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Tumour profiling tests to guide adjuvant chemotherapy decisions in lymph node-positive early breast cancer - Protocol

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1. Name of External Assessment Group (EAG) and project lead

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2. Plain English Summary

Breast cancer is the most commonly diagnosed cancer and the fourth most common cause of cancer related deaths in the UK. During the period 2016-2018, an average of 46,479 women and 319 men were diagnosed with breast cancer in England each year.[1] During the period 2017-2019, an average of 9,509 women and 69 men died from breast cancer in England each year.[2] Treatment usually involves surgery to remove the tumour and any involved lymph nodes. This may be followed by one or more of the following treatments: radiotherapy, endocrine (hormone) therapy, biological therapy and/or chemotherapy.

There are various prognostic tools that help patients and clinicians make treatment decisions by predicting the risk of the disease coming back (recurring) after surgery. These include the Nottingham Prognostic Index (NPI) and PREDICT. PREDICT is recommended in NICE Guideline 101.[3] These tools predict the risk of recurrence, based on pathological information (e.g., tumour size, grade and lymph node status for NPI), plus other factors including oestrogen receptor (ER) status and age for PREDICT. However, it has been suggested that these clinical tools do not predict recurrence and response to treatment particularly well for some patients. This presents a challenge to clinicians in making decisions on whether or not to recommend the use of adjuvant chemotherapy (chemotherapy after surgery) in people with early-stage breast cancer (Stages I, II (A or B) and IIIA[4]).

Tumour profiling, using either gene expression profiling or protein expression profiling (with immunohistochemistry), seeks to identify genes or proteins that may be helpful in assessing disease prognosis and guiding therapy. Improved information on a patient's risk of recurrence (i.e., prognostic risk) and/or likely response to chemotherapy (i.e., predictive benefit) may help target chemotherapy at those patients who will benefit the most. Avoiding chemotherapy in patients at low risk of recurrence, and who would therefore obtain limited benefit, avoids the unpleasant side effects of chemotherapy and reduces expenditure on both the chemotherapy itself and the treatment of these side effects. It is therefore important to understand the benefits offered by these tumour profiling tests compared with existing prognostic tools and whether they represent a good use of National Health Service (NHS) resources.

A previous systematic review and economic evaluation (Harnan *et al.*, 2019[5]) assessed the clinical effectiveness and cost-effectiveness of tumour profiling tests compared with current prognostic tools in guiding the use of adjuvant chemotherapy in women with early breast cancer in England. This report informed recommendations from the National Institute for Health and Care Excellence (NICE) for the use of EndoPredict (EPclin score), Oncotype DX and Prosigna as options for guiding adjuvant chemotherapy decisions for people with ER-positive, human

epidermal growth factor receptor 2 (HER2) negative, lymph node negative (LN-) early breast cancer assessed to be at intermediate risk of recurrence of breast cancer after surgery (Diagnostic Guidance [DG] 34).[6] Two tests - MammaPrint and IHC4 - were not recommended. DG34 did not make any specific recommendations on the use of any of these tumour profiling tests in people with lymph node-positive (LN+) early breast cancer.

This review aims to update the previous report by systematically evaluating the most recent evidence on the use of four of these tumour profiling tests (Oncotype DX, EPclin, Prosigna and MammaPrint) to guide adjuvant chemotherapy treatment decisions in women with ER-positive, HER2-negative, LN+ early breast cancer, including an updated economic evaluation to determine whether these tests represent good value for money for the NHS.

3. Decision problem

3.1 *Purpose of the decision to be made*

The main research question to be addressed 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?"*

This project will update the systematic review and cost-effectiveness analysis[5] that informed considerations for the LN-positive subgroup within NICE DG34.[6]

3.2 *Clear definition of the intervention*

Four tests have been identified by NICE and will be included in this assessment. The use of these interventions should be considered in combination with current clinical decision-making on the use of adjuvant chemotherapy. The four tests included in the assessment are summarised in Table 1.

EndoPredict (Myriad Genetics)

EndoPredict is a Conformité Européene (CE) marked assay that is designed to predict the likelihood of distant recurrence within 10 years of an initial diagnosis of breast cancer. The company claims that EndoPredict can also predict the absolute benefit of chemotherapy. The test is intended for use in pre- and post-menopausal people with early-stage breast cancer with all of the following clinical features:

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

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

EndoPredict requires ribonucleic acid (RNA) samples extracted from formalin-fixed, paraffin-embedded (FFPE) breast cancer tissue. The test can be performed in a local laboratory. It takes approximately 3 to 5 days to receive the test results after the sample has arrived at the laboratory.

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

MammaPrint (Agendia)

MammaPrint is a CE marked microarray that is designed to assess the risk of distant recurrence within 10 years. The company claims that the test also predicts whether a person would benefit from chemotherapy. The test is intended for use in pre- and post-menopausal women with stage I, II or operable stage III breast cancer with the following clinical features:

- HR-positive
- HER2-negative
- Tumour size up to 5cm
- LN-negative or LN-positive (up to 3 positive nodes).

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

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 (NGS) capability. The test requires an FFPE breast cancer tissue sample. 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.

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. A score of more than 0.355 can also be used to indicate ultra-low risk, which the company defines as more than 99% breast cancer-specific survival (BCSS) at 8 years and 97% BCSS at 20 years with 2 to 5 years of tamoxifen treatment.

Oncotype DX Breast Recurrence Score (Exact Sciences)

Oncotype DX Breast Recurrence Score (Oncotype DX) is a CE marked assay designed to quantify the 9-year risk of distant recurrence. The company claims that the test can also predict the likelihood of chemotherapy benefit. The test also reports the underlying tumour biology: ER, progesterone receptor (PR) and HER2 status. The test is intended for use in people with early breast cancer that has the following clinical features:

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

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

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

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

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

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 designed for use in post-menopausal women with early-stage breast cancer that is:

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

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

Prosigna classifies the risk of distant recurrence within 10 years, assuming 5 years of endocrine therapy, based on the Prediction Analysis of Microarray 50 (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 disease (up to 3 positive nodes), a score of 0 to 15 indicates low risk, 16 to 40 indicates intermediate risk, and 41 to 100 indicates 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 current practice.

Table 1: Summary of tumour profiling tests

Test	EndoPredict EPclin score	MammaPrint	Oncotype DX Breast Recurrence Score	Prosigna
Manufacturer	Myriad	Agendia	Exact Sciences	Veracyte
Purpose	Distant recurrence risk and chemotherapy benefit	Distant recurrence risk and chemotherapy benefit	Recurrence risk and chemotherapy benefit	Intrinsic subtype and recurrence risk
Description	12 gene assay (8 cancer genes; RT-qPCR) + clinical factors	70 gene assay (microarray)	21 gene assay (16 cancer genes; RT-qPCR)	50 gene assay (50 cancer genes; direct mRNA counting) + clinical factors
Testing location	Local laboratory	Local laboratory (NGS) or test service (USA)	Test service (USA)	Local laboratory
Stage	Early-stage	Early-stage (Stage I, II or operable Stage III)	Early-stage (Stage I to IIIa)	Early-stage (Stage I to IIIA)
Lymph node status	LN- and LN+ (up to 3 positive nodes)	LN- or LN+ (up to 3 positive nodes)	LN- or LN+ (up to 3 positive nodes)	LN- and LN+ (up to 3 positive nodes, and 4+ nodes)
Hormone receptor status	ER+	HR+	HR+	HR+
HER2 status	HER2-	HER2-	HER2-	HER2- or HER2+
Menopausal status	Pre- and post-menopausal	Pre- and post-menopausal	Pre- and post-menopausal	Post-menopausal only
Test result	Risk category (low, high) Chemotherapy benefit (%) Probability of distant recurrence (%)	Risk category (low, ultra-low, high) Chemotherapy benefit	Recurrence score Chemotherapy benefit Probability of distant recurrence (%)	Risk category (low, intermediate, high) Intrinsic subtype Probability of distant recurrence (%)
Assumptions	Scores assume 5 years of hormonal treatment	Assumes no adjuvant therapy	Score assumes 5 years of endocrine treatment	Score assumes 5 years of endocrine treatment

ER - oestrogen receptor; HER2 - human epidermal growth factor; HR - hormone receptor; LN - lymph node; RT-qPCR - reverse transcription-quantitative polymerase chain reaction; NGS - next generation sequencing; USA - United States of America

3.3 *Populations and relevant subgroups*

The population of interest for this assessment relates to people with ER-positive (and/or PR-positive), HER2-negative, early-stage breast cancer with 1 to 3 positive lymph nodes who are deciding whether to have adjuvant chemotherapy.

The focus of this assessment is patients with Stage I-IIIA disease[4] (See Appendix 9.1 for definitions).

Subgroups

Where evidence allows, the following subgroups may be considered:

- Pre-menopausal women and post-menopausal women
- People predicted to be in low-, intermediate- or high-risk groups using a risk assessment tool (such as PREDICT or NPI), or using clinical and pathological features
- Sex
- People of different ethnicities
- People with comorbidities which mean that they could be particularly affected by the side effects of chemotherapy.

3.4 *Place of the intervention in the treatment pathway*

Tests will be used in the secondary or tertiary care setting to make decisions about adjuvant chemotherapy. Tests predicting the risk of recurrence in a specific population are likely to be used after surgery, in conjunction with other information available about tumour size, grade etc., to guide the use of adjuvant chemotherapy. Use of these tests in the neoadjuvant therapy setting (where chemotherapy would be given as a first step to shrink the tumour before surgery) will not be evaluated within this assessment.

3.5 *Relevant comparators*

The comparator for this appraisal is current decision-making, which may include any tool, or clinical and pathological features, used to assess risk. Clinicopathological tools used in current practice include PREDICT and the NPI.

3.6 *Outcomes*

Relevant outcomes include the following:

Intermediate measures:

- Prognostic ability
- Ability to predict relative benefit from chemotherapy
- Impact of test results on decision-making.

Clinical outcomes:

- Disease-free survival
- Overall survival
- Distant recurrence/distant recurrence-free interval
- Disease-related morbidity and mortality
- Chemotherapy-related morbidity and mortality.

Patient-reported outcomes:

- Health-related quality of life (HRQoL)
- Anxiety.

Costs will be considered from an NHS and Personal Social Services (PSS) perspective. The cost-effectiveness of interventions will be expressed in terms of incremental cost per quality-adjusted life year (QALY) gained. Costs for consideration will include:

- Costs of treating breast cancer, including: drug costs, administration costs, outpatient appointments, supportive care costs and costs associated with treating adverse events
- Costs of the tests, including equipment costs and reagents where applicable
- Costs of staff and associated training, where applicable.

3.7 *Issues for consideration*

Many of the issues encountered during the review undertaken to inform DG34[6] are also likely to apply in this assessment. These are summarised below.

There may be few studies directly comparing the tests head-to-head, or to some comparators, e.g., PREDICT.

The use of clinical and pathological factors alongside the tests will need to be considered in terms of how they are used to target patients to receive tests. The most challenging decisions

are for the patients who are categorised at intermediate-risk by existing prognostic tools, where the decision to undergo chemotherapy or not is most uncertain and additional information would be most beneficial. Existing prognostic tools e.g., NPI or PREDICT may be used to identify subgroups of patients. For instance, NPI identifies a group of patients at intermediate risk, with a NPI score >3.4 and ≤5.4. Similarly, PREDICT calculates the absolute 10-year survival benefit from chemotherapy. The Cambridge Breast Unit (UK) uses this to guide decision-making for adjuvant chemotherapy: benefit of <3% no chemotherapy; benefit of 3-5% chemotherapy discussed as a possible option; benefit >5% chemotherapy recommended. Clinical advice will be sought to identify the most commonly used tool(s) and clarify how these are used to identify subgroups of patients with LN-positive disease.

Clinical and pathological factors are also used alongside the results provided by the tumour profiling tests to guide therapy (either incorporated formally within the test or informally in addition to the test results). This will also be considered, where evidence allows.

The impact of changes in clinical practice around the treatment of early breast cancer e.g., the use of bisphosphonates, the use of extended endocrine therapy (up to 10 years), and the use of abemaciclib after adjuvant chemotherapy, will impact on the baseline risk of recurrence for these patients, but is unlikely to be reflected in the historic evidence base.

The proportion of patients with early breast cancer receiving chemotherapy varies widely between countries; this is likely to impact on the outcome relating to changes in chemotherapy use when using the tests. UK-specific data will therefore be the most relevant in this instance.

3.8 *Areas that are outside the scope of the evaluation and therefore do not require any detailed assessment (e.g., key factors for which evidence is already accepted).*

Areas which will be excluded from this appraisal:

- Patients with micrometastatic disease
- Patients with lymph node-negative disease, or patients with lymph node-positive disease and 4 or more involved nodes
- Patients with HER2-positive disease
- Patients with Stage IIIB/C or IV breast cancer
- The use of chemotherapy in the neoadjuvant setting
- The impact on use or benefit of endocrine therapy or biological therapy.

4. Report methods for assessing the outcomes arising from the use of the interventions

4.1 *Overview of systematic review methodology*

A systematic review of clinical evidence will be undertaken. The review will follow the general principles recommended in CRD's guidance,[7] the PRISMA statement,[8] the NICE Methods Manual[9] and the Cochrane Prognosis Methods Group.[10]

This systematic review will update the previous systematic review (Harnan *et al.*, 2019[5]) conducted for DG34.[6] The previous review covered Oncotype DX, MammaPrint, EndoPredict and Prosigna (plus the IHC4 test which will not be included in the present review). The searches for the previous review were conducted in February 2017. Studies published prior to 2017 will be identified and extracted from the existing review, whilst studies published from 2017 onwards will be identified via an updated search.

Inclusion criteria

4.2 *Population and subgroups*

The relevant population is people with ER-positive (and/or PR-positive), HER2-negative, early stage breast cancer (Stage I, II or IIIA) with 1 to 3 positive lymph nodes.

Studies that recruit a wider population will be included where data are reported for the relevant subgroup separately. Where studies include patients who are non-early stage or who are otherwise out of scope, and no subgroup data are available, the following rule will be applied: if the percentage of patients out of scope is ≤20% then the study will be included (and its contribution to outcome heterogeneity considered), whilst if >20% are out of scope the study will be excluded.

Where evidence allows, the following subgroups may be considered:

- Pre-menopausal women and post-menopausal women
- People predicted to be in low, intermediate or high risk groups using a risk assessment tool (such as PREDICT or NPI), or using clinical and pathological features
- Sex
- People of different ethnicities
- People with comorbidities which mean that they could be particularly affected by the side effects of chemotherapy.

4.3 *Interventions*

The following interventions identified in the NICE scope[6] will be included:

- EndoPredict EPclin score

- MammaPrint
- Oncotype DX Breast Recurrence Score
- Prosigna.

Two of the tests included in the scope (EndoPredict EPclin score and Prosigna) incorporate clinical and pathological features into the test results. However, evidence may be available on test results or versions of the tests which do not formally incorporate clinical and pathological features. The other two tests (MammaPrint and Oncotype DX Breast Recurrence Score) do not formally include clinical and pathological features. However, evidence may exist in which additional algorithms have been used to formally incorporate clinical and pathological features. Where such studies are identified, these will be included in the review, but will be grouped, synthesised and interpreted separately.

Studies using the interventions alone or in conjunction with current decision-making will be included. Current decision-making may include any tool, or clinical and pathological features, used to assess risk. Current clinicopathological tools used in England include PREDICT and NPI. Studies evaluating tests in conjunction with clinicopathological tools which are no longer used in current practice in England, such as Adjuvant! Online, will be considered for inclusion in the review if the data are otherwise relevant.

4.4 *Comparators*

The relevant comparator for the assessment is current decision-making. This may include any tool, or clinical and pathological features, used to assess risk. Clinicopathological tools used in current practice in England include PREDICT and NPI. Studies which include comparators of clinicopathological tools which are no longer used in current practice in England, such as Adjuvant! Online, will be considered for inclusion in the review if the data are otherwise relevant.

End-to-end studies comparing decision-making based on the test versus decision-making using current tools may not be available, in which case different evidence types will be sought and will be linked via the health economic model (see Section 4.6 on study designs).

4.5 *Outcomes*

This section summarises the key outcomes for the assessment as a whole. Some of these will be identified directly from the clinical evidence review, and some from the health economic model, which will link different data types. The subsequent section describing study design

provides more detail on the types of evidence and key study designs which will be sought in the clinical evidence review.

Intermediate measures (these will be sought from the clinical evidence review):

- Prognostic ability
- Ability to predict benefit from chemotherapy
- Impact of test results on decision-making.

Clinical outcomes (these will be estimated using the health economic model; in addition, recurrence and survival will form part of the clinical data on prognostic and predictive ability):

- Disease-free survival
- Overall survival
- Distant recurrence/distant recurrence-free interval
- Disease-related morbidity and mortality
- Chemotherapy-related morbidity and mortality.

Patient-reported outcomes (these will be sought from the clinical evidence review, whilst HRQoL evidence will be incorporated into the health economic model):

- HRQoL
- Anxiety.

4.6 *Types of clinical evidence required and study designs*

This section summarises the types of evidence which will be sought from the clinical evidence review and the main study designs for each. These will be linked in the health economic model in order to inform the clinical effectiveness and cost-effectiveness of the tumour profiling tests versus current decision-making in England.

Types of evidence to be sought within the clinical review:

- End-to-end studies comparing the tests versus current decision-making (if available)
- Prognostic benefit of each test
- Predictive effect of each test for relative benefit of chemotherapy
- Impact of tumour profiling tests on the use of chemotherapy (decision impact)
- HRQoL and anxiety associated with use of the tests.

The following outcomes will not be included in the review:

- Analytical validity of the tests.

The subsequent sections outline each evidence type in more detail and describe the main study designs for each.

End-to-end studies comparing the use of tests versus current decision-making

This type of study would assign patients to decision-making based on the test versus decision-making using current tools. It is unlikely that any/many studies of this design exist. However, there are randomised controlled trials (RCTs) which randomise patients within a particular test risk group/range to either chemotherapy or no chemotherapy; these are described within the sections on prognostic and predictive benefit.

Prognostic benefit of each test

This evidence provides:

- Risk classification probabilities i.e., the proportion of patients allocated to each risk group
- Probability of distant metastases (or survival) per risk group
- Hazard ratios (HRs) for the difference in outcomes between risk groups (both unadjusted and after adjustment for clinical and pathological factors).

The main study designs for this evidence are:

- RCTs which randomise patients within a particular test risk group (or range) to chemotherapy versus no chemotherapy. These studies can provide prognostic data for patients within that risk group/range, but not for patients outside of this range.
- Re-analyses of single arms of older clinical trials with long-term follow-up, where the tests are used on stored tumour samples, and recurrence/survival outcomes are calculated per risk group. When selecting evidence for use in the model, priority may be given to studies which assess more than one of the four tests in a single study, as this will provide a greater degree of consistency of data across the tests.
- Observational studies of the use of the test in practice and recurrence/survival data by test risk group. These studies often provide outcome data only for patients in low-risk groups, or for different risk groups in which patients were treated differently (e.g., more patients received chemotherapy in higher risk groups), which limits their use in assessing the effect of risk group on outcomes. These data will be included initially, but if the volume of data is large then priority will be given to higher quality data (e.g., larger studies, more applicable to practice in England, longer follow-up, data on multiple risk groups).
- The following study type will be excluded: “microarray” or “in silico” studies which do not use the commercial versions of the four tests, but which instead use algorithms

for the genes within a test, and apply these to electronic (in silico) databases of genetic profiles generated from microarray techniques.

Predictive effect of each test for relative benefit of chemotherapy

This evidence provides:

- Data on whether the relative benefit of chemotherapy (i.e., the HR for chemotherapy versus no chemotherapy for recurrence/survival) differs by test risk group.

The main study designs for this evidence are:

- RCTs which randomise patients within a particular test risk group (or range) to chemotherapy versus no chemotherapy. These studies can provide HRs for chemotherapy versus no chemotherapy for patients within that risk group/range, but not for patients outside of this range.
- Re-analyses of older clinical trials of chemotherapy versus no chemotherapy, with long follow-up, where the tests are used on stored tumour samples, and HRs for chemotherapy versus no chemotherapy for recurrence/survival outcomes can be calculated per test risk group. It is likely that there are a limited number of such studies.
- Observational studies of use of the test in practice and recurrence/survival data by test risk group. These studies sometimes provide HRs for chemotherapy versus no chemotherapy, but are subject to limitations as described above; priority will be given to higher quality data (see section on prognostic benefit).

Impact of tumour profiling tests on the use of chemotherapy (decision impact)

This evidence provides either or both:

- Post-test probability of patients receiving chemotherapy dependent on their tumour profiling test risk group (e.g., low, intermediate, high) or test score.
- Pre-test probability of patients receiving chemotherapy under current decision-making.

The main study designs for this evidence are:

- Decision impact studies which assess the chemotherapy decisions/recommendations for patients in different test risk groups, and/or changes to decisions following the test. Priority will be given to studies in LN-positive patients and studies conducted in the UK (or Europe).

HRQoL and anxiety associated with use of the tests

- Studies reporting HRQoL or anxiety associated with use of tumour profiling tests will be summarised as part of the clinical evidence review.

Date and language limits

As noted in Section 3.1, the systematic review will update a previous systematic review (Harnan *et al.*, 2019[5]) conducted to inform NICE DG34.[6] Relevant studies from all dates will be included. Studies published prior to 2017 will be identified and extracted from the existing review, whilst studies published from 2017 onwards will be identified via an update search.

Studies not published in the English language will be included if sufficient PICOS data can be extracted from non-English language full-texts, or from an existing English language abstract. Studies excluded on the basis of language will be listed separately. Non-peer-reviewed reports or abstracts will only be included if the data are presented in a succinct and accessible manner (e.g., a manuscript prepared for submission to a journal), if sufficient methodological details are reported to allow critical appraisal of the study quality, and if results are reported in sufficient detail.

4.7 *Search strategy*

The search strategy for the systematic review will comprise the following main elements:

- Searching of electronic databases, registers and websites
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers and existing systematic reviews.

The databases, trial registers and websites that will be searched include the following:

- MEDLINE and MEDLINE in Process (via Ovid)
- EMBASE (via Ovid)
- Cochrane Database of Systematic Reviews (via Wiley)
- Cochrane Central Register of Controlled Trials (via Wiley)
- HTA Database of the International Network of Agencies for Health Technology Assessment (INAHTA) Web of Science Citation Index Expanded (via Clarivate Analytics)
- Web of Science Conference Proceedings Citation Index (via Clarivate Analytics)
- WHO International Clinical Trials Registry Platform
- Clinicaltrials.gov
- American Society of Clinical Oncology (ASCO)
- European Society for Medical Oncology (ESMO)
- American Association for Cancer Research (AACR)
- European Cancer Organization (ECCO) Congress.

Search terms will include both product names and any alternative names for each of the intervention tests, combined with search terms for breast cancer. Manufacturer website publication lists will also be searched for potentially relevant studies. A draft MEDLINE search strategy is included in Appendix 9.2.

The clinical and cost-effectiveness searches will be limited by date from February 2017 to present. This is the date when searches used in the review to inform DG34[5] were last conducted.

Reference lists of included papers, as well as existing systematic reviews, will be assessed for additional relevant studies. Where necessary and where time allows, authors of eligible studies will be contacted for further information. All searches will be limited to human studies. No limits relating to study design will be applied.

4.8 *Study selection and data extraction strategy*

Study selection

The title and abstract of each record retrieved by the search strategy will be assessed against the inclusion criteria for the review, and irrelevant records will be excluded. The full text of remaining records will be obtained and assessed against the inclusion criteria. Study selection will be conducted by one reviewer. Any studies which give rise to uncertainty will be reviewed by a second reviewer with involvement of a third reviewer when necessary. A 10% sample of the records retrieved by electronic searches will be checked by a second reviewer early in the process to ensure consistency, and any discrepancies will be discussed in order to check adherence to the inclusion criteria.

Data extraction

A data extraction form will be constructed in Microsoft Excel. It may be necessary to use different forms for different study designs. The existing data extraction forms and tables from the earlier review[5] will be used as a template.

Data will be extracted by one reviewer, and checked by a second reviewer. Any disagreements will be resolved through discussion and consultation with a third reviewer where necessary. If time allows, attempts will be made to contact authors for any missing data that are essential to the review. Data from multiple publications of the same study will be extracted as a single study.

As this is an update of a previous systematic review (Harnan *et al.*, 2019[5]) conducted for DG34,[6] studies published prior to 2017 will be identified and extracted from the existing review.

4.9 *Quality assessment strategy*

Studies will be assessed using quality assessment tools relevant to the study design. Tools may be adapted or abbreviated to the specifics of this review, due to time and resource constraints.

For studies that use an RCT design, quality will be assessed using version 2 of the Cochrane Risk of Bias tool (RoB2).[11] For studies that develop and/or validate the tests as prediction models, quality will be assessed using the Prediction model study Risk Of Bias Assessment Tool (PROBAST).[12] The PROBAST tool has been developed specifically for use in systematic reviews of prediction models by the Cochrane Prognosis Methods Group.[10] Any studies that do not fit into the above categories will be assessed using an alternative published tool relevant to the study design, such as the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool.[13]

Studies will be quality assessed by one reviewer, with scores checked by a second. Any disagreements will be resolved through discussion and consultation with a third reviewer where necessary. The impact of the quality of studies on the evidence base will be evaluated through sensitivity analyses in meta-analysis, or through narrative synthesis of the results.

4.10 *Methods of analysis/synthesis*

Interpretation of the evidence base will be conducted with reference to published hierarchies for predictive studies[14-16] and with regard to the ability of the study design to adequately address the decision problem.

For each intervention, studies will be ordered according to population, comparator, outcomes and study design, as well as according to the pre-specified subgroups where data permits. A narrative synthesis will be conducted, drawing on existing high quality systematic reviews where possible. Any comparisons will acknowledge clinical, methodological and statistical heterogeneity.

4.11 *Methods for estimating quality of life – if possible and relevant for the systematic review in question*

Quality of life estimates reported within the clinical literature, i.e., relating to the use of the tests, will be collated as part of the systematic review. Further quality of life data to inform the cost-effectiveness modelling will be identified as part of Section 5.

5. Report methods for synthesising evidence of cost effectiveness

5.1 *Identifying and systematically reviewing published cost-effectiveness studies*

A systematic review of the existing literature assessing the cost-effectiveness of the four identified tests to guide the use of adjuvant chemotherapy in breast cancer management will be undertaken.

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers.

The databases that will be searched include the following:

- MEDLINE and MEDLINE in Process (for latest publications);
- EMBASE;
- Web of Science Citation Index Expanded;
- Web of Science Conference Proceedings Citation Index.

Where applicable, cost-effectiveness studies will be identified using an economic search filter. In addition, relevant cost papers identified from the clinical effectiveness searches will be included in the economic review.

The cost-effectiveness searches will be limited by date from February 2017. This is the date when searches in the published diagnostic guidance (DG34[6]) were last conducted. References of key studies will be checked. Additional searches, for example to inform the health economic model parameters, where required in the course of the project, will be undertaken through consultation between the ScHARR team. Studies will only be included if they address the decision problem set out in the final NICE scope.[6]

5.2 *Evaluation of costs and cost effectiveness*

Only full economic evaluations published in English addressing the cost-effectiveness of the four tests compared with NPI, PREDICT or any adaptations of these tools in clinical practice, or comparing one test against each other, will be critically appraised using published checklists. Cost-effectiveness studies that compare tests with other guidelines such as St Gallen, the National Comprehensive Cancer Network (NCCN) and NIH guidelines will be excluded from the review because of time and resource constraints as these comparators are not directly relevant to the UK context. Studies comparing tests against Adjuvant! Online, will be considered for inclusion in the review if the analysis is otherwise relevant. Existing cost-

effectiveness analyses may also be used to identify sources of evidence to inform structural assumptions and parameter values for the EAG model.

The quality of identified cost-effectiveness studies will be assessed against a critical appraisal checklist based on checklists reported by Drummond *et al.*[17] and Eddy *et al.*[18] (see Appendix 9.4).

5.3 *Adaptation of an existing health economic model*

Tumour profiling tests aim to improve the use of chemotherapy in breast cancer by stratifying patients and identifying those patients who are at high risk of recurrence and/or those who will gain most benefit from chemotherapy. These tests may report information on breast cancer sub-types and/or risk of recurrence/chemotherapy benefit. The focus will be on the risk of recurrence and chemotherapy benefit. Tests predicting the risk of recurrence in a specific population are likely to be used after surgery, in conjunction with other information available such as tumour size and grade, to guide the use of adjuvant chemotherapy.

The objective of the economic evaluation will be to assess the cost-effectiveness of the tests in the adjuvant chemotherapy setting. The cost-effectiveness of these tests in the neoadjuvant setting will not be evaluated. For all four tests (Oncotype DX, Mammaprint, EPclin and Prosigna), prior economic evaluations exist as part of NICE DG34[6] and these will be reviewed and updated as appropriate. It is anticipated that the structure and parameters of the existing EAG model will be used as a starting point and will be updated to take account of new evidence in the LN-positive population. Updates to the model may include any aspect of its structure and parameters, but are likely to include new/additional evidence relating to:

- The prognostic and predictive benefits of each tumour profiling test included in the NICE scope[6] (including risk classification probabilities, distant recurrence rates and relative treatment effects within and across risk classification groups)
- The probability of receiving chemotherapy in current practice and the impact of tumour profiling tests on the use of chemotherapy (decision impact)
- The level of HRQoL associated with disease states and negative HRQoL impacts resulting from the use of adjuvant chemotherapy
- Changes in the breast cancer treatment pathway since the publication of NICE DG34,[6] including the use of abemaciclib in LN- positive early breast cancer (NICE Technology Appraisal 810[19]) and the mix of adjuvant and palliative treatment regimens used in England, and associated costs.
- Life expectancy in the general population
- HRQoL in the general population.

We anticipate that the most commonly used comparators for predicting the risk of recurrence after surgery to guide the use of chemotherapy in England are PREDICT and NPI. We will seek clinical advice in terms of the most appropriate comparator(s) to be reflected in the economic model and the proportion of patients who receive chemotherapy in current NHS practice.

The economic analysis will be undertaken in line with the NICE Reference Case.[9] The model will estimate the incremental cost per QALY gained for each test versus the comparator over a lifetime horizon from the perspective of the UK NHS and PSS. Secondary outcomes (predicted health benefits, costs and impacts on the use of chemotherapy services) will also be presented. Modelling assumptions will be drawn from the literature, supplemented with clinical expert opinion. HRQoL data identified from the systematic review of clinical evidence or from the identified cost-effectiveness papers and/or any recent systematic reviews of quality of life in breast cancer will be used to inform utility values in the model. Costs will be derived from national sources (e.g. NHS Reference Costs,[20] the British National Formulary [BNF][21] the Commercial Medicines Unit (CMU) electronic Market Information Tool [eMIT][22]), relevant literature and data provided by the manufacturers.

It is anticipated that there will be differences in the level and quality of evidence supporting each of the tests. Combining evidence from different studies, based on different methodologies and with different patient characteristics will limit the conclusions that could be drawn from any comparisons that could be made between the analyses. It may therefore be more appropriate to perform separate analyses for each test using the best direct sources of data available for each test; in this case it would not be appropriate to directly compare these analyses. An incremental analysis will be included, only if appropriate and if evidence allows.

In the base case analysis, tests will be assessed in line with their intended use (see Table 1). EndoPredict EPclin score and Prosigna incorporate clinical and pathological features into the test results. However, evidence may be available on test results or versions of the test which do not formally incorporate clinical and pathological features. MammaPrint and Oncotype DX do not formally include clinical and pathological features. However, evidence may exist in which additional algorithms have been used to formally incorporate clinical and pathological features. Where such studies are identified, the impact of this will be explored in sensitivity analyses, where appropriate and feasible.

Deterministic sensitivity analysis will be undertaken to explore the sensitivity of the results to variations in specific input parameters. Scenario analyses will be presented to explore the impact of alternative assumptions and evidence sources. Key scenarios are likely to include

those assessing whether tests provide predictive benefit and the magnitude of these effects across test risk classification groups. Results will be presented for important subgroups for which sufficient evidence exists. Probabilistic sensitivity analysis (PSA) will be undertaken using Monte Carlo sampling. The uncertainty around each parameter will be represented using a probability distribution, with correlation between parameters maintained if identified. Decision uncertainty will be presented using cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs).

A number of approaches will be used to ensure the credibility of the health economic model, including:

- Ensuring that the model is consistent with the NICE Reference Case and published checklists for economic evaluations/models.
- Double-programming the deterministic version of the model by the model author.
- Checking model implementation by a third-party modeller who is not involved in developing the model itself.
- Ensuring the accuracy of model input parameters against their original sources.
- Checking the appropriateness of model input parameters and assumptions with clinical experts.
- Checking the face validity of the model predictions with clinical experts.

6. Handling information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than Thursday 11th May 2023. Data arriving after this date may not be considered.

If the data meet the inclusion criteria for the review, they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by a manufacturer and specified as such will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g., in brackets). Any 'academic in confidence' data provided by the manufacturer, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness model will also be highlighted.

A version of the economic model with confidential information redacted or replaced with dummy data will be provided.

7. Competing interests of authors

None

8. Timetable/milestones

Milestone	Date to be completed
Final date for Manufacturer/sponsor data submissions	11/05/2023
Progress Report	12/07/2023
Draft Assessment Report	25/08/2023
Final Report to NICE	25/09/2023

9. Appendices

9.1 Table of breast cancer stages, compiled from Cancer Research UK[4] and National Breast Cancer Foundation[23]

		Tumour size	Lymph nodes	Spread	
	Stage 0	NR	0	Not spread beyond the tissue of origin	
Early stage invasive breast cancer	Stage 1a	≤2cm	0	Not spread beyond breast	Microscopic invasion of tissue outside the lining of the duct or lobule, but not >1mm
	Stage 1b	0 (ie no tumor) to ≤2cm	0.2-2mm groups of cells in lymph nodes		
	Stage 2a	0 to ≤2cm	>2mm in 1-3 axillary or breast bone lymph nodes		
		>2<5cm	0		
	Stage 2b	>2<5cm	0.2-2mm groups of cells in lymph nodes		
			1-3 axillary or breast bone lymph nodes		
		>5cm	0		
	Stage 3a	Any size, or none	4-9 axillary or breast bone lymph nodes		
		>5cm	0.2-2mm in lymph nodes		
		>5cm	1-3 axillary or breast bone lymph nodes		
	Stage 3b	Any size, or none	≤9 axillary or breast bone lymph nodes,	Chest wall and/or skin, causing swelling or ulcer	
	(inflammatory breast cancer)			Reddening of large portion of skin; warm and may be swollen; cancer cells spread to	

				lymph nodes/skin	
	Stage 3c	Any size, or none.	≥10 axillary LNs10 axillary LNs OR spread to collarbone LNs OR spread to axillary AND breastbone LNs	Chest wall and/or skin, causing swelling or ulceration	
	Stage 4	Any size	Any	Metastasised to other parts of the body	

9.2 Draft search strategy

Search for interventions

2017-present

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to March 10, 2023

#	Searches
1	exp Breast Neoplasms/
2	exp mammary neoplasms/
3	exp breast/
4	exp neoplasms/
5	3 and 4
6	(breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)).mp.
7	(mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullar)).mp.
8	1 or 2 or 5 or 6 or 7
9	(endopredict or epclin or "ep score").mp.
10	(mammaprint or 70-gene or "70-gene").mp.
11	(oncotype or "recurrence score" or 21-gene or "21 gene").mp.
12	(prosigna or pam50 or 50-gene or "50 gene").mp.
13	or/9-12
14	8 and 13
15	limit 14 to yr="2017 -Current"

9.3 Critical appraisal checklist for economic evaluations using key components of the British Medical Journal checklist for economic evaluations (Drummond *et al*) together with the Eddy checklist on mathematical models employed in technology assessments (Eddy 1985)

Reference ID		
Title		
Authors		
Year		
Modelling assessments should include:		**Yes/No**
1	A statement of the problem;	
2	A discussion of the need for modelling vs. alternative methodologies	
3	A description of the relevant factors and outcomes;	
4	A description of the model including reasons for this type of model and a specification of the scope including; time frame, perspective, comparators and setting. *Note: n=number of health states within sub-model*	
5	A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence;	
6	A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships, and distributions) and the data;	
7	A list of parameter values that will be used for a base case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis;	
8	The results derived from applying the model for the base case;	
9	The results of the sensitivity analyses; unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold.	
10	A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect;	
11	A description of the validation undertaken including; concurrence of experts; internal consistency; external consistency; predictive validity.	
12	A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results;	
13	A description of research in progress that could yield new data that could alter the results of the analysis	

10. Additional information that is needed by NETSCC, HTA and NICE. Please send this as a WORD document when you submit your protocol to esptar@nihr.ac.uk

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Timetable/milestones

- Progress report (to NETSCC, HTA who forward it to NICE within 24 hrs): 12/07/2023
- Assessment report (simultaneously to NICE and NETSCC, HTA): 25/09/2023

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