24% had low-grade cancer. Additionally, the EAG identified possible selection bias because people had their test result before agreeing to randomisation, and there was some crossover between trial arms.

Therefore, the results may underestimate the effect of chemotherapy in a wider population with LN-positive breast cancer with higher overall clinical risk. The company highlighted a subgroup analysis of RxPONDER which indicated that the effect of chemotherapy on invasive disease-free survival was non-significant in people with 1 positive node and in people with 2 or 3 positive nodes. The committee felt that the evidence was uncertain, but commented that it is unlikely that more evidence will be generated in this population to reduce this uncertainty. It concluded that the results of SWOG-8814 and RxPONDER together suggest it is likely that Oncotype DX is predictive of chemotherapy benefit in postmenopausal women with ER- or PR-positive, HER2-negative early breast cancer with 1 to 3 positive lymph nodes.

Effect of menopausal status

3.11 The committee heard that it is likely that chemotherapy is more effective in premenopausal women than in postmenopausal women because of the effect of chemotherapy on ovarian function. The RxPONDER trial reported a significant benefit of chemotherapy on 5-year distant recurrence in premenopausal women with RS 0 to 25, but not in postmenopausal women (see section 3.9). Clinical experts stated that chemotherapy can suppress ovarian function in premenopausal women and this may be responsible for the treatment effects seen. So, the committee concluded that Oncotype DX should not be used to help guide chemotherapy decisions for premenopausal women with LN-positive early breast cancer.

3.12 The committee noted that the tests measure the expression of different genes (see sections 2.10 to 2.25). So, the effects of menopausal status seen in studies of Oncotype DX may not be generalisable to the other tumour profiling tests. There was limited data for other tests stratified by menopausal status. Most of the evidence for EndoPredict was in postmenopausal women. Data from MINDACT for MammaPrint was in a mixed population, in which 33% were premenopausal women. Prosigna is only intended for postmenopausal women. Clinical experts agreed that there is a plausible biological explanation for the difference in chemotherapy benefit between pre- and postmenopausal women (see section 3.11). They also highlighted that the risk of incorrectly foregoing chemotherapy is higher in premenopausal women than in postmenopausal

women. So, the committee concluded that EndoPredict and MammaPrint should not be used to help guide chemotherapy decisions in premenopausal women, and that Prosigna is not intended for use in this population.

Effect of test results on chemotherapy decisions

3.13 The committee concluded that evidence on how test results affected chemotherapy decisions could reasonably be generalised between tumour profiling tests. The only available evidence on how test results influenced chemotherapy recommendations or decisions in a LN-positive population was for Oncotype DX. Clinical experts stated that the decision-making process is similar regardless of test identity, and that there are many other factors that can affect decisions on chemotherapy in addition to tumour profiling test results (see section 2.5). The committee recalled that different tests measure the expression of different genes, but that there is some overlap between tests. However, the way different tests define risk groups resulted in large differences in the number of people who would be assigned as having low, intermediate or high risk, even between tests with the same number of risk categories (see section 3.22), so there was some uncertainty. The committee concluded that it was reasonable to use the available data from studies of Oncotype DX to evaluate the other tests, because alternative methods would be more uncertain. More evidence on how the results of tests other than Oncotype DX affect chemotherapy decision making for people with LN-positive early breast cancer would be helpful to reduce uncertainty (see section 3.22).

Effect of ethnicity

3.14 The committee concluded that more evidence was needed on how well tumour profiling tests can predict risk in different ethnic groups (see section 4.1). There was not enough evidence to say whether the ability of tumour profiling tests to predict risk may differ across ethnic groups. In RxPONDER, differences in 5-year invasive disease-free survival within the RS 0 to 25 group were reported according to ethnicity (White, 92%; Black, 87%; Asian, 94%), but no prognostic or predictive data were reported. In a subgroup analysis of the SEER database, the prognostic ability of Oncotype DX was only statistically significant in White

participants, but this was based on small numbers. There was no evidence stratified by ethnicity for other tumour profiling tests.

Men, trans, non-binary and intersex people with breast cancer

3.15 There was very little data on using tumour profiling tests for men with breast cancer. Clinical experts stated that ER- or PR-positive, HER2-negative, LN-positive breast cancer generally responds to treatment with chemotherapy in the same way for men and women. But it is unclear whether tumour profiling tests would have the same prognostic and predictive ability for men and women. No data was identified on using tumour profiling tests for trans, non-binary or intersex people. It is likely that decisions on adjuvant chemotherapy in these populations would be individualised to the person considering their hormonal profile, their circumstances and any gender-affirming treatment, in addition to the factors described in section 2.5. Tumour profiling tests may be used if clinical judgement determines them to be suitable for the person and as part of the shared decision-making process. Further research is needed on the prognostic and predictive ability of tumour profiling tests in these populations (see section 4.1).

Cost effectiveness

Cost effectiveness of EndoPredict

3.16 The committee concluded that EndoPredict was likely to be a cost-effective use of NHS resources when used to guide adjuvant chemotherapy decision making with postmenopausal women. In the EAG's base-case analysis, the probabilistic incremental cost-effectiveness ratio (ICER) for EndoPredict compared with decision making without tumour profiling was £4,113 per quality-adjusted life year (QALY) gained. This result was driven by a small decrease in the number of people having chemotherapy and in the number of people with distant recurrence, and additional costs of testing. With confidential price discounts applied, EndoPredict dominated standard care (it cost less and produced more QALYs). The committee considered a scenario analysis that used an alternative

source for test risk classification probabilities and distant recurrence-free interval (Filipits et al. 2019). In this scenario, EndoPredict was instead dominated by standard care (it cost more and produced fewer QALYs). The EAG noted that the data from Filipits et al. was taken at 15 years, when there were few people remaining in the study. The data used in the base-case analysis (from the TransATAC study) was taken at 10 years. Ten-year data from Filipits et al. produced similar results to the base case. Clinical experts explained that the benefit of chemotherapy is primarily in the first few years, and that the risk of recurrence after 10 years is less likely to be affected by chemotherapy. So, the committee preferred the base-case analysis. The committee recalled that there was no data on how EndoPredict results would affect chemotherapy decisions for people with LN-positive breast cancer, and that interpretation of results may not be generalisable between tests (see section 3.13). It noted that scenario analyses using data from different studies of Oncotype DX to inform impact on chemotherapy decisions did not have a large effect on the cost-effectiveness estimates for EndoPredict. So, although this parameter was uncertain, the committee felt that the conclusions of the economic model were likely to be robust.

Cost effectiveness of MammaPrint

3.17 The committee concluded that MammaPrint was unlikely to be a cost-effective use of NHS resources. In the EAG's base-case analysis, MammaPrint was considered to have prognostic ability only, and was dominated by standard care when used for a population with clinical high risk and mixed menopausal status (33% premenopausal). This result was driven by an increase in the number of people who developed distant recurrence as well as the additional costs of testing, even though there was a large decrease in the number of people having chemotherapy. The company stated that results from the MINDACT trial had been misrepresented, and that if MammaPrint was considered to have predictive ability then it would dominate standard care. The committee recalled that it was uncertain whether MammaPrint was predictive of chemotherapy benefit (see section 3.8). Clinical experts commented that the data from the 33% of premenopausal women in the MINDACT cohort may be obscuring a smaller effect of chemotherapy on distant recurrence in postmenopausal women (see sections 3.11 and 3.12). The company submitted data from an exploratory

subgroup analysis of MINDACT participants with 1 to 3 lymph nodes aged over 50 (n=430), and suggested that the effect of chemotherapy on distant recurrence in this group could be used in the economic model (HR 0.88, 95% CI 0.46 to 1.68). The committee considered this analysis, and noted that the confidence interval included the value used in the EAG's base case (HR 0.71) which was derived from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2012 meta-analysis. The EAG explained that using the MINDACT subgroup analysis HR across both risk groups would imply a lower benefit of chemotherapy overall than was seen in the EBCTCG meta-analysis, which included a much larger population than MINDACT. So, the committee concluded that the EAG's base case was more appropriate.

Cost effectiveness of Oncotype DX

3.18 The committee concluded that Oncotype DX was likely to be a cost-effective use of NHS resources when used to help guide adjuvant chemotherapy decision making with postmenopausal women. In the EAG's base-case analysis, Oncotype DX dominated decision making without tumour profiling in postmenopausal women. However, this was dependent on the assumption that the test has predictive ability for chemotherapy benefit. In scenario analyses in which Oncotype DX had prognostic ability only, testing resulted in reduced costs but also fewer QALYs than standard care (savings of more than £30,000 per QALY lost with confidential price discounts applied). RxPONDER only provided data for people with RS 0 to 25, so model inputs for the RS 26 to 100 group had to be sourced from the TransATAC and SWOG-8814 studies, which used a cutoff of RS 30 for the high-risk group. The committee recalled its discussions on the uncertainty around the predictive ability of Oncotype DX for postmenopausal women (see sections 3.9 and 3.10), and that the effect of chemotherapy was likely overestimated in SWOG-8814 and underestimated in RxPONDER. It noted a scenario analysis, in which the hazard ratio for chemotherapy effect in the RS 0 to 25 group was reduced to 1.0 from 1.12, did not have a large effect on the cost-effectiveness estimates. The committee also noted that the economic model used a constant hazard ratio for the effect of chemotherapy over time. This may overestimate the effect because the greatest benefit of chemotherapy is seen in the first few years (see section 3.16). The EAG provided scenario analyses in which the effect of chemotherapy was lost after 5 or 10 years, and Oncotype DX

remained dominating over current practice. The committee concluded that it was likely that Oncotype DX has some predictive ability for chemotherapy benefit in this population, but that the difference in chemotherapy benefit between risk groups was possibly overestimated in the economic model.

Cost effectiveness of Prosigna

3.19 The committee concluded that Prosigna was likely to be a cost-effective use of NHS resources when used to help guide adjuvant chemotherapy decision making with postmenopausal women. In the EAG's base-case analysis, the probabilistic ICER for Prosigna was £24,547 per QALY gained using list prices. This result was driven by a small decrease in the number of people having chemotherapy and in the number of people with distant recurrence, and additional costs of testing. With confidential price reductions applied, the ICER was below £20,000 per QALY gained. The committee considered several scenario analyses which demonstrated that the ICER was sensitive to factors including sources of key inputs and the effectiveness and cost of chemotherapy. However, in most scenarios the ICER remained below £20,000 per QALY gained.

Impact on chemotherapy services

3.20 The EAG's economic model predicted that using tumour profiling tests would reduce the number of people having chemotherapy. The committee recognised that infusion services are often under a lot of pressure. Clinical experts explained that it is unlikely that reduced numbers of people having chemotherapy for early breast cancer would allow people with other types of cancer to access treatment faster, because generally people do not have to wait long for chemotherapy. However, it could improve patient and staff experience at infusion centres and reduce medical errors. Patient experts emphasised that people with LN-positive breast cancer should not be pressured to forego chemotherapy for capacity reasons, and that they should be offered an initial discussion with an oncologist even if tumour profiling tests suggest that they have a low risk of recurrence. The committee concluded that benefits resulting from reduced use of chemotherapy are already captured in the economic model through reduced costs and chemotherapy-related adverse events, and so did not need to be considered

qualitatively.

3.21 The committee acknowledged that different tests were likely to reduce the number of people having chemotherapy by different amounts, but that EndoPredict, Oncotype DX and Prosigna were all likely to be cost effective compared with not using tumour profiling tests. The EAG's economic model predicted that using Oncotype DX would result in 594 fewer women having chemotherapy per 1,000 tested, whereas with EndoPredict or Prosigna the reduction was around 40. However, the committee noted that there was not enough comparative evidence to compare the tests directly, and that all 3 tests had ICERs below £20,000 per QALY gained when compared to not using tumour profiling tests.

Research considerations

Effect of EndoPredict and Prosigna test results on chemotherapy decisions

3.22 The only available evidence on how test results influenced chemotherapy recommendations or decisions was for Oncotype DX. The committee considered that this data may not be fully generalisable to other tests because they measure the expression of different sets of genes, and because the risk classification probabilities of each test result in different numbers of people being assigned to low-, intermediate- or high-risk groups (see section 3.13). However, uncertainty in this parameter did not have a large effect on the cost-effectiveness results for EndoPredict (see section 3.16). Further evidence on how EndoPredict and Prosigna results affect chemotherapy decisions for people with LN-positive early breast cancer would be helpful to reduce this uncertainty.

OPTIMA

3.23 The OPTIMA trial is an ongoing randomised controlled trial of Prosigna, comparing test-directed chemotherapy use with standard chemotherapy prescribing. The population includes people with a high clinical risk of recurrence

and mostly people with LN-positive cancer (1 to 9 positive nodes). No results have yet been published. The committee recognised that OPTIMA may be able to address some of the uncertainty around the results for Prosigna, and encouraged clinicians to continue to promote enrolment in OPTIMA.

4 Recommendations for further research

4.1 For people with lymph node-positive early breast cancer, more research is needed on the prognostic and predictive ability of tumour profiling tests:

- across different ethnic groups
- in men and trans, non-binary or intersex people.

4.2 Research is needed on the types and formats of information that would help people with lymph node-positive breast cancer to understand all the factors that can support decisions on chemotherapy. Studies could involve people who have experienced the decision-making process.

5 Implementation

NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

In addition, NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered for developing specific research study protocols as appropriate. NICE will also incorporate the research recommendations in section 4 into its guidance research recommendations database and highlight these recommendations to public research bodies.

Exact Sciences, Myriad Genetics and Veracyte have offered their tumour profiling tests to the NHS under access proposals that make each test available to the NHS at a revised price. The proposal prices are commercial in confidence. It is the responsibility of the companies to communicate details of their proposal to the relevant NHS organisations.

The UK National External Quality Assessment Service (NEQAS) has launched a pilot scheme for tumour expression profiling in breast cancer. Laboratories processing the tests can register for the scheme through the UK NEQAS website or by emailing the provider at info@genqa.org.

6 Diagnostics advisory committee members and NICE project team

Committee members

This topic was considered by the diagnostics advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the test to be evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Additional specialist committee members took part in the discussions for this topic:

Specialist committee members

Mark Davies
Consultant in medical oncology and honorary consultant in clinical genetics, South West Wales Cancer Centre

Suzanne Frank
Advanced specialist breast cancer pharmacist, The Christie NHS Foundation Trust

Caroline Graham
Specialist lay committee member

Muireann Kelleher
Consultant medical oncologist, St. George's Healthcare NHS Foundation Trust

Stuart McIntosh
Clinical reader in surgical oncology, Queen's University Belfast

Britta Stordal
Senior Lecturer in medical sciences, Middlesex University London

NICE project team

Each diagnostics evaluation is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.

Jacob Grant
Topic lead

Judith Shore
Technical adviser (until August 2023)

Frances Nixon
Technical adviser (from September 2023)

Toni Gasse
Project manager (until May 2023)

Donna Barnes
Project manager

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