NATIONAL INSTITUTE FOR HEALTH AND CLINCIAL EXCELLENCE

Diagnostics Assessment Programme

Gene expression profiling and expanded immunohistochemistry tests to guide selection of chemotherapy regimes in breast cancer management

Final scope

April 2011

1 Introduction

The Medical Technologies Advisory Committee identified the Randox Breast Cancer Array (Randox BCA), a gene expression profiling test, as potentially suitable for evaluation by the Diagnostics Assessment Programme (DAP) on the basis of a briefing note. The Randox BCA is manufactured by Randox Laboratories Limited. This document has been updated following feedback from attendees at the scoping workshop held on 2 March 2011 and the assessment subgroup meeting held on 11 April 2011. The scope has been extended to include gene expression profiling and expanded immunohistochemistry tests for guiding selection of chemotherapy regimes in breast cancer management. The final scope outlines the approach for assessing the clinical and cost effectiveness components of this evaluation.

2 Target condition/indication

2.1 Breast cancer background

Breast cancer is the most common cancer in women in England. In 2008 there were 39,681 new cases diagnosed, an increase of 1,633 cases compared with 2007 (4%). Just over 10,000 women died from breast cancer in England in 2008, a rate of 26 deaths per 100,000 women. It is the second most common cause of cancer death in women, after lung cancer.

One in eight women will develop breast cancer at some point in their lives. Age is a known risk factor for developing breast cancer. Four out of every five new cases are diagnosed in women aged 50 and over, with cases peaking in the 60 to 64 age group (14% of all new cases).

Earlier detection and improved treatment for breast cancer have meant that survival rates have risen. Although incidence rates for breast cancer increased by more than 85 per cent between 1971 and 2008, mortality rates have fallen by 33% since 1971. Survival from breast cancer is higher than that for cervical cancer and much higher than that of other major cancers in women – lung, colorectal and ovarian.

2.2 Diagnosis

Sections 2.2 through 2.5 have been adapted from NICE clinical guideline – CG80 – Breast cancer (early & locally advanced).

In most cases, whether suspected at breast screening or through presentation to the GP, diagnosis in the breast clinic is made by triple assessment (clinical assessment, mammography and/or ultrasound imaging with core biopsy and/or fine needle aspiration cytology).

2.3 Primary systemic therapy (neoadjuvant therapy)

Neoadjuvant treatment in oncology is defined as additional treatment preceding the main therapy option; surgery is the main therapy option. Optimal management of breast cancer includes local control in the breast and the prevention of metastatic spread. Some patients will have developed occult metastatic spread before clinical or radiological detection of the primary tumour. There are also patients whose tumours at presentation are too large to be considered appropriate for breast conservation. Primary systemic therapy of invasive breast cancer may be offered in an attempt to enable breast conserving treatment and subsequent surgery (mastectomy or wide local excision). Histological examination is usually conducted to inform the treatment decision. Radiotherapy may then be offered according to similar criteria to those patients presenting de novo. Primary systemic treatment involves the use of systemic therapy, either chemotherapy or endocrine therapy, after diagnosis but before definitive surgery. Primary systemic therapy (also referred to as neoadjuvant therapy) can be successfully used to shrink the size of the primary tumour such that breast conservation may be achieved with a good cosmetic result but with a slightly higher risk of local recurrence comapred with mastectomy. Primary systemic therapy can also identify the efficacy of the systemic treatment regimen since the primary tumour is available to monitor response to the therapy. This option is of course not available if the primary tumour has been removed surgically. The use of primary systemic treatment allows targeting of occult metastatic tumour deposits at an earlier stage than the conventional approach of postoperative chemotherapy. Randomised trials of primary systemic therapy have failed to show a significant survival benefit, but more recent studies using current chemotherapy regimens have been able to identify subgroups of patients, such as those achieving complete pathological response at surgery, that have a survival advantage.

2.4 Surgery

Surgery is the mainstay of treatment for invasive breast cancer and is usually used as the first treatment option.

2.5 Postoperative assessment and adjuvant treatment planning

Following surgery, further information is obtained by histological examination, which provides prognostic information including histological grade, nodal status and tumour size. Factors predicting response to specific targeted therapies including hormone receptor and the human epidermal growth factor receptor 2 (HER2) statuses are also evaluated. These prognostic and predictive factors, together with patient characteristics, enable subsequent treatment planning to be undertaken by the breast cancer multidisciplinary team (MDT).

2.5.1 Predictive factors
Hormone receptors

Approximately 70% of invasive breast cancers are oestrogen receptor alpha (ER) positive and the level of ER assessed immunohistochemically provides useful predictive information regarding efficacy of endocrine therapy. ER status therefore forms part of the UK minimum dataset for histopathology reporting of invasive breast cancer. ER status is routinely determined on all invasive breast cancers and reported using a standardised technique (such as the Allred scoring

system). The prediction of likelihood of response of a breast cancer to endocrine therapies using ER assessment is not, however, precise; some patients with ER-positive disease will not respond to endocrine therapies. Additional discriminatory markers to predict response to endocrine agents with greater accuracy may prove useful. Progesterone receptor (PR) status has been considered as such an additional marker, but it does not appear to add useful information in ER-positive tumours. Divergent ER and PR status is uncommon (for example < 5% of cases are ER-negative but PR-positive) and the value of the addition of PR status in this situation in predicting likelihood of response to endocrine therapy is also unclear. Nevertheless, PR examination is routinely performed on all invasive tumours by some laboratories.

HER2 status

The clinical importance of amplification of the human epidermal growth factor receptor gene HER2 in breast cancer was recognised in 1987 and an association with poorer patient outcome was subsequently reported. HER2 positivity (protein over-expression or gene amplification) is seen in approximately 15% of early invasive breast cancer. Women whose breast cancers are HER2-positive may benefit from Trastuzumab therapy. Therefore, the HER2 status of an invasive breast cancer has become an essential part of selection of this therapy. Diagnostic tests for HER2 over-expression and gene amplification include immunohistochemistry (IHC) and fluorescence in situ hybridisation (FISH). Breast cancers are reported as HER2-negative or HER2-positive according to standardized guidelines (i.e. those scoring 3+ by IHC, or 2+ and FISH amplified, as positive).

Determining hormone recptor and HER2 status – Immunohistochemistry

IHC is used to identify specific molecules in the breast cancer sample. Specifically, IHC is commonly used to show whether or not the cancer cells have hormone receptors (ER and/or PR) and/or HER2 receptors on their surface. The tissue is treated with antibodies that bind to the specific molecule. These are made visible under a microscope by using a colour reaction, a radioisotope, colloidal gold, or a fluorescent dye.

- IHC for hormone receptor testing: guidelines for pathology reporting of breast disease recommend that results for the ER/PR be reported as negative or positive and accompanied by an Allred score. This score is based on the sum of two measures including 1) a percentage that tells you how many cells out of 100 stain positive for hormone receptors – a number between 0% (none have receptors) and 100% (all have receptors) is given and 2) a number between 0 and 3 is given to indicate the intensity of their staining. '0' means that no receptors are present, '1' a small number present, '2' a medium number, and '3' a large number.
- IHC for HER2 receptor testing: guidelines for pathology reporting of breast disease recommend that results for HER2 be reported as a semi-quantitative system based on the intensity of reaction product and percentage of membrane positive cells, giving a score range of 0–3+. Samples scoring 3+ are regarded as unequivocally positive, and those scoring 0/1+ as negative. Borderline scores of 2+ require confirmation using another analysis system, ideally fluorescence in situ hybridisation.
- Fluorescence in situ hybridisation (FISH): a laboratory technique used to look at genes or chromosomes in cells and tissues. Pieces of DNA that contain a fluorescent dye are made in the laboratory and added to cells or tissues on a glass slide. When these pieces of DNA bind to specific genes or areas of chromosomes on the slide, they light up when viewed under a microscope with a special light. HER2 FISH testing results are conventionally expressed as the ratio of HER2 signal to chromosome 17 signal. Tumours showing a ratio > 2 should be considered as positive.

Expanded IHC tests are defined as those tests that measure biomarkers other than or in addition to ER, PR and HER2. These tests aim to provide similar information to gene expression profiling tests, in particular, the likelihood of cancer recurrence.

2.5.2 Adjuvant treatment planning

Adjuvant treatment in oncology is defined as additional treatment following the main therapy option; surgery is the main therapy option. While defined in this way, adjuvant treatment is viewed as an integral part of breast cancer management. Such adjuvant therapy typically consists of one or more of radiation, chemotherapy, and/or endocrine therapy/biological therapy. Planning adjuvant treatment is complex and incorporates a variety of prognostic and predictive factors. There are a number of tools to help the MDT with decisions on adjuvant treatment planning which assess prognosis and may estimate potential treatment benefit. These are described in the section on comparators (section 4.3).

2.6 Care pathway

The care pathway for this assessment can be ascertained from existing guidelines. NICE clinical guideline – CG80 – 'Breast cancer (early & locally advanced): diagnosis and treatment' should be used in the first instance. Other guidelines that may provide supplementary information include:

- St Gallen consensus recommendations
- National Comprehensive Cancer Network guidelines (NCCN).

3 Gene expression profiling

Greater understanding of the human genome, and subsequently, the genetic determinants of cancer and other diseases, has led to an array of genetic tests for use in health care. Gene expression profiling (GEP) is a relatively new technology for identifying genes whose activity may be helpful in assessing disease prognosis and guiding therapy.

GEP tests assess the identity and number of messenger RNA (mRNA) transcripts in a specific tissue sample. As only a fraction of the genes encoded in the genome of a cell are expressed by being transcribed into mRNA, GEP provides information about the activity of genes that give rise to these mRNA transcripts. Given that mRNA molecules are translated into proteins, changes in mRNA levels are ultimately related to changes in the protein composition of the cells, and consequently to changes in the properties and functions of tissues and cells (both normal and malignant) in the body.

Various assays are used in the management of breast cancer. These assays investigate the expression of specific panels of genes (also known as a gene profile or gene signature). They work by making use of different techniques to measure mRNA levels in breast cancer specimens including real-time reverse transcription-polymerase chain reaction (RT-PCR) and DNA microarrays. Many of these assays have been designed to measure the risk of cancer recurrence. Other uses of the assays include breast cancer sub-typing (using molecular classification systems), predicting the likely benefit from certain types of therapy (e.g. chemotherapy), or diagnosing breast cancer.

There are various ways of preparing the RNA, and different protocols used to prepare the specimens (e.g. formalin-fixed, paraffin-embedded, snap-frozen and fresh samples). Furthermore, there are varying algorithms that can be used to combine the raw data to obtain a summary measure. All of these factors can affect the reproducibility and reliability of GEP tests.

The complexity of gene profiling has led to numerous efforts to develop IHC markers that are able to provide similar information to that given by GEP tests. One such test is IHC4, which looks for the presence of a proliferation marker, Ki67 in addition to testing for ER, PR and HER2.

The detailed use of gene expression profile tests, for improving chemotherapy choices for breast cancer is not currently covered in NICE guidance.

3.1 Improving chemotherapy choices

Systemic therapy options for breast cancer management include endocrine treatments, targeted biological agents and chemotherapy.

The decision about whether or not to use chemotherapy is a major challenge in breast cancer management. Chemotherapy is defined as the use of cytotoxic medications with the intention of preventing cancer recurrence in patients. Chemotherapy regimens containing Anthracycline have been used routinely in the adjuvant setting. It should be noted that, for the purposes of this assessment, chemotherapy does not include other forms of systemic therapy such as endocrine treatments or targeted biological therapy.

Although chemotherapy can reduce the likelihood of cancer recurrence and death for women with breast cancer, it has considerable adverse effects. Many women with early-stage breast cancer are advised to undergo chemotherapy, however, not all will benefit from it and some may remain free of disease recurrence at 10 years without it.

GEP and expanded IHC tests may be capable of better identifying those patients that are likely and unlikely to benefit from chemotherapy than conventional clinical and pathological risk assessment. Two types of information are most likely to be useful in this context. These are the molecular sub-type of the breast tumour and an indication of the likelihood of cancer recurrence. As well as providing information on the likely outcome/course of the cancer (prognostic information), molecular sub-typing and recurrence risk may also provide information on the likelihood of the patient benefitting from chemotherapy (predictive information). Predictive and prognostic information may be used to inform chemotherapy decisions in breast cancer management. Information on molecular sub-typing and recurrence risk can be found below.

3.1.1 Breast tumour sub-typing using molecular classification systems

Micro-array-based gene expression studies have revealed that, in addition to being clinically heterogeneous, breast cancer is also a molecularly heterogeneous disease. As a result, distinct molecular sub-types of breast cancer that exhibit different gene expression patterns and clinical outcomes have been developed. The prognosis and chemotherapy sensitivity of the various molecular sub-types are different. Luminal-like cancers tend to have the most favourable long-term survival compared with the others, whereas basal-like and HER2-positive tumours have significantly worse long-term survival and are more sensitive to chemotherapy. However, it is important to note that these correlations are expected as there is a strong association between the molecular sub-type and conventional histopathologic variables (namely, ER and HER2 status).

Numerous classification systems have been published. The first of these was described by Perou and colleagues in 2000. Since then, this classification system has been refined to distinguish the luminal group into luminal A and luminal B, and the classification of normal-like is less commonly used as it is believed to be a potential artefact from the initial study. This classification system is commonly cited in the literature and includes the following sub-types, the IHC approximation is provided in brackets (ER = oestrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor 2):

- Luminal A (ER positive and generally HER2 negative)
- Luminal B (ER positive (but a lower number of receptors than luminal A) and generally HER2 negative)
- HER2 amplified (predominantly HER2 positive and ER negative)
- Basal-like (generally ER, PR and HER2 negative (triple negative))
- Unclassified/5NP (generally ER, PR, HER2, EGFR and CK5 negative).

Initial work to identify the molecular sub-types used hierarchical clustering to design a classification model (single sample predictor (SSP)) that allows a breast cancer to be classified using a nearest centroid classifier. Essentially, this means that new tumours are sub-typed based on how similar their gene profile is to tumours used and sub-typed in the initial data-set for the SSP. Several limitations of SSPs have been posited in the literature. These include the effect of the breast tumour samples and genes selected in defining the molecular sub-types. Consequently, it has been observed that different SSPs may not reliably assign the same tumour to the same molecular sub-type. More recently, a sub-type classification model based on a parametric clustering technique defined by three gene modules has been suggested to overcome the challenges of SSPs.

Although there is a body of literature on molecular classification systems, GEP tests used for molecular sub-typing, in most cases, are at the early stages of the validation pathway. Generally, studies of diagnostic test accuracy in defining the molecular sub-types when comapred with the classification based on ER, PR and HER2 status can be found in the literature.

Clinical experts contacted during scoping felt that molecular classification systems showed great potential, however, their views on the impact of these classification systems on treatment decisions (compared with current clinical practice) were mixed. Some experts felt that molecular classification systems were useful for predicting non-response to neoadjuvant chemotherapy. In addition, the basal-like classification captured other individuals with a poor prognosis who may be missed if only using the triple negative (ER/PR/HER2 negative) diagnosis by IHC. Other experts felt that little was known about the concordance between these molecular classifications with their prognostic and predictive value. Clinical experts also felt that if molecular classification systems were to be used in the clinical setting, they would do so as an adjunct to current clinical practice rather than replacing any part of it.

The impact of molecular classification systems on breast cancer management, when added to current clinical practice, is difficult to determine from the published literature. The literature on the use of molecular signatures in predicting non-response (or response) to neoadjuvant chemotherapy suggests that different molecular sub-types respond differently to neoadjuvant chemotherapy. However, it may also be possible to use IHC as a surrogate marker for the molecular classifications. An area of potential benefit may be that of individuals with basal-like breast cancer who are not identified using the triple negative (ER/PR/HER2 negative) diagnosis by IHC. Although figures in the literature vary, triple negatives may account for approximately 7–20% of all breast cancers and it is thought that approximately 85% of all basal type tumours may be triple negatives. The literature suggests that many breast cancer researchers believe that molecular classification systems will change with further subdivision of these sub-types.

At present, molecular classification systems are not routinely used by physicians in the NHS in England. Guidelines on the use of molecular classification systems in breast cancer management were not identified during scoping.

3.1.2 Recurrence risk

Therapeutic decisions for breast cancer management are based on risk estimates. Tests that improve such estimates have the potential to affect clinical outcomes in breast cancer patients either by avoiding unnecessary chemotherapy with its attendant morbidity or by employing it where it might not otherwise have been used, thereby reducing recurrence risk.

Much of the literature on gene expression profile test validation focuses on the analytical validity and clinical validity of those tests that measure recurrence risk. Some tests are further down the validation pathway and may have evidence on the clinical utility of the technology.

Tests measuring recurrence risk combine the measurements of gene expression levels within the tumour to produce a number associated with the risk of disease recurrence. These tests aim to improve on risk stratification schemes based on clinical and pathological factors currently used in clinical practice (see section 4.3).

Existing breast cancer guidelines have recommended the use of gene expression profile tests to help guide chemotherapy treatment decisions. For example, the 2009 (11th) St Gallen consensus meeting publication states 'the Panel supported the use of a validated multigene-profiling assay, if readily available, as an adjunct to high-quality phenotyping of breast cancer in cases in which the indication for adjuvant chemotherapy remained uncertain.'

At present, GEP tests measuring recurrence risk are not routinely used by physicians in the NHS in England.

3.2 Scoping workshop feedback

Scoping workshop attendees felt that both molecular sub-typing and recurrence risk measurements may be used to stratify patients when considering chemotherapy. Attendees felt that these tests may be used with current clinical practice as opposed to replacing any part of current clinical practice.

The extensive use of chemotherapy in breast cancer management was discussed. Attendees felt that patients were over-treated with chemotherapy as it is difficult to identify those patients who are less likely to benefit from its use. This has been noted both anecdotally and in the scientific literature.

Therefore, the scope has been expanded from an evaluation of Randox BCA to include other gene expression profiling tests that are likely to influence the use of chemotherapy in breast cancer management. In addition, attendees felt it was important to include IHC tests that may fulfil this purpose.

Details of the interventions can be found in section 4.2 – *Table 1*.

4   Scope of the evaluation

The assessment has been expanded to include gene expression profiling tests and expanded immunohistochemistry tests that are likely to influence the use of chemotherapy in breast cancer management.

4.1 Population

People diagnosed with early invasive breast cancer.

Note: Although the population for the assessment is broad, some GEP and expanded IHC tests may only be used in a sub-population. For example, women with early-stage invasive breast cancer (stage I, II or III), lymph node negative or positive (up to 3), oestrogen receptor positive or negative and HER2 positive or negative. Additionally, men with breast cancer should also be included in the assessment if data are available on the use of these technologies in men.

4.2 Interventions

Several GEP and expanded IHC tests that are likely to impact the use of chemotherapy in breast cancer management exist. Technologies identified during scoping are summarised in *Table 1*.

TABLE 1 Interventions identified during scoping

Test	Manufacturer	Purpose	Description	Target population*
Gene expression profiling tests				
Randox BCA	Randox Laboratories	Molecular Sub-typing + Recurrence risk	Low density biochip array 23 gene array	All women with breast cancer
Breast Cancer Index	bioTheranostics	Recurrence risk	RT-PCR Assessment of H/I ratio (*HOXB13*: *IL17BR*) and MGI (Molecular Grade Index)	ER+, LN–
MammaPrint	Agendia	Recurrence Risk	MICROARRAY 70 gene array	Early-stage (stage I or II), LN– or LN+ (up to 3), ER+ or ER–
MammaPrint + BluePrint	Agendia	Recurrence risk + Molecular Sub-typing	MICROARRAY 70 gene array + 80 gene array	Early-stage (stage I or II), LN– or LN+ (up to 3), ER+ or ER–
OncotypeDX	Genomic Health	Recurrence risk and Predictive of chemotherapy benefit	RT-PCR 21 gene assay	Early-stage (stage I or II), LN–, ER+ patients who will be treated with hormone therapy
PAM50	ARUP Laboratories Inc.	Recurrence risk and Predictive of chemotherapy benefit	RT-qPCR 55-gene assay	Early-stage (stage I or II), LN–, ER+ patients who will be treated with hormone therapy
Expanded immunohistochemistry tests				
IHC4	N/A	Recurrence risk	IHC test based on ER, PgR, HER2 and Ki67 Plus clinical factors (age, nodal status, tumour size, grade, randomised treatment)	ER+
Mammostrat	Clarient	Recurrence risk	IHC test based on P53, HTF9C, CEACAM5, NDRG1 and SLC7A5 markers	Early-stage (stage I or II), LN–, ER+ patients who will be treated with hormone therapy
NPI+	Nottingham Prognostics	A clinical decision making tool kit for all operable breast cancer patients providing prognostic and therapeutic predictive outputs	A multistep approach combining biological assessed by immunocytochemistry and traditional pathological and clinical variables	All patients with early (stage I or II) invasive breast cancer

*ER+/−=oestrogen receptor positive or negative, LN+/−=lymph node positive or negative.

4.3 Comparators

Two existing algorithms are in use for predicting survival and the utility of adjuvant therapy in breast cancer and should serve as comparators. These include:

1. Nottingham Prognostic Index
2. Adjuvant! Online

Nottingham Prognostic Index (NPI): the NPI is a well-established, validated and widely used method of predicting survival for operable primary breast cancer. This index was based on a retrospective analysis of 9 factors in 387 patients. Only 3 of the factors (tumour size, stage of disease, and tumour grade) remained significant on multivariate analysis. The NPI is calculated as: lymph node (LN) stage (1–3) + grade (1–3) + maximum tumour diameter, giving an observed range of NPI from 2.08 (LN negative, grade 1, 0.4 cm) to 6.8 (LN stage 3, grade 3, size 4.9 cm).

Adjuvant! Online: the Adjuvant! Online computer program is designed to provide estimates of the benefits of adjuvant endocrine therapy and chemotherapy. A version of Adjuvant! Online that will include HER2 status and the potential benefit of Trastuzumab is in development. It is believed that the current version (version 8) may underestimate the risk of mortality and does not take into account the negative impact of HER2 positivity or how this may be affected by Trastuzumab. Patient and tumour characteristics are entered into the program and provide an estimate of the baseline risk of mortality or relapse for patients without adjuvant therapy. Information about the efficacy of different therapy options is derived from Early Breast Cancer Trialists Collaborative Group meta-analyses in order to provide estimates of reduction in risk at 10 years of breast cancer related death or relapse for selected treatments. Results may be displayed and printed in graphical form to aid shared decision-making. Attendees at the scoping workshop suggested that there were some difficulties in applying the Adjuvant! Online data to the UK population.

4.4 Health outcomes

The outcomes of interest are the morbidity and mortality associated with invasive breast cancer and its treatment. These may include:

- Distant recurrence free survival – 10 years
- Health-related quality of life, such as, adverse events associated with chemotherapy

Note: The health outcomes stated above are preferred for use in the assessment. However, the available data may be limited. In such cases, other data may be used. For example, total disease recurrence at 5 years or pathological complete response.

4.5 Healthcare setting

These tests will be assessed for use in the adjuvant setting and are expected to be used in secondary and tertiary care.

Note: the neoadjuvant setting was considered for inclusion in the scope, however, it was anticipated that evidence on the use of these tests in the neoadjuvant setting would be lacking. Therefore, it was decided that the assessment should focus on the adjuvant setting only.

5 Modelling approach

Tests to be included in the economic modelling will need to have sufficient data to allow modelling to proceed. The level of data required will be set by the external assessment group

(EAG). Both predictive and prognostic information may be used to inform chemotherapy decisions. Therefore, the EAG will seek to undertake economic evaluation of tests that provide either or both types of information.

5.1 Modelling possibilities

5.1.1 Molecular sub-typing

Guidelines recommending treatment decisions based on molecular sub-typing have not been uncovered during scoping. To allow the modelling of the role of sub-typing tests it would be necessary to link the accuracy of a diagnostic test to final health outcomes. Distinct molecular sub-types of breast cancer that exhibit different gene expression patterns and clinical outcomes have been developed. The prognosis and chemotherapy sensitivity of the various molecular sub-types are different. However, GEP tests used for molecular sub-typing, in most cases, are at the early stages of the validation pathway. Likely changes in treatment planning resulting from the results of sub-typing tests are as yet unclear.

5.1.2 Recurrence risk

Validation studies exist for the diagnostic technologies dealing with recurrence risk. Data on analytical validity, clinical validity, clinical utility and economic evaluations (described in section 5.2 below) are available in the published literature for certain diagnostic technologies. The availability of these data is expected to make it possible to conduct a thorough assessment.

5.2 Existing Models

Economic models for certain diagnostic technologies exist in the published literature (e.g. for MammaPrint and OncotypeDX). These economic evaluations seek to reclassify the risk category of patients who were initially defined by existing guidelines (e.g. NCCN) using the test in question. Resulting quality adjusted life years (QALYs) and costs have been reported.

5.3 Model structure

Published studies that measure the clinical utility of gene expression profile tests using a prospective study design that follow patients from initial diagnosis through to final health outcomes have not been identified during the scoping phase. Two prospective studies, MINDACT (MammaPrint) and TAILORx (Oncotype), are ongoing. Consequently, it is likely that a linked evidence approach will need to be used in the modelling. That is, outcomes of the diagnostic tests to be assessed will need to be related to changes in final heath outcomes.

5.4 Cost considerations

The Randox BCA is processed locally using the Randox Evidence Investigator Analyser. This analyser can be used to process other biochip arrays available from Randox Laboratories (e.g. ovarian cancer therapy response prediction assay, multiplex pathogen detection arrays for STIs and respiratory infections and drug metabolism SNP assays). At present, this analyser is not widely available in the NHS. Therefore, the Randox BCA will incur non-recurrent set-up costs to purchase the necessary equipment needed to process the test.

Generally, other gene expression profile tests for breast cancer are processed centrally by the manufacturer.

Protocols used to prepare the tumour specimens can vary. These include formalin-fixed, paraffin-embedded, snap-frozen and fresh samples. The costs between these protocols vary significantly and should be considered in the assessment.

5.5 Health outcomes

QALYs will need to be calculated in the economic modelling.

6 Equality issues

None identified during scoping. The population in the scope falls within the provisions of the Equality Act 2010 once a diagnosis of cancer has been made.

7 Implementation

Support tools are developed by the implementation team at NICE. The implementation team does not get involved in developing the guidance recommendations but works alongside the guidance-producing programme, the communications team and field based teams to, among other things, ensure intelligent dissemination of NICE guidance to the appropriate target audiences.

Commissioners will need to know whether there are significant non-recurrent set-up costs associated with the introduction of the interventions listed in *Table 1*, particularly where these are likely to influence the location of services or the size of population they would need to serve.

Appendix A Glossary

Adjuvant therapy

Adjuvant therapy is treatment that is given in addition to (proceeding) the primary (initial) treatment. It is designed to help reach the primary treatment goal (for example, disease eradication). Adjuvant therapy for cancer usually refers to surgery followed by chemotherapy or radiotherapy to help decrease the risk of the cancer recurring (coming back). Adjuvant therapy is considered as an integral part of treatment and is viewed as a non-surgical oncology treatment of (primary) breast cancer by clinicians.

Allred score

The Allred score is a composite of the percentage of cells that stained and the intensity of their staining.

Amplification

In genetics, an increase in the frequency of replication of a DNA segment

Analytic validity

Analytical validity in this context refers to a test's ability to accurately and reliably measure the expression of messenger ribonucleic acid (mRNA) by breast cancer tumour cells. It is usually assessed by determining how much observed measurements provided by the test/technology differ from expected values derived from a standard reference. In the measurement of gene expression, however, there are no standard reference tests and an assessment of the analytical validity of the assays has to be obtained by more indirect methods. This involves an examination of test variability arising from tumour sampling, specimen handling, specimen preparation and biologic variation within and between different samples of the same tumour, and the effect of this on the reproducibility of test when repeated in the same patient, over time.

Biomarkers

A biological molecule used as a marker for a substance or process of interest.

Breast conserving surgery

Surgery in which the cancer is removed together with a margin of normal breast tissue. The whole breast is not removed.

Breast reconstruction

The formation of a breast shape after a total mastectomy, using a synthetic implant or tissue from the woman's body.

Chemotherapy

The use of medication(s) (drugs) that are toxic to cancer cells, given with the aim of killing the cells or preventing or slowing their growth.

Clinical utility

The clinical utility of a gene expression profile relates to its ability to discriminate between those who will have more or less benefit from a therapeutic intervention: the focus in the assessment of clinical utility is outcome. Other utilities which may be considered to be important include the effect of the test on clinical decision making (for example, choice of therapy).

Direct evidence of clinical utility of a gene expression profile can only be provided in context of a randomized clinical trial where benefit can be measured in terms of an improvement of clinical outcomes such as overall survival, disease-free survival, chemotherapy toxicity, or quality of life. Prognostic estimates, though not direct estimates of benefit per se, may provide a crude estimate of benefit which may be relevant for patient decision making. They can also provide an upper limit on the degree of clinical benefit that may be expected.

Clinical validity

Clinical validity is usually defined as the degree to which a test accurately predicts the risk of an outcome (for example, time to distant metastases), as well as its ability to separate/discriminate patients with different outcomes into separate (high and low) risk classes. This is usually reported as the clinical sensitivity and specificity of the test.

Cytotoxic

Toxic to living cells.

DNA microarray

A DNA microarray (also commonly referred to as 'gene chip,' 'DNA chip') is a collection of microscopic DNA spots (defined 'features'), commonly representing single genes or transcripts, arrayed on a solid surface by covalent attachment to chemically suitable matrices, or directly synthesized on them. DNA microarrays use DNA as part of their detection system. Qualitative or quantitative measurements with DNA microarrays use the selective nature of DNA–DNA or DNA–RNA hybridisation under high-stringency conditions and fluorophore-based detection. DNA arrays are commonly used for gene expression profiling, i.e., monitoring expression levels of thousands of genes simultaneously, or for comparative genomic hybridisation.

Endocrine therapy

Treatment of cancer by removing and/or blocking the effects of hormones which stimulate the growth of cancer cells.

External assessment group

An independent group of researchers commissioned by NICE to review the evidence on a group of technologies. The external assessment group includes researchers who assess the quality of studies on the treatments, and health economists who look at whether the treatments are good value for money. The Diagnostics Assessment Committee bases its discussions on the diagnostics assessment report produced by the external assessment group.

Gene expression

Gene expression refers to the translation of the information encoded in a gene into an RNA transcript. Expressed transcripts include messenger RNAs (mRNA) translated into proteins, as well as other types of RNA, such as transfer RNA (tRNA), ribosomal RNA (rRNA), micro RNA (miRNA), and non-coding RNA (ncRNA), that are not translated into protein. Gene expression is a highly specific process by which cells switch genes on and off in a timely manner, according to their state. The study of mRNA expression in a cell is an indirect way to study the proteins counterpart.

Gene expression profiling

This term refers to any genomic techniques that measure the fraction of the genes that is expressed in a specific sample. This definition refers to techniques that allow the assessment of more than one gene at a time, especially microarray and real time RT-PCR.

Gene expression profile/pattern

This is any set of genes for which the expression in a specific sample is known. A gene expression profile may account for a variable number of genes, and the corresponding expression values may be obtained by different techniques. Gene expression profiles can be associated, by various techniques, to phenotypes.

Gene expression signature

This is an equivalent term currently in use to refer to a specific 'gene expression profile,' usually associated with a specific phenotype.

Grading

Assessing the degree of aggressiveness of a malignant tumour based usually on the appearance of its cells under the microscope.

Hierarchical clustering

A method which seeks to build a hierarchy of clusters that involves highly complex computation. In order to decide which clusters should be combined (for agglomerative clustering), or where a cluster should be split (for divisive clustering), a measure of dissimilarity between sets of observations is required.

Histology

An examination of the cellular characteristics of a tissue using a microscope.

Hormone receptor

Proteins with a cell that bind to specific hormones.

Human epidermal growth factor receptor

A molecule on the surface of a cell which interacts with a specific growth factor and helps to control how rapidly the cells grow.

Immunohistochemistry
A technique that uses antibodies to identify specific molecules in tissues which are examined and scored by a pathologist using a microscope.

Invasive breast cancer
Breast cancer where the malignant cells have broken through the lining layer of the normal tissues and extend into the fat and fibrous tissue of the breast.

Lymph nodes
Small structures which act as filters of the lymphatic system. Lymph nodes close to the primary tumour are generally the first site to which cancer spreads.

Malignant
Cancerous cells which can invade into nearby tissue and spread to other parts of the body.

Mammography
The process of taking a mammogram – a soft tissue x-ray of the breast which may be used to evaluate a lump or which may be used as a screening test in women with no signs or symptoms of breast cancer.

Mastectomy
Surgical removal of the breast.

Metastases
Deposits of cancer elsewhere in the body.

Metastasis
Spread of cancer away from the primary site to elsewhere in the body via the bloodstream or the lymphatic system.

Multidisciplinary team
A team with members from different healthcare professions (including for example, oncology, pathology, radiology, nursing).

Nearest centroid classifier
This method computes a standardized centroid for each class. This is the average gene expression for each gene in each class divided by the within-class standard deviation for that gene. Nearest centroid classification takes the gene expression profile of a new sample, and compares it to each of these class centroids. The class whose centroid that it is closest to, in squared distance, is the predicted class for that new sample.

Neoadjuvant therapy
Neoadjuvant therapy is treatment that is given prior to the primary (initial) treatment. Surgery is regarded as the primary treatment in breast cancer.

Occult
Hidden, or difficult to observe directly.

Oestrogen receptor
A protein within breast cancer cells that binds to oestrogens. It indicates that the tumour may respond to endocrine therapies. Tumours rich in oestrogen receptors have a better prognosis than those which are not.

Predictive values/markers

A molecule that is assessed to predict the likely response to a specific treatment, for example oestrogen receptor to predict the likely response to endocrine therapy.

Primary systemic therapy

Systemic therapy given before surgery or radiotherapy.

Progesterone receptor

A protein within cells that binds to progesterone.

Prognosis

A prediction of the likely outcome or course of a disease; the chance of recovery, recurrence or death.

Prognostic factors

Disease characteristics that are correlated with the course of the disease and which are used to predict the likely outcomes.

Real time reverse transcriptase polymerase chain reaction (RT-PCR)

Real-time RT-PCR is a molecular biology technique that allows the amplification and the quantification in real time of defined RNA molecules from specific specimens. This technology has been used for several years in research and clinical settings to measure RNA molecules. In the first step DNA, copies of the investigated RNA molecules present in the template are obtained by a reaction named reverse transcription. Then DNA amplification is obtained using PCR, while the quantification of the accumulating DNA product is accomplished by the use of specific fluorescent reagents. The quantification of the target RNA molecule is based on the analysis of the accumulation curve of the complementary DNA, as measured by the fluorescence detected at each cycle of the reaction.

Reverse transcription

In biochemistry, reverse transcription is the enzymatic reaction induced on by the RNA dependent DNA polymerase. This enzyme, also known as reverse transcriptase, is a DNA polymerase enzyme that copies single-stranded RNA into DNA. This process is the reverse of normal transcription, which involves the synthesis of RNA from DNA.

Single sample predictor

A classification model that enables the sub-type of a single tumour to be identified using a nearest centroid classifier based on the initial hierarchical clustering of a small (typically) data set.

Staging

Clinical description of the size and spread of a patient's tumour, allocated by internationally agreed categories.

Systemic therapy/treatment

Medicine, usually given by mouth or injection, to treat the whole body rather than targeting one specific area.

Transcription

In genetics, the process by which genetic information on a strand of DNA is used to synthesize a strand of complementary RNA.

Translation

In genetics, the process by which a messenger RNA molecule specifies the linear sequence of amino acids on a ribosome for protein synthesis.

Appendix B Abbreviations

BCA	Breast cancer array
CG	Clinical guideline
DAP	Diagnostics Assessment Programme
DNA	Deoxyribonucleic acid
ER	Oestrogen receptor
FISH	Fluorescence in situ hybridisation
GEP	Gene expression profiling
GP	General practitioner
HER2	Human epidermal growth factor receptor 2
IHC	Immunohistochemistry
LN	Lymph node
MDT	Multidisciplinary team
MINDACT	Microarray in node negative and 1-3 positive lymph node disease may avoid chemotherapy
mRNA	Messenger ribonucleic acid
NCCN	National Comprehensive Cancer Network Guidelines
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NPI	Nottingham Prognostic Index
PR	Progesterone receptor
QALY	Quality adjusted life year
RT-PCR	Reverse transcription-polymerase chain reaction
SSP	Single sample predictor
TAILORx	Trial assigning individualised options for treatment (Rx)

Appendix C Related NICE Guidance

Refer to http://guidance.nice.org.uk/Topic/Cancer/Breast.

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Appendix E Equality Impact Assessment

The impact on equality has been assessed during this assessment according to the principles of the NICE Equality scheme.

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1. Have any potential equality issues been identified during the scoping process (scoping workshop discussion, assessment subgroup discussion), and, if so, what are they?

None identified

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2. What is the preliminary view as to what extent these potential equality issues need addressing by the Committee?

N/A

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3. Has any change to the draft scope been agreed to highlight potential equality issues?

N/A

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4. Have any additional stakeholders related to potential equality issues been identified during the scoping process, and, if so, have changes to the stakeholder list been made?

Additional stakeholders have not been identified

Approved by Associate Director (name): Nick Crabb

Date: 26/04/2011

Appendix F Attendees of the assessment subgroup meeting

The following people were in attendance at the assessment subgroup meeting held on 11th April 2011:

	Name of representative	Job Title	Organisation
Standing Committee Members	Ian Cree	Director, NETSCC-EME	National Institute for Health Research
	Christopher Hyde	Professor of Public Health and Clinical Epidemiology	Peninsula Technology Assessment Group (PenTAG)
Specialist Committee Members	Carole Farrell	Nurse Clinician	The Christie NHS Foundation Trust
	Louise Jones	Consultant Clinical Scientist	Health Service Research Unit, University of Aberdeen
	Simon Pain	Consultant Breast and Endocrine Surgeon	Department of General Surgery, Norfolk & Norwich University Hospital
	Rob Stein	Consultant and Senior Lecturer in Oncology	Department of Oncology UCL Hospitals
	Ursula Van Mann	Principal Clinical Scientist	Health Service Research Unit, University of Aberdeen
External Assessment Group arriving at 13:00	Sue Ward	Project Manager & supervisor for economic modelling	ScHARR, The University of Sheffield
	Rachid Rafia	Economic Modeller	
	Alison Scope	Systematic Reviewer	

NICE staff in attendance:

Name	Title
Prof Adrian Newland	Chair, Diagnostics Advisory Committee
Nick Crabb	Associate Director, Diagnostics Assessment Programme
Hanan Bell	Technical Advisor
Jackson Lynn	Project Manager, Diagnostics Assessment Programme
Gurleen Jhuti	Technical Analyst, Diagnostics Assessment Programme
Farouk Saeed	Technical Analyst, Diagnostics Assessment Programme