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Tumour profiling tests to guide adjuvant chemotherapy decisions in lymph node-positive early breast cancer: a systematic review and economic evaluation

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Scientific summary

Tumour profiling tests to guide adjuvant chemotherapy decisions in lymph node-positive early breast cancer: a systematic review and economic evaluation

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Scientific summary

Background

Breast cancer is the most commonly diagnosed cancer in women and the fourth most common cause of cancer-related death in the UK. Most people with lymph node-positive (LN+) breast cancer receive adjuvant chemotherapy due to their increased risk of recurrence. However, chemotherapy is associated with considerable adverse effects. Currently, adjuvant chemotherapy decisions may be informed by clinical and pathological information, sometimes via a risk prediction tool. Improved information on a patient's risk of recurrence (i.e. their prognostic risk) and/or their likely response to chemotherapy (i.e. predictive benefit) may help clinicians to target chemotherapy to patients who will benefit most. Tumour profiling tests aim to improve decisions on chemotherapy use by improving the categorisation of patients according to risk and the identification of patients who will benefit most from chemotherapy.

In 2018, the National Institute for Health and Care Excellence (NICE) published Diagnostics Guidance (DG) No. 34. DG34 recommends the use of Oncotype DX, Prosigna and EndoPredict (EPclin) for guiding chemotherapy decisions in people with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2) negative, lymph node-negative (LN0) early breast cancer, including those with micrometastases. Two other tests assessed in DG34 (MammaPrint and immunohistochemical 4 (IHC4)) were not recommended in the LN0 population. While DG34 also assessed these tests in women with LN+ early breast cancer, the Appraisal Committee did not make any specific recommendations on the use of any test within LN+ patients. This assessment provides an updated systematic literature review and economic analysis of four tumour profiling tests (Oncotype DX, Prosigna, EPclin and MammaPrint) compared to current decision-making in women with ER-positive [and/or progesterone receptor (PR)-positive], HER2-negative, early breast cancer with one to three positive lymph nodes.

Objectives

The main research question is: '*Do tumour profiling tests used for guiding adjuvant chemotherapy decisions in patients with ER-positive (and/or PR-positive), HER2-negative, early-stage breast cancer with 1 to 3 positive lymph nodes represent a clinically effective and cost-effective use of NHS resources?*'

The objectives are:

- To conduct a systematic review of effectiveness and cost-effectiveness of four tumour profiling tests (Oncotype DX, Prosigna, EPclin and MammaPrint).
- To develop a health economic model to assess the cost-effectiveness of tumour profiling tests compared with current decision-making (no testing) on the use of chemotherapy from the perspective of the NHS and Personal Social Services (PSS).

Methods

Clinical evidence review methods

The External Assessment Group (EAG) undertook a systematic review of Oncotype DX, Prosigna, EPclin and MammaPrint for guiding adjuvant chemotherapy decisions in women with ER+/PR+, HER2− early breast cancer where the study population was at least 80% LN+. Studies were identified from the previous review which informed NICE DG34 (searches conducted in 2017) plus an updated search (April 2023) covering MEDLINE, EMBASE, Cochrane, and other sources. Eligible data types included prospective randomised controlled trials (RCTs) and studies of prognostic ability, prediction of relative chemotherapy benefit, impact of tests on chemotherapy decisions (restricted to UK and European studies), and health-related quality of life (HRQoL) and anxiety associated with testing.

Cost-effectiveness methods

The EAG undertook a systematic review of existing economic analyses of Oncotype DX, Prosigna, EPclin and MammaPrint for guiding adjuvant chemotherapy decisions in women with ER+, HER2−, LN+ early breast cancer. Studies included published analyses which were identified within the previous systematic review undertaken to inform NICE DG34 and economic analyses in LN+ populations published since 2017. The EAG also critically appraised economic analyses of Oncotype DX and MammaPrint submitted to NICE by the test manufacturers.

The EAG also developed a de novo health economic model to assess the cost-effectiveness of Oncotype DX, MammaPrint, Prosigna, and EndoPredict (EPclin), each compared against current decision-making. The economic analysis was undertaken from the perspective of the NHS and PSS and was largely based on the model developed to inform NICE DG34, with updates to reflect changes in the breast cancer treatment pathway and updated evidence on the tests identified from the clinical effectiveness review. The EAG model adopts a hybrid decision tree/Markov structure. Model parameter values were informed by the RxPONDER, TransATAC, SWOG-8814 and MINDACT trials, a recent UK decision impact study undertaken in women with LN+ early breast cancer, previous economic models, routine costing sources and other literature. All results presented in this report reflect the list prices of the tumour profiling tests; additional analyses including price discounts for the tests and downstream treatments were provided in a separate confidential appendix to NICE.

Results

Clinical evidence results

Overview of available evidence

In total, 55 articles were included, 42 relating to prognostic and predictive ability, and 13 relating to impact on chemotherapy decisions. Data were reported for two prospective RCTs (RxPONDER and MINDACT). In RxPONDER, LN+ patients with an Oncotype DX Breast Recurrence Score (RS) of 0–25 were randomised to chemotherapy versus no chemotherapy. In MINDACT, patients with discordant MammaPrint risk and clinical risk were randomised to chemotherapy versus no chemotherapy. In addition, the ongoing OPTIMA RCT compares Prosigna test-directed chemotherapy use versus standard chemotherapy use; however, results are not yet available.

Prognostic ability

All four tests demonstrated prognostic ability for determining risk of relapse in LN+ populations, both with and without adjustment for clinical factors.

Prediction of chemotherapy benefit

No predictive data in a LN+ population were identified for Prosigna or EPclin. For Oncotype DX, a reanalysis of the SWOG-8814 RCT using cut-offs of RS < 18 and > 30 indicated no effect of chemotherapy on 10-year disease-free survival in the low-risk group, a non-significant effect in the intermediate-risk group, and a borderline statistically significant effect in the high-risk group, with statistically significant interaction tests in some but not all analyses. The RxPONDER prospective RCT reported no benefit of chemotherapy in post-menopausal patients with an RS of 0–25, but a statistically significant benefit in pre-menopausal patients with an RS of 0–25, while the test for interaction between RS (within the range 0–25) and effect of chemotherapy was not statistically significant in either group. The National Cancer Database reported 5-year overall survival within post-menopausal or older-age subgroups with RS ≤ 25; some analyses showed a statistically significant chemotherapy benefit while others did not. For MammaPrint, prediction of chemotherapy benefit could not be determined from the LN+ subgroup of the MINDACT prospective RCT, because all patients in the clinical high-risk, MammaPrint high-risk group, were offered chemotherapy (there was a non-significant effect of chemotherapy in the LN+ MammaPrint low-risk group). A cohort reanalysis from 2009 reported a non-significant interaction test between MammaPrint score and effect of chemotherapy on breast cancer-specific survival (p = 0.95).

Decision impact

Studies on chemotherapy decisions in LN+ populations in the UK and Europe indicated a net reduction in the percentage of patients recommended chemotherapy pre-test to post-test of between 12% and 75%, with greater reductions in groups with lower RS. All studies used Oncotype DX; no decision impact studies were identified for EPclin, Prosigna or MammaPrint.

Health-related quality of life and anxiety

No studies reported HRQoL or anxiety associated with using tumour profiling tests in a LN+ population. Therefore, studies in a LN0 or mixed nodal status population were briefly summarised, with mixed results regarding the impact of testing and anxiety.

Cost-effectiveness results

The results of the EAG's probabilistic base-case analyses are summarised below.

Oncotype DX

Within the pre-menopausal LN+ population, Oncotype DX is dominated by current decision-making. These results are driven by the estimated reduction in the use of adjuvant chemotherapy due to the test in women who would have benefitted from treatment.

Within the post-menopausal LN+ subgroup, Oncotype DX dominates current decision-making, provided the assumption of predictive benefit holds. These results are driven by an estimated large reduction in the use of adjuvant chemotherapy in women who would not have benefitted from treatment. As was the case with the economic analyses in the LN+ subgroup undertaken to inform DG34, removing this assumption of predictive benefit results in a situation whereby Oncotype DX is dominated by current decision-making, driven by a large reduction in the use of adjuvant chemotherapy in women who would have benefitted from treatment and an increase in the lifetime probability of developing distant metastases (DM). This assumption of predictive benefit remains subject to some uncertainty, and it strongly influences the conclusions of the economic analysis in the post-menopausal LN+ subgroup.

Prosigna

The incremental cost-effectiveness ratio (ICER) for Prosigna versus current decision-making is expected to be £39,357 per quality-adjusted life-year (QALY) gained. The model suggests that the use of Prosigna will result in a small decrease in the use of chemotherapy, a small reduction in the lifetime probability of developing DM and additional net costs due to the cost of the test. The EAG's systematic review did not identify any evidence to support a predictive benefit for Prosigna in the LN+ population.

EndoPredict (EPclin)

The ICER for EPclin versus current decision-making is expected to be £4113 per QALY gained. The model suggests that the use of EPclin will result in a small decrease in adjuvant chemotherapy use, a small reduction in the lifetime probability of developing DM and additional net costs due to the cost of the test. The EAG's systematic review did not identify any evidence to support a predictive benefit for EPclin in the LN+ population.

MammaPrint

MammaPrint is dominated by current decision-making. These results are driven by a large reduction in the use of adjuvant chemotherapy in women who would have benefitted from treatment, an increase in the lifetime probability of developing DM and additional net costs due to the cost of the test. The EAG's systematic review did not identify sufficient evidence to support a predictive benefit for MammaPrint in the LN+ population.

Discussion

Strengths and limitations in the clinical evidence base

Strengths of the clinical evidence base include the fairly substantial evidence for prognostic ability of all four tests. A major limitation is the difficulty in collecting new data on predictive ability, as it is not considered ethical to randomise

patients who are high risk on any test to chemotherapy versus no chemotherapy. Therefore, although there are prospective RCTs for the effect of chemotherapy in low-risk to intermediate-risk patients, data for high-risk patients are limited to retrospective reanalyses of trials, plus observational data in which test results may have influenced treatment. Decision impact data in a LN+ population were only available for Oncotype DX. Anxiety and HRQoL data associated with testing were not identified in a LN+ population.

Strengths and limitations relating to the health economic analysis

The EAG's model has several strengths: the economic analysis is consistent with the NICE Reference Case and relates specifically to the LN+ population under consideration within this appraisal; the model structure is generally consistent with most published economic models of tumour profiling tests as well as the two economic models submitted by the test manufacturers; for each individual test, risk classification probabilities and distant recurrence-free interval estimates have been taken from same source where data permit, which avoids potential spectrum bias; the analysis uses a recent relevant UK decision impact study undertaken in LN+ women; and a broad assessment of uncertainty around all key model inputs has been presented, including testing assumptions around whether Oncotype DX is predictive of chemotherapy benefit.

The EAG's economic analyses are subject to several weaknesses: the economic analyses of Oncotype DX based on RxPONDER indirectly assume a predictive benefit which reflects a plausible clinical assumption about the effect of chemotherapy in women who were excluded from the trial (external data from SWOG-8814 are used to inform the benefit of chemotherapy in women with an RS of > 25), rather than a statistical test of interaction across the full RS spectrum; there are inconsistencies in Oncotype DX RS cut-offs between sources used in the model; the analyses rely on a decision impact study of Oncotype DX to estimate post-test probabilities for all 2- and 3-level tests, which is highly uncertain; and there is insufficient evidence to allow for the economic analyses of EPclin and MammaPrint in an exclusively pre-menopausal subgroup. There is uncertainty around the potential negative effects of chemotherapy on infertility which may not be fully captured in the analysis of Oncotype DX in the pre-menopausal LN+ subgroup. The EAG's analyses of net health benefit provide a means for considering whether any missing health effects are likely to impact on the conclusions drawn from the economic analysis.

Implications for service provision

Oncotype DX, Prosigna and EPclin are already recommended for use in the NHS for women with ER+ (and/or PR+), HER2−, LN0 early breast cancer. Depending on the specific test and population under consideration, tumour profiling may result in fewer women receiving adjuvant chemotherapy (reducing costs and increasing capacity), but this may lead to more women requiring further treatment for DM (increasing costs and reducing capacity).

MammaPrint is not currently recommended for use in the NHS. MammaPrint testing can be undertaken either as an off-site service with samples sent to a laboratory in the USA or through a decentralised testing service for laboratories with next-generation sequencing (NGS) capability. The per-sample pricing of MammaPrint remains the same regardless of testing location. Not all laboratories will have NGS capabilities which has implications for how MammaPrint testing is organised and delivered. For the other tests, only one sample processing approach is available – for Oncotype DX, samples are processed centrally at the Exact Sciences laboratory in the USA, whereas for Prosigna and EPclin, samples are processed in local laboratories.

Suggested research priorities

Research priorities include the following:

- Further studies assessing the ability of all four tests to predict long-term relative chemotherapy benefit in LN+ populations would help to address uncertainty. This may require observational or registry data to assess outcomes across the full range of test scores. In addition, the OPTIMA trial is ongoing, comparing Prosigna test-directed chemotherapy use versus standard chemotherapy use.

- Longer-term studies to further quantify the negative impact of adjuvant chemotherapy using a preference-based instrument would be valuable, to estimate both short-term toxicity and longer-term negative effects, including impacts on fertility in pre-menopausal women.
- Further UK and European studies assessing the impact of tumour profiling tests on recommendations for adjuvant chemotherapy in LN+ populations may reduce uncertainty around clinical impact and cost-effectiveness.
- The integration of tumour profiling tests with decision aid tools to support shared decision-making may constitute a useful research direction.
- The role of tumour profiling tests in older adults, who may be more prone to chemotherapy complications in the context of limited life expectancy, is also a research priority, as is research on test performance in males and in ethnically diverse populations.

Study registration

This study is registered as PROSPERO CRD42023425638.

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