Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence – Protocol

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1. Title of the project:

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

2. Name of TAR team and 'lead'

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3. Plain English Summary

[This will be used on the HTA Programme website and for any appropriate research registers.]

Breast cancer is the most commonly diagnosed cancer in women in England. In 2008 there were 39,681 new cases diagnosed, an increase of 1,633 cases comapred 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 (ONS,

2010). Treatment usually involves surgery to remove the primary tumour and any involved lymph nodes: this may be followed by radiation therapy, endocrine therapy, Trastuzumab and/or chemotherapy depending on tumour and patient variables.

To help guide treatment decision making, several guidelines have been established. The guidelines used in England include the Nottingham Prognostic Index (NPI) and Adjuvant! Online. These guidelines assist clinicians in the selection of the most appropriate treatment for a particular patient. They provide information about prognosis which is largely based on pathological parameters (e.g., tumour size, grade and lymph node status) for NPI with the addition of ER receptor status, age and co-morbidity for Adjuvant! OnLine. However, it has been suggested that these clinical tools do not predict outcome and response to treatment particularly well (Paik, 2007). Different guidelines can give different results and it has been suggested that a large proportion of women with early stage breast cancer are over-treated. This may result in unnecessary use of toxic and expensive chemotherapy for women who derive no benefit or avoidable deaths in women for whom chemotherapy was withheld.

This presents a great challenge to clinicians in estimating prognosis and making therapeutic decisions particularly relating to the decision about whether or not to use adjuvant chemotherapy (chemotherapy after surgery) in women with early stage breast cancer. While chemotherapy may prevent relapse in some, not all women with early stage breast cancer will benefit and some women remain recurrence free at 10 years without chemotherapy. However, a subset of patients with a 'good' prognosis may still develop recurrence after curative surgery and adjuvant therapy.

Detailed multi-parameter cancer profiling, using either gene expression profiling or protein expression profiling (with immunohistochemistry) has been proposed as an approach to address these issues by identifying genes or proteins whose activity may be helpful in assessing disease prognosis and guiding therapy in this group of patients. Improved information on baseline risk (i.e. prognostic risk) and response to chemotherapy (i.e. predictive benefit) may help target chemotherapy on those patients who will benefit the most. Avoiding chemotherapy in patients at low risk of recurrence and who will therefore obtain limited benefit offers the potential for cost savings (in terms of avoided chemotherapy and avoided treatment of adverse events associated with chemotherapy) and the benefit of avoiding the disutility associated with adverse events. Accurately identifying those patients at highest risk of recurrence will maximise the survival gains from chemotherapy.

Since the systematic reviews by Marchionni *et al.* (2008) (search date from 1990 to January 2007) and Smartt (2009) (search date from 2007 to September 2009) several other studies of gene expression profiling have become available.

The aim of this review is to systematically evaluate and appraise the potential clinical and cost effectiveness of using gene or protein expression profiling tests to guide selection of chemotherapy regimes in breast cancer management.

4. Decision problem

[This will appear on the HTA Programme website and appropriate research registers]

4.1 Purpose of the decision to be made

The aim of the assessment is to answer the following research question:

By guiding the selection of chemotherapy regimes in breast cancer management, will using gene or protein expression profiling tests in patients with early stage breast cancer improve health outcomes and quality of life comapred with currently used decision making protocols?

4.2 Clear definition of the intervention

Nine tests have been identified by NICE and will be included in this assessment: six are based on gene expression profiling and three on immunohistochemistry.

The gene expression profiling tests which are included are as follows;

- The Randox Assay (BCA) (Randox Laboratories) is a cDNA-based expression biochip assay that aims to accurately define the clinical sub-types of breast cancer tumours prior to initiating treatment. The target population is all individuals with diagnosed breast cancer.
- MammaPrint (Agendia) is based on microarray technology which uses a 70-gene expression profile. MammaPrint is intended as a prognostic test for women 61 years or younger with primary invasive ER+, or ER-negative (ER–) LN0 breast cancer.
- Blueprint (Agendia) used is used in addition to MammaPrint for molecular sub-typing, is an 80 gene microarray, the target population is patients with early-stage (stage I or II), LN– or LN+ (up to 3), ER+ or ER– breast cancer.
- PAM50 gene expression assay (ARUP Laboratories Inc.) identifies the major intrinsic biological subtypes of breast cancer and generates risk of recurrence (ROR) score.
- OncotypeDX (Genomic Health) quantifies gene expression for 21 genes in breast cancer tissue by RT-PCR. It is intended to predict the likelihood of recurrence in women of all ages with newly diagnosed Stage I or II, ER-positive (ER+) lymph node negative (LN0) breast cancer treated with tamoxifen. The test assigns the breast cancer a recurrence score. The test also looks at the expression of hormone receptor genes, both the estrogen receptor (ER) and progesterone receptor (PR) and can provide an indication of how responsive the cancer is likely to be to hormonal therapy.
- Breast Cancer Index (Biotheranostics) is a RT-PCR assessment of the ratio of expression of 2 genes, HOXB13 and IL17BR and the Molecular Grade Index (MGI) and gives an indication of recurrence risk. The target population are those with ER+ and LN– breast cancer.

The expanded immunohistochemistry tests for protein expression which are included are the IHC4, Mammostrat and Nottingham Prognostic Indicators plus (NPI+).

- IHC4 assesses levels of four key proteins in a breast cancer sample, ER, PgR, HER2 and Ki-67. This permits broad categorisation into the 5 main tumour subtypes which determine treatment and prognosis.
- The Mammostrat® test uses five immunohistochemical markers (SLC7A5, HTF9C, P53, NDRG1, and CEACAM5) to stratify patients into risk groups to inform treatment decisions. These markers are independent of one another and do not directly measure either proliferation or hormone receptor status.
- NPI+ is a biomarker based prognostic assay which integrates 10 predictive biomarkers of long term survival and therapeutic response with existing clinical and molecular pathology knowledge to support individualised clinical decision making.

5. Report methods for synthesis of evidence of clinical effectiveness

A systematic review of the evidence on the clinical effectiveness of gene and protein expression profiling tests to guide selection of chemotherapy regimes in breast cancer management will be

conducted. For two of the tests MammaPrint and OncotypeDX a recent systematic review exists (Smartt, 2009) therefore a summary of this review will be provided plus an update of this review will be conducted by searching for evidence on each of the two named tests and alternative names for each test for the period January 2009 to present date, and from 2002 on the product names and alternative names for the seven remaining tests. The review will be conducted following the general principles recommended in CRD's guidance (CRD, 2009), the PRISMA statement (Liberati *et al.*, 2009), and The NICE Diagnostic Assessment Programme Interim Methods Statement (NICE, 2010).

Unpublished information received from manufacturers will be summarised separately. Unpublished information will only be considered if presented in a structured format, and the method reported in a sufficient detail. Due to the time constraints of the project priority will be given to peer-review articles in press, or submitted to peer-review journals, Other types of unpublished data, including research reports, databases and other non-peer reviewed materials will be considered only if deemed to provide important information by the Assessment Team and if time/resource constraints allow.

5.1 Inclusion and exclusion criteria

The titles and abstracts of records identified by the search strategy will be examined for relevance by one reviewer. Full papers of any potentially relevant records will be obtained where possible and screened by one reviewer. The relevance of each study to the review and the decision to include/exclude studies will be made according to the inclusion criteria detailed below. Any studies which give rise to uncertainty will be reviewed by a second reviewer with involvement of a third reviewer when necessary.

Population

Inclusion criteria: People diagnosed with early invasive breast cancer. Some 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.

Interventions

Inclusion criteria: The assessment will include the gene expression profiling tests and expanded immunohistochemistry tests that have been identified by NICE. Tests to be included are: Randox Breast Cancer Array, MammaPrint + BluePrint, PAM50, MammaPrint, OncotypeDX, Breast Cancer Index, IHC4, Mammostrat and NPI+.

Comparators

The comparator will be current UK clinical practice. This includes the use of Adjuvant! Online or the Nottingham Prognostic Index (NPI), in combination with pathological parameters (eg, tumour size, grade and lymph node status), to predict survival and the utility of adjuvant therapy in breast cancer.

Outcomes

- Analytic validity (ie the ability of the test to accurately and reliably measure the expression of mRNA or proteins by breast cancer tumour cells),
- Clinical validity (ie the degree to which the test could accurately predict the risk of an outcome and discriminate patients with different outcomes),
- Clinical utility in relation to harm, impact on clinical decision making, evidence of improvement in outcomes and health care costs.

- Primary clinical outcomes to include: distant recurrence free survival at 10 years, local recurrence free survival at 10 years, total disease recurrence at 5 years, pathological complete response.
- Secondary outcomes to include: Health-related quality of life, including the impact of adverse events associated with chemotherapy. Reduction in overall chemotherapy use.

Setting

Tests which are used in secondary and tertiary care to make decisions about adjuvant chemotherapy treatment.

Study designs

Inclusion criteria: for the review of clinical effectiveness the best available level of evidence will be included, with priority given to controlled studies if available.

Exclusion criteria: studies will be excluded if they do not meet the inclusion criteria, appear to be methodologically unsound, or do not report methods and/or results in the necessary detail. The following will also be excluded:

- animal models
- preclinical and biological studies
- editorials and opinion pieces
- studies only published in languages other than English unless no other comparable data exist
- reports published as meeting abstracts will be excluded unless comparable data do not exist in full published studies and in such a case will only be included where sufficient methodological details are reported to allow critical appraisal of study quality
- studies applied only to breast cancer biology
- studies relating to these tests only in the neo-adjuvant treatment setting

5.2 Literature searching

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

- Searching of electronic databases;
- Contacting manufacturers;
- Contact with experts in the field;
- Scrutiny of bibliographies of included papers;
- Citation Searching of key papers.

The databases that will be searched include the following:

- MEDLINE and MEDLINE in Process (for latest publications);
- EMBASE;
- The Cochrane Library (including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, CENTRAL, and NHSEED)
- BIOSIS previews;
- Web of Knowledge.

Recent relevant conference proceedings including the St Gallen International Breast Cancer will be screened. In addition, relevant reviews and guidelines will be identified through the following resources: Clinical Evidence, National Institute for Health and Clinical Evidence (NICE) website, NHS Evidence – National Library of Guidelines, SIGN Guidelines, the Guidelines International Network website and the Medicines and Healthcare products Regulatory Agency.

Search terms will take into account product names and any alternative names for each of the tests. Product and alternative product names will be sought from information from manufacturers and their websites, searching full text of potentially included articles, review papers and their reference lists. A draft MEDLINE search strategy is included in Appendix 9.1)

The clinical and cost effectiveness searches will be limited by date from January 2009 to present for the OncotypeDX and MammaPrint (the search strategies from the existing systematic reviews appear to be of good quality and clearly reported and as a result all studies prior to September 2009 should have been identified). A 9 month window of overlap will be used when updating the literature search of these reviews to account for any publications that may not have yet been indexed in major science literature databases when Smartt (2009) conducted her literature search. For the other tests searches will be conducted from 2002 to present date. This date has been identified as a suitable start date by checking previous systematic reviews and submissions of reference lists from manufacturers. The first evidence for the tests included in the previous systematic review (MammaPrint or OncotypeDX) was reported in 2002. As these tests are the most established tests and furthest along the validation pathway, evidence for the subsequent tests will not predate this.

Reference lists of included papers will be assessed for additional relevant studies and where necessary, 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 to the searches.

5.3 Study selection and data extraction strategy

Data will be extracted by one reviewer using a standardised data extraction form and checked by another. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. If time constraints allow, attempts will be made to contact authors for any missing data. Data from multiple publications of the same study will be extracted as a single study. Moreover, as part of this systematic review is an update of two existing reviews, all relevant data will be extracted from the reviews in the first instance, but will be cross checked for accuracy with the original papers. If necessary, additional data will be extracted from the original papers. Supplementary information received directly from manufacturers will be summarised and tabulated separately.

5.4 Quality assessment strategy

The nature of the quality assessment which will be undertaken will depend on the types of studies identified, but will be undertaken using appropriate and established tools.

Although there are no validated tools for the assessment of the quality of tumour marker/ gene expression profiling studies, Smartt (2009) used the general principles of the reporting recommendations for tumour marker prognostic studies (REMARK) to assess the quality of the studies. The REMARK guidelines were developed to encourage transparent and relevant reporting of study design, pre-planned hypotheses, patient and specimen characteristics, assay methods, and statistical analysis methods, in order to help others judge the usefulness of the data presented (McShane, Altman, Sauerbrei *et al*., 2005). However, these guidelines are not fully suited to genetic risk prediction studies. Recently Janseens *et al* (2011) developed a checklist for strengthening the reporting of the genetic risk prediction studies (GRIPS) by building on the principles established by prior reporting guidelines (STREGA, REMARK, STARD). For this review, we will assess the study quality using the relevant sections of the GRIPS reporting guidelines (Janseens *et al*., 2011). The assessment will be performed by one reviewer,

and independently checked by another. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

5.5 Methods of analysis/synthesis

The results of data extraction will be tabulated and discussed as a narrative summary. If sufficient clinically and statistically homogenous data are available, data will be pooled using appropriate meta-analytic techniques to estimate a summary measure of effect on relevant outcomes. Clinical, methodological and statistical heterogeneity will be investigated.

6. Report methods for synthesising evidence of cost-effectiveness

A systematic review of the existing literature studying the cost effectiveness of the nine identified tests to guide selection of chemotherapy regimes in breast cancer management will be undertaken.

6.1 Identifying and systematically reviewing published cost effectiveness studies

Databases to be searched are shown in section 5.2. Cost-effectiveness studies will be identified using an economic search filter. A draft MEDLINE search strategy is presented in Appendix 1 and will be adapted for use in other databases. In addition, relevant cost papers identified from the clinical effectiveness searches will be included in the economic review.

6.2 Evaluation of costs and cost effectiveness

The quality of identified cost-effectiveness studies will be assessed against a critical appraisal checklist adapted from the Drummond (Drummond 1996) and Eddy (Eddy 1985) checklists (Appendix 9.2).

6.3 Development of a health economic model

Preliminary discussion with clinical experts indicates that patients diagnosed with breast cancer follow the diagnosis/treatment pathway described in *Figure 1*. GEP and expanded IHC tests aim to improve the use of chemotherapy in breast cancer by stratifying patients and identifying those patients who will gain most benefit from chemotherapy. These tests may report two types of information – breast cancer sub-types and/or risk of recurrence. Tests developed to provide information on sub-types might be used either before surgery for informing decisions on neo-adjuvant therapy or after surgery for informing decisions on adjuvant chemotherapy. Tests predicting the risk of recurrence in a specific population are likely to be used further down in the treatment pathway after surgery, in conjunction with other information available about tumour size, grade etc, to guide the use of adjuvant therapy.

The objective of the economic evaluation will be to explore the cost effectiveness of tests in the adjuvant chemotherapy setting. The cost effectiveness of these tests in the neo-adjuvant setting will not be evaluated in this evaluation. The feasibility of modelling any individual test will be dependent on the level of evidence available, the robustness of data and time constraints within the project. Tests that do not have fully reported external validation studies (i.e validation on an independent dataset) will not be included in the economic evaluation. Evidence will be required on the impact on adjuvant chemotherapy treatment decisions of the new test, compared with current clinical practice (adjuvant online or NPI). Tests validated for use in predicting chemotherapy benefit will be distinguished from those using prognostic information as a proxy for chemotherapy benefit. 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 if suitable evidence allows.

A preliminary review of the evidence suggests that less robust data are available for the effect of molecular sub-typing tests comapred with the risk of recurrence tests. The potential role of sub-typing tests would be to add additional information into the existing decision making process. For instance information on luminal status may provide an indication of the likelihood of patients responding to chemotherapy. However, it is expected that evidence on the impact of sub-typing on decision-making will be limited or even lacking completely.

We anticipate the appropriate comparators for the risk of recurrence after surgery to guide the use of chemotherapy is expected to be the NPI score, Adjuvant! Online or any adaptation of these tools in clinical practice. It is expected that there might be some variation in clinical practice in the UK.

The primary outcome from the model will be an estimate of the incremental cost per additional quality-adjusted life year (QALY) gained associated with the use of tests to improve the use of chemotherapy in breast cancer. Secondary outcomes (health benefits) will also be presented. Costs and benefits will be captured using a lifetime horizon and modelled in line with the NICE Diagnostic Assessment Programme Interim Methods Statement (NICE, 2010). The model will adopt the perspective of the UK NHS and personal social services (PSS) with costs and benefits discounted at an annual rate of 3.5%. Modelling assumptions will be taken from the literature, supplemented by clinical expert opinion where required. Tests needing fresh samples (such as MammaPrint) may require significant re-organisation of pathology services, with resulting costs. Quality of life data will be reviewed and used to generate the quality adjustment weights required to estimate QALYs. Costs will be derived from national sources (e.g. NHS reference costs, national unit costs, *British National Formulary*) and data provided by the manufacturers.

The development of the model is likely to be an iterative process. A conceptual model will be developed in conjunction with clinical experts to capture the current pathway of care for the diagnosis and management of breast cancer and how the new tests would change the pathway if routinely available in the NHS. The conceptual model will indicate the data requirements which will be sought both from the published literature and within commercial in confidence data held by the manufacturers. The model is likely to evolve following discussions with project stakeholders and the specialist committee members (SCMs), and according to the availability of data. It is anticipated that there may be limited evidence for some of the parameters that will be included in the economic model. Therefore, the uncertainty around the parameter estimates will be modelled to take this into account. A range of scenarios will be presented varying main model assumptions to identify parameters that impact the most the ICER and to represent the uncertainty in parameters estimate. Furthermore, Probabilistic sensitivity analysis (PSA) will also be carried out using Monte Carlo simulation. The uncertainty in each parameter will be represented using a probability distribution. The decision uncertainty will be presented as the probability that each intervention is the most cost-effective for a given cost-effectiveness threshold. Cost-effectiveness acceptability curves will also be presented to illustrate graphically the decision uncertainty.

7. Handling the company submission(s)

All relevant data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 27 May 2011. Data arriving after this date is unlikely to be considered, except data specifically requested by the Assessment team. 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.

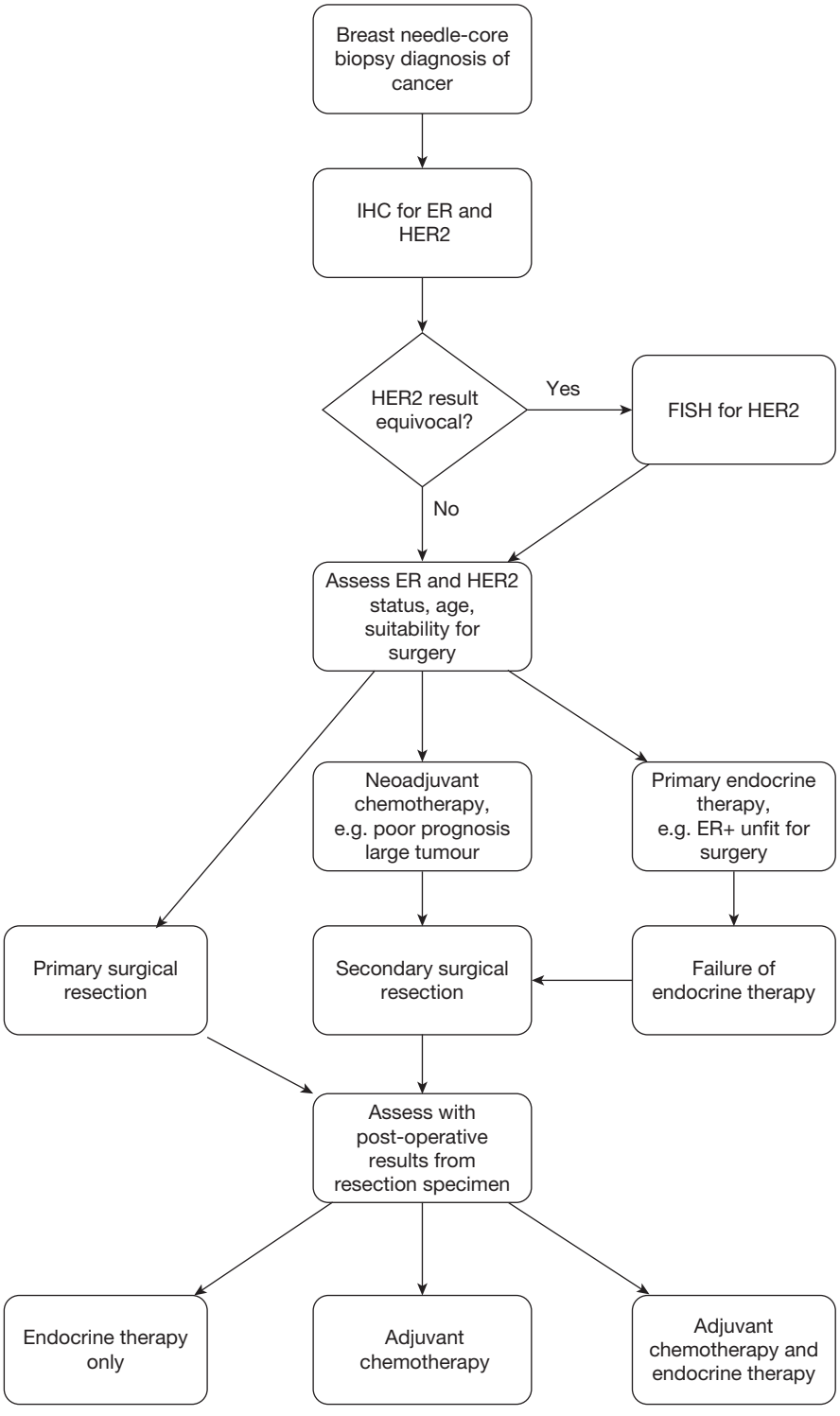

FIGURE 1 Diagnosis and management pathway in breast cancer.

Any economic evaluations included in the company submission, provided it complies with NICE's advice on presentation, will be assessed for clinical relevance, reasonableness of assumptions and appropriateness of the data used in the economic model. If the TAR team judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing a de-novo model

Any 'commercial in confidence' data taken from a company submission, and specified as confidential in the check list, 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 manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

8. Competing interests of authors

None

9. Appendices

9.1 Draft search strategy

Update search for OncotypeDX, and MammaPrint

Date limits = January 2009 – date
Filter = human studies only

1. exp Breast Neoplasms/
2. exp mammary neoplasms/
3. exp "Neoplasms, Ductal, Lobular, and Medullary"/
4. exp breast/
5. exp neoplasms/
6. 4 and 5
7. (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.
8. (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 medullary)).mp.
9. 1 or 2 or 3 or 6 or 7 or 8
10. MammaPrint.mp.
11. 70-gene.mp.
12. gene70.mp.
13. gene?seventy.mp.
14. seventy?gene.mp.
15. amsterdam profile.mp.
16. Oncotype.mp.
17. Oncotype DX.mp.
18. 21-gene.mp.
19. gene21.mp.
20. gene?twentyone.mp.
21. twentyone?gene.mp.
22. GHI Recurrence score.mp.
23. GHI-RS.mp.
24. 92-gene.mp.
25. gene92.mp.
26. gene?ninetytwo.mp.
27. ninetytwo?gene.mp.
28. RT-PCR (adj 5) 21.mp.
29. or/10–28
30. 9 and 29

Search for Randox, Blueprint, PAM50, Breast Cancer Index, IHC4, Mammostrat, and NPI+

Date limits = 2002 – date
Filter = human studies only

1. exp Breast Neoplasms/
2. exp mammary neoplasms/
3. exp "Neoplasms, Ductal, Lobular, and Medullary"/
4. exp breast/
5. exp neoplasms/
6. 4 and 5
7. (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.
8. (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 medullary)).mp.
9. 1 or 2 or 3 or 6 or 7 or 8
10. Randox.mp.
11. Blueprint.mp.
12. 80-gene.mp.
13. gene80.mp.
14. gene?eighty.mp.
15. eighty?gene.mp.
16. PAM50.mp.
17. 50-gene.mp.
18. gene50.mp.
19. gene?fifty.mp.
20. fifty?gene.mp.
21. breast bioclassifier.mp.
22. Breast Cancer Index.mp.
23. Breast cancer gene expression ratio.mp.
24. 2-gene.mp.
25. Two-gene-index.mp.
26. 2-gene-index.mp.
27. Two?gene.mp.
28. gene?two.mp.
29. H?I.mp.
30. H:I.mp.
31. 5-gene.mp.
32. gene5.mp.
33. gene?five.mp.
34. five?gene.mp.
35. 7-gene.mp.
36. seven-gene.mp.
37. gene7.mp.
38. gene?seven.mp.
39. Theros.mp.
40. Biotheranostics.mp.
41. Theros breast cancer index.mp.
42. HOXB13$.mp.
43. homeobox?13$.mp.
44. interleukin?17B$.mp.
45. IL17BR.mp.

46. mammostrat.mp.
47. five-biomarker-assay.mp.
48. IHC4.mp.
49. NPI+.mp.
50. Nottingham prognostic index plus.mp.
51. Nottingham prognostic index +.mp.
52. or/10–51
53. 9 and 52

9.2 Critical appraisal checklist for economic evaluations using key components of the British Medical Journal checklist for economic evaluations (Drummond & Jefferson 1996) 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	

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Timetable/milestones

Progress report (to NETSCC, HTA who forward it to NICE within 24hr): 15 July 2011.

Draft assessment report (simultaneously to NICE and NETSCC, HTA): 22 August 2011.

Assessment Report (simultaneously to NICE and NETSCC, HTA): 19 September 2011.

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